

FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

February 23-24, 2015

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. We are bringing certain compounding issues to this Advisory Committee to obtain the Committee's advice. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The FDA does not intend to issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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I. Withdrawn or Removed List

A. Background

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (**Tab 1**) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from the following three sections of the FD&C Act:

- (1) Section 501(a)(2)(B) (concerning current good manufacturing practice);
- (2) Section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and
- (3) Section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).¹

One of the conditions that must be satisfied to qualify for the exemptions under section 503A of the FD&C Act is that the licensed pharmacist or licensed physician “does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective” (“the withdrawn or removed list”) (section 503A(b)(1)(C)).

In 1998, FDA began to develop the list. FDA published a proposed rule in the Federal Register of October 8, 1998 (63 FR 54082) (**Tab 2**). After the proposed rule published, as required by the statute, FDA consulted the Pharmacy Compounding Advisory Committee about the 60 drug products FDA had proposed for inclusion on the original withdrawn or removed list. In 1999, FDA finalized and codified the withdrawn or removed list at 21 CFR 216.24, explaining that the drug products included on this list “may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act” (64 FR 10944, March 8, 1999) (**Tab 3**).

In the Federal Register of January 4, 2000 (65 FR 256), FDA proposed a rule to amend § 216.24 (2000 proposed rule) (**Tab 4**). Specifically, FDA proposed to add all drug products containing aminopyrine and all drug products containing astemizole to the original list of drug products withdrawn or removed from the market because they have been found to be unsafe or not effective. After the 2000 proposed rule published, three additional drug products (cisapride, grepafloxacin, and troglitazone) were identified as candidates for addition to the list. These five drug products were presented to the Advisory Committee at a meeting held on July 13 and 14, 2000 (65

¹ Section 503A of the FD&C Act does not apply to compounded positron emission tomography (PET) drugs as defined in section 201(ii) of the FD&C Act or radiopharmaceuticals (see section 503A(d) of the FD&C Act). Section 503A also does not apply to drugs intended for use in animals.

FR 40104, June 29, 2000) (**Tab 5**). The Advisory Committee voted to include aminopyrine, astemizole, cisapride, grepafloxacin, and troglitazone to the list of drug products that have been withdrawn or removed from the market because they were found to be unsafe or not effective.

FDA did not complete this rulemaking or further update this rule because of ongoing litigation concerning the validity of section 503A, which was resolved by the enactment of the Drug Quality and Security Act (DQSA) in 2013.²

On July 2, 2014, FDA published a proposed rule to revise and update 21 CFR 216.24 (see 79 FR 37687) (**Tab 6**), which will also apply to outsourcing facilities, a new category of compounder created under the DQSA.³ In reviewing 21 CFR 216.24, FDA determined that the list needed to be updated to reflect drug products that had been withdrawn or removed from the market since the final rule was promulgated in 1999. In the July 2014 proposed rule, FDA recommended the addition of 25 drug products to the list and the modification of one drug already on the codified list (79 FR 37687). Only two drug specific comments were submitted to the docket of the July 2014 proposed rule, one on adenosine phosphate, which is currently included on the list in 21 CFR 216.24, and one on chloramphenicol tablets, 250 milligrams, which was proposed for inclusion in the July 2, 2014 proposed rule.

B. Drugs Proposed for the Withdrawn or Removed List for Which Comments Were Submitted

1. Adenosine Phosphate

The current withdrawn or removed list contains the following entry for adenosine phosphate: All drug products containing adenosine phosphate. FDA received one comment asking that FDA clarify whether the entry for adenosine phosphate on the withdrawn or removed list is intended to include all three forms of adenosine phosphate (mono-, di-, and tri-phosphate) (see Appendix 3 of the attached **2015 FDA Review of Adenosine Phosphate at Tab 7**).

The preamble to the proposed rule published in the Federal Register of October 8, 1998, indicated that FDA previously determined adenosine phosphate, formerly marketed as a component of Adeno for injection, Adco for injection, and other

² Public Law 113-54, Title I (Nov. 27, 2013; 127 Stat. 587).

³ The DQSA added new section 503B of the FD&C Act that created a new category of “outsourcing facilities.” One of the conditions in section 503B of the FD&C Act that must be satisfied for an outsourcing facility to qualify for certain exemptions is that the drug does not appear on a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (see section 503B(a)(4)). Given that nearly identical criteria apply for a drug to be included on the list referred to in section 503A(b)(1)(C) and the list referred to in section 503B(a)(4) of the FD&C Act, FDA proposed to revise and update the list at § 216.24 (21 CFR 216.24) for purposes of both sections 503A and 503B.

drug products, to be neither safe nor effective for its intended uses as a vasodilator and an anti-inflammatory. The preamble noted that in 1973, FDA directed the removal of these drug products from the market (see 63 FR 54082).

After the proposed rule published, FDA consulted the Pharmacy Compounding Advisory Committee about the 60 drug products FDA had proposed for inclusion on the original withdrawn or removed list, including adenosine phosphate. The Advisory Committee briefly discussed the reasons for including adenosine phosphate in the list, and voiced no objections to FDA's proposal to include adenosine phosphate on the withdrawn or removed list.

The language of the current adenosine phosphate entry in 21 CFR 216.24 does not specify that the compounding prohibition is intended to apply only to adenosine monophosphate; instead, it lists adenosine phosphate without any further qualification. However, in light of the comment requesting clarification regarding the adenosine phosphate entry, FDA has assessed whether to modify the entry for adenosine phosphate on the list, and for the reasons described in the attached **2015 FDA Review of Adenosine Phosphate (Tab 7)**, is recommending that adenosine mono-, di- and tri- phosphate be included on the withdrawn or removed list.

2. Chloramphenicol

One of the new drugs products proposed for inclusion on the withdrawn or removed list in the July 2014 proposed rule (79 FR 37,687) was "*All oral drug products containing chloramphenicol.*" As FDA explained in the preamble of the July 2014 proposed rule, FDA has previously determined that an oral drug containing chloramphenicol was withdrawn for reasons of safety or effectiveness. In response to the comment, FDA reviewed the basis for including oral chloramphenicol on the list and for the reasons described in the attached **2015 FDA Review of Oral Chloramphenicol (Tab 8)**, continues to recommend that oral chloramphenicol be included on the withdrawn or removed list.

C. Drugs Proposed for the Withdrawn or Removed List for Which No Comments Were Submitted

The Agency did not receive comments on 24 of the drugs proposed for inclusion on the list in the July, 2014 proposal, nor were comments submitted with regard to the proposal to modify the entry for one of the drugs already on the list, bromfenac sodium. The 24 drugs and bromfenac sodium are listed below along with the background material that formed the basis for the proposal to include them on the list.

1. **Alatrofloxacin mesylate** – All drug products containing alatrofloxacin mesylate.
 - a. FDA Public Health Advisory Letter from Murray M. Lumpkin, M.D., Deputy Center Director (Review Management), Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland, Re: Food and Drug Administration 09 June 1999 Trovan (Trovfloxacin/Alatrofloxacin Mesylate) Interim Recommendations (June 9, 1999) (**Tab 9**)
 - b. Federal Register of June 16, 2006 (71 FR 34940) Revocation of Requirements for Aminopyrine and Dipyrone Merck & Co., Inc., et al.; Withdrawal of Approval of 65 New Drug Applications and 52 Abbreviated New Drug Applications (**Tab 10**)
2. **Aminopyrine** – All drug products containing aminopyrine
 - a. Revocation of Requirements for Aminopyrine and Dipyrone (42 FR 53954, October 4, 1977) (**Tab 11**)
 - b. Materials on Aminopyrine included in the Briefing Information for the July 13 – 14, 2000 Meeting of the Pharmacy Compounding Advisory Committee:
 - i. Revocation of Requirements for Aminopyrine and Dipyrone (42 FR 53954, October 4, 1977) (**Tab 11**)
 - ii. RX Study Bulletin #231 Drug Products containing Dipyrone (**Tab 12**)
3. **Astemizole** - All drug products containing astemizole
 - a. Materials on Astemizole included in the Briefing Information for the July 13 – 14, 2000 Meeting of the Pharmacy Compounding Advisory Committee
 - i. Determination that Astemizole 10mg tablets Were Withdrawn From Sale for Safety Reasons (64 FR 45973, August 23, 1999) (**Tab 13**)
 - ii. FDA Talk Paper, T99-29 (June 21, 1999) Janssen Pharmaceutica Announces the Withdrawal of Hismanal From the Market (**Tab 14**)
 - iii. "Dear Healthcare Provider" Letter from Janssen Pharmaceutica (June 18, 1999) (**Tab 15**)
4. **Bromfenac sodium** - All drug products containing bromfenac sodium except ophthalmic solutions)
 - a. Materials on Bromfenac Sodium included in the Briefing Information for the October 14 – 16, 1998 Meeting of the Pharmacy Compounding Advisory Committee (**Tab 16**)

- b. Federal Register of May 13, 2011 (76 FR 28045) “Determination That XIBROM (Bromfenac Ophthalmic Solution) 0.09% Was Not Withdrawn From Sale for Reasons for Safety or Effectiveness” (**Tab 17**)
- 5. **Cerivastatin sodium** - All drug products containing cerivastatin sodium
 - a. Letter from E. Paul Mac Carthy, MD, Vice President, Head U.S. Medical Science, Bayer Corporation, to Healthcare Professional, Re: Market withdrawal of Baycol (cerivastatin) (August 8, 2001) (**Tab 18**)
- 6. **Cisapride** - All drug products containing cisapride
 - a. Materials on cisapride included in the Briefing Information for the July 13 – 14, 2000 Meeting of the Pharmacy Compounding Advisory Committee
 - i. FDA Talk Paper, T00-14 (March 23, 2000) Janssen Pharmaceutica Stops Marketing Cisapride in the US (**Tab 19**)
 - ii. Janssen Pharmaceutica Press Release (March 23, 2000) (**Tab 20**)
 - iii. *Washington Post* article (March 24, 2000) "Heartburn Drug to Be Pulled"
 - iv. "Dear Healthcare Provider" Letter from Janssen Pharmaceutica (April 12, 2000) (**Tab 21**)
 - b. Letter from Jan Gheuens, MD, PhD, Vice President, Medical Affairs, Janssen Pharmaceutica, to Healthcare Professional (April 12, 2000) (**Tab 22**)
- 7. **Esmolol hydrochloride** - All parenteral drug products containing esmolol HCl that supply 250 mg/milliliter (mL) of concentrated esmolol per 10-mL ampule.
 - a. Federal Register of May 5, 2010 (75 FR 24710) “Determination That BREVIBLOC (Esmolol Hydrochloride) Injection, 250 Milligrams/Milliliter, 10-Milliliter Ampule, Was Withdrawn From Sale for Reasons of Safety or Effectiveness” (**Tab 23**)
- 8. **Etretinate** - All drug products containing etretinate
 - a. Federal Register of September 10, 2003 (68 FR 53384) “Hoffman-La Roche, Inc.; Withdrawal of Approval of a New Drug Application” for TEGISON (**Tab 24**)
- 9. **Gatifloxacin**: All drug products containing gatifloxacin (except ophthalmic solutions)
 - a. Federal Register of February 3, 2006 (71 FR 5858) “Determination That TEQUIN (Gatifloxacin) Injection, 10 Milligrams per Milliliter (200

Milligrams), Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness” (**Tab 25**)

- b. Federal Register of September 9, 2008 (73 FR 52357) “Determination that TEQUIN (Gatifloxacin) Was Withdrawn From Sale for Reasons of Safety or Effectiveness” (**Tab 26**)

10. Grepafloxacin - All drug products containing grepafloxacin

- a. Materials on grepafloxacin included in the Briefing Information for the July 13 – 14, 2000 Meeting of the Pharmacy Compounding Advisory Committee
 - i. Glaxo Wellcome Press Release (October 27, 1999) announcing the voluntary withdrawing of its oral fluoroquinolone antibiotic, Raxar (grepafloxacin) (**Tab 27**)
 - ii. "Dear Healthcare Provider" Letter from Glaxo Wellcome (November 1, 1999) announcing voluntary withdrawing of all licensed formulations of RAXAR (**Tab 28**)
 - iii. *Wall Street Journal* article (October 28, 1999) "Glaxo Removes Raxar Antibiotic From Markets Due to Side Effects"
- b. Federal Register of June 14, 2007 (72 FR 32852) “Otsuka Pharmaceutical Co., Ltd.; Withdrawal of Approval of New Drug Application” (**Tab 29**)
- c. Federal Register of July 9, 2007 (72 FR 37244) “Otsuka Pharmaceutical Col, Ltd.; Withdrawal of Approval of a New Drug Application; Correction” (**Tab 30**)

11. Methoxyflurane - All drug products containing methoxyflurane

- a. Federal Register of August 16, 2001 (66 FR 43017) “Schering Corp, et al.; Withdrawal of Approval of 51 New Drug Applications and 25 Abbreviated New Drug Applications” (**Tab 31**)
- b. Federal Register of September 6, 2005 (70 FR 53019) “Determination That Penthrane (Methoxyflurane) Inhalation Liquid, 99.9 Percent, Was Withdrawn From Sale for Reasons of Safety or Effectiveness” (**Tab 32**)

12. Novobiocin sodium – All drug products containing novobiocin sodium

- a. Federal Register of February 11, 2009 (74 FR 6896) “Apothecon et al.; Withdrawal of Approval of 103 New Drug Applications and 35 Abbreviated New Drug Applications” (**Tab 33**)
- b. Federal Register of January 19, 2011 (76 FR 3143) “Determination That ALBAMYCIN (Novobiocin Sodium) Capsule, 250 Milligrams, Was Withdrawn From Sale for Reasons of Safety or Effectiveness” (**Tab 34**)

13. **Oxycodone hydrochloride** – All extended-release drug products containing oxycodone hydrochloride that have not been determined by FDA to have abuse-deterrent properties
- a. Federal Register of April 18, 2013 (78 FR 23273) “Determination That the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20-553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness” and 11 corresponding reference documents (**Tab 35**)
 - b. References to Federal Register of April 18, 2013 published by the government:
 - i. Reference 1: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (CDC), “Policy Impact: Prescription Painkiller Overdoses” (**Tab 36**).
 - ii. Reference 2: CDC, “Vital Signs: Overdoses of Prescription Opioid Pain Relievers— United States, 1999–2008,” *Morbidity and Mortality Weekly Report*, vol. 60, No. 43, pp. 1487–1492, 2011(**Tab 37**).
 - iii. Reference 3: National Center for Injury Prevention and Control, CDC, “Unintentional Drug Poisoning in the United States” (**Tab 38**).
 - iv. Reference 5: FDA, “FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics” (**Tab 39**).
 - v. Reference 6: FDA, “Draft Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling”(**Tab 40**).
 - vi. Reference 10: CDC, “Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance From the CDC and the U.S. Department of Health and Human Services,” *Morbidity and Mortality Weekly Report*, vol. 61, pp. 1–40, 2012 (**Tab 41**).
 - c. Citations for copyrighted references in the Federal Register of April 18, 2013:
 - i. Reference 4: Jones, C.M., K.A. Mack, and L.J. Paulozzi, “Pharmaceutical Overdose Deaths, United States, 2010,” *Journal of the American Medical Association*, vol. 309, pp. 657–659, 2013.
 - ii. Reference 7: Katz, N., R.C. Dart, E. Bailey, et al., “Tampering With Prescription Opioids: Nature and Extent of the Problem, Health Consequences, and Solutions,” *The American Journal of Drug and Alcohol Abuse*, vol. 37, pp. 205–217, 2011.

- iii. Reference 8: Silva, K., S.M. Schrage, A. Kecojevic, et al., “Factors Associated With History of Non-Fatal Overdose Among Young Nonmedical Users of Prescription Drugs,” *Drug and Alcohol Dependence*, vol. 128, pp. 104–110, 2013.
 - iv. Reference 9: Degenhardt, L., C. Bucello, B. Mathers, et al., “Mortality Among Regular or Dependent Users of Heroin and Other Opioids: A Systematic Review and Meta- Analysis of Cohort Studies,” *Addiction*, vol. 106, pp. 32–51, 2011.
 - v. Reference 11: Alexander, D., K. Alexander, and J. Valentino, “Intranasal Hydrocodone-Acetaminophen Abuse-Induced Necrosis of the Nasal Cavity and Pharynx,” *The Laryngoscope*, vol. 122, pp. 2378–2381, 2012.
- d. Federal Register of August 7, 2013 (78 FR 48177) “Purdue Pharma L.P.; Withdrawal of Approval of a New Drug Application for Oxycontin” (**Tab 42**)
14. **Pemoline** – All drug products containing pemoline
- a. FDA Alert – Information for Healthcare Professionals: Pemoline Tablets and Chewable Tablets (marketed as Cylert) (October 2005) (**Tab 43**)
15. **Pergolide mesylate** – All drug products containing pergolide mesylate
- a. FDA Public Health Advisory – Pergolide (marketed as Permax) (March 29, 2007) (**Tab 44**)
16. **Phenylpropanolamine (PPA)** – All drug products containing PPA
- a. Final Minutes of October 19, 2000 Meeting of the FDA Nonprescription Drugs Advisory Committee “Safety Issues of Phenylpropanolamine (PPA) in Over-the-Counter (OTC) Products” (**Tab 45**)
 - b. FDA Public Health Advisory – Safety of Phenylpropanolamine (November 6, 2000) (**Tab 46**)
 - c. Federal Register of August 14, 2001 (66 FR 42665) “Phenylpropanolamine; Proposal to Withdraw Approval of New Drug Applications and Abbreviated New Drug Applications; Opportunity for a Hearing” (**Tab 47**)
 - d. Federal Register of February 20, 2002 (67 FR 7702) “Mylan Pharmaceuticals et al.; Withdrawal of Approval of 34 Abbreviated New Drug Applications” (**Tab 48**)
 - e. Federal Register of December 22, 2005 (70 FR 75988) “Phenylpropanolamine-Containing Drug Products for Over-the-Counter Human Use; Tentative Final Monographs” (**Tab 49**)

- f. Federal Register of February 20, 2014 (79 FR 9744)
“Phenylpropanolamine; Withdrawal of Approval of 13 New Drug Applications and 7 Abbreviated New Drug Applications” (**Tab 50**)

17. **Polyethylene glycol (PEG) 3350, sodium chloride, sodium bicarbonate, potassium chloride, and bisacodyl** – All drug products containing PEG 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution, and 10 milligrams (mg) or more of bisacodyl delayed-release tablets

- a. Federal Register of August 17, 2011 (76 FR 51037) “Determination That Halflytely and Bisacodyl Tablets Bowel Prep Kit (Containing Two Bisacodyl Delayed Release Tablets, 5 Milligrams) Was Withdrawn From Sale for Reasons of Safety or Effectiveness” (**Tab 51**)

18. **Propoxyphene** – All drug products containing propoxyphene

- a. FDA Drug Safety Communication – FDA Recommends Against Continued Use of Propoxyphene (November 19, 2010) (**Tab 52**)
- b. Federal Register of March 10, 2014 (79 FR 13308) “Xanodyne Pharmaceuticals, Inc., et al.; Withdrawal of Approval of 8 New Drug Applications and 46 Abbreviated New Drug Applications for Propoxyphene Products” (**Tab 53**)
- c. Federal Register of March 10, 2014 (79 FR 13310) “MK Laboratories, Inc., et al.; Proposal To Withdraw Approval of Three Abbreviated New Drug Applications for Propoxyphene Products; Opportunity for a Hearing” (**Tab 54**)

19. **Rapacuronium bromide** – All drug products containing rapacuronium bromide

- a. Letter from Deborah Shapse, MD, Medical Director, Organon, Inc., Re: Voluntary Market Withdrawal of Raplon[®] (rapacuronium bromide) for Injection, All Batches (March 27, 2001) (**Tab 55**)
- b. Federal Register of March 19, 2012 (77 FR 16039) “Abbott Laboratories et al.; Withdrawal of Approval of 35 New Drug Applications and 64 Abbreviated New Drug Applications” (**Tab 56**)

20. **Rofecoxib** – All drug products containing rofecoxib

- a. FDA Public Health Advisory – Safety of Vioxx (September 30, 2004) (**Tab 57**)
- b. Announcement by Merck (worldwide withdrawal of VIOXX) (**Tab 58**)

21. **Sibutramine hydrochloride** – All drug products containing sibutramine hydrochloride

- a. Federal Register of December 21, 2010 (75 FR 80061) “Abbott Laboratories, Inc.; Withdrawal of Approval of a New Drug Application for MERIDIA” (**Tab 59**)

22. **Tegaserod maleate** – All drug products containing tegaserod maleate

- a. FDA Public Health Advisory – Tegaserod maleate (marketed as Zelnorm) (March 30, 2007) (**Tab 60**)
- b. FDA News Release, “FDA Permits Restricted Use of Zelnorm for Qualifying Patients” (July 27, 2007) (**Tab 61**)
- c. FDA Zelnorm (tegaserod maleate) Information, (April 2, 2008) (**Tab 62**)

23. **Troglitazone** - All drug products containing troglitazone

- a. Materials on troglitazone included in the Briefing Information for the July 13 – 14, 2000 Meeting of the Pharmacy Compounding Advisory Committee
 - i. "Dear Pharmacist" Letter from Warner-Lambert Company (March 22, 2000) (**Tab 63**)
 - ii. Warner-Lambert Company Press Release (March 21, 2000) (**Tab 64**)
 - iii. HHS News Press Release (March 21, 2000) Rezulin to Be Withdrawn From the Market (**Tab 65**)
 - iv. *Washington Post* article (March 22, 2000) "Controversial Diabetes Drug Is Withdrawn"

24. **Trovafloxacin mesylate** – All drug products containing trovafloxacin mesylate

- a. FDA Public Health Advisory Letter from Murray M. Lumpkin, M.D., Deputy Center Director (Review Management), Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland, Re: Food and Drug Administration 09 June 1999 Trovan (Trovafloxacin/Alatrofloxacin Mesylate) Interim Recommendations (June 9, 1999) (**Tab 66**)
- b. Federal Register of September 22, 1999 (64 FR 51325) “Wallace Laboratories et al.; Withdrawal of Approval of 18 New Drug Applications and 44 Abbreviated New Drug Applications” (**Tab 67**)
- c. Federal Register of June 16, 2006 (71 FR 34940) “Merck & Co., Inc., et al.; Withdrawal of Approval of 65 New Drug Applications and 52 Abbreviated New Drug Applications” (**Tab 68**)

25. **Valdecoxib** – All drug products containing Valdecoxib

- a. FDA Alert – Information for Healthcare Professionals: Valdecoxib (marketed as Bextra) (April 7, 2005) (**Tab 69**)
- b. Federal Register of August 2, 2013 (78 FR 46984) “Pfizer, Inc.; Withdrawal of Approval of a New Drug Application for BEXTRA” (**Tab 70**)

II. 503A Bulk Drug Substances List

A. Overview of 503A Bulk Drug Substances List

Section 503A of the FD&C Act (**Tab 1**) describes the conditions under which a compounded drug product may be entitled to an exemption from certain sections of the FD&C Act. Those conditions include that the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that (1) comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A. See section 503A(b)(1)(A)(i) of the FD&C Act. Under section 503A(c)(2), the criteria for determining which substances should appear on the 503A bulk drugs list “shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.”

In the *Federal Register* of April 7, 1998 (63 FR 17011) (**Tab 71**), FDA invited all interested persons to nominate bulk drug substances for inclusion on the list of bulk drug substances that can be used in compounding under section 503A. In 1998, FDA received nominations for 41 different drug substances. Ten of these drug substances were the subject of a USP or NF monograph, or components of FDA approved drugs and did not need to go on the list. After evaluating the nominated drug substances and consulting with the Pharmacy Compounding Advisory Committee as required by section 503A, FDA published a proposed rule listing 20 drug substances on the section 503A bulk drug substances list in January 1999 (64 FR 996, January 7, 1999) (**Tab 72**). The proposed rule also described ten nominated drug substances that were still under consideration for the bulk drug substance list. The Pharmacy Compounding Advisory Committee reconvened in May 1999 to discuss drugs included in the proposed rule, in addition to other bulk drug substances (see 64 FR 19791 (April 22, 1999) (**Tab 73**)). However, after the 2002 U.S. Supreme Court decision, FDA suspended its efforts to develop the bulk drugs list under section 503A.

Because of the amount of time that had passed between the publication of the proposed rule and the enactment of the Drug Quality and Security Act, FDA felt it

was necessary to begin again to develop the 503A bulk drug substance list. In the December 4, 2013 *Federal Register* (78 FR 72841) (**Tab74**), FDA published a notice withdrawing the 1999 proposed rule and inviting all interested persons to nominate bulk drug substances for inclusion on a list of bulk drug substances that can be used for compounding under section 503A of the FD&C Act.

Over 2,500 substances were nominated. However, many of those nominations were for a substance that is the subject of a USP monograph or a component of an FDA-approved drug, were not for bulk drug substances used in compounding as active ingredients, or did not include sufficient information to justify inclusion of the nominated substance on the list. To improve the efficiency of the process for developing the list of bulk drug substances that can be used to compound drug products under section 503A, FDA reopened the nomination process in July 2014 (79 FR 37747 (July 2, 2014) (**Tab 75**) and provided more detailed information on what it needs to evaluate a nomination. FDA stated that bulk drug substances that were previously nominated would not be further considered unless they were renominated and those nominations were adequately supported. Substances that were already eligible for use in compounding or that were not adequately supported would not be placed on the list. In response to that solicitation, 65 bulk drug substances were nominated with sufficient supporting information for FDA to evaluate them. FDA is prioritizing these for evaluation and for presentation to the Committee.

In the July 2014 *Federal Register* notice (79 FR 37747) (July 2, 2014) soliciting nominations for this list, FDA proposed that the following criteria would be used to evaluate the nominated substances:

- (1) The physical and chemical characterization of the substance;
- (2) Any safety issues raised by the use of the substance in compounded drug products;
- (3) Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature; and
- (4) The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists.

At the meeting, FDA will ask the Committee to discuss these proposed criteria. FDA will also present six nominated substances that FDA has evaluated using the new proposed criteria. At future meetings FDA will present additional nominated bulk drug substances for the committee's consideration.

B. Substances Nominated for Inclusion on the 503A Bulk Drug Substances List (in order of discussion at the meeting)

1. Thymol iodide

- a. Nominations (**Tab 76**)
 - i. International Academy of Compounding Pharmacists (IACP)
 - ii. American Society of Health-System Pharmacists (ASHP)
 - iii. Fagron
 - iv. National Community Pharmacists Association (NCPA)
- b. FDA Review (**Tab 77**)

2. Silver protein mild

- a. Nominations (**Tab 78**)
 - i. NCPA
 - ii. Fagron
 - iii. IACP
- b. FDA Review (**Tab 79**)

3. Squaric acid dibutyl ester (dibutyl squarate)

- a. Nominations (**Tab 80**)
 - i. IACP
 - ii. Fagron
 - iii. ASHP
 - iv. Professional Compounding Centers of America (PCCA)
 - v. NCPA
- b. FDA Review (**Tab 81**)

4. Diphenylcyclopropenone

- a. Nominations (**Tab 82**)
 - i. ASHP
 - ii. PCCA
 - iii. NCPA
- b. FDA Review (**Tab 83**)

5. Cantharidin

- a. Nominations (**Tab 84**)

- i. NCPA
 - ii. PCCA
 - iii. IACP
 - iv. Fagron
 - v. Submission from Hyman Phelps McNamara
- b. FDA Review (**Tab 85**)

6. Piracetam

- a. Nominations (**Tab 86**)
 - i. NCPA
 - ii. IACP
 - iii. PCCA
- b. FDA Review (**Tab 87**)

Tab 1

Section 503A of the Federal Food, Drug, and
Cosmetic Act (FD&C Act)

of frauds against American manufacturers and has provided the cover for the importation of foreign counterfeit drugs.

“(6) The existing system of providing drug samples to physicians through manufacturer’s representatives has been abused for decades and has resulted in the sale to consumers of misbranded, expired, and adulterated pharmaceuticals.

“(7) The bulk resale of below wholesale priced prescription drugs by health care entities, for ultimate sale at retail, helps fuel the diversion market and is an unfair form of competition to wholesalers and retailers that must pay otherwise prevailing market prices.

“(8) The effect of these several practices and conditions is to create an unacceptable risk that counterfeit, adulterated, misbranded, subpotent, or expired drugs will be sold to American consumers.”

§ 353a. Pharmacy compounding

(a) In general

Sections 351(a)(2)(B), 352(f)(1), and 355 of this title shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding—

(1) is by—

(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or

(B) a licensed physician,

on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

(2)(A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and

(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between—

(i) the licensed pharmacist or licensed physician; and

(ii)(I) such individual patient for whom the prescription order will be provided; or

(II) the physician or other licensed practitioner who will write such prescription order.

(b) Compounded drug

(1) Licensed pharmacist and licensed physician

A drug product may be compounded under subsection (a) of this section if the licensed pharmacist or licensed physician—

(A) compounds the drug product using bulk drug substances, as defined in regulations of the Secretary published at section 207.3(a)(4) of title 21 of the Code of Federal Regulations—

(i) that—

(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States

Pharmacopoeia chapter on pharmacy compounding;

(II) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or

(III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d) of this section;

(ii) that are manufactured by an establishment that is registered under section 360 of this title (including a foreign establishment that is registered under section 360(i) of this title); and

(iii) that are accompanied by valid certificates of analysis for each bulk drug substance;

(B) compounds the drug product using ingredients (other than bulk drug substances) that comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

(C) does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective; and

(D) does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.

(2) Definition

For purposes of paragraph (1)(D), the term “essentially a copy of a commercially available drug product” does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.

(3) Drug product

A drug product may be compounded under subsection (a) only if—

(A) such drug product is not a drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product; and

(B) such drug product is compounded in a State—

(i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or

(ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

The Secretary shall, in consultation with the National Association of Boards of Pharmacy, develop a standard memorandum of understanding for use by the States in complying with subparagraph (B)(i).

(c) Advertising and promotion

A drug may be compounded under subsection (a) of this section only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug, class of drug, or type of drug. The pharmacy, licensed pharmacist, or licensed physician may advertise and promote the compounding service provided by the licensed pharmacist or licensed physician.

(d) Regulations

(1) In general

The Secretary shall issue regulations to implement this section. Before issuing regulations to implement subsections (b)(1)(A)(i)(III), (b)(1)(C), or (b)(3)(A) of this section, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopoeia, pharmacy, physician, and consumer organizations, and other experts selected by the Secretary.

(2) Limiting compounding

The Secretary, in consultation with the United States Pharmacopoeia Convention, Incorporated, shall promulgate regulations identifying drug substances that may be used in compounding under subsection (b)(1)(A)(i)(III) of this section for which a monograph does not exist or which are not components of drug products approved by the Secretary. The Secretary shall include in the regulation the criteria for such substances, which shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.

(e) Application

This section shall not apply to—

- (1) compounded positron emission tomography drugs as defined in section 321(ii) of this title; or
- (2) radiopharmaceuticals.

(f) “Compounding” defined

As used in this section, the term “compounding” does not include mixing, reconstituting, or other such acts that are performed in accord-

ance with directions contained in approved labeling provided by the product’s manufacturer and other manufacturer directions consistent with that labeling.

(June 25, 1938, ch. 675, §503A, as added Pub. L. 105–115, title I, §127(a), Nov. 21, 1997, 111 Stat. 2328.)

EFFECTIVE DATE

Section 127(b) of Pub. L. 105–115 provided that: “Section 503A of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 353a], added by subsection (a), shall take effect upon the expiration of the 1-year period beginning on the date of the enactment of this Act [Nov. 21, 1997].”

§ 353b. Prereview of television advertisements

(a) In general

The Secretary may require the submission of any television advertisement for a drug (including any script, story board, rough, or a completed video production of the television advertisement) to the Secretary for review under this section not later than 45 days before dissemination of the television advertisement.

(b) Review

In conducting a review of a television advertisement under this section, the Secretary may make recommendations with respect to information included in the label of the drug—

(1) on changes that are—

- (A) necessary to protect the consumer good and well-being; or
- (B) consistent with prescribing information for the product under review; and

(2) if appropriate and if information exists, on statements for inclusion in the advertisement to address the specific efficacy of the drug as it relates to specific population groups, including elderly populations, children, and racial and ethnic minorities.

(c) No authority to require changes

Except as provided by subsection (e), this section does not authorize the Secretary to make or direct changes in any material submitted pursuant to subsection (a).

(d) Elderly populations, children, racially and ethnically diverse communities

In formulating recommendations under subsection (b), the Secretary shall take into consideration the impact of the advertised drug on elderly populations, children, and racially and ethnically diverse communities.

(e) Specific disclosures

(1) Serious risk; safety protocol

In conducting a review of a television advertisement under this section, if the Secretary determines that the advertisement would be false or misleading without a specific disclosure about a serious risk listed in the labeling of the drug involved, the Secretary may require inclusion of such disclosure in the advertisement.

(2) Date of approval

In conducting a review of a television advertisement under this section, the Secretary

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(63 FR 54082)

(2) If no paint contamination is detected on the actuator pistons and the moisture indicator of the trim actuator is pink or white, prior to further flight, replace the trim actuator with a new or serviceable trim actuator and either replace or regenerate the desiccant in accordance with the alert service bulletin.

(3) If any paint contamination is detected on the actuator pistons, prior to further flight, remove the paint in accordance with the alert service bulletin.

Note 2: Aviac Technologies, the manufacturer of the desiccant, has issued Identification Procedure for Desiccant DAV/AP98-214, Revision 0, dated April 22, 1998, as an additional source of service information to determine the level of saturation of the desiccant.

(b) Within 2 months after the effective date of this AD, perform a one-time visual inspection to verify installation of the flat gasket in each end of the flex drive, and to determine if the flat gasket is in good condition (i.e., shows no signs of wear), in accordance with Dornier Alert Service Bulletin ASB-328-27-017, Revision 2, dated July 28, 1998.

(1) If the gasket is installed and in good condition, no further action is required by paragraph (b) of this AD.

(2) If the gasket is missing or is installed and not in good condition, prior to further flight, replace the gasket with a new gasket, and torque the nuts, in accordance with the alert service bulletin.

Note 3: Accomplishment of the actions required by paragraphs (a) and (b) of this AD, prior to the effective date of this AD, in accordance with Dornier Alert Service Bulletin ASB-328-27-017, Revision 1, dated October 1, 1997, is considered acceptable for compliance with the applicable actions specified in paragraphs (a) and (b) of this AD.

(c) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, International Branch, ANM-116, FAA, Transport Airplane Directorate. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, International Branch, ANM-116.

Note 4: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the International Branch, ANM-116.

(d) Special flight permits may be issued in accordance with §§ 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Note 5: The subject of this AD is addressed in German airworthiness directive 97-188, dated July 3, 1997.

Issued in Renton, Washington, on October 1, 1998.

Darrell M. Pederson,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 98-26964 Filed 10-7-98; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. 98N-0655]

List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations to include a list of drug products that may not be used for pharmacy compounding pursuant to the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (the act) because they have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective. The list has been compiled under the new statutory requirements of the Food and Drug Administration Modernization Act of 1997 (Modernization Act).

DATES: Comments must be received on or before November 23, 1998.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

President Clinton signed the Modernization Act (Pub. L. 105-115) into law on November 21, 1997. One of the issues addressed in this new legislation is the applicability of the act to the practice of pharmacy compounding. Compounding involves a process whereby a pharmacist or physician combines, mixes, or alters ingredients to create a customized

medication for an individual patient. Section 127 of the Modernization Act, which adds section 503A to the act (21 U.S.C. 353a), describes the circumstances under which compounded drugs qualify for exemptions from certain adulteration, misbranding, and new drug provisions of the act (i.e., 501(a)(2)(B), 502(f)(1), and 505 of the act (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)). Section 127(b) of the Modernization Act provides that section 503A of the act will become effective on November 21, 1998, 1 year from the date of the Modernization Act's enactment.

Section 503A of the act contains several conditions that must be satisfied for pharmacy compounding to qualify for the exemptions under section 503A. One of the conditions is that the licensed pharmacist or licensed physician does not "compound a drug product that appears on a list published by the Secretary in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective."

II. Rulemaking to Establish the List

In accordance with section 503A of the act, FDA has developed a list of drug products that have been withdrawn or removed from the market because they have been found to be unsafe or not effective. Many of the drug products on the list were withdrawn from the market through official proceedings, including publication of a notice in the **Federal Register**. For these drug products, this preamble to the proposed rule includes the reason for the withdrawal and the citation to the official notice of withdrawal. Other products, both approved and unapproved, were removed from the market voluntarily by the manufacturer or application holder, and FDA has information indicating that the reason for the removal was because the product was unsafe or not effective. In such cases, the reason for the removal is provided, and additional sources of information on the drug can be found in the docket identified by the number found in brackets in the heading of this document.

This proposed rule is the first of a series of rulemaking proceedings to establish the list of withdrawn or removed drug products, as the development and issuance of this list will be an ongoing process. The primary focus of this proposed rule is drug products that have been removed or withdrawn for safety reasons. FDA intends that future rulemaking

proceedings will focus on drug products that were withdrawn for reasons of effectiveness, on drug products that are identified as having been withdrawn for reasons of safety or effectiveness after the preparation of this proposed rule, and on additional drug products that will be proposed for inclusion on the list either during the comment period or subsequently.

FDA is specifically seeking comment on whether additional drug products should be added to the list and whether products now on the list should remain on the list. Persons submitting comments recommending that a drug product be added to the list should include appropriate documentation, including any notices published in the **Federal Register**. In addition, individuals and organizations may petition FDA to amend the list at any time through the regular citizen petition process described in 21 CFR 10.30.

After evaluating the comments on this proposed rule and consulting an advisory committee on compounding, as required by section 503A(d)(1) of the act, FDA will issue the list as a final rule which will be codified in the Code of Federal Regulations. The initial list published as a final rule may include all or some of the products proposed for inclusion on the list in this proposal, depending upon the comments received. Additional products will be added to the list through the rulemaking process after the data on the products are evaluated, and after consultation with the advisory committee on compounding.

III. Description of the Proposed Rule

FDA is proposing that the drug products described in this section be included in the list of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective. Compounding a drug product that appears on this list is not covered by the exemption provided in section 503A(a) of the act, and may be subject to enforcement action under sections 501(a)(2)(B), 502(f)(1), and 505 (among other applicable provisions) of the act.

The listings are arranged alphabetically by the established name of the active ingredient contained in the drug product. For many of the drugs, the proprietary or trade name of some or all of the drug products which contained the active ingredient are also given in the preamble paragraphs describing the withdrawn or removed drug products. Some of the drugs listed were withdrawn or removed from the market

based on problems relating only to one dosage form or route of administration. In such cases, the listing for that drug product reflects that fact, e.g., "*Neomycin Sulfate*: Parenteral drug products containing neomycin sulfate." In other cases, the problem is associated with the active ingredient, or appears to relate to other dosage forms or routes of administration, and the listing reflects that fact, e.g., "*Adrenal Cortex*: All drug products containing adrenal cortex." In several instances, a particular formulation, dosage form, or route of administration is explicitly excluded from an entry on the list because there is an approved drug (that has not been withdrawn or removed from the market) that contains the same active ingredient(s) as the drug product that has been withdrawn or removed from the market. In these instances, the listing includes the appropriate qualification, e.g., "*Suprofen*: All drug products containing suprofen (except ophthalmic solutions)."

In several cases, the withdrawn drug products are identified according to the established name of the active ingredient, listed as a particular salt or ester of the active moiety, e.g., "*Dexfenfluramine hydrochloride*: All drug products containing dexfenfluramine hydrochloride." Although the specific listing may be limited to a particular salt or ester, other salts or esters of the active moiety will not qualify for the compounding exemptions in section 503A of the act unless (among other requirements) the particular salt or ester is the subject of a United States Pharmacopeia or National Formulary monograph; is a component of an FDA approved drug; or appears on the FDA list of bulk drug substances that may be used for compounding. (See section 503A(b)(1)(A)(i) of the act).

The list is being proposed as § 216.24 of Title 21 of the Code of Federal Regulations. This new section will be included in a new part, part 216, which is currently intended to include all FDA regulations whose primary purpose is implementation of the pharmacy compounding provisions found in section 503A of the act.

The following drug products are proposed for inclusion in proposed § 216.24. The supporting documentation for each listed drug product may be found in the docket identified by the number found in brackets in the heading of this document. The supporting documentation will be arranged alphabetically according to the established name of the active ingredient of the drug products.

Adenosine phosphate: All drug products containing adenosine phosphate. Adenosine phosphate, formerly marketed as a component of Adeno for injection, Adco for injection, and other drug products, was determined to be neither safe nor effective for its intended uses as a vasodilator and an anti-inflammatory. FDA directed the removal of these drug products from the market in 1973.

Adrenal cortex: All drug products containing adrenal cortex. The low level of corticosteroids found in adrenal cortex injection and adrenal cortex extract were determined to present a substantial risk of undertreatment of serious conditions, such as adrenal cortical insufficiency, burns, and hypoglycemia. FDA determined that adrenal cortex for injection and adrenal cortex extract presented a significant potential hazard and directed the removal of these drug products from the market in January 1978.

Azaribine: All drug products containing azaribine. The use of azaribine, formerly marketed as Triazure tablets, was associated with very serious thromboembolic events. Approval of the new drug application (NDA) for Triazure tablets was withdrawn June 10, 1977 (see the **Federal Register** of June 10, 1977 (42 FR 29998)).

Benoxaprofen: All drug products containing benoxaprofen. The use of benoxaprofen, formerly marketed as Oraflex tablets, was associated with fatal cholestatic jaundice among other serious adverse reactions. The holder of the approved application voluntarily withdrew Oraflex tablets from the market on August 5, 1982.

Bithionol: All drug products containing bithionol. Bithionol, formerly marketed as an active ingredient in various topical drug products, was shown to be a potent photosensitizer with the potential to cause serious skin disorders. Approvals of the NDA's for bithionol drug products were withdrawn on October 24, 1967 (see the **Federal Register** of October 31, 1967 (32 FR 15046)).

Bromfenac sodium: All drug products containing bromfenac sodium. The use of bromfenac sodium, formerly marketed as Duract capsules, was associated with fatal hepatic failure. Duract capsules were voluntarily withdrawn from the market by their manufacturer on June 22, 1998.

Butamben: All parenteral drug products containing butamben. The use of a parenteral drug product containing butamben, formerly marketed as Efocaine, was associated with severe adverse reactions, such as severe tissue slough and transverse myelitis.

Approval of the NDA for Efocaine was withdrawn on August 7, 1964 (see the **Federal Register** of August 14, 1964 (29 FR 11656)).

Camphorated oil: All drug products containing camphorated oil. Products containing camphorated oil were associated with poisoning in infants and young children due to accidental ingestion. FDA directed the removal from the market of drug products containing camphorated oil in 1982 (see 21 CFR 310.526 (1997)).

Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate. Carbetapentane citrate gel, formerly marketed as Candette Cough Jel, was determined not to be safe because the inexact methods of measuring the gel by consumers were potentially dangerous. Approval of the NDA for Candette Cough Jel was withdrawn on November 29, 1972 (see the **Federal Register** of November 29, 1972 (37 FR 25249)).

Casein, iodinated: All drug products containing iodinated casein. Iodinated casein, formerly marketed as a component of Neo-Barine, was associated with thyrotoxic side effects. Approval of the NDA for Neo-Barine was withdrawn October 22, 1964 (see the **Federal Register** of October 28, 1964 (29 FR 14676)).

Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation. Chlorhexidine gluconate topical tincture 0.5%, formerly marketed as Hibitane, was associated with chemical and thermal burns when used as a patient preoperative skin preparation. The drug product was voluntarily removed from the market in early 1984. FDA determined that chlorhexidine gluconate topical tincture 0.5% was removed from the market for reasons of safety (see the **Federal Register** of October 6, 1997 (62 FR 52137)).

Chlormadinone acetate: All drug products containing chlormadinone acetate. Chlormadinone acetate, formerly marketed as a component of the combination drug products Estalor-21 and C-Quens tablets, was associated with the development of mammary tumors in dogs. The manufacturer ceased marketing the drug in 1970 and approvals of the NDA's for Estalor-21 and C-Quens tablets were withdrawn by FDA on March 16, 1972 (see the **Federal Register** of March 16, 1972 (37 FR 5516)).

Chloroform: All drug products containing chloroform. National Cancer Institute studies demonstrated that chloroform is carcinogenic in animals. FDA directed the removal from the

market of drug products containing chloroform in 1976 (see 21 CFR 310.513 (1997)).

Cobalt: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives). FDA found that cobalt salts were not safe or effective for treatment of iron-deficiency anemia. The toxic effects of cobalt salts include liver damage, claudication, and myocardial damage. FDA directed the removal from the market of drug products containing cobalt salts in 1967 (see 21 CFR 250.106 (1997)).

Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride. Dexfenfluramine hydrochloride, formerly marketed as Redux capsules, was associated with valvular heart disease. The manufacturer of dexfenfluramine hydrochloride capsules voluntarily withdrew the drug from the market in September 1997.

Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride. Diamthazole dihydrochloride, formerly marketed as Asterol ointment, powder, and tincture, was associated with neurotoxicity. Approvals of the NDA's for Asterol ointment, powder, and tincture were withdrawn on July 19, 1977 (see the **Federal Register** of July 19, 1977 (42 FR 37057)).

Dibromsalan: All drug products containing dibromsalan. Dibromsalan, formerly marketed in a number of drug products, largely antibacterial soaps, as an antimicrobial, preservative, or for other purposes, was, with other halogenated salicylanilides listed in this proposal, found to be a potent photosensitizer capable of causing disabling skin disorders. FDA directed the removal from the market of drug products containing dibromsalan in 1975 (see § 310.508 (21 CFR 310.508) (1997)).

Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams (mg) or more of diethylstilbestrol per unit dose. Diethylstilbestrol, marketed in various tablet and parenteral drug products, was associated with adenocarcinoma of the vagina in the offspring of the patient when used in early pregnancy. Approvals of the NDA's for these diethylstilbestrol drug products were withdrawn on February 18, 1975 (see the **Federal Register** of February 5, 1975 (40 FR 5384)).

Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate. Dihydrostreptomycin sulfate, formerly marketed in several parenteral drug

products, was associated with ototoxicity. Approvals of the NDA's for dihydrostreptomycin sulfate drug products were withdrawn on July 20, 1970 (see the **Federal Register** of September 3, 1970 (35 FR 13988)).

Dipyrrone: All drug products containing dipyrrone. Dipyrrone, formerly marketed as Dimethone tablets and injection, Protemp oral liquid, and other drug products, was associated with potentially fatal agranulocytosis. Approvals of the NDA's for dipyrrone drug products were withdrawn on June 27, 1977 (see the **Federal Register** of June 17, 1977 (42 FR 30893)).

Encainide hydrochloride: All drug products containing encainide hydrochloride. Encainide hydrochloride, formerly marketed as Enkaid capsules, was associated with increased death rates in patients who had asymptomatic heart rhythm abnormalities after a recent heart attack. The manufacturer of Enkaid capsules voluntarily withdrew the product from the market on December 16, 1991.

Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride. Fenfluramine hydrochloride tablets, formerly marketed as Pondimin tablets, were associated with valvular heart disease. The manufacturer of fenfluramine hydrochloride tablets voluntarily withdrew the drug from the market in September 1997.

Flosequinan: All drug products containing flosequinan. Flosequinan, formerly marketed as Manoplax tablets, was the subject of a study that indicated the drug had adverse effects on survival, and that beneficial effects on the symptoms of heart failure did not last beyond the first 3 months of therapy. After the first 3 months of therapy, patients on the drug had a higher rate of hospitalization than patients taking a placebo. The manufacturer of Manoplax tablets voluntarily withdrew the drug from the market in July 1993.

Gelatin: All intravenous drug products containing gelatin. Gelatin for intravenous use, formerly marketed as Knox Special Gelatine Solution Intravenous-6 percent, was found not to be suitable as a plasma expander because the drug caused increased blood viscosity, reduced blood clotting, and prolonged bleeding time. Approval of the NDA for Knox Special Gelatine Solution Intravenous-6 percent was withdrawn on April 19, 1978 (see the **Federal Register** of April 7, 1978 (43 FR 14743)).

Glycerol, iodinated: All drug products containing iodinated glycerol. Iodinated glycerol, formerly marketed as Iodur Elixir and other drug products, was

found to have carcinogenic potential. FDA directed the removal from the market of drug products containing iodinated glycerol in April 1993.

Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin.

Chorionic gonadotropins of animal origins, formerly marketed as Synapoidin Steri-Vial, were shown to produce allergic reactions. Approval of the NDA for Synapoidin Steri-Vial was withdrawn on July 6, 1972 (see the **Federal Register** of July 6, 1972 (37 FR 13284)).

Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate. Mepazine hydrochloride, formerly marketed as Pacatal tablets, and mepazine acetate, formerly marketed as Pacatal for injection, were associated with granulocytopenia, granulocytosis, paralytic ileus, urinary retention, seizures, hypotension, and jaundice. Approval of the NDA for Pacatal tablets and Pacatal for injection was withdrawn on May 28, 1970 (see the **Federal Register** of May 28, 1970 (35 FR 8405)).

Metabromsalan: All drug products containing metabromsalan. Metabromsalan, formerly marketed in a number of drug products, largely antibacterial soaps, as an antimicrobial, preservative, or for other purposes, was, with other halogenated salicylanilides listed in this proposal, found to be a potent photosensitizer capable of causing disabling skin disorders. FDA directed the removal from the market of drug products containing metabromsalan in 1975 (see § 310.508 (1997)).

Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride. Parenteral methamphetamine hydrochloride, formerly marketed as Methedrine injection and Drinalfa injection and used as an adjunct treatment for weight reduction, was found to have a history of serious abuse and a severe risk of dependence. Approvals of the NDA's for Methedrine injection and Drinalfa injection were withdrawn on March 30, 1973 (see 21 CFR 310.504 (1997)).

Methapyrilene: All drug products containing methapyrilene. Methapyrilene, formerly marketed in many drug products, was shown to be a potent carcinogen. Manufacturers voluntarily withdrew methapyrilene drug products from the market in May and June 1979.

Methopholine: All drug products containing methopholine. Methopholine, formerly marketed as Versidyne tablets, was associated with

ophthalmic changes and corneal opacities in dogs. Approval of the NDA for Versidyne tablets was withdrawn on March 22, 1965 (see the **Federal Register** of March 27, 1965 (30 FR 4083)).

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride. Mibefradil dihydrochloride, formerly marketed as Posicor tablets, was associated with potentially harmful interactions with other drugs. Mibefradil dihydrochloride reduced the activity of certain liver enzymes that are important in helping the body eliminate many other drugs. Inhibiting these enzymes can cause some of these drugs to accumulate to dangerous levels in the body. The manufacturer voluntarily removed Posicor tablets from the market on June 8, 1998.

Neomycin sulfate: All parenteral drug products containing neomycin sulfate. Parenteral neomycin sulfate was found to present toxicity problems when used to irrigate wounds and was found not to be acceptable for the treatment of urinary tract infections due to the availability of newer, safer antibiotics that were as effective as, or more effective than, parenteral neomycin sulfate. Approvals of the marketing applications for parenteral neomycin sulfate were withdrawn on January 5, 1989 (see the **Federal Register** of December 6, 1988 (53 FR 49232)).

Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatologic application). Nitrofurazone, formerly marketed in nasal drops, otic drops, and vaginal suppositories, was associated with mammary neoplasia in rats. Approvals of the NDA's for the nitrofurazone drug products were withdrawn on December 4, 1974, and June 10, 1975 (see the **Federal Register** of December 4, 1974 (39 FR 42018), and May 30, 1975 (40 FR 23502)).

Nomifensine maleate: All drug products containing nomifensine maleate. Nomifensine maleate, formerly marketed as Merital capsules, was associated with an increased incidence of hemolytic anemia. The approved application holder removed Merital capsules from the market on January 23, 1986. FDA published a notice of its determination that Merital capsules were removed from the market for safety reasons (see the **Federal Register** of June 17, 1986 (51 FR 21981)). Approval of the NDA for Merital capsules was withdrawn on March 20, 1992 (see the **Federal Register** of March 20, 1992 (57 FR 9729)).

Oxyphenisatin: All drug products containing oxyphenisatin.

Oxyphenisatin, formerly marketed in Lavema Compound Solution and Lavema Enema Powder, was associated with hepatitis and jaundice. The approvals of the NDA's for Lavema Compound Solution and Lavema Enema Powder were withdrawn on March 9, 1973 (see the **Federal Register** of March 9, 1973 (38 FR 6419)).

Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate. Oxyphenisatin acetate, formerly marketed in Dialose Plus capsules, Noloc capsules, and other drug products, was associated with hepatitis and jaundice. Approvals of the NDA's for the oxyphenisatin acetate drug products were withdrawn on February 1, 1972 (see the **Federal Register** of February 1, 1972 (37 FR 2460)).

Phenacetin: All drug products containing phenacetin. Phenacetin, formerly marketed in A.P.C. with Butalbital tablets and capsules and other drug products, was associated with a high potential for harm to the kidneys and the possibility of hemolytic anemia and methemoglobinemia resulting from abuse. The approvals of the NDA's for the phenacetin drug products were withdrawn on November 4, 1983 (see the **Federal Register** of October 5, 1983 (48 FR 45466)).

Phenformin hydrochloride: All drug products containing phenformin hydrochloride. Phenformin hydrochloride, formerly marketed as D.B.I. tablets, Meltrol-50 capsules, and other drug products, was associated with lactic acidosis. Approvals of the NDA's for the phenformin hydrochloride drug products were withdrawn on November 15, 1978 (see the **Federal Register** of April 6, 1979 (44 FR 20967)).

Pipamazine: All drug products containing pipamazine. Pipamazine, formerly marketed as Mornidine tablets and injection, was associated with hepatic lesions. Approval of the NDA for Mornidine tablets and injection was withdrawn on July 17, 1969 (see the **Federal Register** of July 17, 1969 (34 FR 12051)).

Potassium arsenite: All drug products containing potassium arsenite. Potassium arsenite, formerly marketed as Fowler's Solution (oral), was toxic and highly carcinogenic. FDA determined Fowler's Solution was a new drug in April 1980, and the manufacturers removed the drug product from the market.

Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 mg or more of potassium per dosage unit

(except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion). Concentrated solid oral dosage forms of potassium salt were associated with small bowel lesions. Approvals of NDA's for all solid oral dosage form drug products containing potassium chloride that supply 100 mg or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion) were withdrawn on July 29, 1977, and April 29, 1992 (see the **Federal Register** of July 29, 1977 (42 FR 38644), and April 29, 1992 (57 FR 18157)).

Povidone: All intravenous drug products containing povidone. Povidone, marketed as Polyvinylpyrrolidone in Normal Saline, was found to be unsafe for use as a plasma expander in the emergency treatment of shock because povidone accumulates in the body and may cause storage disease with the formation of granulomas. Povidone also interferes with blood coagulation, hemostasis, and blood typing and cross matching. Approval of the NDA for Polyvinylpyrrolidone in Normal Saline was withdrawn on April 19, 1978 (see the **Federal Register** of April 7, 1978 (43 FR 14743)).

Reserpine: All oral dosage form drug products containing more than 1 mg of reserpine. Reserpine, marketed as Reserpoid tablets, Rau-Sed tablets, and other drug products for the treatment of hypertension and psychiatric disorders, was associated with a greater frequency and severity of adverse effects in strengths greater than 1 mg. Approvals of NDA's, or those portions of NDA's, for solid oral dosage form drug products containing more than 1 mg of reserpine were withdrawn on May 9, 1977 (see the **Federal Register** of April 29, 1977 (42 FR 21844)).

Sparteine sulfate: All drug products containing sparteine sulfate. Sparteine sulfate, formerly marketed as Spartocin injection and Tocosamine sterile solution, was found to have unpredictable effects and was associated with tetanic uterine contractions and obstetrical complications. Approvals of the NDA's for Spartocin injection and Tocosamine sterile solution were withdrawn on August 17, 1979 (see the **Federal Register** of August 7, 1979 (44 FR 46316)).

Sulfadimethoxine: All drug products containing sulfadimethoxine. Sulfadimethoxine, formerly marketed in Madricidin capsules, was associated with Stevens-Johnson syndrome and

fatalities. Approval of the NDA for Madricidin capsules was withdrawn on March 11, 1966 (see the **Federal Register** of March 19, 1966 (31 FR 4747)).

Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use). Sulfathiazole, formerly marketed in Tresamide tablets and several other brands of tablets, was associated with renal complications, rash, fever, blood dyscrasias, and liver damage. Approvals of the NDA's for sulfathiazole tablets were withdrawn on September 28, 1970 (see the **Federal Register** of October 15, 1970 (35 FR 16190)).

Suprofen: All drug products containing suprofen (except ophthalmic solutions). Suprofen, formerly marketed as Suprol capsules, was associated with flank pain syndrome. The manufacturer voluntarily removed Suprol capsules from the market in May 1987.

Sweet spirits of nitre: All drug products containing sweet spirits of nitre. Sweet spirits of nitre, also known as spirit of nitre, spirit of nitrous ether, and ethyl nitrite spirit, was associated with methemoglobinemia in infants. FDA directed the removal from the market of drug products containing sweet spirits of nitre in 1980 (see 21 CFR 310.525 (1997)).

Temafloxacin hydrochloride: All drug products containing temafloxacin hydrochloride. Temafloxacin hydrochloride, formerly marketed as Omniflox tablets, was associated with hypoglycemia in elderly patients, as well as a constellation of multisystem organ involvement characterized by hemolytic anemia, frequently associated with renal failure, markedly abnormal liver tests, and coagulopathy. The approved application holder voluntarily removed Omniflox tablets from the market in Spring 1992. Approval of the NDA for Omniflox tablets was withdrawn on September 25, 1997 (see the **Federal Register** of September 25, 1997 (62 FR 50387)).

Terfenadine: All drug products containing terfenadine. Terfenadine, formerly marketed in Seldane and Seldane-D tablets, was associated with serious heart problems when used concurrently with certain drugs, including certain antibiotics and antifungals. Seldane and Seldane-D tablets were voluntarily removed from the market by their manufacturer in February 1998.

3,3',4',5-tetrachlorosalicylanilide: All drug products containing 3,3',4',5-tetrachlorosalicylanilide. The halogenated salicylanilide 3,3',4',5-tetrachlorosalicylanilide, formerly marketed in a number of drug products,

largely antibacterial soaps, as an antimicrobial, preservative, or for other purposes, was, with other halogenated salicylanilides listed in this proposal, found to be a potent photosensitizer capable of causing disabling skin disorders. FDA directed the removal from the market of drug products containing 3,3',4',5-tetrachlorosalicylanilide in 1975 (see § 310.508 (1997)).

Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 mg/milliliter (mL). Concentrated tetracycline was associated with temporary inhibition of bone growth, permanent staining of the teeth, and enamel hypoplasia in children. FDA amended the antibiotic drug regulations so that drug products containing tetracycline formulated for pediatric use in a concentration greater than 25 mg/mL would not be certified (see the **Federal Register** of October 31, 1978 (43 FR 50676)).

Ticrynafen: All drug products containing ticrynafen. Ticrynafen, formerly marketed as Selacryn tablets, was associated with liver toxicity. Selacryn tablets were voluntarily withdrawn from the market by their manufacturer on January 16, 1980. Approval of the NDA for Selacryn tablets was withdrawn on May 20, 1996 (see the **Federal Register** of May 20, 1996 (61 FR 25228)).

Tribromsalan: All drug products containing tribromsalan. Tribromsalan, formerly marketed in a number of drug products, largely antibacterial soaps, as an antimicrobial, preservative, or for other purposes, was, with other halogenated salicylanilides listed in this proposal, found to be a potent photosensitizer capable of causing disabling skin disorders. FDA directed the removal from the market of drug products containing tribromsalan in 1975 (see § 310.508 (1997)).

Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane. Trichloroethane is potentially toxic to the cardiovascular system and was associated with deaths from misuse or abuse. FDA directed the removal from the market of aerosol drug products intended for inhalation containing trichloroethane in 1977 (see 21 CFR 310.507 (1997)).

Urethane: All drug products containing urethane. Urethane (also known as urethan and ethyl carbamate), formerly marketed as an inactive ingredient in Profenil injection, was determined to be carcinogenic. Approval of the NDA for Profenil

injection was withdrawn on March 28, 1977 (see the **Federal Register** of March 18, 1977 (42 FR 15138)).

Vinyl chloride: All aerosol drug products containing vinyl chloride. The inhalation of vinyl chloride is associated with acute toxicity manifested by dizziness, headache, disorientation, and unconsciousness. FDA directed the removal from the market of aerosol drug products containing vinyl chloride in 1974 (see 21 CFR 310.506 (1997)).

Zirconium: All aerosol drug products containing zirconium. Zirconium, formerly used in several aerosol drug products as an antiperspirant, was associated with human skin granulomas and toxic effects in the lungs and other internal organs of test animals. FDA directed the removal from the market of aerosol drug products containing zirconium in 1977 (see 21 CFR 310.510 (1997)).

Zomepirac sodium: All drug products containing zomepirac sodium. Zomepirac sodium, formerly marketed as Zomax tablets, was associated with fatal and near-fatal anaphylactoid reactions. The manufacturer voluntarily removed Zomax tablets from the market in March 1983.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of \$100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. As discussed in the following paragraphs, the agency believes that this proposed rule is consistent with the regulatory

philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The agency has not estimated any compliance costs or loss of sales due to this proposal because it prohibits pharmacy compounding of only those drug products that have already been withdrawn or removed from the market. Although the agency is not aware of any routine use of these drug products in pharmacy compounding, the agency invites the submission of comments on this issue and solicits current compounding usage data for these drug products.

Unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant economic impact of a regulation on small entities. The agency is taking this action in order to comply with Section 503A of the act. This provision specifically directs FDA to develop a list of drug products that have been withdrawn or removed from the market because such products or components have been found to be unsafe or not effective. Any drug product on this list will not qualify for the pharmacy compounding exemptions under section 503A of the act. The drug products on this list were manufactured by many different pharmaceutical firms, some of which may have qualified under the Small Business Administration (SBA) regulations (those with less than 750 employees) as small businesses. However, since the list only includes those drug products that have already been withdrawn or removed from the market for safety or efficacy concerns, this proposal will not negatively impact these small businesses. Moreover, no compliance costs are estimated for any of these small pharmaceutical firms because they are not the subject of this rule and are not expected to realize any further loss of sales due to this proposal. Further, the SBA guidelines limit the definition of small drug stores or pharmacies to those that have less than \$5.0 million in sales. Again, the pharmacies that qualify as small businesses are not expected to incur any compliance costs or loss of sales due to this regulation because the products have already been withdrawn or removed from the market, and the agency believes that these drugs would be compounded only very rarely, if ever. Therefore, FDA certifies that this rule will not have a significant economic

impact on a substantial number of small entities.

The Unfunded Mandates Reform Act requires (in section 202) that agencies prepare an assessment of anticipated costs and benefits before proposing any expenditure by State, local, and tribal Governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any 1 year. The publication of the list of products withdrawn or removed from the market because they were found to be unsafe or ineffective will not result in expenditures of funds by State, local, and tribal governments or the private sector in excess of \$100 million annually. Because the agency does not estimate any annual expenditures due to the proposed rule, FDA is not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (Pub. L. 104-13) is not required.

VII. Request for Comments

Interested persons may, on or before November 23, 1998, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The agency notes that the comment period in this document is shorter than the 75-day period that is customarily provided by FDA for proposed rules of a technical nature. Likewise, this comment period is less than the 60 days ordinarily provided, as set out in FDA's procedural regulations, § 10.40(b)(2) (21 CFR 10.40(b)(2)). As discussed in the following paragraphs, FDA believes that a 45-day comment period is appropriate in this instance. Executive Order 12889 (58 FR 69681, December 30, 1993), which implemented the North American Free Trade Agreement, states that any agency subject to the Administrative Procedure Act should provide a 75-day comment period for any proposed Federal technical regulation or any Federal sanitary or phytosanitary measure of general application. However, Executive Order 12889 provides an exception to the 75-

day period where the United States considers the measure necessary to address an urgent problem related to the protection of human, plant, or animal health. Similarly, FDA regulations establish a 60-day comment period as ordinary agency practice, but provide that the 60-day period may be shortened if the Commissioner of Food and Drugs finds good cause for doing so.

As discussed in this document, section 503A(a) of the act exempts certain compounded drug products from some specific misbranding and adulteration provisions, as well as the new drug provision, of the act. Section 503A(b)(1)(C) of the act excludes from the exemption drugs that FDA has found were removed from the market or had marketing applications withdrawn because the drug product or some component of the drug product was unsafe or ineffective. Compounding versions of many of these drug products presents a serious risk to human health, either indirectly, because a patient is being provided an ineffective drug product when effective drug products may be available, or directly, due to the toxicity of the drug product. Indeed, many of the drug products listed in this proposed rule have been associated with human fatalities.

Section 127(b) of the Modernization Act provides that section 503A of the act will go into effect on November 21, 1998. If a final regulation issuing the list of drug products that have been withdrawn or removed is not published before November 21, 1998, these drug products may be compounded, exempt from various legal requirements, contrary to the expressed intent of Congress and at a risk to human health. Accordingly, the agency intends to solicit public comment on this proposal, consider the comments submitted, and prepare and publish a final implementing regulation by November 21, 1998. FDA has concluded that the urgency of this matter is sufficient justification for shortening the comment period for this proposal to 45 days, consistent with Executive Order 12889. Similarly, this urgency constitutes good cause within the meaning of § 10.40(b), which justifies shortening the period to 45 days.

List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 216 be added to read as follows:

1. Part 216 is added to read as follows:

PART 216—PHARMACY COMPOUNDING

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

Sec.

216.23 [Reserved]

216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

Authority: 21 U.S.C. 351, 352, 353a, 355, and 371.

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

§ 216.23 [Reserved]

§ 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective. The following drug products may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act:

Adenosine phosphate: All drug products containing adenosine phosphate.

Adrenal cortex: All drug products containing adrenal cortex.

Azaribine: All drug products containing azaribine.

Benoxaprofen: All drug products containing benoxaprofen.

Bithionol: All drug products containing bithionol.

Bromfenac sodium: All drug products containing bromfenac sodium.

Butamben: All parenteral drug products containing butamben.

Camphorated oil: All drug products containing camphorated oil.

Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate.

Casein, iodinated: All drug products containing iodinated casein.

Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation.

Chlormadinone acetate: All drug products containing chlormadinone acetate.

Chloroform: All drug products containing chloroform.

Cobalt: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives).

Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride.

Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride.

Dibromsalan: All drug products containing dibromsalan.

Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams or more of diethylstilbestrol per unit dose.

Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate.

Dipyrene: All drug products containing dipyrene.

Encainide hydrochloride: All drug products containing encainide hydrochloride.

Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride.

Flosequinar: All drug products containing flosequinar.

Gelatin: All intravenous drug products containing gelatin.

Glycerol, iodinated: All drug products containing iodinated glycerol.

Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin.

Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate.

Metabromsalan: All drug products containing metabromsalan.

Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride.

Methapyrilene: All drug products containing methapyrilene.

Methopholine: All drug products containing methopholine.

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride.

Neomycin sulfate: All parenteral drug products containing neomycin sulfate.

Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatologic application).

Nomifensine maleate: All drug products containing nomifensine maleate.

Oxyphenisatin: All drug products containing oxyphenisatin.

Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate.

Phenacetin: All drug products containing phenacetin.

Phenformin hydrochloride: All drug products containing phenformin hydrochloride.

Pipamazine: All drug products containing pipamazine.

Potassium arsenite: All drug products containing potassium arsenite.

Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).

Povidone: All intravenous drug products containing povidone.

Reserpine: All oral dosage form drug products containing more than 1 milligram of reserpine.

Sparteine sulfate: All drug products containing sparteine sulfate.

Sulfadimethoxine: All drug products containing sulfadimethoxine.

Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use).

Suprofen: All drug products containing suprofen (except ophthalmic solutions).

Sweet spirits of nitre: All drug products containing sweet spirits of nitre.

Temafloxacin hydrochloride: All drug products containing temafloxacin hydrochloride.

Terfenadine: All drug products containing terfenadine.

3,3',4',5-tetrachlorosalicylanilide: All drug products containing 3,3',4',5-tetrachlorosalicylanilide.

Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter.

Ticrynafen: All drug products containing ticrynafen.

Tribromsalan: All drug products containing tribromsalan.

Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane.

Urethane: All drug products containing urethane.

Vinyl chloride: All aerosol drug products containing vinyl chloride.

Zirconium: All aerosol drug products containing zirconium.

Zomepirac sodium: All drug products containing zomepirac sodium.

Dated: October 1, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98-26923 Filed 10-2-98; 4:25 pm]

BILLING CODE 4160-01-F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[PA-4076b; FRL-6166-2]

Approval and Promulgation of Air Quality Implementation Plans; Pennsylvania; Approval of VOC and NO_x RACT Determinations for Individual Sources

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA proposes to approve the State Implementation Plan (SIP) revision submitted by the Commonwealth of Pennsylvania for the purpose of establishing volatile organic compound (VOC) and nitrogen oxides (NO_x) reasonably available control technology (RACT) for four (4) major sources located in Pennsylvania. In the Final Rules section of this **Federal Register**, EPA is approving the Commonwealth's SIP revision as a direct final rule without prior proposal because the Agency views this as a noncontroversial SIP revision and anticipates no adverse comments. A detailed rationale for the approval is set

forth in the direct final rule and the accompanying technical support document. If no adverse comments are received in response to this rule, no further activity is contemplated in relation to this rule. If EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. EPA will not institute a second comment period on this action. Any parties interested in commenting on this action should do so at this time. If adverse comments are received that do not pertain to all documents subject to this rulemaking action, those documents not affected by the adverse comments will be finalized in the manner described here. Only those documents that receive adverse comments will be withdrawn in the manner described here.

DATES: Comments must be received in writing by November 9, 1998.

ADDRESSES: Written comments should be addressed to David Campbell, Air Protection Division, Mailcode 3AP11, U.S. Environmental Protection Agency, Region III, 1650 Arch St., Philadelphia, Pennsylvania 19103. Copies of the documents relevant to this action are available for public inspection during normal business hours at the Air Protection Division, U.S. Environmental Protection Agency, Region III, 1650 Arch St., Philadelphia, Pennsylvania 19103; and the Pennsylvania Department of Environmental Protection, Bureau of Air Quality Control, P.O. Box 8468, 400 Market Street, Harrisburg, Pennsylvania 17105.

FOR FURTHER INFORMATION CONTACT: David Campbell, (215) 814-2196, at the EPA Region III office or via e-mail at campbell.dave@epamail.epa.gov. While information may be requested via e-mail, comments must be submitted in writing to the above Region III address.

SUPPLEMENTARY INFORMATION: See the information pertaining to this action, VOC and NO_x RACT determinations for individual sources located in Pennsylvania, provided in the Direct Final action of the same title which is located in the Rules and Regulations Section of this **Federal Register**.

Authority: 42 U.S.C. 7401-7671q.

Dated: September 11, 1998.

W. Michael McCabe,

Regional Administrator, Region III.

[FR Doc. 98-26896 Filed 10-7-98; 8:45 am]

BILLING CODE 6560-50-P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[TN-201-9828b; FRL-6169-7]

Approval and Promulgation of Implementation Plans Tennessee: Approval of Revisions to the Nashville/Davidson County Portion of the Tennessee SIP Regarding Control of Volatile Organic Compounds

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: The EPA proposes to approve revisions to the Nashville/Davidson County portion of the Tennessee State Implementation Plan (SIP) concerning control of volatile organic compounds. The State of Tennessee through the Tennessee Department of Air Pollution Control submitted the revisions to EPA on July 23, 1997. To be consistent with the EPA's Guidelines for "Control of Volatile Organic Compounds Emissions from Stationary Sources," the State of Tennessee amended Regulation No. 7, "Regulation for Control of Volatile Organic Compounds, Section 7-16, Emission Standards for Surface Coating of Miscellaneous Metal Parts and Products" of the Nashville/Davidson County portion of the Tennessee SIP (Nashville SIP).

In the final rules section of this **Federal Register**, the EPA is approving the State of Tennessee SIP revision as a direct final rule without prior proposal because the Agency views this as a noncontroversial revision amendment and anticipates no adverse comments. A detailed rationale for the approval is set forth in the direct final rule. If no adverse comments are received in response to the direct final rule, no further activity is contemplated in relation to this proposed rule. If EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. The EPA will not institute a second comment period on this document. Any parties interested in commenting on this document should do so at this time.

DATES: To be considered, comments must be received by November 9, 1998.

ADDRESSES: Written comments should be addressed to Mr. Gregory O. Crawford at the EPA Regional Office listed below. Copies of documents relative to this action are available for public inspection during normal business hours at the following locations. The interested persons

Tab 3

Federal Register of March 8, 1999
(64 FR 10944)

Olefin polymers	Density	Melting Point (MP) or softening point (SP) (<i>Degrees Centigrade</i>)	Maximum extractable fraction (expressed as percent by weight of the polymer) in <i>N</i> -hexane at specified temperatures	Maximum soluble fraction (expressed as percent by weight of polymer) in xylene at specified temperatures
<p>* 3.7 Ethylene/propylene copolymers, meeting the identity described in paragraph (a)(3)(i) of this section, containing not less than 80 mole-percent of polymer units derived from ethylene and having a minimum viscosity average molecular weight of 95,000 as determined by the method described in paragraph (d)(5) of this section, and a minimum Mooney viscosity of 13 as determined by the method described in paragraph (d)(6) of this section. Ethylene/propylene copolymers described in this item 3.7 are to be used only in blends with other olefin polymers complying with this section, at levels not to exceed 30 percent by weight of the total polymer blend, and in contact with food only of types identified in § 176.170(c) of this chapter, Table 1, under Types I, II, III, IV-B, VI, VII, VIII, and IX. Additionally, optional adjuncts permitted for use in olefin copolymers complying with item 3.4 of this table may be used in the production of this copolymer. *</p>	<p>* Not less than 0.86 *</p>	<p>* * *</p>	<p>* * *</p>	<p>* * *</p>

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Dated: February 23, 1999.

Janice F. Oliver,
*Deputy Director for Systems and Support,
 Center for Food Safety and Applied Nutrition.*
 [FR Doc. 99-5520 Filed 3-5-99; 8:45 am]
 BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. 98N-0655]

List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to include a list of drug

products that may not be used for pharmacy compounding under the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (the act) because they have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective. The list has been compiled under the new statutory requirements of the Food and Drug Administration Modernization Act of 1997 (Modernization Act).

DATES: This rule is effective on April 7, 1999.

FOR FURTHER INFORMATION CONTACT: Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers

Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

Section 127 of the Modernization Act (Pub. L. 105-115), which added section 503A to the act (21 U.S.C. 353a), describes the circumstances under which compounded drugs qualify for exemptions from certain adulteration, misbranding, and new drug provisions of the act (i.e., 501(a)(2)(B), 502(f)(1), and 505 of the act (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)).

Section 503A of the act contains several conditions that must be satisfied for pharmacy compounding to qualify for the exemptions. Section 503A(b)(1)(C) of the act provides that the licensed pharmacist or licensed physician does not "compound a drug product that appears on a list published by the Secretary in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective." Section 503A(d)(1) of the act requires that the list of drug products that have been withdrawn or removed from the market because they were unsafe or not effective be issued as a regulation and that an advisory committee be consulted in the rulemaking process.

In the **Federal Register** of October 8, 1998 (63 FR 54082), FDA proposed a rule to establish the list of drug products that have been withdrawn or removed from the market because they were unsafe or not effective. The primary focus of that initial proposed rule and this final rule is on drug products that have been withdrawn or removed from the market because they were found to be unsafe. FDA may initiate rulemaking to add other drug products to the list that have been withdrawn or removed from the market because they were found to be not effective or to update the list as new information becomes available to the agency regarding products that were removed from the market because they were unsafe. The proposed rule was presented to the Pharmacy Compounding Advisory Committee at a meeting held on October 14 and 15, 1998 (see the **Federal Register** of September 4, 1998 (63 FR 47301)). The committee did not have any adverse comments on the proposed rule and did not suggest any changes.

II. Comments on the Proposed Rule

FDA received comments from consumers, pharmacists, a medical doctor, a pharmaceutical manufacturer,

a pharmaceutical manufacturers' organization, and a committee representing the plaintiffs in a drug product liability class action suit.

1. Two comments questioned FDA's shortening the comment period from 75 to 45 days.

As FDA stated in the preamble to the proposed rule (63 FR 54082 at 54087 to 54088), the agency believes that a shorter comment period was warranted to expedite this rulemaking proceeding because the compounding of many of the drug products on the list would present a serious threat to the public health. Many of the drug products have caused death or life-threatening conditions. Some of the drugs on the list are believed to cause cancer, while others were shown to be toxic to the liver and other organs.

2. One comment objected to the wording of the first sentence of proposed § 216.24, which says "The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective." The comment expressed concerns that the finding that a drug was withdrawn from the market by the manufacturer because it was not safe or effective might be used in a product liability lawsuit against the manufacturer who voluntarily withdrew the drug product from the market. The comment also expressed concerns that fear of having the finding used against them might discourage manufacturers from voluntarily withdrawing drug products when concerns about the drug product's safety and effectiveness have developed.

The agency does not believe it is necessary to change the wording of § 216.24 in response to this comment. Compounding pharmacists and physicians are the intended audience for this rule. The purpose of § 216.24 is to provide these compounders a list of drugs that they may not compound under section 503A of the act. This list is not intended to be used as evidence in a product liability suit, and the addition of language designed to minimize the potential effect of the list in litigation is unnecessary to fulfill its intended purpose.

For the purposes of this rule, FDA has determined that it is not necessary to deviate from the statutory language found in section 503A(b)(1)(C) of the act, which prohibits compounders from compounding "a drug product that appears on a list published by [FDA] in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug

products have been found to be unsafe or ineffective."

The agency wishes to emphasize that the inclusion of a drug product on the list does not mean that the drug product was marketed negligently, was defective, or was marketed in breach of any warranty. Even after exhaustive clinical studies, safety problems may not become apparent until a drug product has been in commercial distribution for a significant amount of time, so the fact that a drug was removed or withdrawn from the market does not mean that the drug was improperly placed in commercial distribution.

3. A large number of comments objected to drug products containing adrenal cortex being placed on the list. One of the comments included a photocopy of an article from the November issue of the magazine *Nutrition & Healing*. This article apparently is the source of much of the content of many of the comments. None of the comments provided any information about the removal of adrenal cortex extract from the market, other than the unsupported statements that the removal of adrenal cortex extract was economically motivated. These comments included unsupported statements that adrenal cortex extract has never been associated with a death or serious adverse event (except for a series of adverse events in 1996 and 1997 associated with contaminated adrenal cortex extract) and that adrenal cortex extract is safer and more effective than the synthetic adrenocortical steroids that have replaced it in medical use. The comments also asserted, without presenting any scientific data or historical information to support the assertion, that FDA acted improperly in directing the removal of drugs containing adrenal cortex from the market because the low levels of corticosteroids found in the drugs presented a substantial risk of undertreatment of serious conditions.

FDA's concerns about the safety of adrenal cortex extract have grown stronger since the drug product was removed from the market in 1978. Adrenal cortex extract is derived from the cortex adrenal glands of domestic food animals, including cattle. In 1986 the disease bovine spongiform encephalopathy (BSE) was identified in cattle. BSE has been found to be epidemic in Great Britain and present in Western Europe and Oman. Hundreds of thousands of cattle have either died or been destroyed as a result of BSE infection. Since that time strong evidence has been developed associating ingestion of tissues from

BSE-infected cattle with the development of new variant Creutzfeldt-Jakob disease (nvCJD) in humans. A patient taking a drug derived from the adrenal cortex of a BSE-infected cow would be running an unacceptable risk of contracting nvCJD. Due to the destruction of BSE-infected cattle and other controls (see the **Federal Register** of August 29, 1994 (59 FR 44591)), the chances of a patient getting nvCJD from adrenal cortex extract are low. However, there is still a risk involved in taking adrenal cortex extract, and that risk must be taken very seriously in light of the fact that nvCJD appears to always be fatal.

Concerning the comments that FDA acted improperly in removing drugs containing adrenal cortex from the market because of a substantial risk of undertreatment of serious conditions, FDA's action was investigated by the General Accounting Office and found to be proper (see "By the Comptroller General, Report to the Honorable Barry M. Goldwater, Jr., House of Representatives of the United States: Adrenal Cortical Extract Taken Off Drug Market" (HRD-81-61, 1981)).

For the reasons stated previously, FDA is keeping drug products containing adrenal cortex on the list of drugs that may not be compounded under section 503A of the act.

4. One comment strongly supported the inclusion of drug products containing dexfenfluramine hydrochloride and fenfluramine hydrochloride on the list.

5. One comment pointed out that there is a hearing request pending before the agency regarding the withdrawal of approval of the applications for neomycin sulfate in sterile vials for injection (see the **Federal Register** of December 6, 1988 (53 FR 49232)) and another pending request for a hearing regarding the withdrawal of approval of the applications for neomycin sulfate for prescription compounding (see the **Federal Register** of December 6, 1988 (53 FR 49231)). A petition for stay of action regarding the two actions mentioned above and regarding a labeling guideline for neomycin sulfate for prescription compounding (see the **Federal Register** of April 15, 1988 (53 FR 12662)) is also pending before the agency.

Because of the complex administrative record on neomycin sulfate currently before the agency and because of the public health need to expedite implementation of this rule, FDA is postponing final action on listing all parenteral drug products containing neomycin sulfate. Parenteral drug products containing neomycin

sulfate may be added to the list at a later date.

III. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of \$100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. As discussed in the paragraphs below, the agency believes that this rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The agency has not estimated any compliance costs or loss of sales due to this final rule because it prohibits pharmacy compounding of only those drug products that have already been withdrawn or removed from the market. The agency is not aware of any routine use of these drug products in pharmacy compounding and received no significant data in response to the request in the preamble to the proposed rule for the submission of comments on this issue and current compounding usage data for these drug products. Additionally, FDA did not receive any comments on compliance costs and loss of sales due to this rule or current compounding usage data for the drug products listed in this rule at the Pharmacy Compounding Advisory Committee meeting held on October 14 and 15, 1998.

Unless an agency certifies that a rule will not have a significant economic

impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant economic impact of a regulation on small entities. The agency is taking this action in order to comply with section 503A of the act. This provision specifically directs the FDA to develop a list of drug products that have been withdrawn or removed from the market because such products or components have been found to be unsafe or not effective. Any drug product on this list will not qualify for the pharmacy compounding exemptions under section 503A of the act. The drug products on this list were manufactured by many different pharmaceutical firms, some of which may have qualified under the Small Business Administration (SBA) regulations (those with less than 750 employees) as small businesses. However, since the list only includes those drug products that have already been withdrawn or removed from the market for safety or efficacy concerns, this final rule will not negatively impact these small businesses. Moreover, no compliance costs are estimated for any of these small pharmaceutical firms because they are not the subject of this rule and are not expected to realize any loss of sales due to this rule. Further, the SBA guidelines limit the definition of small drug stores or pharmacies to those that have less than \$5.0 million in sales. Again, the pharmacies that qualify as small businesses are not expected to incur any compliance costs or loss of sales due to this regulation because the products have already been withdrawn or removed from the market, and the agency believes that these drugs would be compounded only very rarely, if ever. Therefore, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits for it finalizes any rule requiring any expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any 1 year. The publication of the list of products withdrawn or removed from the market because they were found to be unsafe or ineffective will not result in expenditures of funds by State, local, and tribal governments or the private sector in excess of \$100 million annually. Because the agency does not estimate any annual expenditures due to the final rule, FDA is not required to

perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

V. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 216 is added to read as follows:

PART 216—PHARMACY COMPOUNDING

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

Sec.

216.23 [Reserved]

216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

Authority: 21 U.S.C. 351, 352, 353a, 355, and 371.

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

§ 216.23 [Reserved]

§ 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective. The following drug products may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act:

Adenosine phosphate: All drug products containing adenosine phosphate.

Adrenal cortex: All drug products containing adrenal cortex.

Azaribine: All drug products containing azaribine.

Benoxaprofen: All drug products containing benoxaprofen.

Bithionol: All drug products containing bithionol.

Bromfenac sodium: All drug products containing bromfenac sodium.

Butamben: All parenteral drug products containing butamben.

Camphorated oil: All drug products containing camphorated oil.

Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate.

Casein, iodinated: All drug products containing iodinated casein.

Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation.

Chlormadinone acetate: All drug products containing chlormadinone acetate.

Chloroform: All drug products containing chloroform.

Cobalt: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives).

Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride.

Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride.

Dibromsalan: All drug products containing dibromsalan.

Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams or more of diethylstilbestrol per unit dose.

Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate.

Dipyron: All drug products containing dipyron.

Encainide hydrochloride: All drug products containing encainide hydrochloride.

Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride.

Flosequinan: All drug products containing flosequinan.

Gelatin: All intravenous drug products containing gelatin.

Glycerol, iodinated: All drug products containing iodinated glycerol.

Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin.

Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate.

Metabromsalan: All drug products containing metabromsalan.

Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride.

Methapyrilene: All drug products containing methapyrilene.

Methopholine: All drug products containing methopholine.

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride.

Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatologic application).

Nomifensine maleate: All drug products containing nomifensine maleate.

Oxyphenisatin: All drug products containing oxyphenisatin.

Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate.

Phenacetin: All drug products containing phenacetin.

Phenformin hydrochloride: All drug products containing phenformin hydrochloride.

Pipamazine: All drug products containing pipamazine.

Potassium arsenite: All drug products containing potassium arsenite.

Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).

Povidone: All intravenous drug products containing povidone.

Reserpine: All oral dosage form drug products containing more than 1 milligram of reserpine.

Sparteine sulfate: All drug products containing sparteine sulfate.

Sulfadimethoxine: All drug products containing sulfadimethoxine.

Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use).

Suprofen: All drug products containing suprofen (except ophthalmic solutions).

Sweet spirits of nitre: All drug products containing sweet spirits of nitre.

Temafloxacin hydrochloride: All drug products containing temafloxacin.

Terfenadine: All drug products containing terfenadine.

3,3',4',5-tetrachlorosalicylanilide: All drug products containing 3,3',4',5-tetrachlorosalicylanilide.

Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter.

Ticrynafen: All drug products containing ticrynafen.

Tribromsalan: All drug products containing tribromsalan.

Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane.

Urethane: All drug products containing urethane.

Vinyl chloride: All aerosol drug products containing vinyl chloride.

Zirconium: All aerosol drug products containing zirconium.

Zomepirac sodium: All drug products containing zomepirac sodium.

Dated: March 1, 1999.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 99-5517 Filed 3-5-99; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 874

[Docket No. 98N-0249]

Ear, Nose, and Throat Devices; Classification of the Nasal Dilator, the Intranasal Splint, and the Bone Particle Collector

AGENCY: Food and Drug Administration, HHS.

Tab 4

Federal Register of January 4, 2000
(65 FR 256)

dated October 2, 1997, including Appendix 01 (for Model A300–600 series airplanes); as applicable; at the applicable time specified in paragraph (a)(1) or (a)(2) of this AD. Thereafter, repeat the inspection at intervals not to exceed 5 years.

(1) For airplanes with less than 15 years since date of manufacture as of the effective date of this AD: Inspect within 10 years since date of manufacture, or within 12 months after the effective date of this AD, whichever occurs later.

(2) For airplanes with 15 or more years since date of manufacture as of the effective date of this AD: Inspect within 6 months after the effective date of this AD.

Note 2: For Model A300 series airplanes, accomplishment of an eddy current inspection prior to the effective date of this AD in accordance with Airbus Service Bulletin A300–53–0339, dated October 2, 1997, is considered acceptable for compliance with the initial eddy current inspection required by paragraph (a) of this AD.

Corrective Actions

(b) If any crack is detected during any inspection required by paragraph (a) of this AD, prior to further flight, repair the door edge frame in accordance with Airbus Service Bulletins A300–53–0339, Revision 1, dated July 28, 1998 (for Model A300 series airplanes); A310–53–2106 (for Model A310 series airplanes), dated October 2, 1997; or A300–53–6114 (for Model A300–600 series airplanes), dated October 2, 1997; as applicable. Complete replacement of a door edge frame with a new door frame in accordance with the service bulletin constitutes terminating action for the repetitive inspections required by this AD for that door frame only.

Report Requirements

(c) Submit a report of the inspection results (both positive and negative findings) to Airbus Industrie, Customer Services Directorate, 1 Rond Point Maurice Bellonte, 31707 Blagnac Cedex, France, at the applicable time specified in paragraph (e)(1) or (e)(2) of this AD. Information collection requirements contained in this regulation have been approved by the Office of Management and Budget (OMB) under the provisions of the Paperwork Reduction Act of 1980 (44 U.S.C. 3501 *et seq.*) and have been assigned OMB Control Number 2120–0056.

(1) For airplanes on which any inspection is accomplished after the effective date of this AD: Submit the report within 30 days after performing any inspection required by paragraph (a) or (b) of this AD.

(2) For airplanes on which the inspection has been accomplished prior to the effective date of this AD: Submit the report within 10 days after the effective date of this AD.

Alternative Methods of Compliance

(d) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, International Branch, ANM–116, FAA, Transport Airplane Directorate. Operators shall submit their requests through an

appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, International Branch, ANM–116.

Note 3: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the International Branch, ANM–116.

Special Flight Permits

(e) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Note 4: The subject of this AD is addressed in French airworthiness directive 98–123–245(B), dated March 11, 1998.

Issued in Renton, Washington, on December 28, 1999.

D.L. Riggan,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 00–48 Filed 1–3–00; 8:45 am]

BILLING CODE 4910–13–U

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. 99N–4490]

Additions to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations to add two drug products to the list of drug products that may not be used for pharmacy compounding under the exemptions provided by the Federal Food, Drug, and Cosmetic Act (the act) because they have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective.

DATES: Written comments must be received on or before March 20, 2000.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

I. Background

President Clinton signed the Food and Drug Administration Modernization Act (Public Law 105–115) into law on November 21, 1997. One of the issues addressed in the legislation is the applicability of the act to the practice of pharmacy compounding. Compounding involves a process whereby a pharmacist or physician combines, mixes, or alters ingredients to create a customized medication for an individual patient. Section 127 of the Modernization Act, which adds section 503A to the act (21 U.S.C. 353a), describes the circumstances under which compounded drugs qualify for exemptions from certain adulteration, misbranding, and new drug provisions of the act (i.e., sections 501(a)(2)(B), 502(f)(1), and 505 of the act (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)).

Section 503A of the act contains several conditions that must be satisfied for pharmacy compounding to qualify for the exemptions. One of the conditions is that the licensed pharmacist or licensed physician does not “compound a drug product that appears on a list published by the Secretary in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.”

II. Rulemaking to Establish the List

In the **Federal Register** of October 8, 1998 (63 FR 54082), we proposed the original list of drug products that have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective. We published the original list as a final rule in the **Federal Register** of March 8, 1999 (64 FR 10944). You may wish to read these documents for additional information about the list. The two **Federal Register** documents may be found on the Center for Drug Evaluation and Research’s website at <http://www.fda.gov/cder/pharmcomp/default.htm> or the Government Printing Office’s website at http://www.access.gpo.gov/su_docs/aces/aces140.html.

The list was codified as § 216.24 of Title 21 in the Code of Federal Regulations (CFR) (21 CFR 216.24). This is the first time we have proposed to amend the list.

III. Description of this Proposed Rule

We are proposing that the drug products described below be added to

the list of drug products that have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective. Compounding a drug product that appears on the list is not covered by the exemption provided in section 503A(a) of the act, and it may be subject to enforcement action under sections 501(a)(2)(B), 502(f)(1), and 505 (among other applicable provisions) of the act.

Aminopyrine: All drug products containing aminopyrine. Drug products containing aminopyrine were used as an analgesic and an antipyretic. Aminopyrine caused agranulocytosis, a condition characterized by a decrease in the number of certain white blood cells and lesions on the mucous membrane and skin. Some of the cases of agranulocytosis were fatal. In 1964, we declared drug products containing aminopyrine to be new drugs. We invited new drug applications (NDA's) for these drug products, but only for use as an antipyretic in serious situations where other safer drugs could not be used (see 21 CFR 201.311 (42 FR 53954, October 4, 1977)). We received no NDA's for drug products containing aminopyrine, and those unapproved drug products were removed from the market by their manufacturers (see 42 FR 53954).

Astemizole: All drug products containing astemizole. Astemizole tablets were marketed under the trade name Hismanal and were indicated for the relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria. We approved the NDA for astemizole tablets in December 1988. Within a few years of the approval, it was learned that low-level overdoses of astemizole were resulting in life-threatening heart arrhythmias. Patients with liver dysfunction or who were taking other drugs that interfered with the metabolism of astemizole were also found to be at risk of serious cardiac adverse events while taking astemizole. The manufacturer of astemizole tablets, the only astemizole drug product, removed the product from the market on June 18, 1999. We published a notice in the **Federal Register** of August 23, 1999 (64 FR 45973), announcing our determination that astemizole tablets were withdrawn from the market for safety reasons.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore,

neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of \$100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. As discussed below, the agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The agency has not estimated any compliance costs or loss of sales due to this proposed rule because it prohibits pharmacy compounding of only those drug products that have already been withdrawn or removed from the market. Although the agency is not aware of any routine use of these drug products in pharmacy compounding, the agency invites the submission of comments on this issue and solicits current compounding usage data for these drug products.

Unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant economic impact of a regulation on small entities. The agency is taking this action to comply with section 503A of the act. This provision specifically directs us to develop a list of drug products that have been withdrawn or removed from the market because such products or components have been found to be unsafe or not effective. Any drug product on this list will not qualify for the pharmacy compounding exemptions under section 503A of the act.

The drug products that are proposed to be added to the this list were manufactured by several different pharmaceutical firms, some of which may have qualified under the Small Business Administration (SBA) regulations (those with less than 750 employees) as small businesses. However, since the list only includes drug products that have already been withdrawn or removed from the market for safety or efficacy concerns, this proposal will not negatively impact these small businesses. Moreover, no compliance costs are estimated for any of these small pharmaceutical firms because they are not the subject of this rule and are not expected to realize any further loss of sales due to this proposal. Further, the SBA guidelines limit the definition of small drug stores or pharmacies to those that have less than \$5.0 million in sales. Again, the pharmacies that qualify as small businesses are not expected to incur any compliance costs or loss of sales due to this regulation because the products have already been withdrawn or removed from the market, and the agency believes that these drugs would be compounded only very rarely, if ever. Therefore, we certify that this rule will not have a significant economic impact on a substantial number of small entities.

Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any one year. The publication of the list of products withdrawn or removed from the market because they were found to be unsafe or ineffective will not result in expenditures of funds by State, local, and tribal governments or the private sector in excess of \$100 million annually. Because the agency does not estimate any annual expenditures due to the proposed rule, we are not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

VI. Paperwork Reduction Act of 1995

We tentatively conclude that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VII. Request for Comments

Interested persons may, on or before March 20, 2000, submit to the Dockets

Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 216 be amended as follows:

PART 216—PHARMACY COMPOUNDING

1. The authority citation for 21 CFR part 216 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 353a, 355, and 371.

2. Amend § 216.24 by adding alphabetically to the list of drug products "Aminopyrine" and "Astemizole" to read as follows:

§ 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

* * * * *

Aminopyrine: All drug products containing aminopyrine.

Astemizole: All drug products containing astemizole.

* * * * *

Dated: December 10, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 00-76 Filed 1-3-00; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[REG-105606-99]

RIN 1545-AX05

Credit for Increasing Research Activities

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Notice of proposed rulemaking and notice of public hearing.

SUMMARY: This document contains proposed regulations relating to the computation of the credit for increasing

research activities (the research credit) for members of a controlled group and the allocation of the credit under section 41(f) of the Internal Revenue Code. These proposed regulations are intended to provide guidance on the proper method for computing the research credit for members of a controlled group and the proper method for allocating the group credit to members of the group. These proposed regulations reflect changes to section 41 made by the Revenue Reconciliation Act of 1989 (the 1989 Act). This document also provides notice of a public hearing on these regulations.

DATES: Written or electronic comments must be received no later than April 5, 2000. Outlines of topics to be discussed at the public hearing scheduled for April 26, 2000 at 10 a.m. must be received by April 5, 2000.

ADDRESSES: Send submissions to: CC:DOM:CORP:R (REG-105606-99), room 5226, Internal Revenue Service, POB 7604, Ben Franklin Station, Washington, DC 20044. Submissions may be hand delivered Monday through Friday between the hours of 8 a.m. and 5 p.m. to: CC:DOM:CORP:R (REG-105606-99), Courier's Desk, Internal Revenue Service, 1111 Constitution Avenue NW., Washington, DC. Alternatively, taxpayers may submit comments electronically via the Internet by selecting the "Tax Regs" option of the IRS Home Page, or by submitting comments directly to the IRS Internet site at: <http://www.irs.gov/prod/taxregs/reglist.html>. The public hearing will be held in room 2615, Internal Revenue Building, 1111 Constitution Avenue, NW., Washington, DC.

FOR FURTHER INFORMATION CONTACT: Concerning the proposed regulations, Lisa J. Shuman at (202) 622-3120 (not a toll-free number); concerning submission of comments, the hearing, and/or to be placed on the building access list to attend the hearing, La Nita Van Dyke at (202) 622-7190 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Paperwork Reduction Act

The collection of information contained in this notice of proposed rulemaking has been submitted to the Office of Management and Budget for review in accordance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)). Comments on the collection of information should be sent to the Office of Management and Budget, Attn: Desk Officer for the Department of the Treasury, Office of Information and Regulatory Affairs, Washington, DC 20503, with copies to

the Internal Revenue Service, Attn: IRS Reports Clearance Officer, OP:FS:FP, Washington, DC 20224. Comments on the collection of information should be received by March 6, 2000. Comments are specifically requested concerning:

Whether the proposed collection of information is necessary for the proper performance of the functions of the IRS, including whether the information will have practical utility;

The accuracy of the estimated burden associated with the proposed collection of information (see below);

How the quality, utility, and clarity of the information to be collected may be enhanced;

How the burden of complying with the proposed collection of information may be minimized, including through the application of automated collection techniques or other forms of information technology; and

Estimates of capital or start-up costs and costs of operation, maintenance, and purchase of services to provide information.

The collection of information in this proposed regulation is contained in the preamble under the heading "Proposed Effective Date." The information is required by the IRS to ensure that members of a controlled group filing claims for refund based on a change in method of allocating the research credit to members of the group do not together claim in excess of 100% of the credit with respect to prior taxable years.

Estimated total annual reporting burden: 200 hours.

Estimated average annual burden hours per respondent: 20 hours.

Estimated number of respondents: 10.

Estimated frequency of responses: On occasion.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a valid control number assigned by the Office of Management and Budget.

Books or records relating to a collection of information must be retained as long as their contents may become material in the administration of any internal revenue law. Generally, tax returns and tax return information are confidential, as required by 26 U.S.C. 6103.

Background

The research credit provisions originally appeared in section 44F of the Internal Revenue Code of 1954 (the 1954 Code), as added to the 1954 Code by section 221 of the Economic Recovery Tax Act of 1981. Section 471(c) of the Tax Reform Act of 1984 redesignated section 44F as section 30. Section 231

Tab 5

Federal Register of June 29, 2000
(65 FR 40104)

In the **Federal Register** of March 13, 2000 (65 FR 13405), the agency requested comments on the proposed collections of information. No comments were received.

Dated: June 22, 2000.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning, and Legislation.

[FR Doc. 00-16398 Filed 6-28-00; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Pharmacy Compounding Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Pharmacy Compounding Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on July 13 and 14, 2000, 8:30 a.m. to 5 p.m.

Location: CDER Advisory Committee conference room 1066, 5630 Fishers Lane, Rockville, MD.

Contact Person: Jayne E. Peterson or Tony A. Slater, Jr., Center for Drug Evaluation and Research (CDER) (HFD-21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7001, e-mail: PETERSONJ@CDER.FDA.GOV, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12440. Please call the Information Line for up-to-date information on this meeting.

Agenda: On July 13, 2000, the committee will review five drug products for inclusion on a list of drug products that cannot be compounded because they have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (see 21 CFR 216.24 (64 FR 10944, March 8, 1999)) whereby FDA amended its regulations to include such a list of drug products). In the **Federal Register** of January 4, 2000 (65 FR 256), FDA published a proposed rule amending these

regulations to add two drug products to the list: (1) Aminopyrine (all drug products containing aminopyrine) and (2) astemizole (all drug products containing astemizole). In addition to these two drug products, the committee will review the following three drug products: (1) Grepafloxacin (all drug products containing grepafloxacin), (2) troglitazone (all drug products containing troglitazone), and (3) cisapride (all drug products containing cisapride). Beginning at approximately 10 a.m., and continuing on July 14, 2000, at approximately 8:30 a.m., the committee will discuss and provide FDA with advice about drug products that present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of those drug products.

Procedure: Interested persons may present data, information, or views, orally or in writing on issues pending before the committee. Written submissions may be made to the contact person by July 3, 2000. On July 13, 2000, oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. On July 14, 2000, oral presentations from the public will be scheduled between approximately 8:30 a.m. and 9:30 a.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before July 3, 2000, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

FDA regrets that it was unable to publish this notice 15 days prior to the July 13 and 14, 2000, Pharmacy Compounding Advisory Committee meeting. Because the agency believes there is some urgency to bring these issues to public discussion and qualified members of the Pharmacy Compounding Advisory Committee meeting were available at this time, the Commissioner of Food and Drugs concluded that it was in the public interest to hold this meeting even if there was not sufficient time for the customary 15-day public notice.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: June 20, 2000.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 00-16397 Filed 6-28-00; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00D-1313]

Draft Guidance for Industry on How to Use E-Mail to Submit a Notice of Final Disposition of Animals Not Intended for Immediate Slaughter; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of the draft guidance for industry (#86) entitled "How to Use E-Mail to Submit a Notice of Final Disposition of Animals Not Intended for Immediate Slaughter" in the Center for Veterinary Medicine (CVM). This draft guidance is neither final nor is it in effect at this time. The draft guidance document is intended to provide guidance to new animal drug sponsors (sponsors) on how to submit a notice of final disposition of animals not intended for immediate slaughter (NFDA) as an e-mail attachment by Internet. These electronic submissions are part of CVM's ongoing initiative to provide a method for paperless submissions. This draft guidance implements provisions of the Government Paperwork Elimination Act (GPEA).

DATES: Submit written comments on the draft guidance at any time, however, comments should be submitted by August 28, 2000 to ensure their adequate consideration in preparation of the final document. Submit written comments on the information collection requirements by August 28, 2000.

ADDRESSES: Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Comments should be identified with the full title of the draft guidance document and the docket number found in brackets in the heading of this document.

Copies of the draft guidance document entitled "How to Use E-Mail to Submit a Notice of Final Disposition of Animals Not Intended for Immediate Slaughter" may be obtained on the

Tab 6

Federal Register of July 2, 2014
(see 79 FR 37687)

Compliance), those steps must be done to comply with this AD; any steps that are not labeled as RC are recommended. Those steps that are not labeled as RC may be deviated from, done as part of other actions, or done using accepted methods different from those identified in the specified service information without obtaining approval of an AMOC, provided the steps labeled as RC can be done and the airplane can be put back in a serviceable condition. Any substitutions or changes to steps labeled as RC require approval of an AMOC.

(k) Related Information

(1) For more information about this AD, contact Marie Hogestad, Aerospace Engineer, Systems and Equipment Branch, ANM-130S, Seattle Aircraft Certification Office (ACO), FAA, 1601 Lind Avenue SW., Renton, WA 98057-3356; phone: 425-917-6418; fax: 425-917-6590; email: marie.hogestad@faa.gov.

(2) For service information identified in this AD, contact Boeing Commercial Airplanes, Attention: Data & Services Management, P. O. Box 3707, MC 2H-65, Seattle, WA 98124-2207; telephone 206-544-5000, extension 1; fax 206-766-5680; Internet <https://www.myboeingfleet.com>. You may view this referenced service information at the FAA, Transport Airplane Directorate, 1601 Lind Avenue SW., Renton, WA. For information on the availability of this material at the FAA, call 425-227-1221.

Issued in Renton, Washington, on June 24, 2014.

Jeffrey E. Duven,

Manager, Transport Airplane Directorate,
Aircraft Certification Service.

[FR Doc. 2014-15505 Filed 7-1-14; 8:45 am]

BILLING CODE 4910-13-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. FDA-1999-N-0194 (Formerly 99N-4490)]

RIN 0910-AH10

Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; withdrawal of previous proposed rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is proposing to amend its regulations to revise the list of drug products that may not be compounded under the exemptions provided by the Federal Food, Drug, and Cosmetic Act (the

FD&C Act) because the drug products have been withdrawn or removed from the market after the drug products or components of such drug products were found to be unsafe or not effective.

Specifically, the proposed rule would add 25 drug products to this list of drug products and modify the description of one drug product on this list to add an exception. These revisions are necessary because new information has come to the Agency's attention since March 8, 1999, when FDA published the original list as a final rule. FDA is also withdrawing the previous proposed rule regarding additions to this list (see the **Federal Register** of January 4, 2000).

DATES: Submit either electronic or written comments on the proposed rule by September 2, 2014. The January 4, 2000, proposed rule (65 FR 256) is withdrawn as of July 2, 2014.

ADDRESSES: You may submit comments, identified by Agency name and Docket No. FDA-1999-N-0194 and/or Regulatory Information Number (RIN) number 0910-AH10, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name, Docket No. FDA-1999-N-0194, and RIN 0910-AH10 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the "Request for Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Edisa Gozun, Center for Drug Evaluation

and Research (HFD-310), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5199, Silver Spring, MD 20993-0002, 301-796-3110.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from the following three sections of the FD&C Act: (1) Section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).

One of the conditions that must be satisfied to qualify for the exemptions under section 503A of the FD&C Act is that the licensed pharmacist or licensed physician does not compound a drug product that appears on a list published by the Secretary in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (see section 503A(b)(1)(C) of the FD&C Act).

A. Court Decisions Regarding the Pharmacy Compounding Provisions of the FD&C Act

As originally enacted, section 503A of the FD&C Act included prohibitions on the advertising and solicitation of prescriptions for any particular compounded drug, class of drug, or type of drug. Seven compounding pharmacies challenged the advertising and solicitation provisions of section 503A of the FD&C Act as an impermissible regulation of commercial speech. In February 2001, the U.S. Court of Appeals for the Ninth Circuit held that the prohibition on advertising and promotion in section 503A(c) and the provision of section 503A(a) of the FD&C Act that requires that the prescription be "unsolicited," were unconstitutional restrictions on commercial speech. (See *Western States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001).) Furthermore, the Ninth Circuit held that the advertising and solicitation provisions could not be severed from the rest of section 503A and, as a result, found section 503A of the FD&C Act to be invalid in its

entirety. In April 2002, the U.S. Supreme Court affirmed the Ninth Circuit's decision that the advertising and solicitation provisions were unconstitutional; it did not, however, rule on the severability of section 503A of the FD&C Act. (See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).)

In light of these decisions, FDA issued a Compliance Policy Guide in 2002 to provide guidance on FDA's approach concerning the regulation of pharmacy compounding. (See the **Federal Register** of June 7, 2002 (67 FR 39409).)

In September 2004, 10 pharmacies brought suit in the U.S. District Court for the Western District of Texas challenging FDA's authority to regulate compounded drugs. In August 2006, the District Court held, in part, that compounded human drugs are implicitly exempt from the "new drug" definition in section 201(p) of the FD&C Act and, as a result, are not subject to the FD&C Act's new drug approval requirements. (See *Medical Ctr. Pharm. v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006).) The District Court also held that the advertising and solicitation provisions in section 503A of the FD&C Act that the Supreme Court had found to be unconstitutional were severable from the rest of that section.

The Federal Government appealed the decision of the U.S. District Court for the Western District of Texas. In July 2008, the U.S. Court of Appeals for the Fifth Circuit reversed the District Court's finding of an implicit exemption for compounded drugs from the new drug approval requirements in the FD&C Act, holding, instead, that compounded drugs fall within the definition of "new drug" in the FD&C Act and, therefore, are subject to regulation by FDA. (See *Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383 (5th Cir. 2008).) The Fifth Circuit also held that the advertising and solicitation provisions are severable from the rest of section 503A of the FD&C Act, and as a result, the other provisions of section 503A remain in effect.

The Fifth Circuit's severability ruling conflicted with the earlier Ninth Circuit decision, which held that the advertising and solicitation provisions cannot be severed from section 503A of the FD&C Act, and rendered all of section 503A void. Following a fungal meningitis outbreak in September 2012, FDA sought legislation to, among other things, resolve the split in the Circuits to clarify that section 503A of the FD&C Act was valid nationwide.

B. 2013 Drug Quality and Security Act

On November 27, 2013, President Obama signed the Drug Quality and Security Act (Pub. L. 113-54) (DQSA) that contains important provisions relating to the oversight of compounding of human drugs. This new law removes from section 503A of the FD&C Act the provisions that had been held unconstitutional by the U.S. Supreme Court in 2002. By removing these provisions, the new law clarifies that section 503A of the FD&C Act applies nationwide. In addition, the DQSA adds a new section 503B of the FD&C Act (21 U.S.C. 353b) that creates a new category of "outsourcing facilities." Outsourcing facilities, as defined in section 503B of the FD&C Act, are facilities that meet certain conditions described in section 503B, including registering with FDA as an outsourcing facility. If these conditions are satisfied, a drug compounded for human use by or under the direct supervision of a licensed pharmacist in an outsourcing facility is exempt from three sections of the FD&C Act: (1) Section 502(f)(1), (2) section 505, and (3) section 582 (21 U.S.C. 360eee); but not section 501(a)(2)(B). One of the conditions in section 503B of the FD&C Act that must be satisfied to qualify for the exemptions is that the drug does not appear on a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (see section 503B(a)(4)).

Given that nearly identical criteria apply for a drug to be included on the list referred to in section 503A(b)(1)(C) and the list referred to in section 503B(a)(4) of the FD&C Act, FDA is proposing to revise and update the list at § 216.24 (21 CFR 216.24) for purposes of both sections 503A and 503B. Accordingly, the proposed rule that published in the **Federal Register** of January 4, 2000, which would have amended the list in § 216.24, is withdrawn (see **DATES**).

C. Regulatory History of the List

1. Original List

In the **Federal Register** of October 8, 1998 (63 FR 54082), FDA proposed a rule to establish the original list of drug products that have been withdrawn or removed from the market because the drug products or the components of such drug products were found to be unsafe or not effective (1998 proposed rule). The 1998 proposed rule was presented to the Pharmacy Compounding Advisory Committee (Advisory Committee) at a meeting held

on October 14 and 15, 1998 (63 FR 47301, September 4, 1998). The Advisory Committee did not have any adverse comments on the 1998 proposed rule and did not suggest any changes. A transcript of the October 1998 Advisory Committee meeting may be found at the Division of Dockets Management (see **ADDRESSES**) and at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm290713.htm>.

In the **Federal Register** of March 8, 1999 (64 FR 10944), FDA published a final rule that codified the original list in § 216.24 (1999 final rule).

2. 2000 Proposed Rule and Additional Drug Products for the List in § 216.24

In the **Federal Register** of January 4, 2000 (65 FR 256), FDA proposed a rule to amend § 216.24 (2000 proposed rule). Specifically, FDA proposed to add all drug products containing aminopyrine and all drug products containing astemizole to the original list of drug products withdrawn or removed from the market because they have been found to be unsafe or not effective. After the 2000 proposed rule published, three additional drug products (cisapride, grepafloxacin, and troglitazone) were identified as candidates for addition to the list. These five drug products were presented to the Advisory Committee at a meeting held on July 13 and 14, 2000 (65 FR 40104, June 29, 2000). The Advisory Committee voted to include aminopyrine, astemizole, cisapride, grepafloxacin, and troglitazone to the list of drug products that have been withdrawn or removed from the market because they were found to be unsafe or not effective. A transcript of the July 2000 Advisory Committee meeting may be found at the Division of Dockets Management (see **ADDRESSES**) and at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm290713.htm>.

3. New Proposed Rule To Amend the List in § 216.24

This proposed rule would add to § 216.24 the five drug products identified in section I.C.2 and additional drug products that have been withdrawn or removed from the market since the publication of the 1999 final rule because the drug products or components of such drug products were found to be unsafe or not effective. FDA also proposes to modify the description of one drug product contained in the original list to add an exception that would allow the product to be compounded under certain

circumstances. These revisions are necessary to ensure the list of drugs in § 216.24 reflects new information that has come to the Agency's attention since FDA published the original list in the 1999 final rule. As with the original list, the primary focus of this proposed rule is on drug products that have been withdrawn or removed from the market because they were found to be unsafe. FDA may propose at a later date to add other drug products to the list that have been withdrawn or removed from the market because they were found to be not effective, or to update the list as new information becomes available to the Agency regarding products that were removed from the market because they were found to be unsafe.

This proposed rule would replace the 2000 proposed rule. The list set forth in this proposed rule would apply to compounders and outsourcing facilities seeking to qualify for the exemptions under either section 503A or section 503B of the FD&C Act. Accordingly, the 2000 proposed rule to amend § 216.24 is withdrawn. In preparing this proposed rule, FDA has taken into consideration the discussions held by the July 2000 Advisory Committee and that Advisory Committee's vote to include aminopyrine, astemizole, cisapride, grepafloxacin, and troglitazone on the list of drug products that have been withdrawn or removed from the market because they were found to be unsafe or not effective.

Additional nominations for this list can be submitted to FDA for consideration in comments to this proposed rule.

II. Procedural Issue for Comment

Section 503A of the FD&C Act describes the list in section 503A(b)(1)(C) as a list published by the Secretary in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective. This suggests that FDA can develop the 503A(b)(1)(C) list by publishing it in the **Federal Register** and does not need to go through notice and comment rulemaking. Section 503A(c)(1) of the FD&C Act, however, states that the Secretary shall issue regulations to implement section 503A, and that before issuing regulations to implement section 503A(b)(1)(C) pertaining to the withdrawn or removed rule, among other sections, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation

is necessary to protect the public health. In 1998 and 1999, FDA used rulemaking to develop the original list of drug products that had been withdrawn or removed from the market, and consulted the Pharmacy Compounding Advisory Committee about the list. In 2000, FDA also proposed to amend the list through rulemaking after consultation with the Advisory Committee.

Meanwhile, new section 503B of the FD&C Act describes the list in section 503B(a)(4) as a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective. Section 503B(c) of the FD&C Act requires that the Secretary implement through regulations, following consultation with an advisory committee, a list of drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs and therefore may not be compounded under section 503B. (See section 503B(a)(6) of the FD&C Act.) Section 503B does not, however, include any similar requirement for rulemaking or consultation with an advisory committee to establish the list of drugs that may not be compounded under section 503B of the FD&C Act because they have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective.

As noted, FDA plans to publish a single list of drug products (referred to as "the withdrawn or removed list" or "the list") that cannot be compounded for human use under the exemptions provided by either section 503A or 503B of the FD&C Act because they have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective. FDA invites comments on the appropriate procedure to update the list in the future. The Agency believes that the timely sharing of information about safety concerns relating to compounding drugs for human use without undue delay is essential to the protection of public health. FDA is concerned that consulting with the advisory committee and completing the rulemaking process are likely to contribute to substantial delay in updating the list to reflect current safety information. FDA therefore is seeking an alternative procedure to update the withdrawn or removed list in the future. Although FDA is publishing a proposed rule today to add 25 drugs to the list, FDA is also

soliciting public input through this **Federal Register** notice on alternative procedures for updating the list and requests that this input be submitted to FDA for consideration in comments to this proposed rule. FDA will specify in the final rule the procedure it will use to update the list in the future.

III. Description of This Proposed Rule

A. Amendments to Introductory Text

FDA is proposing to add the phrase "or section 503B(a)" to the introductory text of § 216.24 to clarify that drug products included in the list in § 216.24 will not qualify for the exemptions under either section 503A(a) or section 503B(a) of the FD&C Act when compounded.

B. Amendments To Add Drug Products to the List

FDA is proposing to amend § 216.24 to include the 25 drug products described in the following paragraphs that have been withdrawn or removed from the market since the 1999 final rule was published (March 1999) because such drug products or components of such drug products have been found to be unsafe or not effective.

A drug product that is included in the list codified at § 216.24 is not entitled to the exemptions provided in section 503A(a) of the FD&C Act, and is subject to sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act, in addition to other applicable provisions. In addition, a drug that is included in the list codified at § 216.24 is not entitled to the exemptions provided in section 503B(a) of the FD&C Act, and is subject to sections 502(f)(1) and 505 of the FD&C Act, in addition to other applicable provisions.

The listed drugs are ineligible for the exemptions set forth in sections 503A and 503B of the FD&C Act because they have been withdrawn or removed from the market because they were found to be unsafe or not effective. Most drugs on the list may not be compounded in any form. There are, however, two categories of exceptions. In the first category, a particular formulation, indication, dosage form, or route of administration of a drug is explicitly excluded from an entry on the list because an approved drug containing the same active ingredient(s) has not been withdrawn or removed from the market. For such drugs, the formulation, indication, dosage form, or route of administration expressly excluded from the list may be eligible for the exemptions provided in sections 503A and 503B of the FD&C Act. In the second category, some drugs are listed only with regard to certain

formulations, concentrations, indications, routes of administration, or dosage forms because they have been found to be unsafe or not effective in those particular formulations, concentrations, indications, routes of administration, or dosage forms. For drugs that are listed with these types of limitations, any compounding of the drug will be closely scrutinized to ensure that the compounding of the drug does not create a product that is unsafe or not effective. If it appears to do so, FDA may determine that the drug is not entitled to the exemptions provided in sections 503A and 503B of the FD&C Act. Those compounding these particular drugs should take note of the reasons FDA has cited for including a drug on this list, and carefully consider these reasons when considering whether or not to compound a drug that is so listed.

The following drug products are arranged alphabetically by the established names of the active ingredients contained in the drug products and are proposed for inclusion in § 216.24. For many of the drugs, the proprietary or trade name of some or all of the drug products that contained the active ingredient are also given in the preamble paragraphs describing the withdrawn or removed drug products. In several cases, the withdrawn or removed drug products are identified according to the established name of the active ingredient, listed as a particular salt or ester of the active moiety. The following list includes a brief summary of the reasons why each drug product is being proposed for inclusion.

Alatrofloxacin mesylate: All drug products containing alatrofloxacin mesylate. Alatrofloxacin mesylate, formerly marketed as TROVAN Injection, was associated with serious liver injury. On June 9, 1999, FDA announced in a Public Health Advisory that the NDA holder agreed to a limited distribution of TROVAN (alatrofloxacin mesylate) Injection and TROVAN (trovafloxacin mesylate) tablets, 100 milligrams (mg) and 200 mg, to inpatient healthcare facilities (Ref. 1). Subsequently, in the **Federal Register** of June 16, 2006 (71 FR 34940), FDA announced that it was withdrawing the approval of the NDA for TROVAN Injection after the NDA holder notified the Agency that the drug product was no longer marketed and requested that the approval of the NDA be withdrawn.

Aminopyrine: All drug products containing aminopyrine. Aminopyrine was associated with agranulocytosis, a condition characterized by a decrease in the number of certain blood cells and lesions on the mucous membrane and

skin. Some cases of agranulocytosis were fatal. In 1964, FDA declared drug products containing aminopyrine to be new drugs and invited NDAs for these drug products, but only for use as an antipyretic in serious situations where other, safer drugs could not be used. FDA received no NDAs for drug products containing aminopyrine, and those unapproved drug products were removed from the market (see the **Federal Register** of October 4, 1977 (42 FR 53954), and January 4, 2000 (65 FR 256)). Aminopyrine was presented to the Advisory Committee at the July 2000 meeting, and the Advisory Committee voted to include aminopyrine on the withdrawn or removed list (see the **Federal Register** of June 29, 2000 (65 FR 40104)).

Astemizole: All drug products containing astemizole. Astemizole, formerly marketed as HISMANAL 10-mg tablets, was associated with life-threatening heart arrhythmias. Patients with liver dysfunction or who were taking other drugs that interfered with the metabolism of astemizole were also found to be at risk of serious cardiac adverse events while taking astemizole. On June 18, 1999, the NDA holder withdrew HISMANAL (astemizole) 10-mg tablets from the market. In the **Federal Register** of August 23, 1999 (64 FR 45973), FDA announced its determination that HISMANAL (astemizole) 10-mg tablets were removed from the market for safety reasons. (See also the **Federal Register** of January 4, 2000 (65 FR 256).) Astemizole was presented to the Advisory Committee at the July 2000 meeting, and the Advisory Committee voted to include astemizole on the withdrawn or removed list (see the **Federal Register** of June 29, 2000 (65 FR 40104)).

Cerivastatin sodium: All drug products containing cerivastatin sodium. Cerivastatin sodium, formerly marketed as BAYCOL tablets, was associated with increased risk of rhabdomyolysis. Fatal rhabdomyolysis was reported most frequently when used at higher doses, when used in elderly patients, and particularly, with concomitant use of gemfibrozil (LOPID). In an August 8, 2001, "Dear Healthcare Professional Letter," the NDA holder stated that it discontinued the marketing and distribution of all dosage strengths of BAYCOL (Ref. 2).

Chloramphenicol: All oral drug products containing chloramphenicol. Chloramphenicol was formerly marketed as CHLOROMYCETIN (chloramphenicol) Capsules. In a letter dated October 9, 2007, the application holder requested withdrawal of the

ANDA for CHLOROMYCETIN (chloramphenicol) Capsules, 50 mg, 100 mg, and 250 mg. In the **Federal Register** of February 11, 2009 (74 FR 6896), FDA announced that it was withdrawing approval of the ANDA, effective March 13, 2009. Armenpharm, Ltd., submitted a citizen petition dated February 7, 2011 (Docket No. FDA-2011-P-0081), under § 10.30 (21 CFR 10.30), requesting that the Agency determine whether CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, were withdrawn from sale for reasons of safety or effectiveness. After considering the citizen petition, FDA determined that the drug product was withdrawn for reasons of safety or effectiveness. With the approval of additional therapies with less severe adverse drug effects, FDA determined that the risks associated with CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, as then labeled, outweighed the benefits. Furthermore, CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, may cause a number of adverse reactions, the most serious being bone marrow depression (anemia, thrombocytopenia, and granulocytopenia temporally associated with treatment). Additionally, prior to the removal of the capsule drug product from the market, a boxed warning in the prescribing information for both chloramphenicol sodium succinate injection and chloramphenicol capsules stated that serious hypoplastic anemia, thrombocytopenia, and granulocytopenia are known to occur after administration of chloramphenicol. The boxed warning also described fatal aplastic anemia associated with administration of the drug and aplastic anemia attributed to chloramphenicol that later terminated in leukemia. There is published literature that suggests that the risk of fatal aplastic anemia associated with the oral formulation of chloramphenicol may be higher than the risk associated with the intravenous formulation (see the **Federal Register** of July 13, 2012 (77 FR 41412)). FDA is not aware of any oral drug products containing chloramphenicol currently being marketed.

Cisapride: All drug products containing cisapride. Cisapride, formerly marketed as PROPULSID tablets and suspension, was associated with serious cardiac arrhythmias and death. In an April 12, 2000 "Dear Healthcare Professional Letter," the NDA holder stated that it would discontinue marketing the drug as of July 14, 2000, and make the product available only through an investigational limited access program

(Ref. 3). Cisapride was presented to the Advisory Committee at the July 2000 meeting, and the Advisory Committee voted to include cisapride on the withdrawn or removed list (see the **Federal Register** of June 29, 2000 (65 FR 40104)).

Esmolol hydrochloride: All parenteral drug products containing esmolol HCl that supply 250 mg/milliliter (mL) of concentrated esmolol per 10-mL ampule. Esmolol hydrochloride (HCl), 250 mg/mL per 10-mL ampule, formerly marketed as BREVIBLOC Injection 250 mg/mL per 10-mL ampule, was associated with increased risk of medication errors resulting in serious adverse events, including deaths. The NDA holder sent a letter to FDA on June 28, 2007, notifying the Agency that the company had decided to cease the manufacture and distribution of BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule. In a citizen petition dated March 27, 2008 (Docket No. FDA-2008-P-0284), submitted under § 10.30 and in accordance with 21 CFR 314.122 and 314.161, Bedford Laboratories (Bedford) requested that the Agency determine whether BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule, was withdrawn from sale for reasons of safety or effectiveness. In the **Federal Register** of May 5, 2010 (75 FR 24710), FDA announced its determination that BREVIBLOC (esmolol HCl) Injection 250 mg/mL, 10-mL ampule, was withdrawn from the market for safety reasons.

Etretinate: All drug products containing etretinate. Etretinate was formerly marketed as TEGISON Capsules. In a letter dated September 23, 1999, the NDA holder requested that FDA withdraw the approval of the NDA for TEGISON (etretinate) Capsules because it had discontinued marketing the product. The letter also stated that the drug was not withdrawn for safety reasons. However, in an acknowledgement letter dated December 30, 2002, FDA informed the NDA holder that TEGISON (etretinate) Capsules was removed from the market because it posed a greater risk of birth defects than SORIATANE (acitretin), the product that replaced TEGISON (etretinate) Capsules (see the **Federal Register** of September 10, 2003 (68 FR 53384)). Subsequently, in the **Federal Register** of September 10, 2003, FDA announced it was withdrawing approval of the NDA.

Gatifloxacin: All drug products containing gatifloxacin (except ophthalmic solutions). Gatifloxacin was formerly marketed as TEQUIN tablets, injection, and oral suspension. In January 2003, FDA received revised product labeling relating to several

approved supplements for TEQUIN (gatifloxacin). This revised labeling deleted references to TEQUIN injection, 10 mg/mL (200 mg), indicating that this product was no longer being marketed; therefore, the product was moved from the prescription drug product list to the “Discontinued Drug Product List” section of the “Approved Drug Products With Therapeutic Equivalence Evaluations” (the Orange Book). In response to a citizen petition from Apotex Corp. (Docket No. FDA-2005-P-0369),¹ FDA determined, as set forth in the **Federal Register** of February 3, 2006 (71 FR 5858), that TEQUIN injection, 10 mg/mL (200 mg), was not withdrawn for reasons of safety and effectiveness. On May 1, 2006, Public Citizen Research Group submitted a citizen petition (Docket No. FDA-2006-P-0081),² under § 10.30, requesting that FDA immediately ban TEQUIN because of the increased risk of dysglycemia (hypoglycemia, low blood sugar, and hyperglycemia, high blood sugar) in humans. In June 2006, the NDA holder announced that it would no longer market TEQUIN. In the **Federal Register** of September 9, 2008 (73 FR 52357), FDA announced its determination that all dosage forms and strengths of TEQUIN (gatifloxacin) were withdrawn from the market for safety reasons. There are currently approved gatifloxacin ophthalmic solutions on the market. Thus, FDA is proposing to include all drug products containing gatifloxacin, except ophthalmic solutions, on the withdrawn or removed list.

Grepafloxacin: All drug products containing grepafloxacin. Grepafloxacin, formerly marketed as RAXAR tablets, was associated with cardiac repolarization, manifested as QTc interval prolongation on the electrocardiogram, which could put patients at risk of Torsade de Pointes. The NDA holder sent a letter to FDA on March 5, 2003, requesting that FDA withdraw the approval of the NDA for RAXAR tablets, stating that the product was no longer being marketed. In an acknowledgment letter dated June 20, 2003, FDA stated that RAXAR (grepafloxacin) tablets had been removed from the market because of safety concerns. In a followup letter

¹ This citizen petition was originally assigned docket number 2005P-0023/CP1. The number was changed to FDA-2005-P-0369 as a result of FDA's transition to its new docketing system (<http://www.regulations.gov>) in January 2008.

² This citizen petition was originally assigned docket number 2006P-0178. The number was changed to FDA-2006-P-0081 as a result of FDA's transition to its new docketing system (<http://www.regulations.gov>) in January 2008.

dated January 12, 2007, FDA informed the NDA holder that the RAXAR NDA should be withdrawn because of the cardiovascular risks stated previously. The NDA holder sent a letter to FDA on March 20, 2007, agreeing with FDA's determination to initiate the withdrawal of the RAXAR NDA, and FDA subsequently announced that approval of the NDA was withdrawn (see the **Federal Register** of June 14, 2007 (72 FR 32852), and July 9, 2007 (72 FR 37244)). Grepafloxacin was presented to the Advisory Committee at the July 2000 meeting, and the Advisory Committee voted to include grepafloxacin on the withdrawn or removed list (see the **Federal Register** of June 29, 2000 (65 FR 40104)).

Methoxyflurane: All drug products containing methoxyflurane. Methoxyflurane, formerly marketed as PENTHRANE Inhalation Liquid, 99.9 percent, was associated with serious, irreversible, and even fatal nephrotoxicity and hepatotoxicity in humans. In the **Federal Register** of August 16, 2001 (66 FR 43017), FDA announced that it was withdrawing the approval of the NDA after the NDA holder notified the Agency that PENTHRANE (methoxyflurane) Inhalation Liquid was no longer being marketed under the NDA and requested withdrawal of the application. In a citizen petition dated August 25, 2004 (Docket No. FDA-2004-P-0337),³ submitted under § 10.30, and in accordance with § 314.161, AAC Consulting Group requested that the Agency determine whether PENTHRANE (methoxyflurane) Inhalation Liquid, 99.9 percent, was withdrawn from sale for reasons of safety or effectiveness. In the **Federal Register** of September 6, 2005 (70 FR 53019), FDA announced its determination that PENTHRANE Inhalation Liquid, 99.9 percent, was withdrawn from the market for safety reasons.

Novobiocin sodium: All drug products containing novobiocin sodium. Novobiocin sodium, formerly marketed as ALBAMYCIN capsule, 250 mg, was associated with adverse reactions that included relatively common skin reactions, jaundice, hepatic failure, and blood dyscrasias (neutropenia, anemia, and thrombocytopenia). Literature also revealed concerns about the development of novobiocin-resistant *Staphylococci* during treatment and a potential for drug interactions. On June

³ This citizen petition was originally assigned docket number 2004P-0379. The number was changed to FDA-2004-P-0337 as a result of FDA's transition to its new docketing system (<http://www.regulations.gov>) in January 2008.

9, 1999, the NDA holder sent an annual report to FDA that indicated that ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was no longer being manufactured, and on June 27, 2007, the NDA holder sent a letter to FDA notifying the Agency that ALBAMYCIN (novobiocin sodium) capsule, 250 mg, had been discontinued. In the **Federal Register** of February 11, 2009 (74 FR 6896), FDA announced that it was withdrawing approval of the NDA in response to the NDA holder's withdrawal request. Crixmore LLC submitted a citizen petition dated July 9, 2008 (Docket No. FDA-2008-P-0431), under § 10.30, requesting that the Agency determine whether ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was withdrawn from sale for reasons of safety or effectiveness. In the **Federal Register** of January 19, 2011 (76 FR 3143), FDA announced its determination that ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was withdrawn from the market for reasons of safety or effectiveness.

Oxycodone hydrochloride: All extended-release drug products containing oxycodone hydrochloride that have not been determined by FDA to have abuse-deterrent properties. OXYCONTIN (oxycodone hydrochloride) extended-release tablets were approved in multiple strengths under NDA 20-553 in 1995. The formulation was often abused by manipulating the product to defeat its extended-release mechanism, causing the oxycodone to be released more rapidly. This product was voluntarily withdrawn from sale following introduction of a reformulated version, also marketed as OXYCONTIN (oxycodone hydrochloride) extended-release tablets, which was developed with physicochemical properties intended to make the tablets more difficult to manipulate for purposes of abuse or misuse and was approved in multiple strengths under NDA 22-272 in 2010. Several parties submitted citizen petitions under § 10.30, requesting that the Agency determine whether original OXYCONTIN (oxycodone HCl) extended-release tablets were voluntarily withdrawn from sale for reasons other than safety or effectiveness.⁴ In a letter to FDA dated

March 19, 2013, the NDA holder requested withdrawal of approval of NDA 20-553 for original OXYCONTIN. In the **Federal Register** of April 18, 2013 (78 FR 23273), FDA published notice of its determination that original OXYCONTIN, NDA 20-553, was withdrawn from sale for reasons of safety or effectiveness. The notice concluded that "[o]riginal OXYCONTIN . . . poses an increased potential for abuse by certain routes of administration, when compared to reformulated OXYCONTIN. Based on the totality of the data and information available to the Agency at this time, FDA concludes that the benefits of original OXYCONTIN no longer outweigh its risks." In the **Federal Register** of August 7, 2013 (78 FR 48177), FDA announced that it was withdrawing the approval of NDA 20-553. In addition, because the drug approval process is the most appropriate way for FDA to evaluate the effect and labeling of products with potentially abuse-deterrent properties, compounding of opioid products with potentially abuse-deterrent properties will be closely scrutinized.

Pemoline: All drug products containing pemoline. Pemoline, formerly marketed as CYLERT tablets and chewable tablets, was associated with liver failure. FDA determined that the overall risk of liver toxicity from CYLERT and generic pemoline outweighed the benefits of the drug. On October 24, 2005, FDA announced in an FDA Alert that the NDA and ANDA holders chose to stop sales and marketing of CYLERT and generic pemoline in May 2005 (Ref. 4).

Pergolide mesylate: All drug products containing pergolide mesylate. Pergolide mesylate, formerly marketed as PERMAX tablets, was associated with increased risk of heart valve damage. On March 29, 2007, FDA announced in a Public Health Advisory that the NDA and ANDA holders agreed to withdraw PERMAX and generic pergolide mesylate from the market (Ref. 5).

Phenylpropanolamine (PPA): All drug products containing PPA. A study demonstrated that PPA was associated with increased risk of hemorrhagic stroke. On November 6, 2000, FDA announced in a Public Health Advisory that it was taking steps to remove PPA from all drug products and requested that all drug companies discontinue marketing products containing PPA (Ref. 6). In response to FDA's request, companies reformulated their products

to exclude PPA. In a notice published in the **Federal Register** on August 14, 2001 (66 FR 42665), FDA offered an opportunity for a hearing on a proposal to issue an order, under section 505(e) of the FD&C Act, withdrawing approval of 13 NDAs and 8 ANDAs for products containing phenylpropanolamine. (Although the August 14, 2001, notice stated that FDA proposed to withdraw approval of 16 NDAs and 8 ANDAs, the notice listed only 13 NDAs and 8 ANDAs.) FDA withdrew approval of ANDA 71-099 for BROMATAPP Extended-Release Tablets in a notice published in the **Federal Register** of February 20, 2002 (67 FR 7702) after the application holder informed FDA that the product was no longer being marketed and requested withdrawal. In the **Federal Register** of February 20, 2014 (79 FR 9744), FDA announced that the NDA and ANDA products containing PPA were no longer shown to be safe for use under the conditions that formed the basis upon which the applications were approved, and thus the Agency was withdrawing approval of 20 products containing PPA.

Polyethylene glycol (PEG) 3350, sodium chloride, sodium bicarbonate, potassium chloride, and bisacodyl: All drug products containing PEG 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution, and 10 mg or more of bisacodyl delayed-release tablets. PEG 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution, and four bisacodyl delayed-release tablets, 5 mg (20-mg bisacodyl), formerly marketed as HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (20-mg bisacodyl), was associated with ischemic colitis. The NDA holder informed FDA that it ceased to manufacture and market HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (20-mg bisacodyl) as of September 25, 2007. On July 15, 2008, FDA received a citizen petition (Docket No. FDA-2008-P-0412), submitted under § 10.30, from Foley & Lardner LLP. The petition requested that the Agency determine whether HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and four bisacodyl delayed release tablets, 5 mg) (HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (20-mg bisacodyl)), manufactured by Braintree Laboratories, Inc. (Braintree), was withdrawn from sale for reasons of safety or effectiveness. In the **Federal Register** of

⁴ Varam, Inc., Docket No. FDA-2011-P-0473 (June 9, 2011) (10, 15, 20, 30, 40, 50, 80, and 160 mg); Sheppard, Mullin, Richter & Hampton LLP, Docket No. FDA-2010-P-0540 (October 8, 2010) (10, 15, 20, 30, 40, 60, and 80 mg); Lachman Consultant Services, Inc., Docket No. FDA-2010-P-0526 (September 30, 2010) (10, 15, 20, 30, 40, 60, 80, and 160 mg). Lachman also submitted a petition in 2001 concerning just Purdue Pharma LP's 2001

withdrawal of the 160 mg strength, Docket No. FDA-2001-P-0473 (formerly Docket No. 2001P-0426) (September 18, 2001).

March 19, 2010 (75 FR 13292), FDA announced its determination that HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (20-mg bisacodyl) was withdrawn from the market for reasons of safety or effectiveness. Similarly, PEG 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution, and two bisacodyl delayed-release tablets, 5 mg (10-mg bisacodyl), formerly marketed as HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (10-mg bisacodyl), was associated with ischemic colitis. The NDA holder informed FDA that it ceased to manufacture and market HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (10-mg bisacodyl) as of July 17, 2010. On September 23, 2010, FDA received a citizen petition (Docket No. FDA-2010-P-0507), submitted under § 10.30, from Perrigo Company (Perrigo) requesting that the Agency determine whether HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and two bisacodyl delayed release tablets, 5 mg) (HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (10-mg bisacodyl)), manufactured by Brintree, was withdrawn from sale for reasons of safety or effectiveness. In the **Federal Register** of August 17, 2011 (76 FR 51037), FDA announced its determination that HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (10-mg bisacodyl) was withdrawn from the market for reasons of safety or effectiveness.

Propoxyphene: All drug products containing propoxyphene. Propoxyphene, formerly marketed under various names such as DARVON and DARVOCET, was associated with serious toxicity to the heart. In a drug safety communication dated November 19, 2010, FDA announced it had requested that companies voluntarily withdraw propoxyphene from the U.S. market and that FDA was recommending against the continued use and prescribing of the pain reliever propoxyphene because new data showed that the drug can cause serious toxicity to the heart, even when used at therapeutic doses. FDA concluded that the safety risks of propoxyphene outweighed its limited benefits for pain relief at recommended doses. The Agency's recommendation was based on all available data including data from a then-new study that evaluated the effects that increasing doses of propoxyphene have on the heart. The

results of the study showed that when propoxyphene was taken at therapeutic doses, there were significant changes to the electrical activity of the heart which can increase the risk for serious abnormal heart rhythms (Ref. 7). In the **Federal Register** of March 10, 2014 (79 FR 13308), FDA announced that due to this safety risk, the Agency was withdrawing approval of 54 propoxyphene products with agreement from holders of the affected applications. On that date, FDA also published a notice of opportunity for a hearing on its proposal to withdraw approval of three additional propoxyphene products for which FDA had not received correspondence from the application holders requesting that FDA withdraw approval (see the **Federal Register** of March 10, 2014 (79 FR 13310)).

Rapacuronium bromide: All drug products containing rapacuronium bromide. Rapacuronium bromide, formerly marketed as RAPLON for Injection, was associated with the occurrence of bronchospasm. In a letter dated March 27, 2001, the NDA holder announced that it voluntarily withdrew all batches of RAPLON for Injection from the market (Ref. 8). FDA subsequently announced in the **Federal Register** of March 19, 2012 (77 FR 16039) that it was withdrawing the approval of the NDA.

Rofecoxib: All drug products containing rofecoxib. Rofecoxib, formerly marketed as VIOXX, was associated with increased risk of serious cardiovascular events, including heart attack and stroke. On September 30, 2004, FDA announced in a Public Health Advisory that the NDA holder voluntarily withdrew VIOXX from the market (Ref. 9).

Sibutramine hydrochloride: All drug products containing sibutramine hydrochloride. Sibutramine hydrochloride (HCl), formerly marketed as MERIDIA oral capsules, was associated with increased risk of heart attack and stroke. In a letter dated October 12, 2010, the NDA holder requested that FDA withdraw the approval of the NDA for MERIDIA. In an acknowledgment letter dated November 1, 2010, FDA stated that the benefits of MERIDIA (sibutramine HCl) oral capsules no longer outweighed the risks in any identifiable population. FDA subsequently announced in the **Federal Register** of December 21, 2010 (75 FR 80061) that it was withdrawing approval of the NDA.

Tegaserod maleate: All drug products containing tegaserod maleate. Tegaserod maleate, formerly marketed as ZELNORM, was associated with a

higher chance of heart attack, stroke, and worsening heart chest pain that can become a heart attack, compared to a placebo. On March 30, 2007, FDA announced in a Public Health Advisory that the NDA holder agreed to stop selling ZELNORM (Ref. 10). On July 27, 2007, FDA announced that it was permitting the restricted use of ZELNORM (tegaserod maleate) under a treatment investigational new drug (IND) protocol to treat irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in women younger than 55 who meet specific guidelines (Ref. 11). On April 2, 2008, FDA announced that the sponsor of ZELNORM notified FDA that it would no longer provide ZELNORM (tegaserod maleate) under a treatment IND protocol to treat IBS-C and CIC in women younger than 55; however, the sponsor agreed to continue to supply ZELNORM for use in emergency situations (Ref. 12).

Troglitazone: All drug products containing troglitazone. Troglitazone, formerly marketed as REZULIN and PRELAY Tablets, a treatment for type 2 diabetes, was shown to be more toxic to the liver than two other more recently approved drugs that offered a similar benefit. In a letter dated May 1, 2002, the holder of the NDA for REZULIN (troglitazone) Tablets requested that FDA withdraw the NDA for REZULIN (troglitazone) Tablets because it had discontinued marketing the product in March 2000. FDA subsequently announced in the **Federal Register** of January 10, 2003 (68 FR 1469) that it was withdrawing the approval of the NDA for REZULIN. In a letter dated December 31, 2002, the holder of the NDA for PRELAY (troglitazone) Tablets requested that FDA withdraw the approval of the NDA for PRELAY (troglitazone) Tablets because it never marketed the drug and had no plans to market the drug in the future. In the **Federal Register** of August 11, 2003 (68 FR 47581), FDA concluded that PRELAY was voluntarily withdrawn after review of safety data showed that REZULIN was more toxic to the liver than two other more recently approved drugs that offered a similar benefit, and FDA announced that it was withdrawing approval of the NDA for PRELAY. Troglitazone was presented to the Advisory Committee at the July 2000 meeting, and the Advisory Committee voted to include troglitazone on the withdrawn or removed list (see the **Federal Register** of June 29, 2000 (65 FR 40104)).

Trovafloxacin mesylate: All drug products containing trovafloxacin mesylate. Trovafloxacin mesylate,

formerly marketed as TROVAN tablets, 100 mg and 200 mg, was associated with serious liver injury. On June 9, 1999, FDA announced in a Public Health Advisory that the NDA holder agreed to a limited distribution of TROVAN (alatrofloxacin mesylate) Injection and TROVAN (trovafloxacin mesylate) tablets, 100 mg and 200 mg, to inpatient healthcare facilities (Ref. 1). The holders of the NDAs for TROVAN (trovafloxacin mesylate) tablets, 100 mg and 200 mg, and TROVAN/ZITHROMAX COMPLIANCE PAK (trovafloxacin mesylate/azithromycin for oral suspension) notified the Agency that the drug products were no longer marketed and requested that the approval of the NDAs be withdrawn (see the **Federal Register** of September 22, 1999 (64 FR 51325), and June 16, 2006 (71 FR 34940)). FDA announced it was withdrawing approval of the NDAs in the **Federal Register** of September 22, 1999 (64 FR 51325), and June 16, 2006 (71 FR 34940).

Valdecocix: All drug products containing valdecocix. Valdecocix, formerly marketed as BEXTRA, was associated with increased risk of serious cardiovascular events and an increased risk of serious skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other nonsteroidal anti-inflammatory drugs. On April 7, 2005, FDA announced in an FDA Alert that it had concluded that the overall risk versus benefit profile of BEXTRA (valdecocix) was unfavorable and that the NDA holder had voluntarily removed BEXTRA from the market (Ref. 13). In letters dated May 27, 2011, August 8, 2011, and October 31, 2011, the holder of the NDA for BEXTRA (valdecocix) Tablets requested that FDA withdraw the NDA for BEXTRA (valdecocix) Tablets. FDA subsequently announced in the **Federal Register** of August 2, 2013 (78 FR 46984) that it was withdrawing approval of the NDA.

C. Amendment To Modify the Description of a Drug Product on the List

FDA is proposing to amend § 216.24 to modify the description of bromfenac sodium on the list.

Bromfenac sodium: All drug products containing bromfenac sodium (except ophthalmic solutions). The use of bromfenac sodium, formerly marketed as DURACT (bromfenac sodium) Capsules, was associated with fatal hepatic failure. The manufacturer of DURACT Capsules voluntarily withdrew the drug from the market on June 22, 1998 (see the **Federal Register** of October 8, 1998 (63 FR 54082)). On

March 8, 1999, FDA included all drug products containing bromfenac sodium in the list codified at § 216.24 when FDA published the 1999 final rule (64 FR 10944). Since then, FDA has approved bromfenac ophthalmic solutions, and although one of these, XIBROM (bromfenac ophthalmic solution) 0.09%, was discontinued by the NDA holder in 2011, FDA announced its determination in the **Federal Register** of May 13, 2011 (76 FR 28045) that it was not withdrawn for reasons of safety or effectiveness. (See also Docket No. FDA-2011-P-0128.) Approved bromfenac ophthalmic solutions are currently on the market. Thus, FDA is proposing to include all drug products containing bromfenac sodium on the list with an exception for ophthalmic solutions.

For the convenience of the reader, the regulatory text of § 216.24 provided with this proposed rule includes the drug products proposed for addition and modification discussed in this document and the drug products codified by the 1999 final rule.

IV. Environmental Impact

FDA has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612) and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because small businesses are not expected to incur any compliance costs or loss of sales due to this regulation, we propose to certify that this rule will not have a significant

economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. We do not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

This rule proposes to amend § 216.24 concerning pharmacy compounding. Specifically, the proposed rule would add to or modify the list of drug products that may not be compounded under the exemptions provided by sections 503A and 503B of the FD&C Act because the drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective (see section III). The Agency is proposing to add 25 drug products to the list and to modify the description of 1 drug product on the list to add an exception. The Agency is not aware of any routine use of these drug products in pharmacy compounding and, therefore, does not estimate any compliance costs or loss of sales as a result of the prohibition against compounding these drugs for human use. However, the Agency invites the submission of comments and solicits current compounding usage data for these drug products, if they are compounded for human use.

Unless an Agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires Agencies to analyze regulatory options to minimize any significant economic impact of a regulation on small entities. Most pharmacies meet the Small Business Administration definition of a small entity, which is defined as having annual sales less than \$25.5 million for this industry. The Agency is not aware of any routine compounding of these drug products and does not estimate any compliance costs or loss of sales to small businesses as a result of the prohibition against compounding these drugs. Therefore, the Agency proposes to certify that this proposed rule will not have a significant

economic impact on a substantial number of small entities.

VI. Paperwork Reduction Act of 1995

The submission of comments on this proposed rule and the submission of additional nominations for the list that is the subject of this rulemaking would be submissions in response to a **Federal Register** notice, in the form of comments, which are excluded from the definition of “information” under 5 CFR 1320.3(h)(4) of OMB regulations on the Paperwork Reduction Act (i.e., facts or opinions submitted in response to general solicitations of comments from the public, published in the **Federal Register** or other publications, regardless of the form or format thereof, provided that no person is required to supply specific information pertaining to the commenter, other than that necessary for self-identification, as a condition of the Agency’s full consideration of the comment). The proposed rule contains no other collection of information.

VII. Request for Comments

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of comments. Identify comments with the docket number found in the brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

VIII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site addresses in this reference section, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. FDA Public Health Advisory Letter from Murray M. Lumpkin, Deputy Center Director (Review Management), Center for Drug Evaluation and Research, FDA, Re: Food and Drug Administration TROVAN (Trovafloracin/Alatrofloxacin Mesylate) Interim Recommendations (June 9, 1999), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/PublicHealthAdvisories/ucm053103.htm>.
2. Letter from E. Paul Mac Carthy, Vice President, Head U.S. Medical Science, Bayer Corporation, to Healthcare Professional, Re: Market withdrawal of Baycol (cerivastatin) (August 8, 2001), <http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM173692.pdf>.
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List of Subjects in 21 CFR Part 216

Drugs, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, the proposed rule that published on January 4, 2000 (65 FR 256), is withdrawn and it is proposed that 21 CFR part 216 be amended as follows:

PART 216—HUMAN DRUG COMPOUNDING

- 1. The authority citation for 21 CFR part 216 is revised to read as follows:
Authority: 21 U.S.C. 351, 352, 353a, 353b, 355, and 371.
- 2. The heading for part 216 is revised to read as set forth above.
- 3. Section 216.24 is revised to read as follows:

§ 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective. The following drug products may not be compounded under the exemptions provided by section 503A(a) or section 503B(a) of the Federal Food, Drug, and Cosmetic Act:

Adenosine phosphate: All drug products containing adenosine phosphate.

Adrenal cortex: All drug products containing adrenal cortex.

Alatrofloxacin mesylate: All drug products containing alatrofloxacin mesylate.

Aminopyrine: All drug products containing aminopyrine.

Astemizole: All drug products containing astemizole.

Azaribine: All drug products containing azaribine.

Benoxaprofen: All drug products containing benoxaprofen.

Bithionol: All drug products containing bithionol.

Bromfenac sodium: All drug products containing bromfenac sodium (except ophthalmic solutions).

Butamben: All parenteral drug products containing butamben.

Camphorated oil: All drug products containing camphorated oil.

Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate.

Casein, iodinated: All drug products containing iodinated casein.

Cerivastatin sodium: All drug products containing cerivastatin sodium.

Chloramphenicol: All oral drug products containing chloramphenicol.

Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation.

Chlormadinone acetate: All drug products containing chlormadinone acetate.

Chloroform: All drug products containing chloroform.

Cisapride: All drug products containing cisapride.

Cobalt: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives).

Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride.

Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride.

Dibromsalan: All drug products containing dibromsalan.

Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams or more of diethylstilbestrol per unit dose.

Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate.

Dipyron: All drug products containing dipyron.

Encainide hydrochloride: All drug products containing encainide hydrochloride.

Esmolol hydrochloride: All parenteral dosage form drug products containing esmolol hydrochloride that supply 250 milligrams/milliliter of concentrated esmolol per 10-milliliter ampule.

Entretinate: All drug products containing entretinate.

Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride.

Flosequinan: All drug products containing flosequinan.

Gatifloxacin: All drug products containing gatifloxacin (except ophthalmic solutions).

Gelatin: All intravenous drug products containing gelatin.

Glycerol, iodinated: All drug products containing iodinated glycerol.

Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin.

Grepafloxacin: All drug products containing grepafloxacin.

Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate.

Metabromsalan: All drug products containing metabromsalan.

Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride.

Methapyrilene: All drug products containing methapyrilene.

Methopholine: All drug products containing methopholine.

Methoxyflurane: All drug products containing methoxyflurane.

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride.

Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatologic application).

Nomifensine maleate: All drug products containing nomifensine maleate.

Novobiocin sodium: All drug products containing novobiocin sodium.

Oxycodone hydrochloride: All extended-release drug products containing oxycodone hydrochloride that have not been determined by FDA to have abuse-deterrent properties.

Oxyphenisatin: All drug products containing oxyphenisatin.

Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate.

Pemoline: All drug products containing pemoline.

Pergolide mesylate: All drug products containing pergolide mesylate.

Phenacetin: All drug products containing phenacetin.

Phenformin hydrochloride: All drug products containing phenformin hydrochloride.

Phenylpropanolamine: All drug products containing phenylpropanolamine.

Pipamazine: All drug products containing pipamazine.

Polyethylene glycol 3350, sodium chloride, sodium bicarbonate, potassium chloride, and bisacodyl: All drug products containing polyethylene glycol 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution, and 10 milligrams or more of bisacodyl delayed-release tablets.

Potassium arsenite: All drug products containing potassium arsenite.

Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).

Povidone: All intravenous drug products containing povidone.

Propoxyphene: All drug products containing propoxyphene.

Rapacurionium bromide: All drug products containing rapacurionium bromide.

Reserpine: All oral dosage form drug products containing more than 1 milligram of reserpine.

Rofecoxib: All drug products containing rofecoxib.

Sibutramine hydrochloride: All drug products containing sibutramine hydrochloride.

Sparteine sulfate: All drug products containing sparteine sulfate.

Sulfadimethoxine: All drug products containing sulfadimethoxine.

Sulfathiazole: All drug products containing sulfathiazole (except for those formulated for vaginal use).

Suprofen: All drug products containing suprofen (except ophthalmic solutions).

Sweet spirits of nitre: All drug products containing sweet spirits of nitre.

Tegaserod maleate: All drug products containing tegaserod maleate.

Temafloxacin hydrochloride: All drug products containing temafloxacin.

Terfenadine: All drug products containing terfenadine.

3,3',4',5-tetrachlorosalicylanilide: All drug products containing 3,3',4',5-tetrachlorosalicylanilide.

Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter.

Ticrynafen: All drug products containing ticrynafen.

Tribromsalan: All drug products containing tribromsalan.

Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane.

Troglitazone: All drug products containing troglitazone.

Trovafloxacin mesylate: All drug products containing trovafloxacin mesylate.

Urethane: All drug products containing urethane.

Valdecocix: All drug products containing valdecocix.

Vinyl chloride: All aerosol drug products containing vinyl chloride.

Zirconium: All aerosol drug products containing zirconium.

Zomepirac sodium: All drug products containing zomepirac sodium.

Dated: June 25, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-15371 Filed 7-1-14; 8:45 am]

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Tab 7

2015 FDA Review of Adenosine Phosphate



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

Date: January 28, 2015

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SUBJECT: Review of Adenosine Phosphate for the Withdrawn or Removed List

INTRODUCTION

In 1997, the Food and Drug Administration Modernization Act added section 503A to the Federal Food, Drug, and Cosmetic Act (FD&C Act). Section 503A describes the circumstances under which compounded drugs can qualify for exemptions from certain adulteration, misbranding, and new drug provisions.

One of the conditions that must be satisfied to qualify for the exemptions under section 503A of the FD&C Act is that the licensed pharmacist or licensed physician “not compound a drug product that appears on a list published by the Secretary in the *Federal Register* of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective”.¹

In 1998, FDA began to develop the *Withdrawn or Removed List*.² FDA published a proposed rule in the *Federal Register* of October 8, 1998,³ in which FDA indicated, among other things, that it had previously determined that adenosine phosphate (formerly marketed as a component of Adeno for injection, Adco for injection, and other drug products) was neither safe nor effective for its intended uses as a vasodilator and an anti-inflammatory. The notice also stated that in 1973, FDA had directed the removal of these drug products from the market.

After the proposed rule was published, FDA consulted the Pharmacy Compounding Advisory Committee about the 60 drug products FDA had proposed for inclusion on the original Withdrawn or Removed List (Appendix 1 contains the background information that was provided to the Pharmacy Compounding Advisory Committee about adenosine phosphate in 1998). The Advisory Committee briefly discussed the reasons for including adenosine

¹ See section 503A(b)(1)(C).

² In this document, the *Withdrawn or Removed List* refers to the list of drugs set forth in 21 CFR 216.24.

³ See 63 FR 54082.

phosphate on the list (Appendix 2 contains the portion of the transcript from Day 2 of the Advisory Committee that includes the Committee’s discussion about adenosine phosphate). Following this discussion, the Committee voiced no objections to FDA’s proposal to include adenosine phosphate on the Withdrawn or Removed List.

In 1999, FDA finalized and codified the Withdrawn or Removed List at 21 CFR 216.24, explaining that the drug products included on this list “may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act.”⁴ The following entry was included for adenosine phosphate: “All drug products containing adenosine phosphate.”

On July 2, 2014, FDA published a proposed rule to revise and update 21 CFR 216.24,⁵ which will also apply to outsourcing facilities, a new category of compounder created under The Drug Quality and Security Act (DQSA).⁶

In the July 2014 proposed rule, FDA recommended the addition of 25 drug products to the list and the modification of one drug already on the codified list.⁷ Although FDA did not propose any changes to the existing entry for adenosine phosphate, FDA received one comment on the July 2014 proposed rule asking that FDA clarify whether the entry for adenosine phosphate on the Withdrawn or Removed List is intended to include all three forms of adenosine phosphate (mono-, di-, and tri-phosphate) (see Appendix 3).

The language of the current adenosine phosphate entry in 21 CFR 216.24 does not specify that the compounding prohibition is intended to apply to only adenosine monophosphate; instead, it lists adenosine phosphate without any further qualification. However, in light of the comment requesting clarification of the adenosine phosphate entry, FDA decided to reassess whether to modify the entry on the list for adenosine phosphate, and, if so, how to modify it.

As part of this effort, in November 2014, the Office of Regulatory Policy (ORP) in FDA’s Center for Drug Evaluation and Research submitted six consult questions to the Office of New Drugs (OND). OND’s responses to these questions are provided in the following section.

⁴ See 64 FR 10944, March 8, 1999.

⁵ See 79 FR 37687.

⁶ Public Law 113-54, Title I (Nov. 27, 2013; 127 Stat. 587). The Drug Quality and Security Act added new section 503B to the FD&C Act creating a new category of *outsourcing facilities*. One of the conditions in section 503B of the FD&C Act that must be satisfied for an outsourcing facility to qualify for certain exemptions is that the drug not appear on a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (see section 503B(a)(4)). Given that nearly identical criteria apply for a drug to be included on the list referred to in section 503A(b)(1)(C) and the list referred to in section 503B(a)(4) of the FD&C Act, FDA proposed to revise and update the list at § 216.24 (21 CFR 216.24) for purposes of both sections 503A and 503B.

⁷ See 79 FR 37,687.

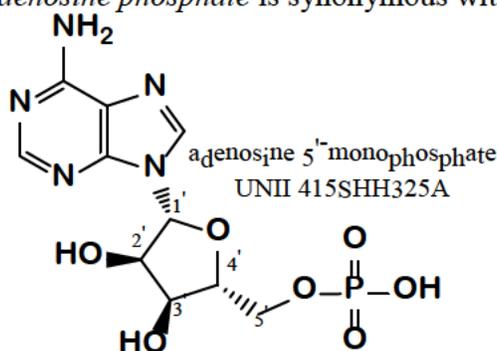
EVALUATION

1. What is the difference between adenosine and adenosine phosphate?

Adenosine is a purine nucleoside composed of a molecule of adenine attached to a ribose sugar molecule, but without a phosphate group.

The term *adenosine phosphates* usually refers to compounds consisting of an adenosine attached at one of the ribose hydroxyl-groups to one, two, three, or more phosphate units. The phosphate units are commonly attached to the 5' hydroxyl group of adenosine; *adenosine monophosphate (AMP)* refers to adenosine 5'-monophosphate; *adenosine diphosphate (ADP)* refers to adenosine 5'-diphosphate; and *adenosine triphosphate (ATP)* refers to adenosine 5'-triphosphate. When the phosphate units are attached to only one of the ribose hydroxyl groups (such as in ATP, ADP, and AMP), the adenosine phosphates can be only in the noncyclic orientation. But the phosphorylation could occur at any position and with any number of phosphates. The general term *adenosine phosphates* could refer to any adenosine that is phosphorylated.

The term *adenosine phosphate*, although ambiguous,⁸ generally refers to adenosine 5'-monophosphate (FDA Unique Ingredient Identifier (UNII) 415SHH325A). For example, as illustrated in the following diagram, FDA's Substance Registration System indicates that the *Preferred Substance Name adenosine phosphate* is synonymous with UNII 415SHH325A.



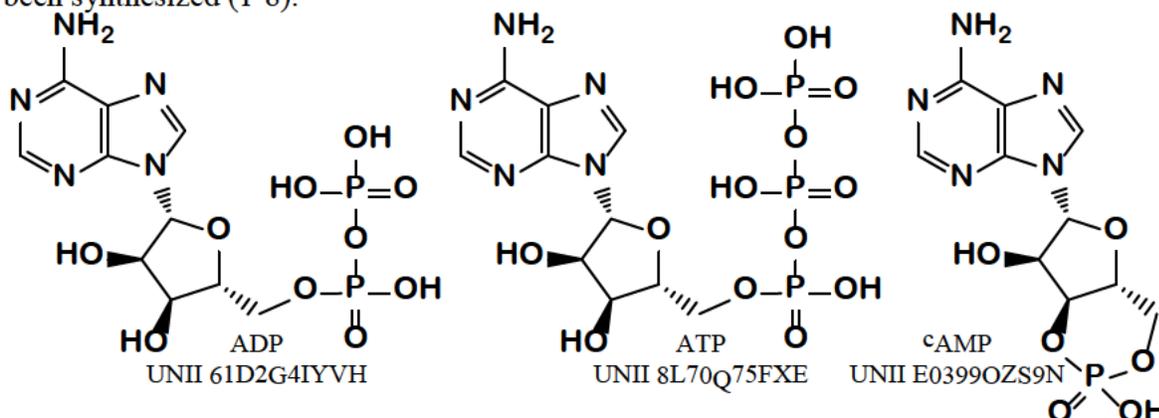
2. Are there only three forms of adenosine phosphate (i.e., mono-, di-, and tri-phosphate)?

A number of other adenosine phosphates are also known to exist endogenously and can have distinct and important functions (e.g., cyclic 3',5'-adenosine monophosphate⁹ [cAMP], adenosine 2' and 3' phosphates [e.g., nicotinamide adenine dinucleotide phosphate and 3'-phosphoadenosine-5'-phosphosulfate]). For example, cAMP, made from ATP by the enzyme

⁸ *Adenosine phosphate* is currently not a Medical Subject Heading (MeSH) in Pubmed. In a Pubmed search, the term *adenosine phosphate* is automatically mapped to two Medical Subject Headings: adenosine monophosphate and adenine nucleotides (the latter is a synonym, alternate form, or other closely related term to adenosine phosphates in MeSH).

⁹ A single phosphate is attached to two hydroxyl groups (3' and 5') of adenosine in cAMP.

adenyl cyclase, is a ubiquitous intracellular second messenger for signal transduction that regulates important cellular function. Furthermore, analogs of AMP, ADP, ATP, cAMP have been synthesized (1-8).



3. Although FDA has previously reviewed and approved products containing adenosine, the products containing adenosine *phosphate* (emphasis added) that were previously removed from the market and which in turn lead to the inclusion of the adenosine phosphate-specific entry in the Withdrawn or Removed List, were unapproved drugs. Can you confirm that FDA has never approved an NDA or ANDA containing adenosine phosphate?

To the best of our knowledge, FDA has never approved an NDA or ANDA containing any adenosine phosphate. A search on January 14, 2015, of the drugs@fda website, the current Orange Book, and the Document Archiving Reporting and Regulatory Tracking System (DARRTS) using the term *adenosine* yielded no evidence of any such drug approval.

4. The background materials on adenosine phosphate provided to the 1998 Advisory Committee (Appendix 1) contain several references to adenosine monophosphate. However, adenosine diphosphate and adenosine triphosphate do not appear to have been specifically addressed in these materials. Given your review of this material, please provide a brief summary of your understanding of any safety concerns (other than a lack of substantial scientific evidence regarding its safety or effectiveness)? Are there safety concerns associated with adenosine monophosphate that post-date 1998 of which you're aware?

Appendix 1 indicates that the risk of *Adenosine Phosphate* 25 mg/mL (assumed to have the similar safety profile of adenosine) was not offset by any known benefit. Dr. Martin's consult review (dated 1971 and cited by Lana Ogram, Director of the Division of Prescription Drug Compliance and Surveillance in her August 7, 1996, memo to Dr. Raymond Lipicky, Director of the Division of Cardio-Renal Drug Products) raised the issue of the lack of efficacy for adenosine 5' monophosphate. In addition, a consult review by Dr. Fenichel (in a memorandum dated August 8, 1996, to Ms. Ogram, also included in Appendix 1) discussing safety of *Adenosine Phosphate* 25 mg/mL cited the "nontrivial incidences" of potentially fatal cardiac dysrhythmias and bronchospasm of the two non-phosphorylated adenosine products approved in the United States.

Indeed, despite adenosine's short half-life, the labeling of both products (Adenocard [NDA 19937] and Adenoscan [NDA 20059]) recommends that appropriate resuscitative measures be available when these products are used because of these side effects (i.e., high degree heart block, cardiac arrest, ventricular arrhythmia, and myocardial infarction). In addition, the transcript of the second day of the 1998 Pharmacy Compounding Advisory Committee meeting (relevant portion included in Appendix 2) indicate that although the committee was not aware of any specific safety concern with any adenosine phosphates, the committee did not object to listing adenosine phosphate (singular) in the Withdrawn or Removed List.

To address the question of any safety concerns associated with adenosine monophosphates since 1998, OND has requested all available and relevant documents on investigational new drug (IND) applications submitted to FDA that studied adenosine monophosphate investigational products. To date, OND is not aware of any new safety concerns associated with adenosine monophosphate as of 1998.

5. Are you aware of any evidence to suggest that the safety concerns FDA has regarding adenosine monophosphate would not be applicable to any other specific form of adenosine phosphate (i.e., di-, tri- or others)? Alternatively, is there any evidence to suggest that the safety concerns FDA has regarding adenosine phosphate would be *limited* to any particular form of adenosine phosphate? Please describe if you have any additional information regarding other safety concerns associated with adenosine diphosphate or adenosine triphosphate.

The non-phosphorylated adenosine and adenosine 5' phosphate molecules are rapidly generated or metabolized from one another by ectonucleotidases and adenosine kinase (9). We are not aware of any evidence to suggest that the safety concerns FDA has regarding adenosine monophosphate would not be applicable to these non-cyclic adenosine phosphates.

ATP, as a disodium salt, appears to be approved in several countries (e.g., France, Japan) for indication(s) similar to that of adenosine approved in the United States (10, 11). However, safety reporting systems (and data collection) may vary across countries and postapproval safety may be underreported. Even so, searches of medical literature through Pubmed and EMBASE suggest a similar safety profile between ATP, non-phosphorylated adenosine, and AMP. Serious adverse events reported with ATP, such as one 50 sec asystole event with "symptoms of clinical death"(12) or ventricular arrhythmias (13), were consistent with that of non-phosphorylated adenosine. Reported adverse events (including hypotension, dyspnea, and slowing of heart rate) are expected pharmacologic or adverse effects of adenosine. Furthermore, ten articles of relevance in the clinical trial literature describing advanced cancer patients treated with infusional adenosine triphosphate at doses of between 20 mcg/kg/min and 100 mcg/kg/min, reported toxicities (including cardiopulmonary symptoms such as chest tightness, dyspnea and flushing), also consistent with those previously described for adenosine (14-23).

Although AMP, ADP, and ATP¹⁰ may share a similar pharmacologic profile with adenosine, the currently limited information does not exclude possible additional adverse events unique to a specific adenosine phosphate. Receptor binding profiles can differ, even for the naturally occurring adenosine 5' phosphates (i.e., AMP, ADP, and ATP), and insufficient information exists on pharmacologic downstream effects. For example, unlike AMP, upon release from platelets, ADP plays a role in initiating thrombus formation. Thus, in vitro and ex vivo studies demonstrate that a pharmacologic dose of ADP may raise clinical safety concerns about thrombotic events, such as myocardial infarction and stroke (24, 25).

However, cAMP and cAMP analogs could have different safety issues than adenosine because they are metabolized differently than ATP, ADP, and AMP, which are quickly metabolized to adenosine outside the cell (9, 26). For example, exogenously administered 8-chloro-adenosine 3',5'-cyclic monophosphate (8-Cl-cAMP), an analog of cAMP is enzymatically converted to 8-Cl-adenosine, which enters the cell and causes cytotoxicity and potential genotoxicity (2, 3, 28, 29). Because 8-CL-cAMP induces growth inhibition and differentiation, it was studied as a cancer treatment (27). That said, each individual cyclic AMP analog's safety profile is in part dependent upon its structure.

6. In light of your responses to the questions listed above and the information considered, do you recommend that the entry for adenosine phosphate currently included on the Withdrawn or Removed List be modified and, if so, how should the entry be described? Please include your rationale for your recommendation.

Based on the information currently available, we believe that the entry on the Withdrawn or Removed List for adenosine phosphate should be modified to clarify that it includes *adenosine 5'-monophosphate*, *adenosine 5'-diphosphate (ADP)*, and *adenosine 5'-triphosphate (ATP)*. The *Federal Register* notice for the 1998 proposed rule stated that adenosine monophosphate was “determined to be neither safe nor effective for its intended uses as a vasodilator and an anti-inflammatory.” We do not have any new safety information to alleviate the existing safety concerns for adenosine monophosphate, nor is FDA aware of any evidence to suggest that the safety concerns FDA has regarding AMP would not be applicable to ADP and ATP, which, like adenosine 5'-monophosphate, are rapidly generated or metabolized from one another by ectonucleotidases and adenosine kinase. Finally, FDA has not seen any evidence of efficacy on ADP for ATP. For these reasons, we recommend that the entry on the Withdrawn or Removed List be updated to state:

Adenosine phosphates: all drug products containing adenosine 5'-monophosphate (AMP), adenosine 5'-diphosphate (ADP), and adenosine 5'-triphosphate (ATP).

FDA is aware that cyclic AMP analogs could pose different safety risks than AMP, ADP, or ATP. FDA is pursuing further research on the cyclic AMP analogs and may propose further modifications to this entry in the future to address these other forms.

¹⁰ However, in vitro studies suggest that non-hydrolyzable analogs of ATP can have a different pharmacologic profile than adenosine (8).

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Appendix 1

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : ALL REGIONAL FOOD AND DRUG DIRECTORS
AND DISTRICT DIRECTORS
ATTN: NAS/NRC COORDINATORS
COMPLIANCE BRANCH CHIEFS

DATE: March 9, 1977

DLC-Rx Drug Study
Bulletin #226

FROM : Prescription Drug Compliance Branch, HFD-515
Division of Drug Labeling Compliance

SUBJECT: Adenosine Alone or in Combination.
Request for District Follow-Up.

We are preparing to implement follow-up to firms marketing adenosine preparations alone or in combination with other drugs which are regarded to be new drugs and are not covered by approved New Drug Applications.

This action is based upon a lack of substantial scientific evidence that products containing adenosine alone, or in combination with other ingredients, are generally recognized as safe and effective for any labeled indication and are, therefore, regarded to be new drugs within the meaning of Section 505 of the Act.

In the past, regulatory letters have issued against isolated adenosine single entity products in addition to a previous class action against adenosine with vitamin B-12 combination products (Drug Study Bulletins #122 & 160). It has come to our attention that usual reference sources contain several adenosine preparations. Therefore, we are now seeking to clear the market of any such remaining violative products via a class action.

Please submit FD-3055's for the following firms and products, and for any other such products of which you are aware, for which FD-3055's are not on file.

BOSTON DISTRICT:

My-B-Den

Miles Laboratories
West Haven, CT

DETROIT

Adenc

Fellows Medical Division
Chromalloy, Inc.
Oak Park, MI

KANSAS CITY DISTRICT

Adenosine B-12 Gel
Adenosine Gel Forte

Douglas Pharmacal Industries, Inc.
Lenexa, KS

LOS ANGELES DISTRICT

Mycasine Gel

Garter-Glogau
(formerly Myers-Carter Labs)
Glendale, AZ

NEW ORLEANS DISTRICT

Adenosine Phosphate

Ambort Medical, Inc.
Little Rock, AR

PHILADELPHIA DISTRICT

ADCO

Foy Laboratories
Wernersville, PA



Albert Lavender, Chief
Prescription Drug Compliance Branch

PRIORITY : HIGH
HIA-DCC No.: : BD-300-199
PROJECT CODE : 52
ESTIMATED TIME : 48 HOURS
REPLY REQUESTED BY : 3/25/77
PROJECT OFFICER : A.K. YELLEN
TELEPHONE NUMBER : 8-443-4206

A

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : ALL REGIONAL FOOD AND DRUG DIRECTORS
AND DEPUTY REGIONAL FOOD AND DRUG DIRECTORS
ATTENTION: NAS/NRC COORDINATORS

DATE: November 9, 1973

DRO Drug Study
Bulletin # 160

FROM : DESI Regulatory Control Staff (BD-317)
Compliance Evaluation Branch
Division of Regulatory Operations
SUBJECT: Adenosine - B12 Combination Drugs
See DRO Drug Study Bulletin # 122

FD 3033's submitted by District Offices disclosed a number of Adenosine-5-Monophosphate/Vitamin B12 combinations on the market. A file search showed that there are no approved NDA's for such a combination nor are they the subject of a DESI review.

Because a medical evaluation shows that injectable combinations containing "Adenosine-5-Monophosphate" and "Vitamin B12" are neither safe nor effective for their intended uses, i.e. - vasodilators, anti-inflammatory agents, etc. we have implemented a class action follow-up against this drug combination under DESI procedures.

We have issued letters on October 31, 1973 to 47 firms as manufacturers or distributors of injectable Adenosine-B12 combination drugs requesting that they discontinue marketing and a statement of intentions with respect to their removal of all outstanding stocks from the market down to the retail level.

Attached are copies of the letters issued to firms in your district and an information copy of the letter to districts in which no letters have been issued to date.

DRO will monitor the firms' replies, furnish districts with copies of such replies and issue assignments where indicated.

FD 3033's should be submitted on any other products marketed within the last two years but not previously reported, so that DRO letters may issue to these firms, if warranted.

We have brought to each firm's attention, where applicable, the Federal Register announcement of October 15, 1971 "General Policy on Fixed Combinations" (Reg 3.86).

Albert Lavender
Albert Lavender, Chief
DESI Regulatory Control Staff (BD-317)

Program Priority: High
Estimated Time: 8 Hours
Charge to: DESI BD-300-199
Reply Requested by : COB December 31, 1973
Project Officer: Paul Worden

Telephone: 301-443-4209

Enclosures



DATE: AUG 7 1996

FROM: Lana Ogram 
Director, Division of Prescription Drug Compliance
and Surveillance

SUBJECT: Request for Safety Assessment for Adenosine
Phosphate Injectable

TO: Dr. Raymond Lipicky
Director, Division of Cardio-Renal Drug Products

We are seriously considering the issuance of a regulatory action against an unapproved product, Adenosine Phosphate 25mg/ml. Its route of administration is by intramuscular injection, and is indicated for the symptomatic relief of varicose vein complications with stasis dermatitis. We are most concerned about any potential risk involving this product. Before we can implement regulatory action, a safety assessment is necessary.

On January 21, 1971 Dr. Edgar J. Martin, BD-350 did a literature assessment relating to the safety of Adenosine-Vit B12 injectable and Adenosine Phosphate injectable. (TAB A). As a result of his assessment three Drug Study Bulletins were issued.

Adenosine in combination with other active ingredients such as Vitamin B-12, was the subject of Drug Study Bulletins #122 in 1972 (TAB B) and #160 in 1973. (TAB C)

In 1977 Drug Study Bulletin # 226 (TAB D) was issued to remove from the market place Adenosine alone or in combination. However, Adenosine Phosphate 25mg/ml is found to be marketed today without the benefit of an approved application. It is this product that is the subject of this request.

=

Page 2 - Dr. Raymond Lipicky

In 1996 Steris Laboratories Inc., Phoenix, AZ is the only manufacturer of Adenosine Phosphate 25 mg/ml (TAB E). Based on a search of our available references, we found that this product was not marketed prior to 1962. We believe that this product is an unapproved new drug.

Please advise on any safety concerns you might have regarding Adenosine Phosphate 25 mg/ml. We are available to meet with you and discuss this request at your convenience if you feel it would be helpful.

While we recognize your heavy work load, we ask your cooperation for an expeditious response.

If you need additional information you may contact Sonia Crisp at 594-0101.

Attachments

TAB A

RE: Adano: LMS-VIS B12 Intestable 5 AMP

Summary: The article is a new drug. The safety of the article has never been tested by contrived studies, and safety and efficacy have not been established by scientifically credible observations. We are not aware how to write adequate directions for its use. The article is misbranded for several causes:

There are no rational theoretical grounds and no credible clinical evidences that the label recommended administration of adenosine-5-monophosphoric acid (SAMF) is effective for the intended purposes. The label is false, or misleading, or deceptive in that it (1) suggests and/or claims SAMF therapeutic effectiveness in certain conditions and (2) quotes 4 literature references as support of its clinical claims while these references contain no credible support for the claims of efficacy, and two of them are not even pertinent to the claims for which they are quoted.

The drug is not mentioned in representative texts such as Success, R. L. Diseases of the Skin, The C. V. Mosby Co., St. Louis, 1956.

Allen, A. C. The Skin. Gruen and Stratton publ. 1967, 2nd ed:
Remington's Pharmaceutical Sciences, 13th ed. Mack Publ. Co. Easton,
Pa., 1965. Grollman, A. Pharmacology and Therapeutics, 6th ed. Lea
Febiger, Philadelphia, 1965.

Previous FDA statements hold true:

A similar article was rated misbranded, and it was noted that its
efficacy was not established, _____ Dr.

_____ objected against another similar article,

_____ We believe the label claims are not acceptable
in the opinion of medical experts.

REVIEW

Label reference #1. Buell, M. V. and M. E. Perkins. J. Biol. Chem
76:95, 1928. Chemical analytical data on 5AMP determination in blood.
The study does not provide any physiological or medical information
and is not designed for such purposes.

Reference #2. A. Rocchino. Relief from pruritus following upon
administration of adenylic acid. Proc. Soc. expt. Biol. Med. 71:3
1949.

_____ The statements are vague testimonials
an uncontrolled study. The study is designed with an irrational
of pruritus. The author finally states "... there is much yet to

done clinically and in the laboratory before the full implications of adenylic acid administration to human beings can be evaluated . . ."

Rostenberg, A. et al. Failure of adenosin-5-monophosphate to affect favorably pruritus of atopic dermatitis, J. Invest. Dermat. 14:401, 1950

and Sawicky, H. H. et al. Adenosine-5-monophosphate (My-B-Den) for the relief of pruritus, J. Invest. Dermat. 17:265, 1951

tested Rottino's claims in controlled experiments, and found SAMP was useless in the treatment of pruritus. The label, revised in 1964, is false and misleading in that it fails to give proper consideration to Rostenberg's and Sawicky's findings.

Reference No. 3. Palmer, L. and S. Waldman. The use of adenosine-5-monophosphate in the treatment of acute subdeltoid

bursitis. New York State J. Med. 52:1774, 1952. An uncontrolled

experiment; the paper is unconvincing in its claim of SAMP efficacy

in bursitis treatment. The paper also supports its claims by refer

to Rottino's alleged results with SAMP in pruritus

but fails to mention that Rottino's findings were not confirmed by

Rostenberg and Sawicky

Thus the paper by

Palmer and Waldman is scientifically inadequate and lacks credibil

Both Palmer and Waldman stated in recent telephone conversations t

they had ceased using SAMP since other drugs do a better job.

Reference No. 4. Vilter, W. R. et al. J. Lab. Clin. Med. 27:527, 1941

The paper is not convincing since it has no, or only inadequate, controls, and its statistics are false. The authors claim they studied "29 selected patients with nutritional deficiency disease. The count of the patients shows that only 26 had such diseases while 3 "had no evidence of nutritional deficiency" and served as controls. There was no control group within the malnourished series. Even if the paper were scientifically acceptable it would not support the label claims. As shown in the following details the label is false and misleading in that it states and/or suggests that the paper support its claims:

1. The paper gives statistics on the authors experience with intravenous 5AMP medication. In contrast, the label indication is for intramuscular use only and warns specifically against intravenous use.

2. The paper specifically states the usefulness of its 5AMP treatment is limited to malnourished patients with pellagra and peripheral neuritis. The label is false and misleading in that it conceals these limitations.

3. The paper specifically states that its 5AMP treatment is lacking efficacy in persons who have no nutritional deficiency. The label is false and misleading in that it conceals this restriction of the paper:

Mills, J. and E. H. Mensted. Lancet 1, 237, 1951. "Vitamin B12 in pernicious anaemia.

The article does not mention 5AMP

or anything that could be related to SAMP. The label is false and misleading in that it states or suggests that this paper supports its SAMP claims.

Edgar J. Martin, M.D., BD-350



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

Date: 8 August 1996
From: Robert R. Fenichel, HFD-110
Subject: Adenosine Phosphate 25 mg/ml
To: Lana Ogram, HFD-333

This will respond to your memo of 7 August to Raymond Lipicky.

Adenosine Phosphate 25 mg/ml is not familiar to this Division, but we have approved two different intravenous adenosine preparations from Fujisawa USA, one to terminate certain arrhythmias (ADENOCARD[®], given as a bolus of 6-12 mg) and one as an adjunct to cardiac nuclear imaging using ²⁰¹Th (ADENOSCAN[®], given as a 6-minute infusion of 0.14 mg/kg/min, working out to a total of 60 mg in a 70-kg patient).

Because of adenosine's extraordinarily short half-life (less than 10 seconds), these preparations have turned out to be relatively safe. Nevertheless, they are associated with nontrivial incidences of

- cardiac dysrhythmias, including ventricular fibrillation, complete heart block, and cardiac arrest, **sometimes fatal**; and
- bronchospasm, especially (but not only) in known asthmatics, rarely requiring respiratory support. I think there may have been a few deaths in this category too.

Because of these hazards, the labeling of ADENOCARD includes the recommendation that "[a]ppropriate resuscitative measures should be available."

This Division has no experience with intramuscular administration of any formulation of adenosine, and we cannot comment on the possibility of untoward local effects (sterile abscesses, for example). Degradation of circulating adenosine is so rapid that true intramuscular administration is probably harmless (and valueless), with serum levels effectively unchanged from those endogenously present, but that is not the end of the story. Attempted intramuscular administration will always result in a certain incidence of inadvertent intravenous injection, with all of the risks noted above.

Such risks may be acceptable, if they are offset by **demonstrated benefits**. We have not attempted to replicate Dr. Martin's scholarship, but we doubt that any such benefits have ever been properly attributed to Adenosine Phosphate 25 mg/ml.

Please let us know if we can be of any further assistance.

* This recommendation is, I just noticed, not present in the labeling of ADENOSCAN. It should be.

Appendix 2

P R O C E E D I N G S

8:32 AM

DR. JUHL: If I could have you take your seats so we can get started, I would like to begin day 2 of the Pharmacy Advisory Compounding Advisory Committee meeting.

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- .
- .
- .

DR. JUHL: If we could all refer to the Federal Register notice that was faxed to us titled List of Drug Products that Have Been Withdrawn or Removed from the Market for Reasons of Safety or Efficacy, and towards the end, and your page numbers may be different than mine there is a list of the drugs and their special conditions and the wording for that.

On mine it is the last two pages of that document.

Other comments on the development of the list per se, and then we will go to specific agents if there are additional questions?

Seeing none, I feel the need, also, to commend you for putting this list together. I am sure people got very dusty down in the basement looking at the old records, and it is a very useful thing for the agency to have for a number of reasons, but for this purpose as well, and there seems to be less area for wiggle and concern over this list than the bulks list for which we are, also, grateful.

Let me poll the group now and I don't want to discuss, I just want the names of products that you would like further information about, and then we will kind of take them in turn.

So, I will just write a list. Are there products, starting with David that you want us to discuss further or you want further information?

MR. LIEBMAN: Off the top of my head, no. I think they have done an excellent job.

DR. JUHL: Bill?

DR. RODRIGUEZ: Likewise.

DR. ALLEN: I believe the only thing possibly would be the adenosine phosphate. You might refer to that, but that is about all.

DR. JUHL: Okay, we will put that on the list.

Judy?

MS. RIFFEE: Nothing.

DR. JUHL: Garnet?

DR. PECK: Nothing else.

DR. JUHL: Larry?

MR. TRISSEL: I am still thumbing real fast.

DR. JUHL: Okay. Elizabeth?

DR. MC BURNEY: I would just like to clarify because I was going to put tetracycline on it, and I would like to ask George, we can have our pharmacist compound oral suspension of tetracycline; it just cannot be for pediatric patients, is that correct, in the dosage that is listed here?

CAPT. SCOTT: Right in the dosage of no more than 25 milligrams per milliliter.

DR. MC BURNEY: All right, then I have none to add to the list.

Thank you.

DR. JUHL: Larry?

MR. TRISSEL: I, also, had a tag on adenosine phosphate because I could not find any specific notation of the safety issue in here regarding it.

DR. JUHL: Okay, we will put that on the list then.

Anna?

MS. MC CLAIN: Nothing to add.

DR. JUHL: Bill?

MR. RUSHO: Nothing to add.

DR. JUHL: Sarah?

MS. SELLERS: Nothing.

DR. JUHL: Joan? Carmen?

Adenosine phosphate, the floor is open for discussion on that topic. Larry has mentioned he would like to know about the specific safety issue and what was the other question, Loyd, was that yours?

DR. ALLEN: I believe it has some alternative uses now.

DR. JUHL: Okay, and the listing for this compound, adenosine phosphate as recorded in the Federal Register restricts all drug products containing adenosine phosphate.

CAPT. SCOTT: The information that we had indicated that the action was based on a lack of substantial evidence that adenosine alone or in combination with other ingredients generally recognized as safe and effective for any indication and I believe they were using it as a vasodilator and for anti-inflammatory properties that it may have been believed to have.

There was some work done within the division. We requested the reviewing division to respond to the safety of this drug, and it is very close to the adenosine which is approved except it is the salt, the adenosine phosphate, and

the adenosine by itself can cause cardiac dysrhythmias, sometimes fatal bronchospasms. It was just that this drug from my understanding it was injected and being injected intramuscularly I believe, and it has a very, very short half life, and it was not I think due to the lack of efficacy they could not find it was really getting into the body, into the system to really provide any type of relief for what they were trying to treat, and so I think by virtue of that it was one of those cases where because of the lack of effectiveness that they could find that there was a safety problem indirectly.

DR. JUHL: I understand this is a drug that was never approved via NDA.

CAPT. SCOTT: No.

DR. JUHL: It was a drug that was marketed as a non-approved?

CAPT. SCOTT: That is correct.

DR. JUHL: It was not grandfathered. It was simply not taken through the regulatory process at all?

CAPT. SCOTT: As far as I know there was never an approved NDA for adenosine phosphate. That is correct.

MR. TRISSEL: Did I understand you to say that adenosine itself was marketed as approved?

CAPT. SCOTT: Adenosine is, yes.

MR. TRISSEL: So, just the phosphate formulation --

CAPT. SCOTT: Adenosine salt has never been approved; that is correct.

DR. JUHL: I am not familiar. Adenosine itself is used how?

CAPT. SCOTT: Adenocard(?) which is used for supraventricular

tachycardia, I believe.

DR. JUHL: That is via the parenteral route as well then?

CAPT. SCOTT: Yes, direct IV injection, and because it has such a short half life it has to be given, well, it is recommended in the labeling to be given IV because it works directly and with a very short period of time.

MS. SELLERS: Used mostly in the emergency setting, and it is a dangerous drug itself because of the AV no-bar(?) but my only question would be if it is used as an injectable, if you miss the muscle and get it into a vein systemically it could be --

CAPT. SCOTT: I think that was the concern that was raised from the medical officer that it does have severe side effects if not used properly, plus I think the only experience that we had was that it was being injected IM which because it only lasts in the body 10 to 15 seconds it is obviously not going to really work in the IM route, and so it is basically like giving a placebo for some of the indications I believe that they were using were quite serious, and it was not having the effect. So, by having a lack of effectiveness it was indirectly a safety problem.

DR. JUHL: Loyd, you said that you had knowledge of it being used in something else?

DR. ALLEN: I don't have any direct knowledge. I would like to defer to some of the other pharmacists or physicians or someone in the audience that might have, but I have just heard that it has been used for some alternative --

DR. JUHL: Parenterally?

DR. ALLEN: I believe parenterally.

DR. JUHL: Is anyone else able to add to the confusion here?
Would anyone like to speak for the drug being excluded from this list?

MR. TRISSEL: I haven't heard anything that would make me believe that it is any different than any other drug on this list. It doesn't seem to be the use in compounding that was identified by the sponsor, and it fits all the other criteria of this list. So, I wouldn't see any reason to make a special exception of it.

DR. JUHL: Seeing no other comments I would presume that would indicate the will of the Committee on this particular product and are those who may have been leafing through during the discussion finding notes in your binder that would want you to consider, have us consider any other products on this list?

Seeing none of those, are there other things that the agency would like us to address?

MS. AXELRAD: I don't think we have any other issues right now.

DR. JUHL: Let me look at my watch. I think we will conclude early today which I hope doesn't disappoint anyone.

(Laughter.)

Appendix 3

PUBLIC SUBMISSION

As of: July 23, 2014
Received: July 03, 2014
Status: Draft
Category: Health Professional - A0007
Tracking No. 1jy-8d0e-w1ng
Comments Due: September 02, 2014
Submission Type: Web

Docket: FDA-1999-N-0194

Additions to the List of Drug Products Have Been Withdrawn

Comment On: FDA-1999-N-0194-0001

Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

Document: FDA-1999-N-0194-DRAFT-0003

Comment from Anonymous Anonymous, NA

Submitter Information

Name: Anonymous Anonymous

Organization: NA

General Comment

Can the list be clarified for adenosine phosphate? There are 3 forms of adenosine phosphate (mono-, di-, and tri-phosphate). It is not clear whether the list is intended to include all 3 forms of just the mono-phosphate.

Tab 8

2015 FDA Review of Oral Chloramphenicol



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: January 30, 2015

FROM: Yuliya Yasinskaya, M.D.
Medical Officer
Division of Anti-Infective Products, Office of Antimicrobial Products,
CDER

THROUGH: Sumathi Nambiar, M.D., M.P.H.
Division Director
Division of Anti-Infective Products, Office of Antimicrobial Products,
CDER

Ed Cox, M.D., M.P.H.
Office Director
Office of Antimicrobial Products
CDER

SUBJECT: Inclusion of oral chloramphenicol on the "Withdrawn or Removed List"
codified at 21 CFR 216.24

TO: Pharmacy Compounding Advisory Committee

Introduction

The Food and Drug Administration Modernization Act of 1997 added section 503A to the Federal Food, Drug, and Cosmetic Act (FD&C Act) that describes the circumstances under which compounded drugs can qualify for exemptions from certain adulteration, misbranding, and new drug provisions.

One of the conditions that must be satisfied to qualify for the exemptions under section 503A of the FD&C Act is that the licensed pharmacist or licensed physician "does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective" ("the withdrawn or removed list") (section 503A(b)(1)(C)).

In 1999, FDA finalized and codified the withdrawn or removed list at 21 CFR 216.24 (64 FR 10944, March 8, 1999).

On July 2, 2014, FDA published a proposed rule to revise and update 21 CFR 216.24 (see 79 FR 37687 in Appendix 2), which will also apply to outsourcing facilities, a new

category of compounder created under the Drug Quality and Security Act (DQSA) that was enacted on November 27, 2013.¹ In reviewing 21 CFR 216.24, FDA determined that certain substantive revisions to the list were necessary because new information has come to the Agency's attention since March 8, 1999, when FDA published the original list as a final rule. In the July 2014 proposed rule, FDA recommended the addition of 25 drug products to the list and the modification of one drug already on the codified list (79 FR 37,687). One of the new drug products proposed for inclusion was "*All oral drug products containing chloramphenicol.*" FDA provided the following rationale for this proposal in the July 2014 Federal Register notice:

Chloramphenicol was formerly marketed as Chloromycetin (chloramphenicol) Capsules. In a letter dated October 9, 2007, the application holder requested withdrawal of the ANDA for Chloromycetin (chloramphenicol) Capsules, 50 mg, 100 mg, and 250 mg. In the Federal Register of February 11, 2009 (74 FR 6896), FDA announced that it was withdrawing approval of the ANDA, effective March 13, 2009. Armenpharm, Ltd., submitted a citizen petition dated February 7, 2011 (Docket No. FDA-2011-P-0081), under § 10.30 (21 CFR 10.30), requesting that the Agency determine whether Chloromycetin (chloramphenicol) Capsules, 250 mg, were withdrawn from sale for reasons of safety or effectiveness. After considering the citizen petition, FDA determined that the drug product was withdrawn for reasons of safety or effectiveness. With the approval of additional therapies with less severe adverse drug effects, FDA determined that the risks associated with Chloromycetin (chloramphenicol) Capsules, 250 mg, as then labeled, outweighed the benefits. Furthermore Chloromycetin (chloramphenicol) Capsules, 250 mg, may cause a number of adverse reactions, the most serious being bone marrow depression (anemia, thrombocytopenia, and granulocytopenia temporally associated with treatment). Additionally, prior to the removal of the capsule drug product from the market, a boxed warning in the prescribing information for both chloramphenicol sodium succinate injection and chloramphenicol capsules stated that serious hypoplastic anemia, thrombocytopenia, and granulocytopenia are known to occur after administration of chloramphenicol. The boxed warning also described fatal aplastic anemia associated with administration of the drug and aplastic anemia attributed to chloramphenicol that later terminated in leukemia. There is published literature that suggests that the risk of fatal aplastic anemia associated with the oral formulation of chloramphenicol may be higher than the risk associated with the intravenous

¹ The DQSA added new section 503B of the FD&C Act that created a new category of "outsourcing facilities." One of the conditions in section 503B of the FD&C Act that must be satisfied for an outsourcing facility to qualify for certain exemptions is that the drug does not appear on a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (see section 503B(a)(4)). Given that nearly identical criteria apply for a drug to be included on the list referred to in section 503A(b)(1)(C) and the list referred to in section 503B(a)(4) of the FD&C Act, FDA proposed to revise and update the list at § 216.24 (21 CFR 216.24) for purposes of both sections 503A and 503B.

formulation (see the Federal Register of July 13, 2012 (77 FR 41412)). FDA is not aware of any oral drug products containing chloramphenicol currently being marketed.

The documents referenced above -- the Federal Register notice from 2009; the citizen petition from 2011 along with the corresponding supplement; the consult response from OAP/DAIP regarding the citizen petition; the Agency's 2012 response to the citizen petition along with the accompanying Federal Register notice from 2012 -- are all attached here in Appendices (1, 2, 3, and 4 respectively).

FDA received one comment on the proposal to include chloramphenicol in the withdrawn or removed list (see Appendix 5). The comment requested that FDA "reconsider and reclassify Chloramphenicol 250 mg tablets labeling for tropical [sic] medical use and packaging changes; rather than withdraw from the market place for developing nations [World Health Organization,] WHO list of drug use." The commenter stated that chloramphenicol 250 mg is used to control hemorrhagic fever like illnesses (e.g., Lassa Fever, Ebola) and also stated that control and survival benefits outweigh the risks of thrombocytopenia and aplastic anemia in the already anemic patient when used in the short term appropriately.

In light of this comment to the docket regarding the proposed chloramphenicol entry, FDA is reassessing whether to include this product on the list, and if so, how to describe the entry. Once the withdrawn or removed list is finalized, the effect of a drug being included on this list is that the drug may not be compounded under the exemptions provided by the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Most drugs on the list may not be compounded in any form and still qualify for these exemptions, but some entries would prohibit only some types of compounding. For example, some drugs may be listed only with regard to certain formulations, concentrations, indications, routes of administration or dosage forms because the drug has been found to be unsafe or ineffective only in those particular formulations, concentrations, indications, routes of administration, or dosage forms, and other drug products containing the active ingredient remain on the market. The proposed entry for chloramphenicol was restricted to all *oral* drug products containing chloramphenicol.

Review

The Division of Anti-Infective Products (the Division) was asked to provide input on whether chloramphenicol should be included on the list of drugs in 21 CFR 216.24 that should not be compounded and, if yes, on how the drug should be described on the list.

Three questions were asked of the Division:

- (1) Based on the information currently available, do you have reason to expect that the safety issues that were identified in the July 14, 2014, Federal Register notice as having been associated with chloramphenicol capsules, 250 mg, namely anemia, thrombocytopenia

and granulocytopenia would also be associated with other oral versions of chloramphenicol of different dosage forms and strengths? Please explain.

DAIP Response: Oral chloramphenicol formulations, regardless of the specific oral forms and strengths, are expected to have a safety profile similar to that of chloramphenicol capsules, 250 mg, as the active moiety in these formulations is chloramphenicol. The cases described in the publication by Wallerstein et al² had received liquid or other oral forms of chloramphenicol. The authors conclude that the risk of death from aplastic anemia due to chloramphenicol was dose-independent (total treatment doses varied from 3 grams in 3 days to 19 g in 14 days; the publication did not describe the strength of the capsules/liquid in all cases).

- (2) Please assess the commenter's claim that the control and survival benefits chloramphenicol tablets 250 mg offer when used to control hemorrhagic fever like illnesses such as Lassa and Ebola outweigh the risks of thrombocytopenia and aplastic anemia in the already anemic patient when used in the short term. Does the evidence available to you at this time allow you to conclude that the benefits associated with chloramphenicol tablets, 250 mg, outweigh the risks when used to control hemorrhagic fever like illnesses such as Lassa Fever and Ebola?

DAIP Response: We are not aware of any evidence that chloramphenicol has antiviral activity against causative agents of viral hemorrhagic fever, including Ebola. A PubMed search conducted on November 7, 2014 for key words: chloramphenicol AND hemorrhagic fever, chloramphenicol AND Ebola did not yield any publications that would suggest its activity against or utility in treatment of hemorrhagic fever, including Ebola. Chloramphenicol's mechanism of antibacterial action is by binding to the 50S subunit of the bacterial ribosome, a structure not found in viruses. Therefore, there is no putative mechanism to expect antiviral activity.

- (3) In light of your responses to the questions listed above and the information considered, do you recommend that chloramphenicol be included on the withdrawn or removed list and, if so, how should the entry be described (e.g., "All oral drug products containing chloramphenicol")? Please include your rationale for your recommendation.

DAIP Response: We recommend including oral chloramphenicol on the withdrawn or removed list and conclude that the proposed entry "All oral drug products containing chloramphenicol" is acceptable. The rationale for limiting the listing to the oral formulations of chloramphenicol has been previously discussed in the Division's June 14, 2012 consult response by Dr. Dmitri Iarikov (included in Appendix 3) regarding the

² Wallerstein RO et al. JAMA 1969 Jun 16;208(11):2045-50.

Citizen Petition from Armenpharm, Ltd. dated June 7, 2011 (FDA-2011-P-0081) requesting that FDA determine whether Chloromycetin (Chloramphenicol) Capsules, 250 mg was withdrawn from sale for reasons of safety or effectiveness. In addition, the risk of death due to chloramphenicol-induced aplastic anemia appears to be independent of the strength or oral dosage form of the drug, and is moiety specific.

Appendix 1

more accurately describe the information collection content.

Section 2(c) of The Medical Device User Fee Stabilization Act of 2005 (Public Law 109-43) amends section 502(u) of the act by limiting the provision to reprocessed single-use devices (SUDs) and the manufacturers who reprocess them. Under the amended provision, if the original SUD or an attachment to it prominently and conspicuously bears the name of the manufacturer, then the reprocessor of the SUD is required to identify itself by name, abbreviation, or symbol, in a prominent and conspicuous manner on the device or attachment to the device. If the original SUD does not

prominently and conspicuously bear the name of the manufacturer, the manufacturer who reprocesses the SUD for reuse, may identify itself using a detachable label that is intended to be affixed to the patient record.

The requirements of section 502(u) of the act impose a minimal burden on industry. This section of the act only requires the manufacturer, packer, or distributor of a device to include their name and address on the labeling of a device. This information is readily available to the establishment and easily supplied. From its registration and premarket submission database, FDA estimates that there are 10 establishments that distribute

approximately 1,000 reprocessed SUDs. Each response is anticipated to take 0.1 hours resulting in a total burden to industry of 100 hours.

In the **Federal Register** of November 17, 2008 (73 FR 67873), FDA published a 60-day notice requesting public comment on the information collection provisions. The agency received one comment in support of the collection of information stating that it is necessary to help reproducers of SUDs comply with section 502(u) of the act. The comment further stated that the estimated reporting burden did not appear excessive.

FDA estimates the burden of this collection of information as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN¹

Section of the Act	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
502(u)	10	100	1,000	.1	100

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: January 26, 2009.
Jeffrey Shuren,
Associate Commissioner for Policy and Planning.
 [FR Doc. E9-2902 Filed 2-10-09; 8:45 am]
BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
 [Docket No. FDA-2009-N-0026]

Apothecon et al.; Withdrawal of Approval of 103 New Drug Applications and 35 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of 103 new drug applications (NDAs) and 35 abbreviated new drug applications (ANDAs) from multiple applicants. The holders of the applications notified the agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

DATES: Effective March 13, 2009.

FOR FURTHER INFORMATION CONTACT: Florine P. Purdie, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6366,

Silver Spring, MD 20993-0002, 301-796-3601.

SUPPLEMENTARY INFORMATION: The holders of the applications listed in the table in this document have informed FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications. The applicants have also, by their requests, waived their opportunity for a hearing.

Application No.	Drug	Applicant
NDA 7-335	Pronestyl (procainamide hydrochloride (HCl)) Capsules and Injection	Apothecon, c/o Bristol-Myers Squibb Co., P.O. Box 4000, Princeton, NJ 08543-4000
NDA 7-935	Phenergan (promethazine HCl) Tablets	Wyeth Pharmaceuticals, Inc., P.O. Box 8299, Philadelphia, PA 19101-8299
NDA 9-193	Cogentin (benztropine mesylate) Tablets	Merck & Co., Inc., Sunneytown Pike, P.O. Box 4, BLA-20, West Point, PA 19486
NDA 9-986	Deltasone (prednisone) Tablets	Pharmacia & Upjohn Co., c/o Pfizer, Inc., 235 East 42d St., New York, NY 10017
NDA 10-374	Medihaler-Epi (epinephrine bitartrate)	3M Pharmaceuticals, 3M Center, Bldg. 0275-05-W-12, St. Paul, MN 55144-1000
NDA 10-375	Medihaler-ISO (isoproterenol)	Do.
NDA 10-598	Bendectin (doxylamine succinate and pyridoxine HCl) Tablets	Sanofi-Aventis, 300 Somerset Corporate Blvd., Bridgewater, NJ 08807-0977

Application No.	Drug	Applicant
NDA 10-796	Harmony (deserpidine) Tablets	Abbott Laboratories, 200 Abbott Park Rd., Abbott Park, IL 60064-6154
NDA 10-800	Tralgon (acetaminophen) Elixir	Bristol-Myers Squibb Co., P.O. Box 4000, Princeton, NJ 08543-4000
NDA 10-927	Phosphotope (sodium phosphates solution USP) Oral Solution	Bracco Diagnostics, P.O. Box 5225, Princeton, NJ 08543-5225
NDA 10-928	Aureotope (gold injection)	Do.
NDA 11-161	Aristocort (triamcinolone) Tablets	Astellas Pharma US, Inc., Three Parkway North, Deerfield, IL 60015-2537
NDA 11-467	Trancopal (chlormezanone) Tablets	Sanofi-Aventis
NDA 11-721	Neptazane (methazolamide) Tablets	Lederle Laboratories, c/o Wyeth Pharmaceuticals, Inc., P.O. Box 8299, Philadelphia, PA 19101-8299
NDA 11-751	Prolixin (fluphenazine HCl) Injection and Tablets	Apothecon, c/o Bristol-Myers Squibb Co.
NDA 11-832	Vasodilan (isoxsuprine HCl)	Do.
NDA 12-097	Kenalog in Orabase (triamcinolone acetonide dental paste USP)	Do.
NDA 12-164	Naturetin (bendroflumethiazide USP), 2.5 milligrams (mg), 5 mg, and 10 mg	Do.
NDA 12-515	Kenacort (triamcinolone diacetate) Syrup	Bristol-Meyers Squibb Co.
NDA 13-296	Duo-Medihaler (phenyleprine bitartrate and isoproterenol HCl)	3M Pharmaceuticals
NDA 13-601	Mucomyst (acetylcysteine solution USP)	Apothecon, c/o Bristol-Myers Squibb Co.
NDA 14-715	Triavil (perphenazine and amitriptyline HCl) Tablets	New River Pharmaceuticals, Inc., 2200 Kraft Dr., suite 2050, Blacksburg, VA 24060
NDA 15-419	Hippotope (iodohippurate sodium I-131 injection USP)	Bracco Diagnostics
NDA 16-033	Vontrol (diphenidol HCl) Tablets, 25 mg	GlaxoSmithKline, Five Moore Dr., P.O. Box 13398, Research Triangle Park, NC 27709
NDA 16-090	Rubratope-60 (cyanocobalamin CO-60)	Bracco Diagnostics
NDA 16-224	Robengatope (rose bengal sodium I-131 injection USP)	Do.
NDA 16-727	Prolixin Decanoate (fluphenazine decanoate) Injection	Bristol-Myers Squibb Co.
NDA 16-783	Vascoray (iothalamate meglumine, 52% and iothalamate sodium, 26% injection)	Tyco Healthcare/Mallinckrodt Inc., P.O. Box 5840, St. Louis, MO 63134-0840
NDA 16-906	Technetope II (technetium Tc-99m sodium pertechnetate sterile generator)	Bracco Diagnostics
NDA 16-923	Tesuloid (technetium Tc-99m sulfur colloid kit)	Do.
NDA 16-929	FUDR (floxuridine) Injection, 500 mg/5 milliliters (mL)	Hospira, Inc., 275 North Field Dr., Lake Forest, IL 60045-5046
NDA 16-996	Hyperstat (diazoxide) Injection	Schering Corp., 2000 Galloping Hill Rd., Kenilworth, NJ 07033
NDA 17-024	Strotopo (strontium nitrate Sr-85) Injection	Bracco Diagnostics
NDA 17-045	Renotec (technetium Tc-99m ferpenetate kit)	Do.
NDA 17-047	Sethotope (selenomethionine Se-75) Injection	Do.
NDA 17-269	Chlormerodrin Hg-197 Injection	Do.
NDA 17-339	Minitec (technetium Tc-99m sodium pertechnetate generator)	Do.

Application No.	Drug	Applicant
NDA 17-371	Pronestyl (procainamide HCl) Tablets	Apothecon, c/o Bristol-Myers Squibb Co.
NDA 17-395	Intropin (dopamine HCl) Injection, 40 mg/mL, 80 mg/mL, and 160 mg/mL	Hospira, Inc.
NDA 17-598	Septra (trimethoprim and sulfamethoxazole) Oral Suspension	Monarch Pharmaceuticals, Inc., 501 5th St., Bristol, TN 37620
NDA 17-685	Conray 325 (iothalamate sodium)	Mallinckrodt Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
NDA 17-787	Radionuclide-Labeled (I-125) Fibrinogen Sensor	Abbott Laboratories
NDA 17-834	Albumotope-LS (albumin aggregated iodinated I-131-serum)	Bracco Diagnostics
NDA 17-902	Renovue-65 (iodamide meglumine) Injection, 65%	Do.
NDA 17-903	Renovue-Dip (iodamide meglumine) Injection	Do.
NDA 17-931	Iletin I (insulin pork)	Eli Lilly & Co., Lilly Corporate Center, Indianapolis, IN 46285
NDA 17-932	Protamine Zinc and Iletin I (insulin suspension protamine zinc beef/pork)	Do.
NDA 17-935	Ultralente Iletin I (insulin zinc suspension extended beef/pork)	Do.
NDA 17-936	NPH Iletin I (insulin suspension isophane beef/pork)	Do.
NDA 17-943	Proloprin (trimethoprim) Tablets, 100 mg and 200 mg	Monarch Pharmaceuticals, Inc.
NDA 17-970	Nolvadex (tamoxifen citrate) Tablets	AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, P.O. Box 8355, Wilmington, DE 19803-8355
NDA 17-979	Heparin Sodium Injection USP	Abraxis Pharmaceutical Products, Riverway One, 6133 North River Rd., suite 500, Rosemont, IL 60018
NDA 18-017	Blocadren (timolol maleate) Tablets	Merck & Co., Inc., UG2C-50, P.O. Box 1000, North Wales, PA 19454-1099
NDA 18-061	Timolide (timolol maleate and hydrochlorothiazide) Tablets, 10 mg/25mg	Do.
NDA 18-076	Cholovue (iodoxamate meglumine) Injection, 40.3%	Bracco Diagnostics
NDA 18-077	Cholovue (iodoxamate meglumine) for Infusion	Do.
NDA 18-116	Cyclocort (amcinonide) Cream, 0.1%	Astellas Pharma US, Inc.
NDA 18-211	Ditropan (oxybutynin chloride) Syrup, 5 mg	Ortho-McNeil-Janssen Pharmaceuticals, Inc., 1000 U.S. Highway 202, P.O. Box 3000, Raritan, NJ 08869-0602
NDA 18-344	Iletin II (insulin purified pork)	Eli Lilly & Co.
NDA 18-345	NPH Iletin II (insulin suspension isophane purified pork)	Do.
NDA 18-346	Protamine, Zinc, and Iletin II (insulin suspension protamine zinc purified pork)	Do.
NDA 18-347	Lente Iletin II (insulin zinc suspension purified pork)	Do.
NDA 18-354	Ortho-Novum 10/11-21 and 10/11-28 (norethindrone and ethinyl estradiol) Tablets	Ortho-McNeil Pharmaceutical, Inc., c/o Johnson & Johnson Pharmaceutical Research & Development, LLC, 920 Rt. 202 South, P.O. Box 300, Raritan, NJ 08869
NDA 18-452	Septra (sulfamethoxazole and trimethoprim) Injection	Monarch Pharmaceuticals, Inc.

Application No.	Drug	Applicant
NDA 18-476	Protamine, Zinc, and Iletin II (insulin suspension protamine zinc purified beef)	Eli Lilly & Co.
NDA 18-477	Lente Iletin II (insulin zinc suspension purified beef)	Do.
NDA 18-478	Regular Iletin II (insulin purified beef)	Do.
NDA 18-479	NPH Iletin II (insulin suspension isophane purified beef)	Do.
NDA 18-498	Cyclocort (amcinonide) Ointment, 0.1%	Astellas Pharma US, Inc.
NDA 18-537	Tridil (nitroglycerin) Injection	Hospira, Inc.
NDA 18-831	Tracrium (atracurium besylate) Injection	Hospira, Inc.
NDA 18-873	Mexitil (mexiletine HCl) Capsules, 150 mg, 200 mg, and 250 mg	Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Rd., P.O. Box 368, Ridgefield, CT 06877-0368
NDA 18-922	Lodine (etodolac) Capsules and Tablets	Wyeth Pharmaceuticals, Inc.
NDA 19-085	Atrovent (ipratropium bromide) Aerosol	Boehringer Ingelheim Pharmaceuticals, Inc.
NDA 19-166	Regular Insulin (insulin zinc suspension beef) Injection	Eli Lilly & Co.
NDA 19-167	NPH Insulin Beef (insulin zinc suspension beef)	Do.
NDA 19-529	Humulin BR (insulin recombinant human)	Do.
NDA 19-729	Cyclocort (amcinonide) Lotion, 0.1%	Astellas Pharma US, Inc.
NDA 19-816	Oruvail (ketoprofen) Extended-Release Capsules	Wyeth Pharmaceuticals, Inc.
NDA 19-890	Stadol (butorphanol tartrate) Nasal Spray	Bristol-Myers Squibb Co.
NDA 19-965	Novolin L (insulin zinc suspension recombinant human)	Novo Nordisk, Inc., 100 College Road West, Princeton, NJ 08540
NDA 20-152	Serzone (nefazodone HCl) Tablets	Bristol-Myers Squibb Co.
NDA 20-219	Livostin (levocabastine HCl) Ophthalmic Suspension, 0.05%	Novartis Pharmaceuticals Corp., One Health Plaza, East Hanover, NJ 07936-1080
NDA 20-225	Indur (isosorbide mononitrate) Extended-Release Tablets, 30 mg, 60 mg, and 120 mg	Schering Corp.
NDA 20-326	Neutrexin (trimetrexate glucuronate) Injection, 25 mg and 200 mg vials	MedImmune Oncology, Inc., One MedImmune Way, Gaithersburg, MD 20878
NDA 20-377	Cordarone (amiodarone HCl), Injection, 50 mg/mL	Wyeth Pharmaceuticals, Inc.
NDA 20-429	Orudis KT (ketoprofen) Tablets, 12.5 mg	Wyeth Consumer Healthcare, Five Giralda Farms, Madison, NJ 07940
NDA 20-584	Lodine XL (etodolac) Extended-Release Tablets	Wyeth Pharmaceuticals, Inc.
NDA 20-698	MiraLax (polyethylene glycol 3350) Powder for Solution	Braintree Laboratories, Inc., 60 Columbian Street West, P.O. Box 850929, Braintree, MA 02185-0929
NDA 20-784	Nasacort HFA (triamcinolone acetonide) Nasal Spray	Sanofi-Aventis
NDA 20-974	Prozac (fluoxetine HCl) Tablets	Eli Lilly & Co.
NDA 21-028	Velosulin BR (insulin recombinant injection)	Novo Nordisk, Inc.
NDA 21-369	Codeprex (codeine polistirex and chlorpheniramine polistirex) Extended-Release Suspension	UCB, Inc., 1950 Lake Park Dr., Smyrna, GA 30080
NDA 21-387	Pravigard Pak (copackaged) (pravastatin sodium and aspirin) Tablets	Bristol-Meyers Squibb Co.

Application No.	Drug	Applicant
ANDA 40-305	Meperidien HCl Injection USP, 10 mg/mL	Hospira, Inc.
NDA 50-155	Chloromycetin Sodium Succinate (chloramphenicol sodium succinate for injection USP)	Parkedale Pharmaceuticals, Inc., c/o King Pharmaceuticals, Inc., 501 5th St., Bristol, TN 37620
NDA 50-205	Chloromycetin (chloramphenicol) Otitic Solution	Do.
NDA 50-285	Mycifradin (neomycin sulfate) Oral Suspension	Pharmacia & Upjohn Co., c/o Pfizer, Inc.
NDA 50-339	Albamyacin (novobiocin sodium) Capsules	Do.
NDA 50-435	Geocillin (carbenicillin indanyl sodium) Tablets, 382 mg	Pfizer, Inc., 235 East 42d St., New York, NY 10017
NDA 50-504	Mandol (cefamandole nafate) Injection	Eli Lilly & Co.
NDA 50-589	Cefizox (ceftizoxime sodium)	Astellas Pharma US, Inc.
NDA 50-621	Suprax (cefixime) Tablets, 200 mg and 400 mg	Lederle Laboratories, c/o Wyeth Pharmaceuticals, Inc.
NDA 50-622	Suprax (cefixime) Powder for Suspension	Do.
ANDA 60-591	Chloromycetin (chloramphenicol capsules USP), 50 mg, 100 mg, and 250 mg	Parkedale Pharmaceuticals, Inc., c/o King Pharmaceuticals, Inc.
ANDA 61-922	Vidarabine Monohydrate Micronized Powder, Sterile	Do.
ANDA 62-655	Tazidime (ceftazidime for injection USP)	Eli Lilly & Co.
ANDA 63-350	Amikacin Sulfate Injection USP, 50 mg base/mL and 250 mg base/mL	Hospira, Inc.
ANDA 70-847	Metoclopramide Injection USP, 5 mg base/mL	Hospira, Inc.
ANDA 71-291	Metoclopramide Injection USP, 5 mg base/mL	Do.
ANDA 71-364	Acetylcysteine Solution USP	Do.
ANDA 71-365	Acetylcysteine Solution USP	Do.
ANDA 71-645	Droperidol Injection USP, 2.5 mg/mL	Do.
ANDA 73-272	Albuterol Inhalation Aerosol	IVAX Pharmaceuticals Ireland, c/o IVAX Pharmaceuticals, Inc., Two University Plaza, suite 220, Hackensack, NJ 07601
ANDA 74-966	Fluphenazine Decanoate Injection, 25 mg/mL	Hospira, Inc.
ANDA 75-106	Diltiazem HCl Injection, 5 mg/mL	Do.
ANDA 75-242	Labetalol HCL Injection, 5 mg/mL	Do.
ANDA 75-342	Butorphanol Tartrate Injection USP, 1 mg/mL and 2mg/mL	Do.
ANDA 75-396	Midazolam HCl Injection	Do.
ANDA 75-484	Midazolam HCl Injection, 5 mg base/mL	Do.
ANDA 75-571	Enalaprilat Injection, 1.25 mg/mL	Do.
ANDA 75-669	Famotidine Injection, 10 mg/mL	Do.
ANDA 75-705	Famotidine Injection, 10 mg/mL	Do.
ANDA 75-816	Calcitriol Injection	Do.
ANDA 75-830	Milrinone Lactate Injection, 1 mg base/mL	Do.
ANDA 75-108	Amiodarone HCl Injection, 50 mg/mL	Do.
ANDA 76-233	Paclitaxel Injection	Do.
ANDA 76-473	Carboplatin for Injection USP	Do.

Application No.	Drug	Applicant
ANDA 76-978	Ondansetron HCl and Dextrose Injection	Do.
ANDA 77-362	Amlodipine Besylate Tablets	King and Spalding, U.S. Agent for Genpharm Inc., 1700 Pennsylvania Ave., NW., Washington, DC 20006-4706
ANDA 77-925	Meloxicam Tablets, 7.5 mg and 15 mg	Roxane Laboratories, Inc., 1809 Wilson Rd., Columbus, OH 43228
ANDA 85-153	Alkergot (ergoloid mesylates) Sublingual Tablets, 0.5 mg	Sandoz, Inc., 227-15 North Conduit Ave., Laurelton, NY 11413
ANDA 85-916	Diethylpropion HCl Tablets, 25 mg	Do.
ANDA 86-172	Meclizine HCl Tablets, 12.5 mg	Do.
ANDA 86-174	Meclizine HCl Tablets, 25 mg	Do.
ANDA 86-184	Sulfasalazine Tablets, 500 mg	Do.
ANDA 87-417	Alkergot (ergoloid mesylates) Sublingual Tablets, 1 mg	Do.
ANDA 89-565	Vinblastine Sulfate Injection, 10 mg/vial	Hospira, Inc.

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) and under authority delegated to the Director, Center for Drug Evaluation and Research, by the Commissioner of Food and Drugs, approval of the applications listed in the table in this document, and all amendments and supplements thereto, is hereby withdrawn, effective March 13, 2009.

Dated: January 12, 2009.

Douglas C. Throckmorton,

Deputy Director, Center for Drug Evaluation and Research.

[FR Doc. E9-2901 Filed 2-10-09; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA2008E0091; Docket No. FDA2008E0099; Docket No. FDA2008E0204]

Determination of Regulatory Review Period for Purposes of Patent Extension; MACROPLASTIQUE IMPLANTS

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for MACROPLASTIQUE IMPLANTS and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of applications to the Director of Patents and Trademarks, Department of Commerce, for the

extension of patents which claim that medical device.

ADDRESSES: Submit written comments and petitions to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6222, Silver Spring, MD 20993-0002, 301-796-3602.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100-670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For medical devices, the testing phase begins with a clinical investigation of the device and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the device and continues until permission to market the device is granted. Although only a portion of a regulatory review period may count

toward the actual amount of extension that the Director of Patents and Trademarks may award (half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a medical device will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(3)(B).

FDA recently approved for marketing the medical device MACROPLASTIQUE IMPLANTS. MACROPLASTIQUE IMPLANTS are indicated for transurethral injection in the treatment of adult women diagnosed with stress urinary incontinence (SUI) primarily due to intrinsic sphincter deficiency (ISD). Subsequent to this approval, the Patent and Trademark Office received patent term restoration applications for MACROPLASTIQUE IMPLANTS (U.S. Patent Nos. 5,258,028; 5,336,263; and 5,571,182) from Uroplasty, Inc., and the Patent and Trademark Office requested FDA's assistance in determining these patents' eligibilities for patent term restoration. In a letter dated May 6, 2008, FDA advised the Patent and Trademark Office that this medical device had undergone a regulatory review period and that the approval of MACROPLASTIQUE IMPLANTS represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for MACROPLASTIQUE IMPLANTS is 2,651 days. Of this time, 1,973 days occurred during the testing phase of the

Appendix 2



Armenpharm, Ltd.

49 South Ridge Road,
P.O. Box D1400
Pomona, NY 10970

Telephone: 845-354-7077 • Fax: 845-354-2808

2011 FEB 28 9:44
info@armenpharm.com

February 7, 2011

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

Subject: Citizen Petition
ANDA: 060851, Chloramphenicol Capsules USP, 250 mg

Dear Sir/Madam:

The undersigned submits this Citizen Petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act and 21 CFR §§ 10.20, 10.30, 314.122 and 314.161 to request that the Commissioner of Food and Drug Administration (FDA) make a determination as to whether Chloramphenicol Capsules 250 mg was withdrawn from sale for reasons other than safety or effectiveness and grant permission to relist application number A060851, Abbreviated New Drug Application (ANDA) for Chloramphenicol Capsules USP, 250 mg, applicant Armenpharm, Ltd.

A. Action Requested

The petitioner requests that the Commissioner of FDA declare that Chloramphenicol Capsules USP, 250 mg is suitable to relist the drug product in the current edition of "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) and make the determination Chloramphenicol Capsules USP, 250 mg was withdrawn from sale for reasons other than safety or effectiveness. Please refer to Attachment I for a copy of the current electronic edition of the Orange Book, listing application number A060851 Chloramphenicol Capsules, 250 mg, proprietary name Mychel and applicant Armenpharm in the "Discontinued Drug Product List".

The petitioner, Armenpharm, Ltd., requests the Agency to publish a formal notice in the Federal Register relisting Chloramphenicol Capsules USP, 250 mg as an approved drug product for Armenpharm, Ltd. and publish in the current edition of "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) the marketing status as current for ANDA 060851, Chloramphenicol Capsules 250 mg with the proprietary name Mychel.

FDH-2011-P-0081

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B. Statement of Ground

Armenpharm, Ltd., plans to submit a Prior Approval Application for an alternate manufacturing and distribution site for Chloramphenicol Capsules USP, 250 mg. Attachment II contains letters dated September 23, 1991 and October 23, 1991 from Armenpharm, Ltd. to FDA requesting withdraw of Supplement S-003 to abbreviated antibiotic drug application (AADA) 60-851 for Chloramphenicol Capsules USP, 250 mg in order to allow Armenpharm, Ltd. to resubmit a Prior Approval Supplement (PAS) utilizing another more competent manufacturer. In addition, Attachment II contains a letter from FDA dated November 8, 1991 stating Armenpharm's request to withdraw supplement S-003 has been accepted and "withdrawal does not prejudice any future filing of the application" and Armenpharm "may request that the information, in the application that you have withdrawn, be considered in connection with any resubmission".

Chloramphenicol Capsules USP, 250 mg was not withdrawn for safety or effectiveness. The drug product was withdrawn due to the manufacturer no longer marketing the drug product. Federal Register Volume 74, No. 27, February 11, 2009 [Docket No. FDA-2009-N-0026] in Attachment III lists the Reference Listed Drug (RLD), Chloromycetin (chloramphenicol capsules USP), 50 mg, 100 mg, and 250 mg, ANDA 60-591, applicant Parkedale Pharmaceuticals, Inc, c/o King Pharmaceuticals, Inc. as having notified the agency in writing that the drug product was no longer marketed and requested that the approval of the application be withdrawn.

Chloramphenicol is currently approved in an injectable dosage form. Please refer to Attachment IV for a current copy of the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for approval of application number A062365 having the active ingredient, chloramphenicol sodium succinate. Therefore, chloramphenicol is currently in an approved drug product and the applications for an oral solid dosage form, Chloramphenicol Capsules USP, 250 mg were only removed and placed in the discontinued section of the Orange book because manufacturers were no longer marketing the drug product and not removed due to safety or effectiveness of the drug product.

In an effort to combat antibiotic resistance An Interagency Task Force on Antimicrobial Resistance (TFAR) was initiated in 1999 following a congressional hearing on the topic of "Antimicrobial Resistance: Solutions to a Growing Public Health Problem". Currently 10 federal agencies participate as members of the Task Force. FDA co-chairs, along with the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), the Task Force also includes the Agency for Healthcare Research and Quality (AHRQ), Centers for Medicare and Medicaid Services (CMS), the Health Resources and Services Administration (HRSA), the Department of Agriculture (USDA), the Department of Defense, the Department of Veterans Affairs, and the Environmental Protection Agency. In 2001, the U.S. Agency for International Development joined the Task Force to help address global antimicrobial resistance issues. Please refer to Attachment V for additional information concerning TFAR from Centers for Disease Control and Prevention (CDC) and FDA.



Armenpharm, Ltd.

On December 12 and 13, 2007, the Interagency Task Force on Antimicrobial Resistance updated the action plan. The revised action plan is currently being finalized and will be available for public comment in 2010. To date, it has not been posted.

Successful management of current antimicrobials, and the continued development of new ones, is vital to protecting human and animal health against infectious microbial pathogens. Approximately two million people acquire bacterial infections in U.S. hospitals each year, and 90,000 die as a result. About 70 percent of those infections are resistant to at least one drug. The trends toward increasing numbers of infection and increasing drug resistance show no sign of abating. Resistant pathogens lead to higher health care costs because they often require more expensive drugs and extended hospital stays. Resistant infections impact clinicians practicing in every field of medicine. The problem is not limited to hospitals. Community-acquired infections are also frequently resistant to multiple antibiotics, such as community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), common respiratory pathogens including *Streptococcus pneumoniae*, and gram-negative bacilli, which can infect humans through food.

Armenpharm, Ltd. recently contracted with JMI Laboratories for determination of *in vitro* potency of Chloramphenicol and comparators when tested against various microorganisms. Please refer to Attachments VI, VII and VIII, for reports. In Attachment VI, JMI Laboratories tested Chloramphenicol and comparator antimicrobial agents against Community-Acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA). Chloramphenicol appears to be more effective (93-100%) than oxacillin (0%) and erythromycin (0%) against various Community-Acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA). In Attachment VII, JMI Laboratories tested Chloramphenicol and comparator antimicrobial agents against *Staphylococcus aureus* and *Clostridium difficile*. Chloramphenicol appears to be more effective (89.7- 99.4%) than oxacillin (51.5-58.1%), levofloxacin (6.6-93.0%), erythromycin (4.8-86.2%), and clindamycin (52.3-96.6%) against various strains of *Staphylococcus aureus* and *Clostridium difficile*. In Attachment VIII, JMI Laboratories tested Chloramphenicol and comparator antimicrobial agents against Enterobacteriaceae strains carrying emerging resistance mechanisms. Chloramphenicol is not effective against enteric bacteria unless used in huge amounts. Other drugs were more effective at much smaller doses.

Armenpharm, Ltd. would like Chloramphenicol Capsules USP, 250 mg relisted in order to submit a PAS for the drug product. The petitioner believes there is a need for use of an antibiotic as a "last resort" for microorganisms resistant to other antibiotics. Chloramphenicol is no more dangerous, and in one case has less serious side effects than other approved antibiotics used in connection with MRSA. The serious need for additional drugs in the healthcare physicians armamentarium has been recognized by FDA and FDA has asked industry to do exactly what the petitioner has done here. Microorganisms have not developed a resistance by having been exposed to Chloramphenicol Capsules USP, 250 mg in several decades. Chloramphenicol appeared to be more effective, 93-100% than several other antimicrobial agents currently on the market against Community-Acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA).



Armenpharm, Ltd.

The petitioner is including the last approved package insert in Attachment IX and a side by side comparison with Armenpharm's updated proposed labeling including addition of the following sections, Microbiology, Warning, Pregnancy, Nursing Mothers, Pediatric Use, Geriatric Use, Information for Patients and updated Dosage and Administration with an Adults section, Pediatric Patients section and Neonates section can be found in Attachment X. The source of the new text is based on Chloramphenicol Sodium Succinate Injection (Monarch Pharmaceuticals, Inc.) posted on DailyMed, National Library of Medicine.

C. Environmental impact

The petitioner claims categorical exclusion from requirements to prepare an environmental assessment under 21 CFR §25.31 (a). To the best of its knowledge there is no information that indicates extraordinary circumstances exist for filing an EA.

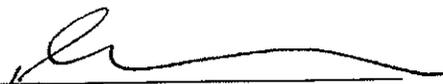
D. Economic impact

In accordance with 21 CFR § 10.30(b), the petitioner will, upon request by the Commissioner, submit economic impact information.

E. Certification

The undersigned certifies that, to the best of his knowledge, this petition includes all information and views on which the Petition relies, and it includes representative data and information known to the petitioner which are unfavorable to the Petition.

Sincerely,



Arthur P. Bedrosian
President
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2011 APR 18 A 11: 24

April 15, 2011

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

**Subject: Citizen Petition, Supplement
Chloramphenicol Capsules USP, 250 mg**

Dear Sir/Madam:

Armenpharm, Ltd. submits this supplement to the Citizen Petition submitted on February 7, 2011. The petitioner erroneously requested the Commissioner of Food and Drug Administration (FDA) to make a determination on their application, A06085 instead of the Reference Listed Drug, application A060591.

The undersigned submits this Citizen Petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act and 21 CFR §§ 10.20, 10.30, and 314.161 to request that the Commissioner of Food and Drug Administration (FDA) make a determination as to whether the Reference Listed Drug Chloromycetin[®] (Chloramphenicol Capsules, 250 mg), application number A060591, applicant Parke-Davis, was withdrawn or withheld from sale for reasons other than safety or effectiveness.

A. Action Requested

The petitioner requests that the Commissioner of FDA determine whether the Reference Listed Drug Chloromycetin[®] (Chloramphenicol Capsules, 250 mg), application number A060591, applicant Parke-Davis, has been voluntarily withdrawn or withheld from sale for reasons other than safety or effectiveness.

The petitioner, Armenpharm, Ltd., requests the Agency to publish a formal notice in the Federal Register announcing its determination that Chloromycetin[®] (Chloramphenicol Capsules, 250 mg) was not withdrawn from sale for reasons of safety or effectiveness, thus allowing abbreviated new drug applications (ANDAs) to refer to this drug product and allow FDA to continue to approve ANDAs that refer to the drug product, Chloramphenicol Capsules, 250 mg, as long as they meet relevant legal and regulatory requirements.

FDA-2011-P-0081

SUP

B. Statement of Ground

Please refer to the Citizen petition submitted on February 7, 2011.

C. Environmental impact

The petitioner claims categorical exclusion from requirements to prepare an environmental assessment under 21 CFR §25.31 (a). To the best of its knowledge there is no information that indicates extraordinary circumstances exist for filing an EA.

D. Economic impact

In accordance with 21 CFR § 10.30(b), the petitioner will, upon request by the Commissioner, submit economic impact information.

E. Certification

The undersigned certifies that, to the best of his knowledge, this petition includes all information and views on which the Petition relies, and it includes representative data and information known to the petitioner which are unfavorable to the Petition.

Sincerely,



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Appendix 3



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: June 14, 2012

FROM: Dmitri Iarikov, MD, Medical Officer, Division of Anti-Infective Products

THROUGH: John Farley, MD, Acting Division Director, Division of Anti-Infective Products

SUBJECT: Safety and Efficacy Relisting Petition for chloramphenicol capsules 250 mg, proprietary name Mychel

TO: Nicole K. Mueller, HFD-7

Summary

We have concluded that chloramphenicol capsules 250 mg, proprietary name Chloromycetin, ANDA #60591, approval date December 8, 1950, was withdrawn from sale for reasons of safety.

This determination was made in accordance with 21 CFR 314.161 and in response to a consult request received from the Office of Regulatory Policy (ORP). ORP generated the consult request in response to a citizen petition submitted by Armenpharm, Ltd.

We carefully reviewed our files for records concerning the withdrawal of chloramphenicol capsules from sale and examined relevant literature and data for postmarketing adverse events and efficacy for this drug product. Our review finds that the risks of chloramphenicol capsules, as currently labeled, outweigh the benefits. We have reviewed the prescribing information for chloramphenicol sodium succinate injection (Monarch Pharmaceuticals, April 2007) and the prescribing information for chloramphenicol capsules, U.S.P. (Rachelle Laboratories Inc., September 1983) and concluded that the labeling for chloramphenicol capsules is not adequate. A sponsor seeking to reintroduce chloramphenicol capsules would also need to submit non-clinical and possibly clinical data to address the safety concern of aplastic anemia, particularly the concern regarding cytotoxic metabolites after oral administration.

Adverse Drug Effects

Chloramphenicol causes a number of adverse reactions, but the most serious adverse effect is bone marrow depression (anemia, thrombocytopenia, and granulocytopenia temporally associated with treatment). A boxed warning in the prescribing information for both chloramphenicol sodium succinate injection and chloramphenicol capsules, U.S.P. states that serious hypoplastic anemia, thrombocytopenia, and

granulocytopenia are known to occur after administration of chloramphenicol. Labeling recommends extensive safety monitoring: baseline blood studies should be followed by periodic blood studies approximately every two days during therapy.

The boxed warning also describes fatal aplastic anemia associated with administration of the drug. As noted in the boxed warning, laboratory studies "cannot be relied on to detect bone marrow depression prior to the development of aplastic anemia" The risk of dying from aplastic anemia following administration of chloramphenicol has been estimated to range from one in 21,671 to one in 40,800. A statewide surveillance study showed a 13-fold increased risk of dying from aplastic anemia associated with chloramphenicol use [1]. In some of the cases reported in this study, aplastic anemia occurred several months or years after chloramphenicol administration. There is published literature which suggests that the risk of fatal aplastic anemia associated with the oral formulation of chloramphenicol may be higher than the risk associated with the intravenous formulation. While this observation may be related to greater use of the oral formulation of chloramphenicol after it was first introduced in 1948, published literature also describes a biologically plausible mechanism for this observation (chloramphenicol metabolites produced by intestinal bacteria after administration of the oral formulation which may be cytotoxic in the bone marrow [2, 3]). A sponsor seeking to reintroduce the oral formulation of chloramphenicol would need to submit non-clinical and possibly clinical data to address the safety concern of aplastic anemia, particularly the concern regarding chloramphenicol metabolites after oral administration.

The boxed warning also states that there are reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Chloramphenicol is listed as reasonably anticipated to be a human carcinogen in the 12th Report on Carcinogens, a congressionally mandated public health document (see Attachment 1). Abnormal cell differentiation into lymphoblastic-leukemia-like cells, inhibition of apoptosis, and increase in cancer cell invasion have been proposed as mechanisms that may contribute to carcinogenesis with chloramphenicol [4, 5].

The chloramphenicol injection and capsule prescribing information state that excessive blood levels may result from administration of the recommended doses of chloramphenicol to patients with impaired liver or kidney function. For patients with impaired liver or kidney function, labeling recommends that, "The dosage should be adjusted accordingly, or preferably, the blood concentration should be determined at appropriate intervals"

Because of the potential for adverse drug effects, the prescribing information for chloramphenicol capsules stated that chloramphenicol must be used only in serious infections for which less potentially dangerous drugs are ineffective and contraindicated. Labeling recommends *in vitro* sensitivity testing, "so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests" Should chloramphenicol capsules be reintroduced, additional labeling and implementation of a Risk Evaluation Mitigation Strategy (REMS) would be necessary to ensure that the oral formulation of the drug is not used in patients for whom the risks outweigh the benefits and ensure adequate safety monitoring of patients, particularly in the outpatient setting.

Efficacy

-
1. Wallerstein RO et al. *JAMA* 1969 Jun 16;208(11):2045-50.
 2. Holt R. *Lancet* 1967;1(7502): 1259-1260.
 3. Yunis AA. *Am J Med.* Sep 1989; 87(3N):44N-48N.
 4. Li CH et al. *Toxicol Sci.* Jul 2010;116(1):140-150.
 5. Yuan ZR, Shi Y. *Cancer Res.* Jun 15 2008;68(12):4875-4881.

The Indications and Usage sections include the following conditions:

- a. Acute infections caused by *Salmonella typhi*
- b. *Salmonella* species
- c. *H. influenzae*, specifically meningeal infections
- d. *Rickettsia*
- e. Lymphogranuloma-psittacosis group
- f. Various Gram-negative bacteria causing bacteremia, meningitis, or other serious Gram-negative infections
- g. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents.
- h. Cystic Fibrosis Regimens

At the time of the approval of chloramphenicol, there was significant unmet need. With the approval of additional therapeutic options with less severe adverse drug effects, the risk benefit of chloramphenicol has changed. In clinical practice, chloramphenicol has been largely replaced by fluoroquinolones, cephalosporins and macrolides for the treatment of typhoid fever, by cephalosporins and vancomycin for treatment of bacterial meningitis, by tetracyclines and fluoroquinolones for treatment of *Rickettsia*, and by macrolides and fluoroquinolones for treatment of *Chlamydia* infections. A variety of alternative agents with activity against *Pseudomonas aeruginosa* (cephalosporins, fluoroquinolones, aminoglycosides, carbapenems) are now used for treatment of cystic fibrosis patients as well as other infections with Gram-negative bacteria. For some approved indications such as Rocky Mountain spotted fever and meningitis due to *Salmonella*, there are published literature reports that the use of chloramphenicol has been associated with poorer clinical outcomes and higher mortality compared to other antibacterials [6, 7].

The Petitioner emphasized a potential use of oral chloramphenicol for the treatment of infections caused by community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). However, despite *in vitro* activity against *Staphylococcus* species, chloramphenicol has to our knowledge not been studied in clinical trials for the treatment of MRSA-associated infections. There are antibacterial drugs which are approved for the treatment of serious bacterial infections caused by MRSA (e.g. linezolid, vancomycin, daptomycin).

The petitioner has also implied that chloramphenicol can be used for the treatment of *Clostridium difficile* infection. No clinical data on the treatment of *Clostridium difficile* infection with chloramphenicol is available and the drug is not approved for this indication.

Adequacy of Labeling

A use of chloramphenicol capsules for which the benefits may possibly outweigh the risks would be in patients with serious bacterial infections with very limited antibacterial drug treatment options who may desire to switch from intravenous to by mouth therapy following an initial course of intravenous chloramphenicol treatment. As noted under Adverse Drug Effects (above), we have determined that the labeling for chloramphenicol capsules U.S.P. is inadequate as a Risk Evaluation Mitigation Strategy (REMS) would be required to ensure that the benefits of the drug outweigh its risks. The REMS would likely include a Medication Guide and Elements to Assure Safe Use including restricted distribution.

6. Holman RC et al. *J Infect Dis.* Dec 1 2001;184(11):1437-1444.

7. Owusu-Ofori A, Scheld WM. *Int J Infect Dis.* Mar 2003;7(1):53-60.

Required Studies

We also considered whether any preclinical or clinical studies of safety or effectiveness would be necessary before chloramphenicol oral capsules were reintroduced to the market. As noted under Adverse Drug Effects (above), a sponsor seeking to reintroduce the oral formulation of chloramphenicol would need to submit non-clinical and possibly clinical data to address the concern regarding chloramphenicol metabolites after oral administration.

Conclusion

Based on the analysis of published literature on the use of oral chloramphenicol and review of records related to the withdrawal from sale of Chloramphenicol Capsules, 250 mg, we conclude that the drug was withdrawn from sale for reasons of safety, that the latest version of the approved labeling is not adequate to ensure that the benefits outweigh the risks, and that additional non-clinical and possibly clinical data is needed before reintroduction of chloramphenicol capsules.

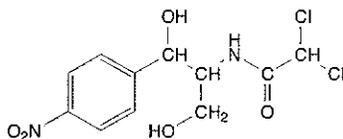
Attachment 1

Chloramphenicol

CAS No. 56-75-7

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)



Carcinogenicity

Chloramphenicol is *reasonably anticipated to be a human carcinogen*, based on limited evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous case reports have shown leukemia to occur after medical treatment for chloramphenicol-induced aplastic anemia, and three case reports have documented the occurrence of leukemia after chloramphenicol therapy in the absence of intervening aplastic anemia (IARC 1990). A case-control study in China found an increased risk of leukemia in children who had been treated with chloramphenicol; the risk increased significantly with increasing number of days the drug was taken (Shu *et al.* 1987, 1988). Two case-control studies found large but statistically nonsignificant increases in the risk of aplastic anemia associated with use of chloramphenicol in the six months before the onset of aplastic anemia (Issaragrisil *et al.* 1997, Laporte *et al.* 1998). However, two other case-control studies found no association between the use of chloramphenicol and the risk of leukemia in adults, suggesting that children may be a particularly susceptible subgroup (Zheng *et al.* 1993, Doody *et al.* 1996). One case-control study found an association between chloramphenicol use and increased risk of soft-tissue sarcoma (Zahm *et al.* 1989). Considered together, the many case reports implicating chloramphenicol as a cause of aplastic anemia, the evidence of a link between aplastic anemia and leukemia, and the increased risk of leukemia found in some case-control studies support the conclusion that chloramphenicol exposure is associated with an increased risk of cancer in humans.

Studies on Mechanisms of Carcinogenesis

Chloramphenicol inhibits protein synthesis in the mitochondria of mammalian cells (by binding to ribosomes), which accounts for the sensitivity of proliferating tissues, such as those that promote the formation of blood cells, to its toxicity. Anemia, including aplastic anemia, is a recognized hazard associated with chloramphenicol treatment in humans. In genotoxicity studies, chloramphenicol gave mainly negative results in bacterial systems and mixed results in mammalian systems. The most consistently positive results were observed for cytogenetic effects in mammalian cells, including DNA single-strand breaks and increased frequencies of sister chromatid exchange and chromosomal aberrations. Overall, chloramphenicol appears to be genotoxic (NTP 2000). Several studies have suggested that dehydrochloramphenicol, a chloramphenicol metabolite produced by intestinal bacteria, may be responsible for DNA damage and carcinogenicity (Isildar *et al.* 1988a,b, Jimenez *et al.* 1990, Kitamura *et al.* 1997). This metabolite can undergo nitroreduction in the bone marrow and has been shown to cause DNA single-strand breaks in bone-marrow cells. Mitochondrial abnormalities caused by chloramphenicol are similar to those observed in preleukemia, sug-

gesting that mitochondrial DNA is involved in the pathogenesis of secondary leukemia.

Cancer Studies in Experimental Animals

No adequate studies of the carcinogenicity of chloramphenicol in experimental animals were identified. In male mice given chloramphenicol by intraperitoneal injection in combination with busulfan (the known human carcinogen 1,4-butanediol dimethanesulfonate), the incidence of lymphoma was significantly higher than in mice receiving either busulfan or chloramphenicol alone (Robin *et al.* 1981).

Properties

Chloramphenicol is a naturally occurring antibiotic derivative of dichloroacetic acid that is a white to grayish or yellowish-white fine crystalline powder at room temperature. It is soluble in water and very soluble in methanol, ethanol, butanol, ethyl acetate, chloroform, and acetone. It is fairly soluble in ether, but insoluble in benzene, petroleum ether, and vegetable oils (IARC 1990, HSDB 2009). It is stable under normal shipping and handling conditions (Akron 2009). The biologically active form of chloramphenicol is levorotatory (Chambers 2001). Physical and chemical properties of chloramphenicol are listed in the following table.

Property	Information
Molecular weight	323.1
Melting point	150°C to 152°C
Log K_{ow}	1.14
Water solubility	25 g/L at 25°C
Vapor pressure	1.7×10^{-12} mm Hg at 25°C

Source: HSDB 2009.

Use

Chloramphenicol is an antimicrobial agent with restricted use, because it causes blood abnormalities. It is used to combat serious infections for which other antibiotics are either ineffective or contraindicated. It can be used against gram-positive cocci and bacilli and gram-negative aerobic and anaerobic bacteria (Burnham *et al.* 2000). Chloramphenicol has been used since the 1950s to combat a wide range of microbial infections, including typhoid fever, meningitis, and certain infections of the central nervous system (IARC 1990). It currently is used in eye ointments and drops to treat superficial ocular infections involving the conjunctiva or cornea, in topical ointments or drops to treat the external ear or skin, in tablets for oral administration, and in intravenous suspensions to treat internal infections (FDA 2009, MedlinePlus 2009). Chloramphenicol has also been used in veterinary medicine as a highly effective and well-tolerated broad-spectrum antibiotic. Because of its tendency to cause blood abnormalities in humans, the U.S. Food and Drug Administration in 1997 banned its use in food-producing animals. Chloramphenicol continues to be used to treat both systemic and local infections in cats, dogs, and horses (FDA 1997, Brooks 2008).

Production

Chloramphenicol is produced naturally by the bacterium *Streptomyces venezuelae*. It may be produced by chemical synthesis followed by a step to isolate stereoisomers. A fermentation process also has been described that does not require separation of stereoisomers (IARC 1990). Chloramphenicol was first produced in the United States in 1948 (IARC 1990). Annual U.S. production was estimated to exceed 908 kg (2,000 lb) in 1977 and 1979 (HSDB 2009). In 2009, chloramphenicol was produced by 16 manufacturers worldwide, including 11 in India, 1 in China, 2 in East Asia, and 2 in Europe (SRI 2009). U.S.

imports of chloramphenicol were estimated at 8,150 kg (17,970 lb) in 1977 and 8,200 kg (18,080 lb) in 1979 (HSDB 2009). Since 1989, annual imports of chloramphenicol and its derivatives have remained at or below 16,000 kg (35,000 lb), averaging 8,000 kg (18,000 lb) from 1989 to 2004. Over the same period, annual U.S. exports of chloramphenicol were less than 53,000 kg (117,000 lb) except in 1993, when 1.9 million kilograms (4 million pounds) were exported. No exports were reported for 1998 or 2000 (USITC 2009). In 2002, less than 10,000 lb of chloramphenicol (U.S. production plus imports) was reported under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule; no inventory update reports for chloramphenicol were filed before 2002 (EPA 2004).

Exposure

The primary routes of human exposure to chloramphenicol are oral and dermal, through its use as a drug. Exposure also may occur through inhalation, dermal contact, ingestion, or contact with contaminated water or soil (HSDB 2009). For adults, a typical dosage of chloramphenicol is 50 to 100 mg/kg of body weight per day, divided into four oral or intravenous doses (MedlinePlus 2009). Chloramphenicol also is used in ophthalmic ointments, solutions, and drops. It usually is taken for two to five days or until the infection is diminished. For many infections, continued treatment with chloramphenicol after the infection has resolved is suggested, for periods ranging from 48 hours for eye infections to 8 to 10 days for typhoid fever. No information was found on the number of prescriptions currently written for chloramphenicol in the United States. Children, especially newborns and young infants, metabolize chloramphenicol much more slowly than do adults. Pediatric doses must be lower so as to avoid gray-baby syndrome; this syndrome is characterized by cardiovascular collapse in infants, apparently caused by accumulation of active, unconjugated chloramphenicol in the serum, resulting from low inactivation through glucuronide conjugation in the liver (Chambers 2001). Initial dosages are 25 mg/kg of body weight every 24 hours for infants under one week old, 25 mg/kg every 12 hours for infants aged one to four weeks, and 50 mg/kg every 6 hours for children weighing less than about 25 kg (55 lb) (Sills and Boenning 1999).

Chloramphenicol can be detected in blood serum, plasma, cerebrospinal fluid, and urine. It is rapidly absorbed from the gastrointestinal tract and is distributed extensively through the human body, regardless of administration route. It has been found in the heart, lung, kidney, liver, spleen, pleural fluid, seminal fluid, ascitic fluid, and saliva. Upon metabolism, chloramphenicol yields *D*-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol and chloramphenicol- β -*D*-glucuronide (IARC 1990). Following degradation of chloramphenicol by intestinal bacteria via amidolysis, 18 metabolites were observed, the major ones being 2-amino-1-(*p*-nitrophenyl)-1,3-propanediol and its *p*-aminophenyl reduction by-product (HSDB 2009). Approximately 90% of chloramphenicol is excreted in urine, mostly as metabolites, including conjugated derivatives; only 15% is excreted as the parent compound (IARC 1990). The half-life of chloramphenicol in adult humans ranges from 1.6 to 4.6 hours. Peak levels appear two to three hours after oral administration of chloramphenicol. In adults given eight 1-g doses, once every six hours, the average peak serum level was 11.2 μ g/mL one hour after the first dose and 18.4 μ g/mL after the fifth dose. Mean serum levels ranged from 8 to 14 μ g/mL over the 48-hour period (Burnham *et al.* 2000). In infants, chloramphenicol's half-life is much longer, ranging from 10 to more than 48 hours in infants aged one to eight days and from 5 to 16 hours in infants aged eleven days to eight weeks (IARC 1990).

Chloramphenicol is released to the environment and may be found in various waste streams as a result of its use as a medicinal and re-

search antimicrobial agent. Chloramphenicol may also be isolated from *S. venezuelae* in the soil (HSDB 2009). If released to air, chloramphenicol will exist primarily as an aerosol and will be removed mainly through dry deposition. Chloramphenicol in the atmosphere reacts with photochemically produced hydroxyl radicals, with a half-life of 12 hours. If released to water, chloramphenicol will be essentially nonvolatile. Adsorption to sediment and bioconcentration in aquatic organisms are not expected to be important processes. If released to soil, chloramphenicol is expected to have high mobility. It is not expected to evaporate from either dry or wet soils. Various studies indicate that chloramphenicol may biodegrade in soil and water. It was found to degrade in adapted activated waste sludge (HSDB 2009).

Occupational exposure during the manufacture of chloramphenicol may occur through inhalation, dermal contact, or ingestion (HSDB 2009). Medical and veterinary personnel who administer drugs containing chloramphenicol also may be exposed (Burnham *et al.* 2000, Brooks 2008).

Regulations

Food and Drug Administration (FDA)

Chloramphenicol is a prescription drug subject to specific labeling requirements. Extra-label use of chloramphenicol in food-producing animals is prohibited. Chloramphenicol in ophthalmic and topical dosage form and in tablet form must not be used in animals producing meat, eggs, or milk.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DMITRI IARIKOV
06/14/2012

JOHN J ALEXANDER
06/14/2012

JOHN J FARLEY
06/14/2012

Appendix 4



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

JUL 13 2012

2012 JUL 16 P 1:39

Arthur P. Bedrosian
President
Armenpharm, Ltd.
49 South Ridge Road
P.O. Box D1400
Pomona, NY 10970

Re: Docket No. FDA-2011-P-0081

Dear Mr. Bedrosian:

This letter responds to your citizen petition received on February 8, 2011, requesting that the Food and Drug Administration (FDA) determine whether Chloromycetin (Chloramphenicol) Capsules, 250 Milligrams (mg) was withdrawn from sale for safety or efficacy reasons.

The FDA has reviewed its records and determined that Chloromycetin (Chloramphenicol) Capsules, 250 mg was withdrawn from sale for reasons of safety or effectiveness. Accordingly, the FDA will remove Chloromycetin (Chloramphenicol) Capsules, 250 mg from the list of drug products published in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). FDA will not accept or approve abbreviated new drug applications (ANDAs) that refer to this drug product.

Enclosed is a copy of the *Federal Register* notice that announces the FDA determination. If you require any further information, do not hesitate to contact me at (301) 796-3507.

Sincerely,

Nikki Mueller
Office of Regulatory Policy
Center for Drug Evaluation and Research

Enclosure

FDA-2011-P-0081

2012 JUL 16

AET

drug product is equivalent to withdrawing the drug from sale.

Lachman Consultant Services, Inc., submitted a citizen petition dated March 14, 2012 (Docket No. FDA-2012-P-0271), under 21 CFR 10.30, requesting that the Agency determine whether TOPOTECAN INJECTION (topotecan hydrochloride) 1 mg (base)/1 mL, 3 mg (base)/3 mL, 4 mg (base)/4 mL, was withdrawn from sale for reasons of safety or effectiveness.

After considering the citizen petition and reviewing Agency records, and based on the information we have at this time, FDA has determined under § 314.161 that TOPOTECAN INJECTION (topotecan hydrochloride) 1 mg (base)/1 mL, 3 mg (base)/3 mL, 4 mg (base)/4 mL, was not withdrawn for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that TOPOTECAN INJECTION (topotecan hydrochloride) 1 mg (base)/1 mL, 3 mg (base)/3 mL, 4 mg (base)/4 mL, was withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of TOPOTECAN INJECTION (topotecan hydrochloride) 1 mg (base)/1 mL, 3 mg (base)/3 mL, 4 mg (base)/4 mL, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. We have found no information that would indicate that this product was withdrawn from sale for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list TOPOTECAN INJECTION (topotecan hydrochloride) 1 mg (base)/1 mL, 3 mg (base)/3 mL, 4 mg (base)/4 mL, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to TOPOTECAN INJECTION (topotecan hydrochloride) 1 mg (base)/1 mL, 3 mg (base)/3 mL, 4 mg (base)/4 mL, may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: July 10, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2012-17090 Filed 7-12-12; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-P-0081]

Determination That CHLOROMYCETIN (Chloramphenicol) Capsules, 250 Milligrams, Were Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that CHLOROMYCETIN (chloramphenicol) Capsules, 250 milligrams (mg), were withdrawn from sale for reasons of safety or effectiveness. The Agency will not accept or approve abbreviated new drug applications (ANDAs) for chloramphenicol capsules, 250 mg.

FOR FURTHER INFORMATION CONTACT: Nikki Mueller, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6312, Silver Spring, MD 20993-0002, 301-796-3601.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or

if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, are the subject of ANDA 60-591, held by Parkedale Pharmaceuticals, and initially approved on December 8, 1950. CHLOROMYCETIN is an antibiotic indicated to treat only serious infections for which less potentially dangerous drugs are ineffective or contraindicated.

In a letter dated October 9, 2007, Parkedale Pharmaceuticals requested withdrawal of ANDA 60-591 for CHLOROMYCETIN (chloramphenicol) Capsules, 50 mg, 100 mg and 250 mg. In the Federal Register of February 11, 2009 (74 FR 6896), FDA announced that it was withdrawing approval of ANDA 60-591, effective March 13, 2009, and moved the drug to the "Discontinued Drug Product List" section of the Orange Book.

Armenpharm, Ltd., submitted a citizen petition dated February 7, 2011 (Docket No. FDA-2011-P-0081), under 21 CFR 10.30, requesting that the Agency determine whether CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, were withdrawn from sale for reasons of safety or effectiveness.

After considering the citizen petition, and based on the information we have at this time, FDA has determined under § 314.161 that CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, were withdrawn for reasons of safety or effectiveness. We have carefully reviewed Agency records concerning the withdrawal of CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. At the time of the approval of CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, there was significant unmet medical need. With the approval of additional therapies with less severe adverse drug effects, FDA has determined that the risks associated with CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, as currently labeled, outweigh the benefits. Most importantly, CHLOROMYCETIN

(chloramphenicol) Capsules, 250 mg, may cause a number of adverse reactions, the most serious being bone marrow depression (anemia, thrombocytopenia, and granulocytopenia temporally associated with treatment). A boxed warning in the prescribing information for both chloramphenicol sodium succinate injection and chloramphenicol capsules states that serious hypoplastic anemia, thrombocytopenia, and granulocytopenia are known to occur after administration of chloramphenicol. The drug product labeling recommends extensive safety monitoring, including baseline blood studies followed by periodic blood studies approximately every 2 days during therapy. The boxed warning also describes fatal aplastic anemia associated with administration of the drug and aplastic anemia attributed to chloramphenicol that later terminated in leukemia. There is published literature which suggests that the risk of fatal aplastic anemia associated with the oral formulation of chloramphenicol may be higher than the risk associated with the intravenous formation.

FDA has also reviewed the latest approved labeling for the product and has determined that this labeling is inadequate and a Risk Evaluation and Mitigation Strategy (REMS) would be required to ensure that the benefits of the drug outweigh its risks. The REMS may include Elements to Assure Safe Use, including restricted distribution, and a Medication Guide could be required as part of the labeling. FDA has determined that additional nonclinical and possibly clinical studies of safety and efficacy would be necessary before CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, could be considered for reintroduction to the market.

Accordingly, the Agency will remove CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to this drug product.

Dated: July 10, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2012-17091 Filed 7-12-12; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-D-0530]

Draft Guidance for Industry and Food and Drug Administration Staff; Medical Devices: The Pre-Submission Program and Meetings With FDA Staff; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of the draft guidance entitled "Medical Devices: The Pre-Submission Program and Meetings with FDA Staff." The purpose of this guidance is to describe the Pre-Submission program (formerly the pre-Investigational Device Exemption (IDE) program) for medical devices reviewed in the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER). In addition, the guidance provides recommendations regarding information that should be included in a Pre-Submission Package. This guidance also describes the procedures that CDRH and CBER intend to follow when industry representatives or application sponsors request a meeting with review staff. This draft guidance is not final nor is it in effect at this time.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment of this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by October 11, 2012. Submit either written or electronic comments on this collection of information by September 11, 2012.

ADDRESSES: Submit written requests for single copies of the draft guidance document entitled "Medical Devices: The Pre-Submission Program and Meetings with FDA Staff" to the Division of Small Manufacturers, International and Consumer Assistance, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4613, Silver Spring, MD 20993-0002; or Office of Communication, Outreach and Development (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.

Send one self-addressed adhesive label to assist that office in processing your request, or fax your request to 301-847-8149. See the **SUPPLEMENTARY INFORMATION** section for information on electronic access to the guidance.

Submit electronic comments on the draft guidance to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Identify comments with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT:

Angela Krueger, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 1666, Silver Spring, MD 20993-0002, 301-796-6380; or

Stephen Ripley, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, 301-827-6210.

SUPPLEMENTARY INFORMATION:

I. Background

Since its establishment in 1995, the pre-IDE program has been a successful resource for both medical device applicants and the FDA. Originally, this program was designed to provide applicants a mechanism to obtain FDA feedback on future IDE applications prior to their submission. Over time, the pre-IDE program evolved to include feedback on other device submission program areas, such as Premarket Approval (PMA) applications, Humanitarian Device Exemption (HDE) applications, and Premarket Notification (510(k)) Submissions, as well as to address questions related to whether a clinical study requires submission of an IDE. The purpose of this guidance is to update the pre-IDE program to reflect this broader scope and make important modifications to reflect changes in the premarket program areas as a result of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85). This guidance also broadens the scope of the program to include those devices regulated by CBER. Accordingly, FDA is changing the name for this program from the pre-IDE program to the Pre-Submission (Pre-Sub) program.

The main purpose of the Pre-Sub program remains the same as the pre-IDE program: to facilitate providing advice to applicants when they have specific questions during product development and early protocol

Appendix 5

Gary Gray Pharmacist dba COMPLEX

(b) (6)

2014 SEP -4 P 1:04

August 22, 2014 (Resending August 26, 2014)

Division of Dockets Management (HFA-305) – FDA
FDA- 5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: ANDA Chloramphenicol 250 mg, formerly marketed as Chloromycetin
CDER Docket No. FDA-1999-N-0194 and/or RIN number 0910-AH10

Dear Edisa Gozsun

I am writing as a clinical pharmacist to petition FDA to reconsider and reclassify Chloramphenicol 250 mg tablets labeling for tropical medical use and packaging changes; rather than withdraw from the market place for developing nations WHO list of drug use. Chloramphenicol 250 mg tablets control hemorrhagic fever like illnesses (Lassa Fever, Ebola, etc.) affecting Sierra Leone and Liberia diamond mining hemoglobin depleted co-joined endemic nation's patients presenting fever, somnolence, and watery tar-like diarrhea.

Control and survival benefits out-weigh the risks of thrombocytopenia and aplastic anemia in the all ready anemic (2^ointestinal parasites) patient when used short term appropriately. Appropriate would be 12 tablet unit-dose package 3 day supply with Hesperian – like patient information in English, Spanish and French supplemental 3 day oral rehydration need – why and instructions how to mix “a little salt + a little sugar” into water pictures.

California published Hesperian Organization “Where there is No Doctor” does illiterate developing nation instruction well. It was the most helpful tropical medicine reference for me as Peace Corps Volunteer traveling Sierra Leone in 1980 to 1982, consulting and ordering CHASL drugs for 18 rural health clinics and 6 hospitals for the Christian Medical Commission Essential Basic Drug Project and developing nations by WHO leadership. I learned a lot – it was a good time. If I can be of further assistance, please email or call me.

Best



Gary Gray, Clinical Pharmacist
California License #24141

Enc. Credentials

Proprietary and Confidentiality Disclaimer: This information is intended only for the use of the individual or entity named above. The authorized recipient of this information is prohibited from disclosing this information to any other party. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or action taken in reliance on the contents of these documents is strictly prohibited. Inform Gary Gray at (b) (6) and call (b) (6)

1983 to 2013 Clinical hospital experienced - California and Arizona

- Kaweah Delta District Hospital – Visalia, California 1998 - 2013
- Adventist Hospital – Ukiah, California 2013 - 2013.
- Eisenhower Hospital - Palm Springs, California 1996 -1997.
- Lincoln Hospital – Phoenix, Arizona 1987 - 1995.
- Northern Arizona Hospitals 1983 - 1986.

1980 to 1982 US Peace Corps Volunteer experience - West Africa

- Pharmacy Director for Christian Health Association of Sierra Leone CHASL – West Africa to set up a centralized pharmacy warehouse and IV compounding facility for CHASL members with capacity for stocking eight hospitals and eighteen rural health clinics with essential basic drugs and IV fluids.
- Implemented successful new procedure for ordering drugs and IV fluids saving CHASL members a significant amount in contributed funding from international relief organizations.
- Worked closely with Catholic Relief Services CRS clearing drug consignments through customs for CHASL members.
- Established CHASL Pharmacy accounting systems, budget projections and financial statements.
- Opened up line of communications between CHASL and CHASL members with European and United States international suppliers.
- Established CHASL essential basic drug formulary listing envisioned by The Christian Medical Commission CMC, World Council of Churches WCC Geneva Switzerland.

1966 to 1979 Pharmacist owner and operator – Arizona and California

- Moore Drug Company - Flagstaff, Arizona 1973 - 1979.
- West Anaheim Pharmacy - Anaheim, California 1966 - 1972.

1944 to 1965 Educational experience – Arizona and California

- Gary completed a six year degree of study in pharmacy at the University of Arizona, Tucson Arizona and awarded Bachelor of Science (BS) Pharmacy in the spring of 1965.
- Course studies included (semesters): (1) botany, (1) zoology, (2) physics, (2) chemistry-inorganic focus, (2) chemistry-organic focus, (1) chemistry-qualitative analysis focus, (1) chemistry-quantitative analysis focus, (1) biochemistry, (2) physiology, (1) pharmaceutical focused inorganic chemistry, (2) pharmaceutical focused organic chemistry, (2) pharmaceutical dispensing, (2) pharmacology, (2) pharmacognosy - that study of pharmacology dealing with plant medicinal substances and (2) work/study cancer desert plant collection/extraction research Tucson, Arizona 1961 - 1965.
- Gary completed pre-Pharmacy study at Fullerton College - Fullerton, California 1959 - 1961.
- [REDACTED] (b) (6)
- Gary graduated [REDACTED] (b) (6) High School [REDACTED] (b) (6)
- [REDACTED] (b) (6)
- Gary was born [REDACTED] (b) (6) to [REDACTED] (b) (6) and [REDACTED] (b) (6)
- [REDACTED] (b) (6)

2000, proposed rule (65 FR 256) is withdrawn as of [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: You may submit comments, identified by Agency name and Docket No. FDA-1999-N-0194 and/or Regulatory Information Number (RIN) number 0910-AH10, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name, Docket No. FDA-1999-N-0194, and RIN 0910-AH10 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the "Request for Comments" heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Advisory Committee voted to include astemizole on the withdrawn or removed list (see the Federal Register of June 29, 2000 (65 FR 40104)).

Cerivastatin sodium: All drug products containing cerivastatin sodium. Cerivastatin sodium, formerly marketed as BAYCOL tablets, was associated with increased risk of rhabdomyolysis. Fatal rhabdomyolysis was reported most frequently when used at higher doses, when used in elderly patients, and particularly, with concomitant use of gemfibrozil (LOPID). In an August 8, 2001, "Dear Healthcare Professional Letter," the NDA holder stated that it discontinued the marketing and distribution of all dosage strengths of BAYCOL (Ref. 2).

Chloramphenicol: All oral drug products containing chloramphenicol. Chloramphenicol was formerly marketed as CHLOROMYCETIN (chloramphenicol) Capsules. In a letter dated October 9, 2007, the application holder requested withdrawal of the ANDA for CHLOROMYCETIN (chloramphenicol) Capsules, 50 mg, 100 mg, and 250 mg. In the Federal Register of February 11, 2009 (74 FR 6896), FDA announced that it was withdrawing approval of the ANDA, effective March 13, 2009. Armenpharm, Ltd., submitted a citizen petition dated February 7, 2011 (Docket No. FDA-2011-P-0081), under § 10.30 (21 CFR 10.30), requesting that the Agency determine whether CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, were withdrawn from sale for reasons of safety or effectiveness. After considering the citizen petition, FDA determined that the drug product was withdrawn for reasons of safety or effectiveness. With the approval of additional therapies with less severe adverse drug effects, FDA determined that the risks associated with CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, as then labeled, outweighed the benefits. Furthermore, CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, may cause a number of adverse reactions, the most serious being bone marrow depression (anemia, thrombocytopenia, and granulocytopenia temporally

associated with treatment). Additionally, prior to the removal of the capsule drug product from the market, a boxed warning in the prescribing information for both chloramphenicol sodium succinate injection and chloramphenicol capsules stated that serious hypoplastic anemia, thrombocytopenia, and granulocytopenia are known to occur after administration of chloramphenicol. The boxed warning also described fatal aplastic anemia associated with administration of the drug and aplastic anemia attributed to chloramphenicol that later terminated in leukemia. There is published literature that suggests that the risk of fatal aplastic anemia associated with the oral formulation of chloramphenicol may be higher than the risk associated with the intravenous formulation (see the Federal Register of July 13, 2012 (77 FR 41412)). FDA is not aware of any oral drug products containing chloramphenicol currently being marketed.

Cisapride: All drug products containing cisapride. Cisapride, formerly marketed as PROPULSID tablets and suspension, was associated with serious cardiac arrhythmias and death. In an April 12, 2000 "Dear Healthcare Professional Letter," the NDA holder stated that it would discontinue marketing the drug as of July 14, 2000, and make the product available only through an investigational limited access program (Ref. 3). Cisapride was presented to the Advisory Committee at the July 2000 meeting, and the Advisory Committee voted to include cisapride on the withdrawn or removed list (see the Federal Register of June 29, 2000 (65 FR 40104)).

Esmolol hydrochloride: All parenteral drug products containing esmolol HCl that supply 250 mg/milliliter (mL) of concentrated esmolol per 10-mL ampule. Esmolol hydrochloride (HCl), 250 mg/mL per 10-mL ampule, formerly marketed as BREVIBLOC Injection 250 mg/mL per 10-mL ampule, was associated with increased risk of medication errors resulting in serious adverse events, including deaths. The NDA holder sent a letter to FDA on June 28, 2007,

Tab 9

FDA Public Health Advisory Letter from
Murray M. Lumpkin June 9, 1999

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For Consumers

Food and Drug Administration 09 June 1999 Trovan (Trovafloracin / Alatrofloracin Mesylate)

INTERIM RECOMMENDATIONS

Trovan (trovafloracin / alatrofloracin) was approved by FDA in 1997 for the treatment of a wide variety of infections.

Based on new safety data related to serious liver injury, described below, the Food and Drug Administration is today advising physicians that the drug Trovan should be reserved for use ONLY in the treatment of patients who meet ALL of the following treatment criteria:

- Have at least one of the following infections that is judged by the treating physician to be serious and life- or limb-threatening:
 - nosocomial pneumonia,
 - community acquired pneumonia,
 - complicated intra-abdominal infections (including post-surgical infections)
 - gynecologic and pelvic infections, or
 - complicated skin and skin structure infections, including diabetic foot infections;
- Receive their initial therapy in an in-patient health care facility (i.e., hospital or long-term nursing care facility); and
- The treating physician believes that, even given the new safety information, the benefit of the product for the patient outweighs the potential risk.

In most cases, it is expected that therapy in these patients would begin with the intravenous formulation of Trovan. Due to the bioavailability of oral Trovan, patients who have stabilized clinically on IV therapy may be switched to oral Trovan to complete their course of therapy, if deemed appropriate by the treating physician. In some patients with these kinds of serious and life- or limb-threatening infections, oral Trovan may be considered appropriate initial therapy. Use of oral Trovan to treat less serious infections is not warranted.

Therapy with Trovan beyond 14 days duration generally should not be used, because the risk of liver injury may increase substantially with exposure beyond 14 days. Trovan should be discontinued prior to 14 days of therapy if the patient experiences any clinical signs or symptoms of liver dysfunction, including fatigue, anorexia, yellowing of the skin and eyes, severe stomach pain with nausea and vomiting, or dark urine.

NEW SAFETY DATA

No reports of hepatic failure, liver transplant, or death due to possible hepatic etiology were reported in the 7000 patients in the pre-marketing clinical trials database exposed to Trovan. It is estimated that approximately 2,500,000 patients have received Trovan since approval for marketing. Following marketing of Trovan in the United States in February 1998, FDA began receiving reports of patients who experienced serious hepatic reactions in association with the use of the product. In July of 1998, FDA had worked with Trovan's manufacturer to add information about hepatic toxicity to the Precautions section of Trovan's package insert.

Since that time, FDA has received reports of over 100 cases of clinically symptomatic liver toxicity in patients receiving Trovan. Some of these patients developed serious liver injury leading to liver transplant and/or death. At present, FDA is aware of 14 cases of acute liver failure that are strongly associated with Trovan exposure. Four of these patients required liver transplant (one of

whom subsequently died). Five additional patients died of liver-related illness. Three patients recovered without transplantation, and the final outcome is still pending on two patients. These numbers of patients with acute liver failure, although few, represent a rate that appears to be significantly higher than would be expected to occur idiopathically in the general population - despite the under-reporting of cases that generally occurs to our post-marketing surveillance system.

Trovan-associated liver failure appears to be unpredictable. It has been reported with both short-term (as little as 2 days exposure) and longer-term drug exposure; therefore the efficacy of liver function monitoring in acceptably managing this risk is uncertain.

Trovan use exceeding 2 weeks duration appears to be associated with a substantially increased risk of acute liver failure.

Liver failure has also been reported following Trovan re-exposure.

These uncommon but very serious adverse reactions are typical of drug toxicities which, because of their rarity, may not always be detectable in clinical trials databases. However, such toxicities may become apparent after marketing when the product is used in a significantly broader population. As such, these adverse reactions are the types of important, new safety information the post-marketing spontaneous reporting system is designed to detect, as it did in this case.

CONCLUSIONS

FDA does not wish to deprive patients and physicians of access to effective antimicrobials, if the risks associated with these drugs can be managed successfully by other means. Based on the new safety data presently available to the agency and based on the availability of alternative products to treat other less serious indications for which this product was originally approved, FDA is issuing the interim recommendations outlined above.

FDA and Pfizer have agreed to a program that will limit the distribution of Trovan to in-patient health care facilities (hospitals and long-term nursing care facilities). Pfizer will be communicating in the near future with appropriate pharmacies to provide directions concerning possible return of their present inventories of Trovan.

FDA believes that this risk management program will better ensure that Trovan is used in clinical situations in which its benefits can be expected to outweigh its presently known risks. In this manner, FDA believes that Trovan can continue to be made available to those patients who may need it for treatment of serious and life- or limb-threatening infections, while minimizing other patients' risk of exposure to the product.

FDA advises patients presently taking Trovan NOT to discontinue their therapy until they have discussed their treatment options with their physician.

FDA and the manufacturer will continue to collect and evaluate data on Trovan's safety and will continue to assess the drug's benefit/risk profile. As further information or recommendations about Trovan become available, FDA will continue to inform the health care and patient communities.

FDA requests that any suspected adverse events thought associated with Trovan be reported to the agency through MedWatch, FDA's adverse event reporting system. Reports may be submitted to FDA by telephone (800-332-1088), by fax (800-332-0178) or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, Maryland 20857. Reports can also be filed via the Internet at www.fda.gov/medwatch¹. Reports may also be filed directly to the manufacturer.

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, Maryland

Page Last Updated: 12/09/2011

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Links on this page:

1. <http://www.fda.gov/medwatch>

Tab 10

Federal Register of June 16, 2006
(71 FR 34940)

and resultant under-utilization; *Form Number*: CMS-R-52 (OMB#: 0938-0386); *Frequency*: Recordkeeping and Reporting—Annually; *Affected Public*: Business or other for-profit and Federal government; *Number of Respondents*: 4,757; *Total Annual Responses*: 4,757; *Total Annual Hours*: 160,702.

To obtain copies of the supporting statement and any related forms for the proposed paperwork collections referenced above, access CMS Web site address at <http://www.cms.hhs.gov/PaperworkReductionActof1995>, or E-mail your request, including your address, phone number, OMB number, and CMS document identifier, to Paperwork@cms.hhs.gov, or call the Reports Clearance Office on (410) 786-1326.

Written comments and recommendations for the proposed information collections must be mailed or faxed within 30 days of this notice directly to the OMB desk officer: OMB Human Resources and Housing Branch, Attention: Carolyn Lovett, New Executive Office Building, Room 10235,

Washington, DC 20503. Fax Number: (202) 395-6974.

Dated: June 9, 2006.

Michelle Shortt,

*Director, Regulations Development Group,
Office of Strategic Operations and Regulatory
Affairs.*

[FR Doc. E6-9479 Filed 6-15-06; 8:45 am]

BILLING CODE 4120-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2006N-0222]

Merck & Co., Inc., et al.; Withdrawal of Approval of 65 New Drug Applications and 52 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing

approval of 65 new drug applications (NDAs) and 52 abbreviated new drug applications (ANDAs) from multiple applicants. The holders of the applications notified the agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

DATES: Effective June 16, 2006.

FOR FURTHER INFORMATION CONTACT:

Florine P. Purdie, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: The holders of the applications listed in the table in this document have informed FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications. The applicants have also, by their requests, waived their opportunity for a hearing.

Application No.	Drug	Applicant
NDA 1-645	Vitamin B6 (pyridoxine hydrochloride (HCl))	Merck & Co., Inc., 770 Sumneytown Pike, P.O. Box 4, BLA-20, West Point, PA 19486-0004
NDA 5-521	Heparin Sodium Injection USP	Eli Lilly and Co., Lilly Corporate Center, Indianapolis, IN 46285
NDA 5-657	Tubocurarine Chloride Injection USP	Bristol-Myers Squibb Co., P.O. Box 4500, Princeton, NJ 08543-4500
NDA 5-794	Sultrin Triple Sulfa Cream and Triple Sulfa Tablets	Ortho-McNeil Pharmaceutical, Inc., 1000 U.S. Highway 202, P.O. Box 300, Raritan, NJ 08869-0602
NDA 6-012	Folvron (folic acid and iron)	Lederle Laboratories, 401 North Middleton Rd., Pearl River, NY 10965
NDA 7-149	Rubramin (cyanocobalamin) Tablets and Capsules	Bristol-Myers Squibb Co.
NDA 7-504	Acthar (corticotropin for injection)	Aventis Pharmaceuticals, Inc., 200 Crossing Blvd., BX 2-309E, Bridgewater, NJ 08807
NDA 7-794	Neothylline (dyphylline)	Teva Pharmaceuticals USA, 1090 Horsham Rd., P.O. Box 1090, North Wales, PA 19454
NDA 9-176	Cortril (hydrocortisone) Topical Ointment	Pfizer Global Pharmaceuticals, 235 East 42nd St., New York, NY 10017
NDA 10-028	Equanil (meprobamate) Tablets	Wyeth Pharmaceuticals, P.O. Box 8299, Philadelphia, PA 19101-8299
NDA 10-093	Biphetamine (dextroamphetamine and amphetamine) Capsules	Celltech Pharmaceuticals, Inc., 755 Jefferson Rd., P.O. Box 31710, Rochester, NY 14603
NDA 10-513	Ketonil (amino acids and electrolytes)	Merck & Co., Inc.
NDA 10-787	Iron Dextran Injection	Aventis Pharmaceuticals, Inc.
NDA 10-799	Dimetane (brompheniramine maleate) Tablets and Extendabs	Wyeth Consumer Healthcare, 5 Giralda Farms, Madison, NJ 07940
NDA 11-340	Cerumenex (triethanolamine polypeptide oleate-condensate), 10%	The Purdue Frederick Co., 1 Stamford Forum, Stamford, CT 06901-3431

Application No.	Drug	Applicant
NDA 11-960	Aristocort (triamcinolone diacetate) Syrup	Astellas Pharma US, Inc., 3 Parkway North, Deerfield, IL 60015-2548
NDA 11-984	Decadron Phosphate (dexamethasone sodium phosphate) Sterile Ophthalmic Solution	Merck & Co., Inc.
NDA 12-122	Glucagon (glucagon HCl) for Injection	Eli Lilly & Co.
NDA 12-281	Robaxial (methocarbamol USP and aspirin USP) Tablets	A.H. Robins Co., c/o Wyeth Pharmaceuticals, P.O. Box 8299, Philadelphia, PA 19101-8299
NDA 12-649	Periactin (cyproheptadine HCl)	Merck & Co., Inc.
NDA 12-703	Elavil (amitriptyline HCl) Tablets	AstraZeneca Pharmaceuticals, 1800 Concord Pike, P.O. Box 8355, Wilmington, DE 19803-8355
NDA 12-704	Elavil (amitriptyline HCl) Injection	Do.
NDA 13-220	Periactin (cyproheptadine HCl) Syrup, 2 milligrams (mg)/5 milliliters (mL)	Merck & Co., Inc.
NDA 13-400	Aldomet (methyldopa) Tablets	Do.
NDA 13-401	Aldomet (methyldopate HCl) Injection, 50 mg/mL	Do.
NDA 13-413	Dexacort Phosphate (dexamethasone sodium phosphate) in Respihaler	Celltech Pharmaceuticals, Inc.
NDA 16-016	Aldoclor-150 and -250 (methyldopa and chlorothiazide) Tablets, 250 mg/150 mg and 250 mg/250 mg	Merck & Co., Inc.
NDA 16-030	Bayer 8 Hour Aspirin and Measurin Aspirin (aspirin extended-release tablets), 650 mg	Bayer Healthcare, LLC, 36 Columbia Rd., P.O. Box 1910, Morristown, NJ 07962-1910
NDA 16-099	Atromid-S (clofibrate) Capsules	Wyeth Pharmaceuticals
NDA 16-745	Jergens Antibacterial Deodorant (triclocarban, 1%) Soap	Kao Brands Co., 2535 Springs Grove Ave., Cincinnati, OH 45214-1773
NDA 16-888	Selsun Blue (selenium sulfide) Cream/Shampoo, 1%	Abbott Laboratories, 625 Cleveland Ave., Columbus, OH 43215-1724
NDA 17-569	Renoquid (sulfacytine) Tablets	Glenwood LLC, 111 Cedar Lane, Englewood, NJ 07631
NDA 17-573	Vanceril (beclomethasone dipropionate) Inhalation Aerosol	Schering Corp., 2000 Galloping Hill Rd., Kenilworth, NJ 07033
NDA 17-659	Alupent (metaproterenol sulfate) Inhalation Solution, 5%	Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Rd., P.O. Box 368, Ridgefield, CT 06877-0368
NDA 17-781	Diprosone (betamethasone dipropionate) Lotion	Schering Corp.
NDA 17-820	Dobutrex (dobutamine HCl) Sterile Injection	Eli Lilly & Co.
ANDA 18-023	Lactated Ringer's Injection USP	B. Braun Medical, Inc., 2525 McGaw Ave., P.O. Box 19791, Irvine, CA 92623-9791
ANDA 18-026	5% Dextrose and 0.9% Sodium Chloride (NaCl) Injection	Do.
ANDA 18-046	10% Dextrose Injection USP	Do.
ANDA 18-047	10% Dextrose and 0.9% NaCl Injection USP	Do.
ANDA 18-184	0.45% NaCl Injection USP	Do.
ANDA 18-186	1/6 Molar Sodium Lactate Injection USP in Plastic Container	Do.
ANDA 18-197	Ibuprofen Tablets	BASF Corp., 8800 Line Ave., Shreveport, LA 71106
ANDA 18-252	Isolyte S (multi-electrolyte injection) Injection	B. Braun Medical, Inc.
ANDA 18-256	5% Dextrose in Ringer's Injection	Do.
NDA 18-257	Tonocard (tocainide HCl) Tablets, 400 mg and 600 mg	AstraZeneca Pharmaceuticals

Application No.	Drug	Applicant
ANDA 18-274	Isolyte S (multi-electrolyte injection) with 5% Dextrose in Plastic Container	B. Braun Medical, Inc.
NDA 18-389	Aldomet (methyldopa) Oral Suspension, 250 mg/5 mL	Merck & Co., Inc.
NDA 18-682	TZ-3 (1% tioconazole) Dermal Cream	Pfizer, Inc., 235 East 42nd St., New York, NY 10017
NDA 18-686	Normodyne (labetalol HCl USP) Injection, 5 mg/mL	Schering Corp.
NDA 18-687	Normodyne (labetalol HCl USP) Tablets	Do.
ANDA 18-721	Ringer's Injection USP	B. Braun Medical, Inc.
NDA 18-754	Orudis (ketoprofen) Capsules, 25 mg, 50 mg, and 75 mg	Wyeth Pharmaceuticals
NDA 18-792	Neopham (amino acids) Injection	Hospira, Inc., 275 North Field Dr., Dept. 389, Bldg. 2, Lake Forest, IL 60045
NDA 18-901	Aminess (essential amino acids injection with histidine)	Do.
NDA 18-911	Heparin Sodium in 5% Dextrose Injection and Heparin Sodium in NaCl Injection	Do.
NDA 19-083	Theophylline and 5% Dextrose Injection	B. Braun Medical, Inc.
NDA 19-107	Protropin (somatrem) for Injection	Genentech, Inc., 1 DNA Way MS1242, South San Francisco, CA 94080-4990
ANDA 19-138	Alphatrex (betamethasone dipropionate cream USP) 0.05%	Savage Laboratories, 60 Baylis Rd., Melville, NY 11747
ANDA 19-143	Alphatrex (betamethasone dipropionate ointment USP) 0.05%	Do.
NDA 19-383	Proventil (albuterol sulfate extended-release tablets USP) Repetabs	Schering Corp.
NDA 19-401	Pseudo-12 Suspension (pseudoephedrine polistirex extended-release suspension)	Celltech Pharmaceuticals, Inc.
NDA 19-523	Cysteine HCl Injection USP, 7.25%	Hospira, Inc.
NDA 19-589	Vancenase AQ (beclomethasone dipropionate) Nasal Spray	Schering Corp.
NDA 19-621	Ventolin (albuterol sulfate) Syrup	GlaxoSmithKline Pharmaceuticals, 5 More Dr., P.O. Box 13358, Research Triangle Park, NC 27709
NDA 20-035	Ergamisol (levamisole HCl) Tablets	Johnson & Johnson Pharmaceutical Research and Development, LLC, c/o Janssen Pharmaceutical Products, LP, 1125 Trenton-Harbourton Rd., K1-02B, Titusville, NJ 08560-0200
NDA 20-176	VitaPed (multivitamins)	Hospira, Inc.
NDA 20-338	Differin (adapalene) Solution, 0.1%	Galderma Laboratories, LP, 14501 North Freeway, Fort Worth, TX 76177
NDA 20-759	Trovan (trovafloxacin mesylate) Tablets, 100 mg and 200 mg	Pfizer, Inc.
NDA 20-760	Trovan (alatrofloxacin mesylate) Injection	Do.
NDA 20-847	Esclim (estradiol extended-release film) Transdermal System	Women First Healthcare, Inc., 380 Lexington Ave., New York, NY 10168
NDA 20-962	Emla (2.5% lidocaine and 2.5% prilocaine) Anesthetic Disc	AstraZeneca Pharmaceuticals
ANDA 40-023	Adrucil (fluorouracil injection USP), 50 mg/mL	Sicor Pharmaceuticals, Inc., 19 Hughes, Irvine, CA 92618
ANDA 40-147	Leucovorin Calcium Injection USP, 10 mg (base)/mL	Hospira, Inc.
NDA 50-039	Garamycin (gentamicin sulfate) Ophthalmic Solution	Schering Corp.

Application No.	Drug	Applicant
NDA 50-091	Chloroptic (chloramphenicol ophthalmic solution USP), 0.5%	Allergan, Inc., 2525 Dupont Dr., P.O. Box 19534, Irvine, CA 92623-9534
NDA 50-322	Neodecadron (neomycin sulfate and dexamethasone sodium phosphate) Sterile Ophthalmic Solution	Merck & Co., Inc.
NDA 50-368	Ilotycin (erythromycin) Ophthalmic Ointment	Eli Lilly & Co.
NDA 50-571	CefMax (cefmenoxime HCl) Injection	TAP Pharmaceutical Products, Inc., 675 North Field Dr., Lake Forest, IL 60045
NDA 50-648	Clindamycin Phosphate Injection in 5% Dextrose	Baxter Healthcare Corp., Route 120 & Wilson Rd., Round Lake, IL 60073
ANDA 60-429	Sumycin Capsules (tetracycline HCl capsules USP)	Apothecon, c/o Bristol-Myers Squibb Co., P.O. Box 4500, Princeton, NJ 08543-4500
ANDA 62-480	Gentacidin Solution (gentamicin sulfate ophthalmic solution USP)	Novartis Pharmaceuticals Corp., 1 Health Plaza, Bldg. 118, East Hanover, NJ 07936-1080
ANDA 62-597	Mytrex (nystatin and triamcinolone acetonide cream USP) 100,000 units/gram (g) and 1 mg/g	Savage Laboratories
ANDA 62-601	Mytrex (nystatin and triamcinolone acetonide ointment USP) 100,000 units/g and 1 mg/g	Do.
ANDA 62-750	Pipracil (piperacillin for injection), 2 g, 3 g, and 4 g	Wyeth Pharmaceuticals, Inc.
ANDA 63-186	Cephalexin Capsules USP, 250 mg and 500 mg	Apothecon, c/o Bristol-Myers Squibb Co.
ANDA 64-084	Sterile Bleomycin Sulfate for Injection USP, 15 and 30 units/vial	Sicor Pharmaceuticals, Inc.
ANDA 70-083	Ibuprofen Tablets USP, 400 mg	BASF Corp.
ANDA 70-099	Ibuprofen Tablets USP, 600 mg	Do.
ANDA 70-273	Alphatrex (betamethasone dipropionate lotion USP), 0.05%	Savage Laboratories
ANDA 70-745	Ibuprofen Tablets USP, 800 mg	BASF Corp.
ANDA 72-621	Acetylcysteine Solution USP, 10%	Roxane Laboratories, Inc., P.O. Box 16532, Columbus, OH 43216
ANDA 72-622	Acetylcysteine Solution USP, 20%	Do.
ANDA 72-995	Metoclopramide HCl Oral Solution, 10 mg/mL	Do.
ANDA 73-562	Diffunisal Tablets USP, 250 mg	Do.
ANDA 73-563	Diffunisal Tablets USP, 500 mg	Do.
ANDA 74-166	Toposar (etoposide injection USP), 20 mg/mL	Sicor Pharmaceuticals, Inc.
ANDA 74-541	Cimetidine HCl Oral Solution, 30 mg/5 mL	Roxane Laboratories, Inc.
ANDA 74-663	Acyclovir Sodium for Injection USP, 500 mg base/vial and 1 g base/vial	Hospira, Inc.
ANDA 75-179	Nabumetone Tablets	Copley Pharmaceutical, Inc., 1090 Horsham Rd., P.O. Box 1090, North Wales, PA 19454
ANDA 75-875	Carbamazepine Oral Suspension USP, 100 mg/5 mL	Taro Pharmaceutical Industries, Ltd., c/o Taro Pharmaceuticals, U.S. Agent, 5 Skyline Dr., Hawthorne, NY 10532
ANDA 80-643	Diphenhydramine HCl Elixir USP, 25 mg/10 mL	Roxane Laboratories, Inc.
ANDA 81-225	Adrucil (etoposide injection USP), 50 mg/mL	Sicor Pharmaceuticals, Inc.
ANDA 83-261	Pentobarbital Sodium Injection USP	Wyeth Pharmaceuticals
ANDA 83-383	Diucardin (hydroflumethiazide tablets USP) Tablets, 50 mg	Do.

Application No.	Drug	Applicant
ANDA 84-015	Bleph-10 (sulfacetamide sodium ophthalmic ointment USP) Ophthalmic Ointment, 10%	Allergan, Inc.
ANDA 84-514	Dilor (diphylline tablets USP), 200 mg	Savage Laboratories
ANDA 84-751	Dilor-400 (diphylline tablets USP), 400 mg	Do.
ANDA 85-035	Diphenoxylate HCl and Atropine Sulfate Tablets USP, 2.5 mg and 0.025 mg	R & S Pharma, LLC, 8407 Austin Tracy Rd., Fountain Run, KY 42133
ANDA 85-961	Methocarbamol Tablets USP, 500 mg	Clonmel Healthcare Ltd., c/o STADA Pharmaceuticals, Inc., U.S. Agent, 5 Cedar Brook Dr., Cranbury, NJ 08512
ANDA 85-963	Methocarbamol Tablets USP, 750 mg	Do.
ANDA 86-899	Isoetharine HCl Inhalation Solution USP, 1%	Roxane Laboratories, Inc.
ANDA 87-450	Chlorthalidone Tablets USP, 50 mg	Clonmel Healthcare Ltd.
ANDA 87-451	Chlorthalidone Tablets USP, 25 mg	Do.
ANDA 87-500	Aminophylline Tablets USP, 100 mg	Roxane Laboratories, Inc.
ANDA 87-501	Aminophylline Tablets USP, 200 mg	Do.
ANDA 88-253	T-Phyl (theophylline) Extended-Release Tablets, 200 mg	The Purdue Frederick Co.

Therefore, under section 505(e), of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), and under authority delegated to the Director, Center for Drug Evaluation and Research, by the Commissioner of Food and Drugs, approval of the applications listed in the table in this document, and all amendments and supplements thereto, is hereby withdrawn, effective June 16, 2006.

Dated: May 23, 2006.

Douglas C. Throckmorton,

Deputy Director, Center for Drug Evaluation and Research.

[FR Doc. E6-9440 Filed 6-15-06; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003E-0254]

Determination of Regulatory Review Period for Purposes of Patent Extension; INSPRA

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for INSPRA and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks,

Department of Commerce, for the extension of a patent that claims that human drug product.

ADDRESSES: Submit written comments and petitions to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100-670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the human drug product becomes effective and runs until the approval phase begins. The approval phase starts with the initial

submission of an application to market the human drug product and continues until FDA grants permission to market the product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted, as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product INSPRA (epiprenone). INSPRA is indicated for the treatment of hypertension. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for INSPRA (U.S. Patent No. 4,559,332) from Novartis Corp., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated June 16, 2003, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of INSPRA represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for

Tab 11

Revocation of Requirements for
Aminopyrine and Dipyrone
(42 FR 53954, October 4, 1977)

venting product related injury to children, the handicapped, and senior citizens.

(7) *Probability of exposure to hazard.* The Commission may also consider several other things which can help to determine the likelihood that a consumer would be injured by a product thought to be hazardous. These are the number of units of the product that are being used by consumers, the frequency with which such use occurs, and the likelihood that in the course of typical use the consumer would be exposed to the identified risk of injury.

(8) *Additional criteria.* Additional criteria may arise that the staff believes warrant the Commission's attention. The Commission encourages the inclusion of such criteria for its consideration in establishing priorities. The Commission recognizes that incontrovertible data related to the criteria identified in this policy statement may be difficult to locate or develop on a timely basis. Therefore, the Commission may not require extensive documentation on each and every criterion before making a decision. In addition, the Commission emphasizes that the order of listing of the criteria in this policy is not intended to indicate either the order in which they are to be considered or their relative importance. The Commission will consider all the criteria to the extent feasible in each case, and as interactively or jointly as possible.

(Sec. 4, (15 U.S.C. 2053), 86 Stat. 1210; as amended by sec. 4, Pub. L. 94-284)

Effective date: October 4, 1977.

Dated: September 28, 1977.

RICHARD E. RAPPS,
Secretary, Consumer Product
Safety Commission.

[FR Doc.77-29108 Filed 10-3-77;8:45 am]

[4110-03]

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER C—DRUGS: GENERAL

[Docket No. 76N-0311]

PART 201—LABELING

Revocation of Requirements for Aminopyrine and Dipyrone

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This rule revokes the regulation describing the conditions that must be met for the continued marketing of aminopyrine and dipyrone. This is being done because there are no approved new drug applications (NDA's) for either of these drug products.

DATES: Effective November 3, 1977. Comments by November 3, 1977.

ADDRESS: Written comments to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

Nathan M. Kight, Bureau of Drugs (HFD-30), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857. (301-443-3640).

SUPPLEMENTARY INFORMATION:

In a statement of policy published in the FEDERAL REGISTER of November 17, 1964 (29 FR 15364) under 21 CFR 3.44 (now 21 CFR 201.311), and amended in the FEDERAL REGISTER of October 11, 1967 (32 FR 14101), the Commissioner of Food and Drugs declared aminopyrine and dipyrone to be new drugs approvable for use only for their antipyretic effect in serious or life-threatening situations where either salicylates or similar drugs are known to be ineffective, or where the benefit-to-risk considerations for dipyrone are acceptable. Applications were approved for dipyrone, but none were received for aminopyrine, which is not known to be marketed in the United States.

Dipyrone is an analgesic antipyretic drug produced in both oral and parenteral forms. It is a sodium sulfonate derivative of aminopyrine and has similar properties.

The Director of the Bureau of Drugs issued a notice of opportunity for hearing in the FEDERAL REGISTER of September 3, 1976 (41 FR 37386) proposing to withdraw approval of NDA's for drug products containing dipyrone on grounds of lack of evidence of safety. In response to the notice, two firms submitted requests for hearing and requests for extension of time to file supporting data. The Food and Drug Administration denied both requests for an extension of time. One of the firms later withdrew its request for hearing. The other elected not to submit the supporting data and analysis that are required by 21 CFR 314.200 and, therefore, its request for hearing was denied. A third firm, though not electing to request a hearing for its products, did request an extension of time to file a hearing request and submitted a published study to demonstrate the safety of dipyrone. The study was reviewed and found not to be relevant to the safety issue on the basis of which the drug products containing dipyrone were being withdrawn. The request for an extension of time was denied. A notice was published in the FEDERAL REGISTER of June 17, 1977 (42 FR 30893) withdrawing approval effective June 27, 1977, of all NDA's for drug products containing dipyrone. Inasmuch as there are no approved NDA's for drugs to which § 201.311 applies, the Commissioner concludes that this regulation should be revoked.

In consideration of the foregoing, the Commissioner finds for good cause that notice and public procedure are impracticable, unnecessary, and contrary to the public interest. Interested persons may, on or before November 3, 1977, file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857, four copies of

written comments, identified with the docket number found in brackets in the heading of this document. Comments received may be seen in the office of the Hearing Clerk between the hours of 9 a.m. and 4 p.m., Monday through Friday. Any changes in this regulation justified by such comments will be the subject of a further amendment.

§ 201.311 [Reserved]

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 502 (f) and (l) and 701(a), 52 Stat. 1051 as amended, 1055 (21 U.S.C. 352 (f) and (l) and 371(a)) and under authority delegated to the Commissioner (21 CFR 5.1), Part 201 is amended by revoking

§ 201.311 Aminopyrine or dipyrone drug preparations for human use; directions and warnings.

Effective date. This revocation shall be effective on November 3, 1977.

(Secs. 502 (f), (l), 701(a), 52 Stat. 1051 as amended, 1055 (21 U.S.C. 352(f), (l), 371(a)).)

Dated: September 28, 1977.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner
for Compliance.

[FR Doc.77-29076 Filed 10-3-77;8:45 am]

[4110-03]

SUBCHAPTER E—ANIMAL DRUGS, FEEDS, AND RELATED PRODUCTS

PART 522—IMPLANTATION OR INJECTABLE DOSAGE FORM NEW ANIMAL DRUGS NOT SUBJECT TO CERTIFICATION

Iron Hydrogenated Dextran Injection

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: The animal drug regulations are amended to reflect approval of a new animal drug application filed by Medico Industries, Inc., providing for use of iron hydrogenated dextran injection for the prevention and treatment of iron deficiency anemia in baby pigs.

EFFECTIVE DATE: October 4, 1977.

FOR FURTHER INFORMATION CONTACT:

Jack C. Taylor, Bureau of Veterinary Medicine (HFV-136), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857 (301-443-5247).

SUPPLEMENTARY INFORMATION: In accordance with section 512(d) of the Federal Food, Drug, and Cosmetic Act, Part 522 (21 CFR 522) is amended to reflect approval of a new animal drug application (NADA 106-772V) filed by Medico Industries, Inc., Elwood, Kans. 66024. In addition, the section is editorially revised.

In compliance with the freedom of information regulations and § 514.11(c) (2) (ii) of the animal drug regulations

Tab 12

RX Study Bulletin #231 Drug Products
containing Dipyrone

Rx Drug Study Bulletin #231

DATE: November 4, 1977

TO: All REGIONAL FOOD & DRUG DIRECTORS
AND DISTRICT DIRECTORS
ATTN: NAS/NRC COORDINATORS
COMPLIANCE BRANCH CHIEFS

FROM Prescription Drug Compliance Branch, HFD-313
Division of Drug Labeling Compliance

SUBJECT Drug Products Containing Dipyrone

Re: Federal Register of June 17, 1977

On November 4, 1977, a Regulatory Letter was issued to firms believed to be manufacturers, repackers, or distributors of drug products for human use containing dipyrone as a follow-up to the Federal Register notice of June 17, 1977. The letter requested the firms' intentions regarding discontinuance of marketing and removal of outstanding stocks from the market.

BACKGROUND:

Prompted by an increasing number of reports (between 1962 and 1964) of fatal agranulocytosis associated with aminopyrine and dipyrone (a sodium sulfonate derivative of aminopyrine) containing drugs, the Commissioner of Food and Drugs convened an ad hoc committee to study these drugs. As a result of their findings, the Commissioner concluded that these drugs were unsafe and were regarded as misbranded under Section 502 of the Federal Food, Drug, and Cosmetic Act when labeled or advertised for routine use as antipyretics or analgesics, and that such preparations were new drugs and might be approved as safe and effective for marketing on the basis of New Drug Applications containing restricted labeling and indications for use. Their use was to be restricted to their antipyretic effect in serious life where salicylates or similar drugs were known to be ineffective, contraindicated, or not tolerated. This resulted in promulgation of Part 201.311 of the CFR which declared all of these drugs to be new drugs and provided the labeling restrictions and indications for use.

Subsequently, thirteen cases of blood dyscrasia associated with the use of dipyrone were reported to FDA during the period from 1966 through 1975. Then of the thirteen cases were identified as agranulocytosis and four of the cases resulted in death.

In view of the toxicity of dipyrone, substantiated by the above, and the present availability of effective orally administered alternative drug products (e.g., aspirin and acetaminophen) and nonpharmacologic methods of antipyretic therapy, the Director of the Bureau of Drugs published a Notice of Opportunity for Hearing in the Federal Register of September 3, 1976 (41 FR 37386) proposing the withdrawal of all NDA's (17) currently held for

Page 2 - DLC-Rx Drug Study Bulletin #231

dipyrone by nine different manufacturers. Subsequently, in the Federal Register of June 17, 1977 (42 FR 30893) a final order was published to withdraw all NDA's for human drugs containing dipyrone in that the drug had not been shown to be safe for use upon the basis of which the applications were approved. In addition, all drug products that were identical, related, or similar to one of the drug products previously holding an approved NDA were subject to the notice.

The effective date of the announcement was June 27, 1977, and shipments thereafter in interstate commerce of the drugs listed in that notice, or of any identical, related, or similar product, not the subject of an approved NDA, was unlawful based on Section 505.

Part 201.311 of the CFR will be deleted as a result of withdrawal of the approvals for these NDA's. Attached are copies of the letter issued to firms in your District, and an information copy of the form letter to those Districts with no applicable firms. The Division of Drug Labeling Compliance will monitor the firms' replies, furnish the District with copies of such replies, and issue assignments where indicated. Although this is not a DESI drug, the same procedures for follow-up will be utilized.

Please submit labeling and FD-3033's for any additional drug products for human

use containing dipyrone or aminopyrine so that we may institute follow-up where indicated.

Albert Lavender, Chief
Prescription Drug Compliance Branch

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

November 4, 1977

REGULATORY LETTER

CERTIFIED

File No.: 77-HFD-313-
PRODUCT:

Gentlemen:

This letter is in reference to the drug product listed above which you market containing aminopyrine or dipyrone.

Title 21 of the Code of Federal Regulations Part 3.44, recodified as 21 CFR 201.311, copy enclosed, declared all drug preparations for human use containing aminopyrine or dipyrone to be new drugs and subject to the requirements of Section 505 of the Federal Food, Drug, and Cosmetic Act. New evidence of clinical experience, not contained in New Drug Applications filed pursuant to Section 505, or not available until such applications were approved, evaluated together with the evidence available when the applications were approved, showed that such drugs are not shown to be safe for use under the conditions of use on the basis of which the applications were approved as set forth in that regulation.

The Food and Drug Administration published in the Federal Register of September 3, 1976 (41 FR 37386) a Notice of Opportunity for Hearing proposing to withdraw approval of the New Drug Applications for drug products for human use that contained dipyrone, a sodium sulfonate derivation of aminopyrine. The action was taken on the basis of new reports of agranulocytosis, sometimes fatal, associated with the use of dipyrone and because of the present availability of effective alternative drug products and effective non-pharmacologic therapy that have less potential for risk.

The Notice stated that the failure of the manufacturer or distributor of any identical, related, or similar drug product to submit objections and a request for hearing would result in the withdrawal of approval of the New Drug Applications and in regulatory action against all such products. The Food and Drug Administration received no objections or requests for hearing from you pursuant to that Notice with respect to the drug product listed above. Subsequently, on June 17, 1977, a notice was published in the (42 FD 30893), withdrawing approval of the New Drug Applications of all dipyrone and aminopyrine containing products. Copies of both these Federal Register notices are enclosed.

Page 2 - Regulatory Letter (Dipyrone)

It is the opinion of the Food and Drug Administration that your drug product listed above is identical, related, or similar to the drugs for which the New Drug Applications have been withdrawn pursuant to the Federal Register notice of June 17, 1977. Accordingly, continued marketing of the above named drug product without an approved New Drug Application constitutes a violation of Section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355. It is our position that such drugs have not been shown to be safe for use upon the basis of which the applications were approved, and pursuant to the authority set forth in Section 505(e), the above notices were published.

We request that you reply within ten (10) days after receipt of this letter, stating the action you will take to discontinue the marketing of your product listed above, and any identical or similar products containing aminopyrine or dipyrone which you may market. If any significant stocks of the drug remain in trade channels at this time, we will require that they be recalled down to the retail level. If such corrective action is not promptly undertaken, the Food

and Drug Administration is prepared to initiate legal action to enforce the law. The Federal Food, Drug, and Cosmetic Act provides for seizure of illegal products, injunction against the manufacturer or distributor of such products, and criminal prosecution of individuals and companies who manufacture or distribute illegal products (21 U.S.C. 332 and 334).

We request that your reply include (1) an estimate of the size and frequency of shipments within the past 12 months; (2) an estimate of the amount of the drug listed above that is in inventory under your control and that which remains in channels of distribution outside your control; (3) in the event that you have already discontinued marketing this drug product, the date of discontinuance; and (4) your intentions with respect to the disposition of your inventory and the withdrawal of outstanding stocks from trade channels.

Your reply should be directed to Michael A. Chappel, Project Officer, Prescription Drug Compliance Branch (HFD-313), Division of Drug Labeling Compliance, Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland, 20857.

Sincerely yours,

T.E. Byers
Associate Director for Compliance
Bureau of Drugs

Enclosures:
FR 9/3/76
FR 6/17/77
21 CFR 201.311

Tab 13

Determination that Astemizole 10mg tablets
Were Withdrawn From Sale for Safety
Reasons (64 FR 45973, August 23, 1999)

ANNUAL BURDEN ESTIMATES

Instrument	Number of respondents	Number of responses per respondent	Average burden hours per response	Total burden hours
Online IRG	54	18	.3	292

Estimated Total Annual Burden Hours: 292.

In compliance with the requirements of Section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, the Administration for Children and Families is soliciting public comment on the specific aspects of the information collection described above. Copies of the proposed collection of information can be obtained and comments may be forwarded by writing to the Administration for Children and Families, Office of Information Services, 370 L'Enfant Promenade, SW, Washington, DC 20447, Attn: ACF Reports Clearance Officer. All requests should be identified by the title of the information collection.

The Department specifically requests comments on: (a) whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility; (b) the accuracy of the agency's estimate of the burden of the proposed collection of information; (c) the quality, utility, and clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques or other forms of information technology. Consideration will be given to comments and suggestions submitted within 60 days of this publication.

Dated: August 17, 1999.

Bob Sargis,

Acting Reports Clearance Officer.

[FR Doc. 99-21747 Filed 8-20-99; 8:45 am]

BILLING CODE 4184-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration**

[Docket No. 99N-2532]

Determination That Astemizole 10-Milligram Tablets Were Withdrawn From Sale for Safety Reasons

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that astemizole 10-milligram (mg) tablets (Hismanal) were withdrawn from sale for safety reasons. The agency will not accept or approve abbreviated new drug applications (ANDA's) for astemizole 10-mg tablets.

FOR FURTHER INFORMATION CONTACT: Andrea C. Masciale, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of approved innovator drug products under an ANDA procedure. ANDA sponsors generally must show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a drug that was previously approved under a new drug application (NDA). Sponsors of ANDA's are not required to repeat the extensive clinical testing necessary to gain approval of an NDA. The only data from investigations required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products with Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book." Under FDA regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (§ 314.162 (21 CFR 314.162)). FDA may not approve an ANDA that does not refer to a listed drug (21 CFR 314.92(a)).

Astemizole 10-mg tablets (Hismanal) are the subject of approved NDA 19-402, currently held by Janssen

Pharmaceutica (Janssen). In 1988, FDA approved the NDA for Hismanal tablets for the relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria. On June 18, 1999, Janssen withdrew Hismanal tablets from sale in the United States. The agency's review of the withdrawal of astemizole 10-mg tablets (Hismanal) from the market has considered the sponsor's explanation of the basis for the withdrawal of the product and information available to the agency regarding Hismanal. The current evidence supports the conclusion under § 314.161 (21 CFR 314.161) that astemizole 10-mg tablets (Hismanal) were withdrawn from the market for safety reasons.

The agency has determined, under § 314.161, that astemizole 10-mg tablets (Hismanal) were withdrawn from the market for safety reasons. Accordingly, the agency will remove astemizole 10-mg tablets (Hismanal) from the "Orange Book" (§ 314.162). FDA will not accept or approve ANDA's that refer to this drug product.

Dated: August 13, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 99-21813 Filed 8-20-99; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration**

[Docket No. 99N-2670]

Antiviral Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Antiviral Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Dates and Time: The meeting will be held on November 2 and 3, 1999, from 8:30 a.m. to 5 p.m. Interested persons and organizations may submit written comments by September 30, 1999, to the Dockets Management Branch (address below).

Location and Addresses: Holiday Inn, The Ballrooms, Two Montgomery Village Ave., Gaithersburg, MD. Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Contact Person: Rhonda W. Stover or John B. Schupp, Center for Drug Evaluation and Research, (HFD-21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7001, or the FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12531. Please call the Information Line for up-to-date information on this meeting.

Agenda: Presentations and committee discussions will address issues related to testing for development of resistant human immunodeficiency virus (HIV-1), with an emphasis on its potential role in antiretroviral drug development. The primary objectives of these deliberations are to obtain advisory committee recommendations on the amount and type of resistance data needed to support both preclinical and clinical development of antiretroviral drugs and product labeling. This 2-day meeting will explore the following scientific issues: (1) Performance characteristics of genotypic and phenotypic assays, (2) definitions of antiviral drug resistance, (3) relationships between the development of mutations or reduced susceptibility and treatment outcome, and (4) available evidence supporting the clinical utility of testing for the development of antiviral drug resistance. In order to prepare presentations and discussions for the meeting, the agency is requesting interested persons to submit in writing the following types of relevant data, information, and views:

- Pre-clinical and/or clinical trial data on the relationship between the development of HIV mutations and changes in susceptibility to antiviral therapies.
- Prospective or retrospective clinical trial data on the relationship between genotype and/or phenotype and treatment outcome.
- Proposals for incorporating HIV resistance testing in clinical trial design.
- Proposals for utilizing information derived from HIV resistance testing to support product labeling.

These submissions should contain the following docket number, 99N-2670, and should be made to the Dockets Management Branch address provided previously in this document.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by October 27, 1999. Oral presentation from the public will be scheduled between approximately 1 p.m. and 2 p.m. on November 3, 1999. Time allotted for each presentation may be limited. Written submissions may be made to the contact person by October 27, 1999. Those desiring to make formal oral presentations should notify the contact person before October 27, 1999, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: August 13, 1999.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 99-21729 Filed 8-20-99; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Oncologic Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Oncologic Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on September 16 and 17, 1999, 8 a.m. to 5 p.m.

Location: Holiday Inn, Kennedy Grand Ballroom, 8777 Georgia Ave., Silver Spring, MD.

Contact Person: Karen M. Templeton-Somers, Center for Drug Evaluation and Research (HFD-21), Food and Drug

Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7001, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12542. Please call the Information Line for up-to-date information on this meeting.

Agenda: On September 16, 1999, the committee will discuss: (1) New drug application (NDA) 21-053, UFT® (tegafur and uracil) Capsules, Bristol-Myers Squibb Co., indicated, with leucovorin calcium tablets, for the first-line treatment of metastatic colorectal cancer; and (2) NDA 50-772, Evacet™ (doxorubicin HCl liposome injection), The Liposome Co., Inc., indicated for the first-line treatment of metastatic breast cancer in combination with cyclophosphamide. On September 17, 1999, the committee will discuss: (1) NDA 20-262/S-033, TAXOL® (paclitaxel) Injection, Bristol-Myers Squibb Co., indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard combination therapy; and (2) biologics license application (BLA) 97-1001, Roferon®-A, Hoffman-La Roche Inc., indicated for use as adjuvant treatment of surgically resected malignant melanoma without clinical evidence of nodal disease, American Joint Committee on Cancer stage II (Breslow thickness > 1.5 millimeter, N0). In addition, FDA will provide an update on the preliminary results of EST 1690 (ECOG intergroup study of INTRON A for the adjuvant treatment of melanoma) for discussion by the committee.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by September 8, 1999. Oral presentations from the public will be scheduled between approximately 8:15 a.m. and 8:45 a.m., and between approximately 1:15 p.m. and 1:30 p.m. on September 16, 1999, and between approximately 8:15 a.m. and 8:45 a.m., and between approximately 1:15 p.m. and 1:30 p.m. on September 17, 1999. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before September 8, 1999, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation. After the scientific presentations, a 30-minute open public session will be conducted for interested persons who have submitted their

Tab 14

FDA Talk Paper, T99-29 (June 21, 1999)
Janssen Pharmaceutica Announces the
Withdrawal of Hismanal From the Market

FDA TALK PAPER

*Food and Drug Administration
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857*

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T99-29	Print Media:	301-827-6242
June 21, 1999	Broadcast Media:	301-827-3434
	Consumer Inquiries:	888-INFO-FDA

JANSSEN PHARMACEUTICA ANNOUNCES THE WITHDRAWAL OF HISMANAL FROM THE MARKET

Janssen Pharmaceutica, Inc., of Titusville, N.J., has announced that it is voluntarily withdrawing the prescription antihistamine, Hismanal (astemizole) 10 mg., from the market.

Since the drug's approval in 1988, new adverse reaction data has required a series of labeling changes and warnings. In light of the choices of other prescription antihistamines now available, and the overall risk benefit profile of this drug, FDA supports the decision of the company to withdraw the product.

Patients who have been taking Hismanal for their allergy symptoms should consult with their doctors to determine an appropriate alternative treatment.

####

[FDA HOME PAGE](#)

Tab 15

"Dear Healthcare Provider" Letter from
Janssen Pharmaceutica (June 18, 1999)

U.S. Food and Drug Administration

DISCLAIMER

FDA posts safety alerts, public health advisories, press releases and other notices from companies as a service to health professionals, consumers and other interested parties. Although FDA approves medical products, FDA does not endorse either the product or the company.

This is the retyped text of a letter from Janssen Pharmaceutica. Contact the company for a copy of any referenced enclosures.

June 18, 1999

Dear Health Care Professional:

Janssen Pharmaceutica would like to inform you that we have decided to voluntarily discontinue the manufacturing, distribution and marketing of **HISMANAL**[®] (astemizole) 10 mg Tablets. We have informed the U.S. Food and Drug Administration. HISMANAL is an antihistamine indicated for relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria. The company is taking this action after careful consideration of the antihistamine class, which includes multiple alternative medications.

Physicians who currently have patients taking HISMANAL should consider future alternative treatment. Pharmacists who receive prescriptions for patients taking HISMANAL should contact the prescriber to discuss alternative treatment.

Please see full Prescribing Information enclosed including Box Warning. If you or your patients require additional medical information, please contact our Health Care Professionals at Janssen One to One[™] Customer Action Center at 1-800-JANSSEN (526-7736) 8:00 A.M. to 8:00 P.M. Eastern Time, Monday through Friday.

Sincerely,

Jan Gheuens, M.D.
Vice President, Medical Affairs
Janssen Pharmaceutica

JPI-HS-286

Janssen at Washington Crossing
1125 Trenton-Harbourton Road
Post Office Box 200
Titusville, New Jersey 08560-0200

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Tab 16

Materials on Bromfenac Sodium included
in the Briefing Information for the October
14 – 16, 1998 Meeting of the Pharmacy
Compounding Advisory Committee

FDA TALK PAPER

*Food and Drug Administration
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857*

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T98-36
June 22, 1998

Print Media: 301-327-6242
Broadcast Media: 301-327-3434
Consumer Inquiries: 800-532-4440

WYETH-AYERST LABORATORIES ANNOUNCES THE WITHDRAWAL OF DURACT FROM THE MARKET

Wyeth-Ayerst Laboratories of St. Davids, Pa. has announced that it is voluntarily withdrawing the analgesic, Duract (bromfenac) from the market. The action follows postmarketing reports of rare severe liver failure in patients in whom the drug was used for extended periods of time which was not in accordance with labeling instructions. The following may be used to respond to questions.

Duract, a non-steroidal anti-inflammatory drug (NSAID), was submitted to the Agency in 1994 and was approved in July 1997 for short term management of acute pain (use for 10 days or less). It was never approved as a treatment for longer term use for chronic conditions such as osteoarthritis or rheumatoid arthritis.

No cases of serious liver injury were reported in clinical trials, however, because there was a higher incidence of liver enzyme elevations in patients treated long term in clinical trials, the product was approved for use for 10 days or less. The information about the elevated liver enzymes was included in the product labeling.

After Duract was marketed, FDA and the company received reports of several cases of rare severe hepatitis and liver failure (some requiring transplantation) in patients taking the drug for more than 10 days.

In February 1998, in response to the reports of severe liver failure (and transplants), FDA and the company strengthened the warnings in Duract's labeling with a special black box warning and Wyeth-Ayerst issued a Dear Doctor letter. The revised label re-emphasized that patients should not take the drug for more than 10 days and alerted physicians and other health care professionals to the cases of severe hepatitis and liver failure (and cases in which patients required a transplant) in patients who had taken Duract.

Despite these efforts, the agency and the company continued to receive reports of severe injuries and death with long term use of Duract.

Given the availability of other therapies, FDA and Wyeth-Ayerst concluded that it would not be practical to implement the restrictions necessary to assure the safe use (less than 10 days) of Duract. The company and FDA agreed that it would be prudent to withdraw the drug from the market. Wyeth-Ayerst is advising doctors to discontinue prescribing and dispensing Duract immediately.

FDA is also advising patients to contact their doctors with any questions about use of the drug. Wyeth-Ayerst is providing the new information in a Dear Doctor letter to physicians, pharmacists,

and health care professionals. Questions from patients or health care professionals about the withdrawal of Duract can be addressed to Wyeth-Ayerst's hotline at 1-800-281-9260.

For more information about the withdrawal of Duract from the market, see:

- ["Dear Healthcare Professional" letter](#)
- [Wyeth-Ayerst press release](#)
- ["Questions and Answers for Withdrawal of Duract."](#)

FDA HOME PAGE

This is the retyped text of a Press Release from Wyeth-Ayerst Laboratories.

FOR IMMEDIATE RELEASE

Contacts:

Douglas Petkus (610) 971-4980

or

Audrey Ashby (610) 971-5823

DURACT VOLUNTARILY WITHDRAWN

Postmarketing reports of rare, but serious liver events associated with long-term use

ST. DAVIDS, PA -- JUNE 22, 1998 -- Wyeth-Ayerst Laboratories, a division of American Home Products Corporation (NYSE:AHP), today announced the voluntary market withdrawal of DURACT (bromfenac sodium capsules), a nonsteroidal anti-inflammatory analgesic indicated for the short-term (10 days or less) management of acute pain.

The company is taking this action based on postmarketing reports of severe hepatic failure resulting in four deaths and eight liver transplants. All but one of those 12 cases involved patients using DURACT for longer than 10 days -- the maximum recommended duration of treatment. The exception involved a patient with pre-existing significant liver disease.

"We believe this voluntary action is in the best interest of patients," says Dr. Philip de Vane, Vice President, Clinical Affairs and North American Medical Director, Wyeth-Ayerst Laboratories.

"While we continue to believe that DURACT is safe and effective when used for 10 days or less, rare but serious adverse events have been associated with DURACT when used for longer periods."

DURACT was introduced in July 1997, and approximately 2.5 million prescriptions have been dispensed -- the great majority of these for 10 days or less. In February 1998, the company and the Food and Drug Administration agreed on labeling changes to further emphasize that DURACT should be used for 10 days or less. These changes were initiated in response to earlier reports of serious events associated with longer-term use.

"Although the revised labeling reduced the number of prescriptions of longer duration and the reports of severe liver events, it did not eliminate them," says Dr. de Vane. "The company has now concluded that further steps to limit use of a potent NSAID pain reliever such as DURACT to just 10 days would not be feasible or effective. In light of these circumstances, as well as the availability of other therapies, Wyeth-Ayerst has decided to withdraw the product."

Wyeth-Ayerst has sent letters of notification to more than 600,000 health care professionals in the United States. They are being advised to stop prescribing and dispensing DURACT immediately. In addition, they have been asked to consider contacting patients who may be using the product longer than 10 days or who have a history of liver disease, and advise these patients to discontinue treatment. Patients are advised to discuss concerns related to DURACT with their physician.

A special information line, 1-800-281-9260, is available to provide answers to questions about DURACT.

Wyeth-Ayers Laboratories, a division of American Home Products Corporation, is a major research-oriented pharmaceutical company.

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This is the retyped text of a letter from Wyeth-Ayerst Laboratories.

June 22, 1998

Dear Healthcare Professional:

Wyeth-Ayerst Laboratories announced today the voluntary market withdrawal of DURACT (bromfenac sodium capsules), a nonsteroidal anti-inflammatory analgesic indicated for the short-term (10 days or less) management of acute pain. The company is taking this action based on postmarketing reports of severe hepatic failure, resulting in four deaths and eight liver transplants.

Approximately 2.5 million prescriptions have been dispensed since DURACT was launched in July 1997. The great majority of those prescriptions were for 10 days or less, a duration of treatment which we continue to believe is safe and effective. All but one of the 12 reported deaths and transplants occurred among the relatively small percentage of patients who took DURACT for more than 10 days. The exception was a person who had pre-existing significant liver disease.

In February 1998, Wyeth-Ayerst Laboratories and the Food and Drug Administration agreed on labeling changes to further emphasize that DURACT should be used for 10 days or less. These changes were initiated in response to earlier reports of serious hepatic events associated with longer-term use. After this action, the number of prescriptions for longer duration use, as well as the number of reported serious hepatic events, was reduced but not completely eliminated. The company has now concluded that further steps to limit use of a potent NSAID analgesic such as DURACT to just 10 days would not be feasible or effective. In light of these circumstances, as well as the availability of other therapies, Wyeth-Ayerst has decided to withdraw this product.

Please discontinue prescribing and dispensing DURACT immediately. You should consider contacting patients who may be taking DURACT for longer than 10 days or who have a history of liver disease. Any such patients should discontinue DURACT treatment. You or your patients may call 1-800-281-9260 with any questions regarding DURACT.

Sincerely,

Philip J. de Vane, M.D.
Vice President, Clinical Affairs
and North American Medical Director

(More information attached)

Sample Returns

Return DURACT samples to:

Wyeth-Ayerst Laboratories
Eaglepointe Center
55 North Pottstown Pike
Eagle, PA 19480

For UPS Shipping information, or if you have any other questions, please call Wyeth-Ayerst Laboratories at 1-800-281-9260.

Pharmacists will receive additional correspondence within the next few days concerning returning product for credit.

Wyeth-Ayerst Laboratories

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Tab 17

Federal Register of May 13, 2011
(76 FR 28045)

Dated: May 9, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011-11744 Filed 5-12-11; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2010-N-0355]

Agency Information Collection Activities; Announcement of Office of Management and Budget Approval; Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a collection of information entitled "Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements" has been approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995.

FOR FURTHER INFORMATION CONTACT: Denver Presley, Office of Information Management, Food and Drug Administration, 1350 Piccard Dr., PI50-400B, Rockville, MD 20850, 301-796-3793.

SUPPLEMENTARY INFORMATION: In the *Federal Register* of September 27, 2010 (75 FR 59266), the Agency announced that the proposed information collection had been submitted to OMB for review and clearance under 44 U.S.C. 3507. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. OMB has now approved the information collection and has assigned OMB control number 0910-0606. The approval expires on February 28, 2014. A copy of the supporting statement for this information collection is available on the Internet at <http://www.reginfo.gov/public/do/PRAMain>.

Dated: May 4, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011-11743 Filed 5-12-11; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-P-0128]

Determination That XIBROM (Bromfenac Ophthalmic Solution) 0.09% Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that XIBROM (bromfenac ophthalmic solution) 0.09% was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for bromfenac ophthalmic solution 0.09% if all other legal and regulatory requirements are met.

FOR FURTHER INFORMATION CONTACT: Patrick Raulerson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6368, Silver Spring, MD 20993-0002, 301-796-3522.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, a drug is removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA

for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

XIBROM (bromfenac ophthalmic solution) 0.09% is the subject of NDA 021664 held by ISTA Pharmaceuticals, Inc. (Ista), approved March 24, 2005. XIBROM is a topical nonsteroidal anti-inflammatory drug for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.

In a citizen petition dated March 1, 2011, and in a letter dated March 3, 2011, Ista informed FDA that it had discontinued shipping XIBROM (bromfenac ophthalmic solution) 0.09% as of February 28, 2011. Ista took the position that XIBROM (bromfenac ophthalmic solution) 0.09% had been discontinued for safety reasons.

After considering the citizen petition and reviewing Agency records, FDA determined under § 314.161 that XIBROM (bromfenac ophthalmic solution) 0.09% was not withdrawn for reasons of safety or effectiveness. We described the basis for this determination in our letter response to Ista's citizen petition (available on <http://www.regulations.gov> under Docket No. FDA-2011-P-0128).

Accordingly, the Agency will continue to list XIBROM (bromfenac ophthalmic solution) 0.09% in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to XIBROM (bromfenac ophthalmic solution) 0.09% may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: May 9, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011-11745 Filed 5-12-11; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-N-0005; FDA 225-09-0014]

Memorandum of Understanding Between the Food and Drug Administration and the International Anesthesia Research Society for the Strategies for Mitigating Anesthesia Related Neuro-Toxicity in Tots Public-Private Partnership

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is providing notice of an amendment to memorandum of understanding (MOU) 222-09-0014 between the International

Anesthesia Research Society (IARS) and FDA. The purpose of this MOU is to establish the framework for collaboration between the parties and to support their shared interest of promoting the safe use of anesthetics and sedatives in children. This is an amendment to this MOU to rename the SAFEKIDS (Safety of Key Inhaled and Intravenous Drugs in Pediatrics) Public-Private Partnership (PPP) to SmartTots (Strategies for Mitigating Anesthesia Related Neuro-Toxicity in Tots) PPP.

DATES: The agreement became effective March 17, 2011.

FOR FURTHER INFORMATION CONTACT:

Wendy R. Sanhai, Office of the Commissioner, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, rm. 4128, Rockville, MD 20857, 301-796-8518, Fax: 301-827-5891, Wendy.sanhai@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: In March 2009, FDA launched the SAFEKIDS Initiative to address major gaps in scientific information about the effects of anesthetics and sedatives on neurocognitive development of infants and young children. Under the framework of the SAFEKIDS Initiative,

FDA and IARS entered into MOU 222-09-0014 to develop the SAFEKIDS PPP—a collaboration among multiple stakeholders to support shared interest of promoting the safe use of anesthetics and sedatives in children.

Per this announcement, the SAFEKIDS Initiative has been renamed the FDA Pediatric Anesthesia Safety Initiative (PASI). As such, all activities supported under the former SAFEKIDS Initiative, including existing projects funded by FDA, will now be supported under PASI.

The amended MOU is intended to revise MOU 222-09-0014 to reflect the official renaming of the FDA-IARS PPP to SmartTots PPP.

In accordance with 21 CFR 20.108(c), which states that all written agreements and MOUs between FDA and others shall be published in the **Federal Register**, the Agency is publishing notice of this MOU.

Dated: May 9, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

BILLING CODE 4160-01-P

225-09-0014

MEMORANDUM OF UNDERSTANDING BY AND BETWEEN THE

UNITED STATES FOOD AND DRUG ADMINISTRATION (FDA)

AND THE

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY (IARS)

FOR

THE STRATEGIES FOR MITIGATING ANESTHESIA RELATED NEURO-TOXICITY IN TOTS

PUBLIC-PRIVATE PARTNERSHIP (SMARTTOTS PPP)

Tab 18

Letter from E. Paul Mac Carthy Re: Market
withdrawal of Baycol (cerivastatin)
(August 8, 2001)

IMPORTANT DRUG WARNING**Pharmaceutical
Division****August 8, 2001****E. Paul MacCarthy M.D., F.R.C.P.I.**
Vice President
Head U.S. Medical Science**Re: Market withdrawal of Baycol (cerivastatin)**

Dear Healthcare Professional:

I am writing to inform you of very important new safety information about Baycol (cerivastatin) and rhabdomyolysis.

Rhabdomyolysis is a serious, potentially fatal, adverse effect of all statin drugs, including Baycol. It can occur with statin monotherapy, though the risk appears to be increased significantly by concomitant use of gemfibrozil (Lopid).

Our ongoing scrutiny of post-marketing reports of rhabdomyolysis, including fatalities, has revealed an increased reporting rate of rhabdomyolysis with Baycol relative to other statins, especially when gemfibrozil is co-prescribed. These data also suggest an increased reporting rate of rhabdomyolysis at the 0.8 mg dose of Baycol alone.

Bayer Corporation has already placed a contraindication in the Baycol product prescribing information sheet against co-prescription with gemfibrozil and issued letters to healthcare professionals warning against co-prescription of these two drugs. Despite these and other actions, Bayer has continued to receive reports of rhabdomyolysis when gemfibrozil is prescribed as a co-medication. Since the co-prescription of Baycol and gemfibrozil has continued despite communications by Bayer against this practice, the company has decided to take the following voluntary action to prevent further cases of rhabdomyolysis:

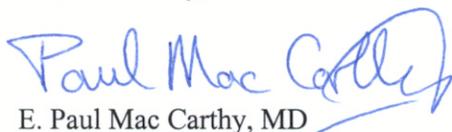
Effective immediately, Bayer has discontinued the marketing and distribution of all dosage strengths of Baycol. Patients who are currently taking Baycol should have their Baycol discontinued and be switched to an alternative therapy.

Bayer is taking this action as part of an ongoing commitment to patients and their healthcare providers to ensure patient safety.

It is important that you forward any adverse event information associated with the use of Baycol to Bayer Corporation at 1-800-288-8371. You can also report the information directly to the FDA via the MedWatch system at 1-800-FDA-1088, by mail (using a postage paid form), or the internet at www.fda.gov/medwatch.

If you have further questions regarding this action on Baycol, please contact Bayer Customer Service at 1-800-758-9794.

Yours sincerely,



E. Paul MacCarthy, MD
Vice President,
Head U.S. Medical Science

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2498
Fax: 203 812-5138
paul.maccarthy.b@bayer.com

Tab 19

FDA Talk Paper, T00-14 (March 23, 2000)
Janssen Pharmaceutica Stops Marketing
Cisapride in the US

FDA TALK PAPER

*Food and Drug Administration
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857*

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T00-14
March 23, 2000

Print Media: 301-827-6242
Broadcast Media: 301-827-3434
Consumer Inquiries: 888-INFO-FDA

JANSSEN PHARMACEUTICA STOPS MARKETING CISAPRIDE IN THE US

Janssen Pharmaceutica Inc., of Titusville, N.J., has announced that it has decided to stop marketing cisapride (Propulsid) in the United States as of July 14, 2000. The effective date of the voluntary action is intended to provide adequate time for patients and physicians to make alternative treatment decisions.

Cisapride is a prescription drug treatment approved only for severe nighttime heartburn experienced by adult patients with gastroesophageal reflux disease (GERD) that does not adequately respond to other therapies.

As of December 31, 1999, use of cisapride has been associated with 341 reports of heart rhythm abnormalities including 80 reports of deaths. Most of these adverse events occurred in patients who were taking other medications or suffering from underlying conditions known to increase risk of cardiac arrhythmia associated with cisapride.

Patients who are currently prescribed cisapride are urged to promptly contact their health care providers to discuss alternative treatments.

Physicians who are treating patients with severely debilitating conditions for whom they believe the benefits of the cisapride may still outweigh its risks are encouraged to contact Janssen at 1-800-JANSSEN. The company will continue to make the drug available to patients who meet specific clinical eligibility criteria for a limited-access protocol.

Since the drug's approval in 1993, Cisapride's labeling has been revised several times (most recently in January 2000, see [FDA Talk Paper T00-6](#)) to inform health care professionals and patients about the drug's risks. Despite these risk management efforts, the firm decided in consultation with the Food and Drug Administration that continued general US prescription access to the drug poses unacceptable risks.

A public advisory committee meeting, previously scheduled for April 12 to discuss ways to reduce the occurrence of adverse events associated with cisapride, has been cancelled.

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[FDA News Page](#) | [FDA Home Page](#)

Office of Public Affairs
Hypertext uploaded by [tg](#) 2000-MAR-23.

Tab 20

Janssen Pharmaceutica Press Release
(March 23, 2000)

ELECTRONIC MAIL MESSAGE

Sensitivity: COMPANY CONFIDENTIAL

Date: 24-Mar-2000 07:50am EST
From: Brad Leissa
LEISSAB
Dept: HFD-590 CRP2 S337
Tel No: 301-827-2186 FAX 301-827-2325

TO: 173 addressees

Subject: PROPULSID (CISAPRIDE) limited-access program

Janssen Pharmaceutica Press Release

LIMITED-ACCESS PROGRAM ANNOUNCED IN UNITED STATES TO ENSURE APPROPRIATE USE OF PROPULSID (CISAPRIDE)

Product No Longer To Be Promoted in United States

March 23, 2000 - Titusville, NJ - A limited-access program will be initiated for Propulsid (cisapride) tablets and suspension, and the product will no longer be marketed in the United States, it was announced today by Janssen Pharmaceutica of Titusville, NJ. Propulsid is a prescription treatment approved by the Food and Drug Administration (FDA) for symptomatic treatment of adults with nighttime heartburn due gastroesophageal reflux disease (GERD).

Under the new program, Propulsid will remain available to appropriate patients for whom other therapies are not effective and who meet clearly defined eligibility criteria. These criteria are being established in close collaboration with the FDA.

Information on the limited-access program will be sent to physicians across the country in April, and enrollment will begin May 1. However, to assure that the medication is available to patients during the transition, distribution will continue until July 14, and the product will remain in pharmacies until mid August. Patients who have current prescriptions for Propulsid are advised to speak with their doctors.

Since the U.S. approval of Propulsid in 1993, there have been a number of serious cardiovascular side effects in individuals who also were taking certain contraindicated medications or who had specific underlying health conditions. In an effort to ensure that the drug was being prescribed safely and appropriately, labeling changes were initiated over the past several years, making the prescribing information as detailed and specific as possible.

Despite these warnings, some inappropriate use has continued in the United States. Janssen and the FDA now believe the best way to address this situation is to limit access to the medication, while ensuring that appropriate patients who have exhausted other treatment options can still benefit from it. Propulsid remains safe and effective for the vast

...safety of patients when used according to the approved prescribing
...information.

Details regarding how the limited-access program will work -- including
eligibility criteria and the application process -- are currently being
developed by Janssen in consultation with the FDA. In the meantime,
consumers and health-care professionals with questions may call
1-800-JANSSEN from 9 a.m. to 5 p.m. Monday to Friday, Eastern Standard
Time.

Tab 21

"Dear Healthcare Provider" Letter from
Janssen Pharmaceutica (April 12, 2000)

U.S. Food and Drug Administration

DISCLAIMER: FDA posts safety alerts, public health advisories, press releases and other notices from companies as a service to health professionals, consumers and other interested parties. Although FDA approves medical products, FDA does not endorse either the product or the company.

This is the retyped text of a letter from Janssen Pharmaceutica. Contact the company for a copy of any referenced enclosures.

April 12, 2000

Dear Healthcare Provider,

Janssen Pharmaceutica would like to inform you of important changes regarding Propulsid (cisapride) Tablets and Suspension. Because of the risk of serious cardiac arrhythmias and death associated with the use of Propulsid in certain patients, Janssen, in consultation with the FDA, has decided to discontinue marketing Propulsid as of July 14, 2000 and make it available only through an investigational limited access program. Propulsid has been associated with serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. From July 1993 through December 1999, 341 such cases have been spontaneously reported, including 80 deaths. In approximately 85% of these cases the events occurred when Propulsid was used in patients with known risk factors.

Over the past few years, Janssen has implemented labeling changes and sponsored educational programs to help assure the safe and appropriate use of Propulsid. However, the level of adverse event reporting and risks associated with the drug did not sufficiently decrease. Consequently, Janssen has decided to stop marketing the drug and make it available only through an investigational limited access program. Physicians should discuss with patients their current medical condition and the option of stopping Propulsid and, if needed, the possible use of alternative therapies (such as lifestyle modifications and/or use of acid reducing agents).

For patients who fail other treatment options and who meet clearly defined eligibility criteria, Janssen is establishing an investigational limited access program. Enrollment in the investigational limited access program will begin May 1, 2000. Janssen will market the product until July 14, 2000, and the product will remain available through pharmacies until approximately mid-August 2000. Between now and July 14, 2000, physicians should reassess the need for Propulsid in each patient given the risks of the drug and available alternatives.

The following are the three treatment protocols for the investigational limited access program:

- Adults: Gastroesophageal reflux disease (GERD), gastroparesis, pseudo-obstruction, and severe chronic constipation
- Pediatrics: Refractory GERD (associated with failure to thrive, asthma, bradycardia, apnea, or other serious conditions) or pseudo-obstruction
- Neonates: Feeding intolerance

In order for patients to be enrolled in the program they must have failed all standard therapeutic

modalities and have undergone an appropriate diagnostic evaluation, including radiologic examinations or endoscopy. In addition, physicians must perform baseline screening tests, including laboratory tests and ECG to screen for contraindicated risk factors. A physician evaluation, laboratory tests, and ECG must be repeated at regular intervals according to the protocol.

The prescribing physician participating in the limited access program must be board eligible or certified in one or more of the following areas: internal medicine (including gastroenterology and cardiology), family practice, pediatrics (including neonatology) or surgery. The patient must also be under the care of a gastroenterologist by consultation, if the prescribing physician is not a gastroenterologist. Since the above protocols reflect investigational uses of Propulsid, institutional review board approval, completion of a Form FDA 1572, and signed informed consent are required.

Janssen, in consultation with the FDA, is currently finalizing all program materials. Physicians interested in enrolling patients or obtaining further information regarding the investigational limited access program should **call toll-free 1-877-795-4247 beginning May 1, 2000.**

All serious adverse events related to Propulsid's use must be reported to Janssen at 1-800-JANSSEN (526-7736) or to the FDA MedWatch Program by phone 1-800-FDA-1088, by fax 1-800-FDA-0178, by mail (using postage-paid form) MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or via www.FDA.gov/medwatch.

Please refer to the enclosed package insert for full prescribing information, including Boxed Warning. Please note that the package insert has not been revised and is enclosed for your reference and use over the next few months. For additional medical information concerning Propulsid, please call Janssen at 1-800-JANSSEN (526-7736) from 9 AM to 5 PM Eastern Time, Monday through Friday.

Sincerely,

Jan Gheuens, MD, PhD
Vice President, Medical Affairs
Janssen Pharmaceutica

Janssen Pharmaceutica Products, L.P. 2000
01-MC-XXX

Janssen Pharmaceutica
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560
1-800-JANSSEN (526-7736)

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Tab 22

Letter from Jan Gheuens, MD, PhD, Vice
President, Medical Affairs, Janssen
Pharmaceutica, to Healthcare Professional
(April 12, 2000)

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Safety

Propulsid (cisapride) Dear Healthcare Professional Letter Apr 2000

FDA posts safety alerts, public health advisories, press releases and other notices from companies as a service to health professionals, consumers and other interested parties. Although FDA approves medical products, FDA does not endorse either the product or the company.

This is the retyped text of a letter from Janssen Pharmaceutica. Contact the company for a copy of any referenced enclosures.

April 12, 2000

Dear Healthcare Provider,

Janssen Pharmaceutica would like to inform you of important changes regarding Propulsid (cisapride) Tablets and Suspension. Because of the risk of serious cardiac arrhythmias and death associated with the use of Propulsid in certain patients, Janssen, in consultation with the FDA, has decided to discontinue marketing Propulsid as of July 14, 2000 and make it available only through an investigational limited access program. Propulsid has been associated with serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. From July 1993 through December 1999, 341 such cases have been spontaneously reported, including 80 deaths. In approximately 85% of these cases the events occurred when Propulsid was used in patients with known risk factors.

Over the past few years, Janssen has implemented labeling changes and sponsored educational programs to help assure the safe and appropriate use of Propulsid. However, the level of adverse event reporting and risks associated with the drug did not sufficiently decrease. Consequently, Janssen has decided to stop marketing the drug and make it available only through an investigational limited access program. Physicians should discuss with patients their current medical condition and the option of stopping Propulsid and, if needed, the possible use of alternative therapies (such as lifestyle modifications and/or use of acid reducing agents).

For patients who fail other treatment options and who meet clearly defined eligibility criteria, Janssen is establishing an investigational limited access program. Enrollment in the investigational limited access program will begin May 1, 2000. Janssen will market the product until July 14, 2000, and the product will remain available through pharmacies until approximately mid-August 2000. Between now and July 14, 2000, physicians should reassess the need for Propulsid in each patient given the risks of the drug and available alternatives.

The following are the three treatment protocols for the investigational limited access program:

- Adults: Gastroesophageal reflux disease (GERD), gastroparesis, pseudo-obstruction, and severe chronic constipation
- Pediatrics: Refractory GERD (associated with failure to thrive, asthma, bradycardia, apnea, or other serious conditions) or pseudo-obstruction
- Neonates: Feeding intolerance

In order for patients to be enrolled in the program they must have failed all standard therapeutic modalities and have undergone an appropriate diagnostic evaluation, including radiologic examinations or endoscopy. In addition, physicians must perform baseline screening tests, including laboratory tests and ECG to screen for contraindicated risk factors. A physician evaluation, laboratory tests, and ECG must be repeated at regular intervals according to the

protocol.

The prescribing physician participating in the limited access program must be board eligible or certified in one or more of the following areas: internal medicine (including gastroenterology and cardiology), family practice, pediatrics (including neonatology) or surgery. The patient must also be under the care of a gastroenterologist by consultation, if the prescribing physician is not a gastroenterologist. Since the above protocols reflect investigational uses of Propulsid, institutional review board approval, completion of a Form FDA 1572, and signed informed consent are required.

Janssen, in consultation with the FDA, is currently finalizing all program materials. Physicians interested in enrolling patients or obtaining further information regarding the investigational limited access program should **call toll-free 1-877-795-4247 beginning May 1, 2000.**

All serious adverse events related to Propulsid's use must be reported to Janssen at 1-800-JANSSEN (526-7736) or to the FDA MedWatch Program by phone 1-800-FDA-1088, by fax 1-800-FDA-0178, by mail (using postage-paid form) MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or via www.FDA.gov/medwatch.

Please refer to the enclosed package insert for full prescribing information, including Boxed Warning. Please note that the package insert has not been revised and is enclosed for your reference and use over the next few months. For additional medical information concerning Propulsid, please call Janssen at 1-800-JANSSEN (526-7736) from 9 AM to 5 PM Eastern Time, Monday through Friday.

Sincerely,

Jan Gheuens, MD, PhD
Vice President, Medical Affairs
Janssen Pharmaceutica

Janssen Pharmaceutica Products, L.P. 2000
01-MC-XXX

Janssen Pharmaceutica
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560
1-800-JANSSEN (526-7736)

Page Last Updated: 08/03/2009

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Links on this page:

Tab 23

Federal Register of May 5, 2010
(75 FR 24710)

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹—Continued

21 CFR Section	Form Number	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
807.93		2,000	1	2,000	0.5	1,000
Totals						309,333

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

FDA has based these estimates on conversations with industry and trade association representatives, and from internal review of the documents listed in table 1 of this document.

Dated: April 29, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2010-10576 Filed 5-4-10; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2008-P-0284]

Determination That BREVIBLOC (Esmolol Hydrochloride) Injection, 250 Milligrams/Milliliter, 10-Milliliter Ampule, Was Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that BREVIBLOC (esmolol hydrochloride (HCl)) Injection, 250 milligrams (mg)/milliliter (mL), 10-mL ampule, was withdrawn from sale for reasons of safety or effectiveness. This determination means the agency will not accept or approve abbreviated new drug applications (ANDAs) for esmolol HCl injection, 250 mg/mL, 10-mL ampule.

FOR FURTHER INFORMATION CONTACT:

Olivia A. Pritzlaff, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6308, Silver Spring, MD 20993-0002, 301-796-3601.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for

which they are seeking approval contains the same active ingredient in the same strength and dosage form as the “listed drug,” which is a version of the drug that was previously approved under a new drug application (NDA). ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of an NDA. The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is generally known as the “Orange Book.” Under FDA regulations, drugs are removed from the list if the agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (section 505(j)(7)(C) of the act; 21 CFR 314.162).

FDA will not approve an ANDA if the listed drug has been withdrawn from sale for safety or effectiveness reasons (section 505(j)(4)(I) of the act). Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. A drug that has been withdrawn from the market for safety or effectiveness reasons is not a listed drug (21 CFR 314.3(b)). FDA may not approve an ANDA that does not refer to a listed drug.

BREVIBLOC (esmolol HCl) Injection is the subject of NDA 19-386, held by Baxter Healthcare Corp. (Baxter). BREVIBLOC is a beta₁-selective adrenergic receptor-blocking agent with a short duration of action. BREVIBLOC is approved for the treatment of supraventricular tachycardia. BREVIBLOC is also indicated for treatment of intraoperative and

postoperative tachycardia and/or hypertension.

Baxter currently markets 4 product presentations of BREVIBLOC Injection—10-mg/mL and 20-mg/mL ready-to-use vials and 10-mg/mL and 20-mg/mL premixed injection bags. Baxter has discontinued marketing the following two product presentations of BREVIBLOC (esmolol HCl) Injection:

- In 2003, Baxter discontinued BREVIBLOC (esmolol HCl) Injection, 10 mg/mL (formulation without sodium chloride), and FDA determined that this presentation of BREVIBLOC Injection was not withdrawn from sale for reasons of safety or effectiveness (69 FR 47155, August 4, 2004).

- In 2007, Baxter discontinued BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule. In a letter dated June 28, 2007, Baxter informed the agency that the company had decided to cease manufacture and distribution of BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule, because the product demonstrated a higher risk of medication errors that may potentially result in serious outcomes. Baxter observed that serious adverse events were associated with the following medication errors:

- Mixups between the ready-to-use 10-mg/mL vial and the 250-mg/mL, 10-mL ampule concentrate;
- Use of undiluted 250-mg/mL, 10-mL ampule concentrate;
- Dilution calculation errors with the 250-mg/mL, 10-mL ampule concentrate; and

- Administration of the wrong drug.

In a Dear Healthcare Professional letter dated August 20, 2007, Baxter stated that their decision to cease manufacture of BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule, was made after thorough review of adverse event reports, clinical usage studies, input from clinicians, and initiatives to reduce medication errors.

In a citizen petition dated March 27, 2008 (Docket No. FDA-2008-P-0284), submitted under 21 CFR 10.30 and in accordance with 21 CFR 314.122 and 314.161, Bedford Laboratories (Bedford) requested that the agency determine

whether BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule, was withdrawn from sale for reasons of safety or effectiveness. Bedford noted that Baxter has publicly stated that the product was discontinued due to safety issues surrounding medication errors and asked the agency to determine the cause of the discontinuation.

We have carefully reviewed our files for records concerning the withdrawal from sale of BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule, including the NDA file for this drug product. We have also independently evaluated relevant literature and data for possible postmarketing adverse event reports. FDA's review shows that the product was withdrawn from sale because of reports of serious adverse events, including deaths.

Although the application holder has made several labeling revisions (including a warning sticker on the ampule) and issued Dear Healthcare Provider letters to reduce the potential for medication errors, there have been additional reports of medication errors. In addition, alternative presentations of the product are available that are not associated with the same potential for medication errors.

After considering the citizen petition (and comments submitted) and reviewing agency records concerning the drug product, analyses of adverse event reports, and relevant literature, FDA has determined under § 314.161 that BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule, was withdrawn from sale for reasons of safety or effectiveness. FDA has reviewed the latest approved labeling for BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule, and has determined that this labeling is inadequate to reduce medication errors to an acceptable level. FDA has determined that Human Factors studies (i.e., Failure Mode and Effects Analysis and usability studies to test the product in a typical practice setting) are necessary before this product could be considered for reintroduction to the market.

Therefore, the agency has determined, under § 314.161, that BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule, was withdrawn from sale for reasons of safety. BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule, will be removed from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule.

Dated: April 30, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2010-10559 Filed 5-4-10; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration

Fiscal Year (FY) 2010 Funding Opportunity

AGENCY: Substance Abuse and Mental Health Services Administration, HHS.

ACTION: Notice of intent to award a Single Source Grant to the grantee of the Technical Assistance Center for Mental Health Promotion and Youth Violence Prevention.

SUMMARY: This notice is to inform the public that the Substance Abuse and Mental Health Services Administration (SAMHSA) intends to award approximately \$620,000 for up to three years to the grantee of the Technical Assistance Center for Mental Health Promotion and Youth Violence Prevention. This is not a formal request for applications. Assistance will be provided only to the current grantee of the Technical Assistance Center for Mental Health Promotion and Youth Violence Prevention based on the receipt of a satisfactory application that is approved by an independent review group.

Funding Opportunity Title: SM-10-018.

Catalog of Federal Domestic Assistance (CFDA) Number: 93.243.

Authority: Section 520A of the Public Health Service Act, as amended.

Justification: Only an application from the grantee for the Technical Assistance Center for Mental Health Promotion and Youth Violence Prevention will be considered for funding under this announcement. Three-year funding has become available to assist because this funding supplement is intended to support the technical assistance needs of Project LAUNCH grantees to be newly funded in FY 2010. The current grantee provides technical assistance to the other cohorts for Project LAUNCH and is in a unique position to address the grant implementation needs of communities to be funded this fiscal year. There is no other potential organization with the required access and expertise.

Eligibility for this program supplement is restricted to the current

grantee, Technical Assistance Center for Mental Health Promotion and Youth Violence Prevention. This supplement will serve to maximize efficiencies created under the current services infrastructure. It would be inefficient and duplicative to fund additional technical assistance services for Project LAUNCH grantees through a second organization.

Contact: Shelly Hara, Substance Abuse and Mental Health Services Administration, 1 Choke Cherry Road, Room 8-1095, Rockville, MD 20857; telephone: (240) 276-2321; E-mail: shelly.hara@samhsa.hhs.gov.

Toian Vaughn,

SAMHSA Committee Management Officer.

[FR Doc. 2010-10502 Filed 5-4-10; 8:45 am]

BILLING CODE 4162-20-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2004-N-0451] (formerly Docket No. 2004N-0226)

Food and Drug Administration Modernization Act of 1997: Modifications to the List of Recognized Standards, Recognition List Number: 023

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing a publication containing modifications the agency is making to the list of standards FDA recognizes for use in premarket reviews (FDA recognized consensus standards). This publication, entitled "Modifications to the List of Recognized Standards, Recognition List Number: 023" (Recognition List Number: 023), will assist manufacturers who elect to declare conformity with consensus standards to meet certain requirements for medical devices.

DATES: Submit written or electronic comments concerning this document at any time. See section VII of this document for the effective date of the recognition of standards announced in this document.

ADDRESSES: Submit written requests for single copies of "Modifications to the List of Recognized Standards, Recognition List Number: 023" to the Division of Small Manufacturers, International, and Consumer Assistance, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66,

Tab 24

Federal Register of September 10, 2003
(68 FR 53384)

Programs (HFA-250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-1223.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of June 11, 2003 (68 FR 34979), the agency announced that the proposed information collection had been submitted to OMB for review and clearance under 44 U.S.C. 3507. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. OMB has now approved the information collection and has assigned OMB control number 0910-0021. The approval expires on August 31, 2006. A copy of the supporting statement for this information collection is available on the Internet at <http://www.fda.gov/ohrms/dockets>.

Dated: September 3, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03-22958 Filed 9-9-03; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 1994P-0036]

Agency Information Collection Activities; Announcement of Office of Management and Budget Approval; Food Labeling; Trans Fatty Acids in Nutrition Labeling; Nutrient Content Claims and Health Claims

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a collection of information entitled "Trans Fatty Acids in Nutrition Labeling; Nutrient Content Claims and Health Claims" has been approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995.

FOR FURTHER INFORMATION CONTACT: Peggy Robbins, Office of Management Programs (HFA-250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-1223.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of July 11, 2003 (68 FR 41434 at 41497), the agency announced that the proposed information collection had been submitted to OMB for review and clearance under 44 U.S.C. 3507. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it

displays a currently valid OMB control number. OMB has now approved the information collection and has assigned OMB control number 0910-0515. The approval expires on July 31, 2006. A copy of the supporting statement for this information collection is available on the Internet at <http://www.fda.gov/ohrms/dockets>.

Dated: September 3, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03-22959 Filed 9-9-03; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003N-0075]

Agency Information Collection Activities; Announcement of Office of Management and Budget Approval; Administrative Detention and Banned Medical Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a collection of information entitled "Administrative Detention and Banned Medical Devices" has been approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995.

FOR FURTHER INFORMATION CONTACT: Peggy Robbins, Office of Management Programs (HFA-250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-1223.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of June 25, 2003 (68 FR 37846), the agency announced that the proposed information collection had been submitted to OMB for review and clearance under 44 U.S.C. 3507. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. OMB has now approved the information collection and has assigned OMB control number 0910-0114. The approval expires on August 31, 2006. A copy of the supporting statement for this information collection is available on the Internet at <http://www.fda.gov/ohrms/dockets>.

Dated: September 3, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03-22960 Filed 9-9-03; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003N-0198]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Requirements for Medicated Feed Mill License; Correction

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; correction.

SUMMARY: The Food and Drug Administration (FDA) is correcting a notice that appeared in the **Federal Register** of August 8, 2003 (68 FR 47331). The document announced the submission of the proposed collection of information entitled "Requirements for Medicated Feed Mill License" to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995. The document was published with an inadvertent error. This document corrects that error.

DATES: Effective September 10, 2003.

FOR FURTHER INFORMATION CONTACT: Denver Presley, Office of Information Resources Management (HFA-250), Food and Drug Administration, 5600 Fishers Lane, rm. 4B-41, Rockville, MD 20857, 301-827-1472.

SUPPLEMENTARY INFORMATION: In FR Doc. 03-20201, appearing on page 47331 in the **Federal Register** of Friday, August 8, 2003, the following correction is made:

1. On page 47332, in the second column, the title "Medicated Feed Mill License Application—21 CFR Part 515 (OMB Control Number 0910-0037)" is corrected to read "Medicated Feed Mill License Application—21 CFR Part 515 (OMB Control Number 0910-0337)".

Dated: September 3, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03-22957 Filed 9-9-03; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003N-0384]

Hoffmann-La Roche, Inc.; Withdrawal of Approval of a New Drug Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of a new drug application (NDA) for TEGISON (etretinate) Capsules held by Hoffmann-La Roche, Inc., 340 Kingsland St., Nutley, NJ 07110. Hoffmann-La Roche has requested that approval of this application be withdrawn because the product is no longer marketed, thereby waiving its opportunity for a hearing.

DATES: Effective September 10, 2003.

FOR FURTHER INFORMATION CONTACT: Florine P. Purdie, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: In a letter dated September 23, 1999, Hoffmann-La Roche requested that FDA withdraw approval of NDA 19-369 for TEGISON (etretinate) Capsules, stating that it had discontinued marketing the product. The letter also stated that TEGISON had been replaced by NDA 19-821 for SORIATANE (acitretin) and that TEGISON was not withdrawn for safety reasons. In FDA's acknowledgment letter of December 30, 2002, the agency informed Hoffmann-La Roche that TEGISON (etretinate) Capsules, a treatment for psoriasis, was removed from the market, under § 314.150(d) (21 CFR 314.150(d)), because it poses a greater risk of birth defects than SORIATANE (acitretin), the product that replaced TEGISON. Acitretin, the active metabolite of etretinate, has a much shorter half-life than etretinate. Thus, acitretin poses a risk of serious birth defects for a shorter period of time than etretinate after a woman stops taking the drug product. Hoffmann-La Roche waived its opportunity for a hearing, provided under § 314.150(a) and (b).

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(e)) and under authority delegated to the Director, Center for Drug Evaluation and Research (21 CFR 5.105(a)), approval of NDA 19-369, and all amendments and supplements thereto, is hereby withdrawn, effective September 10, 2003.

Distribution of this product in interstate commerce without an approved application is illegal and subject to regulatory action (see sections

505(a) and 301(d) of the act (21 U.S.C. 355(a) and 331(d)).

Dated: August 5, 2003.

Steven K. Galson,

Deputy Director, Center for Drug Evaluation and Research.

[F.R. Doc. 03-22956 Filed 9-9-03; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Technical Electronic Product Radiation Safety Standards Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Technical Electronic Product Radiation Safety Standards Committee.

General Function of the Committee: To provide advice on technical feasibility, reasonableness, and practicality of performance standards for electronic products to control the emission of radiation under 21 U.S.C. 360kk(f).

Date and Time: The meeting will be held on October 1, 2003, from 8:30 a.m. to 5 p.m.

Location: Hilton Washington DC North/Gaithersburg, Salons A and B, 620 Perry Pkwy., Gaithersburg, MD.

Contact Person: Richard Kaczmarek, Center for Devices and Radiological Health (HFZ-240), Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850, 301-594-0865, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12399. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committee will hear an informal review of ongoing activities associated with electronic products.

Following the overview, FDA will discuss proposed amendments to the U.S. performance standard for sunlamp products (21 CFR 1040.20) and certain initiatives of international standards

organizations concerning sunlamp products.

In the afternoon, there will be a presentation regarding proposed amendments to the diagnostic x-ray system performance standard (21 CFR 1020.30). Following this, the final topic will be public health considerations of x-ray security screening systems and the development of policies for safe use of these systems.

Background information on the discussion topics will be posted under the Technical Electronic Product Radiation Safety Standards Committee (TEPRSSC) Docket site at <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>. (Click on the year 2003 and scroll down to TEPRSSC.)

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by September 19, 2003. Oral presentations from the public will be scheduled between approximately 10:45 a.m. and 11:30 a.m., and between 3 p.m. and 3:45 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before September 19, 2003, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Persons attending FDA's advisory committee meetings are advised that the agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact Shirley Meeks, Conference Management Staff, at 301-594-1283, ext. 105, at least 7 days in advance of the meeting.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: September 3, 2003.

Peter J. Pitts,

Associate Commissioner for External Relations.

[F.R. Doc. 03-22961 Filed 9-9-03; 8:45 am]

BILLING CODE 4160-01-S

Tab 25

Federal Register of February 3, 2006
(71 FR 5858)

mental health issues, in particular, was found to be one of the weakest in the CFRs. Areas of interest for research may examine CPS procedures for identifying and responding to children's mental health issues as well as the prevalence, type and severity of mental health problems among children identified in State child welfare systems. In addition, findings from the National Survey of Child and Adolescent Well-Being (NSCAW) show that high rates of mental health problems among parents, coupled with low rates of identification and referral, is a serious issue. CB is interested in research that examines mental health services to parents.

Program Evaluation of Priority Area Initiatives (or Evaluation of Programs Addressing Administration Priorities): The current Administration has focused funding in areas of healthy marriage promotion, fatherhood initiatives, community and faith-based organizations and youth development in ensuring the healthy development of children. CB is interested in research to evaluate programs employing these strategies to prevent child abuse and neglect. Research topics may include the evaluation of the effectiveness of these programs as well as the dissemination of promising practices.

Secondary Data Analysis: CB encourages the utilization of existing data sources particularly the use of service data through the National Child Abuse and Neglect Data System (NCANDS). CB is interested in secondary data analyses using NCANDS focusing on service utilization, recurrence and perpetrators.

Service utilization: While not all States provide complete service data to NCANDS, for those States that do provide complete service data, the following areas could be examined: The services that are most often provided to victims of maltreatment; differences in service patterns that exist between children who are first-time victims and children who are repeat victims; differences in service patterns that exist between child victims who remain in their homes and those who are removed; and the variations in service patterns within States according to county characteristics.

Recurrence: To date, recurrence has largely been examined for six-month periods using NCANDS data. The Office of the Assistant Secretary for Planning and Evaluation undertook a longitudinal analysis of NCANDS data examining repeated CPS involvement. Using a multiyear dataset of 1,396,998 children, this research examined the proportion of reported children who re-reported,

the proportion of child victims who had a recurrence of maltreatment and the factors associated with these repeated events. The findings showed that re-reporting was relatively common—about one-third of children had at least one repeated report of maltreatment within a five-year period. For the most part, the same factors were related to both re-reporting of all reported children and recurrence among victims of maltreatment. Findings were also similar when analyses examined only the presence of a single subsequent event or the number and type of multiple subsequent events. Both re-reporting and recurrence occurred more frequently among younger children. Re-reporting and recurrence were more likely to occur in a short time following the initial maltreatment report, usually within a few months. Most children who experienced more than one re-report or re-victimization experienced these events within a short time after the initial event. Areas for further research might examine: Factors that are predictive of a second investigation; report sources that are the most likely to be associated with a second investigation; services that decrease subsequent investigation; and services that decrease subsequent victimization.

Perpetrators: CB continues to be interested in perpetrators, with the notion that understanding who this group is and what their characteristics are, can help to inform more effective intervention and prevention efforts. The Office of the Assistant Secretary for Planning and Evaluation undertook an analysis of NCANDS data examining some of these questions. The analysis focused on male perpetrators of child maltreatment and identifies clear subgroups of male perpetrators. The findings suggest that interventions of all types may need to be more highly differentiated for these different groups. Follow-up of interest includes research to gain a clearer picture of how the various categories of perpetrators fit within households to provide insights into the service and recidivism outcomes.

C. Field Initiated Research on Child Abuse and Neglect

The generation of new knowledge for understanding critical issues in child abuse and neglect improves prevention, identification, assessment and treatment. Research areas to be addressed may be those that will expand the current knowledge base, build on prior research, contribute to practice enhancements, inform policy, improve science and provide insights into new approaches to the assessment,

prevention, intervention and treatment of child maltreatment (i.e., physical abuse, sexual abuse, emotional maltreatment or neglect) on any of the topics listed in (A) Legislative Topics, (B) Other Topics, above, or any other child maltreatment topic.

In addition to the topics cited above, practitioners and researchers are encouraged to propose other relevant subjects for research topics in child abuse and neglect.

Joan E. Ohl,

Commissioner, Administration on Children, Youth and Families.

[FR Doc. E6-1480 Filed 2-2-06; 8:45 am]

BILLING CODE 4184-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2005P-0023]

Determination That TEQUIN (Gatifloxacin) Injection, 10 Milligrams per Milliliter (200 Milligrams), Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that TEQUIN (gatifloxacin) injection, 10 milligrams (mg) per milliliter (mL) (200 mg), was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for gatifloxacin injection, 10 mg/mL (200 mg).

FOR FURTHER INFORMATION CONTACT: Elaine Tseng, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (the 1984 amendments) (Pub. L. 98-417), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is typically a version of the drug that was previously approved. Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise

necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book." Under FDA regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

Under 21 CFR 314.161(a)(1), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

TEQUIN (gatifloxacin) injection, 10 mg/mL (200 mg), is the subject of approved NDA 21-062 held by Bristol-Myers Squibb. TEQUIN (gatifloxacin) injection, 10 mg/mL (200 mg), is an antibiotic used to treat adults with lung, sinus, or urinary tract infections.

FDA approved the NDA for TEQUIN (gatifloxacin) injection, 10 mg/mL (200 mg) and 10 mg/mL (400 mg), on December 17, 1999. On January 27, 2003, FDA received revised product labeling relating to several approved supplements for TEQUIN (gatifloxacin). This revised labeling deleted references to TEQUIN (gatifloxacin) injection, 10 mg/mL (200 mg), indicating that this product was no longer being marketed. Therefore, it was moved from the prescription drug product list to the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness.

Apotex Corp., submitted a citizen petition dated January 13, 2005 (Docket No. 2005P-0023/CP1), under 21 CFR 10.30, requesting that the agency determine whether TEQUIN (gatifloxacin) injection, 10 mg/mL (200 mg), was withdrawn from sale for reasons of safety or effectiveness. After considering the citizen petition and reviewing agency records, FDA has determined that TEQUIN (gatifloxacin)

injection, 10 mg/mL (200 mg), approved under NDA 21-062, was not withdrawn from sale for reasons of safety or effectiveness. The petitioner identified no data or other information suggesting that TEQUIN (gatifloxacin) injection, 10 mg/mL (200 mg), was withdrawn from sale as a result of safety or effectiveness concerns. FDA's independent evaluation of relevant literature and data has not uncovered anything that would indicate that this product was withdrawn for reasons of safety or effectiveness. Accordingly, the agency will continue to list TEQUIN (gatifloxacin) injection, 10 mg/mL (200 mg), in the "Discontinued Drug Product List" section of the Orange Book. ANDAs that refer to TEQUIN (gatifloxacin) injection, 10 mg/mL (200 mg), may be approved by the agency.

Dated: January 27, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. E6-1475 Filed 2-2-06; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2004E-0389]

Determination of Regulatory Review Period for Purposes of Patent Extension; SURPASS

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for SURPASS and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that animal drug product. **ADDRESSES:** Submit written comments and petitions to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Claudia V. Grillo, Office of Regulatory Policy (HFD-013), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 240-453-6681.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417)

and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100-670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For animal drug products, the testing phase begins on the earlier date when either a major environmental effects test was initiated for the drug or when an exemption under section 512(j) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b(j)) became effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the animal drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for an animal drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(4)(B).

FDA recently approved for marketing the animal drug product SURPASS (diclofenac sodium). SURPASS is indicated for the control of pain and inflammation associated with osteoarthritis in tarsal, carpal, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal (hock, knee, fetlock, and pastern) joints in horses. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for SURPASS (U.S. Patent No. 4,937,078) from Mezei Associates, Ltd., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated April 8, 2005, FDA advised the Patent and Trademark Office that this animal drug product had undergone a regulatory review period and that the approval of SURPASS represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

Tab 26

Federal Register of September 9, 2008
(73 FR 52357)

scheduled for the meeting; or you may contact the Board's Web site at <http://www.federalreserve.gov> for an electronic announcement that not only lists applications, but also indicates procedural and other information about the meeting.

Board of Governors of the Federal Reserve System, September 5, 2008.

Robert deV. Frierson,

Deputy Secretary of the Board.

[FR Doc. E8-20989 Filed 9-5-08; 4:15 pm]

BILLING CODE 6210-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA-2006-P-0081 (formerly Docket No. 2006P-0178) and FDA-2005-P-0369 (formerly Docket No. 2005P-0023)]

Determination That TEQUIN (Gatifloxacin) Was Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that TEQUIN (gatifloxacin) Tablets, Injection, and Oral Suspension, were withdrawn from sale for reasons of safety or effectiveness. This

determination means that FDA will not accept or approve abbreviated new drug applications (ANDAs) for gatifloxacin oral tablets, injection, or oral suspension that refer to any previously approved dosage forms and strengths of TEQUIN (gatifloxacin).

FOR FURTHER INFORMATION CONTACT:

Elena Cohen, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6228, Silver Spring, MD 20993-0002, 301-796-3602.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved under a new drug application (NDA). ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of an NDA. The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal

Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book." Drugs are removed from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (section 505(j)(7)(C) of the act; § 314.162 (21 CFR 314.162)).

FDA will not approve an ANDA if the listed drug has been withdrawn from sale for safety or effectiveness reasons (section 505(j)(4)(I) of the act). Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. A drug that has been withdrawn from the market for safety or effectiveness reasons is not a listed drug (21 CFR 314.3(b)). FDA may not approve an ANDA that does not refer to a listed drug. FDA currently has pending one or more ANDAs that refer to TEQUIN (gatifloxacin).

Bristol-Myers Squibb Co. (BMS) is the holder of three NDAs¹ for TEQUIN tablets, injection, and oral suspension as listed in the following table:

TABLE 1.—APPROVED TEQUIN PRODUCTS

NDA No.	Active Ingredients	Strength	Dosage Form/Route
21-061	Gatifloxacin	200 milligrams (mg)	Tablet; oral
21-061	Gatifloxacin	400 mg	Tablet; oral
21-062	Gatifloxacin	Equivalent to 10 mg/milliliter (mL) (200 mg)	Injectable; injection
21-062	Gatifloxacin	400 mg/40 mL (10 mg/mL)	Injectable; injection
21-062	Gatifloxacin in dextrose 5% in plastic container	200 mg/100 mL (2 mg/mL)	Injectable; injection
21-062	Gatifloxacin in dextrose 5% in plastic container	400 mg/200mL (2 mg/mL)	Injectable; injection
21-678	Gatifloxacin	200 mg/5 mL	Suspension; oral

TEQUIN is an antibacterial drug indicated for the treatment of infections

due to susceptible strains of designated microorganisms in the following

conditions: Acute bacterial exacerbation of chronic bronchitis; acute sinusitis;

¹ On December 17, 1999, FDA approved NDAs 21-061 and 21-062 for community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute bacterial sinusitis, uncomplicated urinary tract infections, complicated urinary tract infections, pyelonephritis, and uncomplicated gonorrhea. The December 17, 1999, approval letter also stated that indications for uncomplicated skin

and skin structure infections were approvable pending the submission of certain postmarketing data. For administrative purposes, the agency assigned administrative NDAs 21-404 (TEQUIN Tablets) and 21-405 (TEQUIN Injections) for the treatment of uncomplicated skin and skin structure infections. BMS provided a complete response, and upon approval on October 17, 2002, NDAs 21-404

and 21-405 were retired by FDA. The approvals and all other submissions for the treatment of uncomplicated skin and skin structure infections were incorporated in the original NDAs, 21-061 and 21-062. NDAs 21-404 and 21-405 are not listed in the Orange Book, but can be found through a search at Drugs@FDA.

community-acquired pneumonia; uncomplicated skin and skin structure infections; uncomplicated and complicated urinary tract infections; pyelonephritis; uncomplicated urethral and cervical gonorrhea; and acute, uncomplicated rectal infections in women.

In January 2003, FDA received revised product labeling relating to several approved supplements for TEQUIN (gatifloxacin). This revised labeling deleted references to TEQUIN injection, 10 milligrams/milliliter (mg/mL) (200 mg), indicating that this product was no longer being marketed; therefore, the product was moved from the prescription drug product list to the "Discontinued Drug Product List" section of the Orange Book. In response to a citizen petition from Apotex Corp. (Docket No. FDA-2005-P-0369),² FDA stated, in the **Federal Register** of February 3, 2006 (71 FR 5858), that TEQUIN injection, 10 mg/mL (200 mg), was not withdrawn for reasons of safety and effectiveness.

On May 1, 2006, Public Citizen Research Group submitted a citizen petition (Docket No. FDA-2006-P-0081),³ under 21 CFR 10.30, requesting that FDA immediately ban TEQUIN because of the increased risk of dysglycemia (hypoglycemia, low blood sugar, and hyperglycemia, high blood sugar) in humans. Public Citizen states that it reached its conclusion based on: (1) The relatively high numbers and rates of gatifloxacin-associated dysglycemia adverse event reports calculated from data collected by FDA's Adverse Event Reporting System (AERS) and Health Canada's Adverse Drug Reaction Monitoring Program; (2) a study by Park-Wyllie et al., published in March 2006 in the *New England Journal of Medicine*, that showed that patients (diabetic and nondiabetic) receiving gatifloxacin had approximately 17 times the odds of having a hyperglycemic episode and 4 times the odds of having a hypoglycemic episode compared to those taking macrolide antibiotics; and (3) the relatively high numbers and rates of gatifloxacin-associated dysglycemic events in the manufacturer's safety studies in uninfected patients and other studies in infected patients, including clinical trials, cohort studies, case-

control studies, postmarketing surveillance studies, and case reports.

In June 2006, BMS announced that it would no longer market TEQUIN. In light of pending ANDAs and the citizen petition, FDA examined whether all TEQUIN products, including TEQUIN (gatifloxacin) injection, 10 mg/mL (200 mg), were withdrawn from the market for reasons of safety or effectiveness. After considering the citizen petition and reviewing agency records concerning the drug product, analyses of AERS reports, and relevant literature, FDA has determined under § 314.161 that TEQUIN was withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will remove all TEQUIN products from the Orange Book (§ 314.162). FDA will not accept or approve ANDAs that refer to these drug products.

Therefore, the agency has determined, under § 314.161, that all dosage forms and strengths of TEQUIN (gatifloxacin) listed in the table of this document were withdrawn from sale for reasons of safety. TEQUIN (gatifloxacin) will be removed from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to any dosage form or strength of TEQUIN (gatifloxacin).

Dated: September 2, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8-20938 Filed 9-8-08; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2004-N-0451] (formerly FDA-2004-N-0226)

Food and Drug Administration Modernization Act of 1997: Modifications to the List of Recognized Standards, Recognition List Number: 020

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing a publication containing modifications the agency is making to the list of standards FDA recognizes for use in premarket reviews (FDA recognized consensus standards). This publication, entitled "Modifications to the List of Recognized Standards, Recognition List Number: 020" (Recognition List Number: 020), will assist manufacturers

who elect to declare conformity with consensus standards to meet certain requirements for medical devices.

DATES: Effective September 9, 2008. Submit written or electronic comments concerning this document at any time.

ADDRESSES: Submit written requests for single copies of "Modifications to the List of Recognized Standards, Recognition List Number: 020" to the Division of Small Manufacturers, International and Consumer Assistance, Center for Devices and Radiological Health (CDRH) (HFZ-220), Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850. Send two self-addressed adhesive labels to assist that office in processing your requests, or fax your request to 240-276-3151. Submit written comments concerning this document, or recommendations for additional standards for recognition, to the contact person (see **FOR FURTHER INFORMATION CONTACT**). Submit electronic comments to standards@cdrh.fda.gov. This document may also be accessed on FDA's Internet site at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/cdrhnew.cfm>. See section VI of this document for electronic access to the searchable database for the current list of FDA recognized consensus standards, including Recognition List Number: 020 modifications and other standards related information.

FOR FURTHER INFORMATION CONTACT: Carol L. Herman, Center for Devices and Radiological Health (HFZ-84), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 240-276-8714.

SUPPLEMENTARY INFORMATION:

I. Background

Section 204 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115) amended section 514 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360d). Amended section 514 allows FDA to recognize consensus standards developed by international and national organizations for use in satisfying portions of device premarket review submissions or other requirements.

In a notice published in the **Federal Register** of February 25, 1998 (63 FR 9561), FDA announced the availability of a guidance entitled "Recognition and Use of Consensus Standards." The document described how FDA would implement its standard recognition program and provided the initial list of recognized standards.

Modifications to the initial list of recognized standards, as published in

² This citizen petition was originally assigned docket number 2005P-0023/CP1. The number was changed to FDA-2005-P-0369 as a result of FDA's transition to its new docketing system (*Regulations.gov*) in January 2008.

³ This citizen petition was originally assigned docket number 2006P-0178. The number was changed to FDA-2006-P-0081 as a result of FDA's transition to its new docketing system (*Regulations.gov*) in January 2008.

Tab 27

Glaxo Wellcome Press Release
(October 27, 1999) announcing the
voluntary withdrawing of its oral
fluoroquinolone antibiotic, Raxar
(grepafloxacin)

Press Release

27 October 1999 **Glaxo Wellcome voluntarily withdraws Raxar (Grepafloxacin)**

Glaxo Wellcome plc announces that it is voluntarily withdrawing its oral fluoroquinolone antibiotic, Raxar (grepafloxacin), with immediate effect, as a result of emerging safety concerns. In coming to this decision the company has recognised the need to strike a balance between the therapeutic benefits of the medicine, the potential risk of side effects, and the availability of alternative treatments.

An estimated 2.65 million patient treatments have been prescribed since Raxar was first marketed in August 1997. In line with the company's practice, Glaxo Wellcome has monitored the safety profile of Raxar since launch, and has observed a small number of severe cardiovascular events among patients. While the reported incidence of such cardiovascular events is infrequent, the company is no longer convinced that the benefits of Raxar outweigh the potential risk to patients, given the availability of alternative antibiotics.

Glaxo Wellcome has discussed the safety profile of Raxar with the appropriate regulatory authorities and cardiovascular medical specialists. The decision to withdraw the medicine has been taken on the recommendation of Glaxo Wellcome's senior medical review group, and the company is in the process of informing doctors and pharmacists of the decision in countries where Raxar is marketed.

Raxar is indicated for the treatment of a variety of infections including pneumonia, bronchitis, and some sexually transmitted infections. Glaxo Wellcome licensed Raxar from Otsuka in 1996, and currently markets the medicine in tablet form in over 30 countries, primarily in Europe, North America and Latin America. A co-marketing agreement exists between the two companies in Spain. The medicine is marketed as Raxar or Vaxar.

Glaxo Wellcome is a research-based company whose people are committed to fighting disease by bringing innovative medicines and services to patients throughout the world and to the healthcare providers who serve them.

For further information health professionals may call 1-888-825-5249 (added by MedWatch, FDA)

Tab 28

"Dear Healthcare Provider" Letter from
Glaxo Wellcome (November 1, 1999)
announcing voluntary withdrawing of all
licensed formulations of RAXAR

U.S. Food and Drug Administration

DISCLAIMER: FDA posts safety alerts, public health advisories, press releases and other notices from companies as a service to health professionals, consumers and other interested parties. Although FDA approves medical products, FDA does not endorse either the product or the company.

This is the retyped text of a letter from Glaxo Wellcome. Contact the company for a copy of any referenced enclosures.

November 1, 1999

Dear Health Care Provider:

Withdrawal of Product: RAXAR((grepafloxacin HCl) 600 mg Tablets, 400 mg Tablets, and 200 mg Tablets

Glaxo Wellcome has voluntarily withdrawn all licensed formulations of RAXAR and the product is no longer available from pharmacies.

RAXAR is a fluoroquinolone antibiotic indicated for the treatment of infections caused by strains of bacteria susceptible to grepafloxacin in the following diseases: community-acquired pneumonia; acute bacterial exacerbations of chronic bronchitis; uncomplicated gonorrhea (urethral in males and endocervical and rectal in females); non-gonococcal urethritis and cervicitis.

Glaxo Wellcome has recently concluded an extensive review of the safety of RAXAR and determined that due to an effect of RAXAR on cardiac repolarization, manifested as QT interval prolongation on the electrocardiogram (ECG), some patients may be at risk of a very rare but serious ventricular arrhythmia known as torsade de pointes when treated with the product.

Although torsade de pointes has been reported very rarely in patients taking RAXAR, it is considered by the Company that the therapeutic benefit of treatment with RAXAR may be outweighed by the potential risk to patient safety, especially given the availability of alternative treatments.

For patients already commenced on a course of RAXAR, careful consideration should be given to switching the patient to an alternative antibiotic therapy.

If you have any samples of RAXAR in your possession, you may either contact Glaxo Wellcome to request self-addressed, postage-paid boxes to facilitate returning samples to Glaxo Wellcome, or you may dispose of any remaining RAXAR samples in the usual and customary way that you dispose of expired or damaged samples.

If you would like to request boxes, or for more information, please contact the Glaxo Wellcome Customer Response Center at telephone number 1-888-TALK-2-GW (888-825-5249).

Sincerely,

Richard S. Kent, MD
Vice President - US Medical Operations
Glaxo Wellcome Inc.

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Tab 29

Federal Register of June 14, 2007
(72 FR 32852)

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹—Continued

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
Request for reconsideration of a decision	5	1 time for each application	5	2	10
Request for review—(user fee appeal officer)	2	1 time for each application	2	2	4
Total					60

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

Based on FDA's database system, there are an estimated 250 sponsors of products subject to ADUFA. However, not all sponsors will have any submissions in a given year and some may have multiple submissions. The total number of waiver requests is based on the number of submission types received by FDA in fiscal year 2003. FDA's Center for Veterinary Medicine estimates 30 waiver requests that include the following: 5 significant barriers to innovation, 1 fee exceed cost, 5 free choice feeds, 10 minor use or minor species, 2 small business waiver requests, 5 requests for reconsideration of a decision, and 2 requests for user fee appeal officer. The estimated hours per response are based on past FDA experience with the various waiver requests in FDA's Center for Drug Evaluation and Research. The hours per response are based on the average of these estimates.

Dated: June 7, 2007.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. E7-11425 Filed 6-13-07; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2007N-0221]

Otsuka Pharmaceutical Co., Ltd.; Withdrawal of Approval of a New Drug Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of a new drug application (NDA) for RAXAR (grepafloxacin hydrochloride (HCl)) Tablets held by Otsuka Pharmaceutical Co., Ltd. (Otsuka), c/o Otsuka Pharmaceutical Development & Commercialization, Inc.,

2440 Research Blvd., Rockville, MD 20850. Otsuka has voluntarily requested that approval of this application be withdrawn because the product is no longer marketed, thereby waiving its opportunity for a hearing.

DATES: Effective June 14, 2007.

FOR FURTHER INFORMATION CONTACT: Florine P. Purdie, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: In a letter dated March 5, 2003, Otsuka requested that FDA withdraw approval of NDA 20-695 for RAXAR (grepafloxacin HC1) Tablets, stating that the product was no longer being marketed. In FDA's acknowledgment letter of June 20, 2003, the agency informed Otsuka that RAXAR (grepafloxacin HCl) Tablets, indicated for the treatment of a variety of infections, had been removed from the market because of safety concerns; in its follow-up letter of January 12, 2007, the agency also informed Otsuka that it had determined that the RAXAR NDA should be withdrawn under § 314.150(d) (21 CFR 314.150(d)) because of its effect on cardiac repolarization, manifested as QTc interval prolongation on the electrocardiogram, which could put patients at risk of Torsade de Pointes. In its letter of March 20, 2007, Otsuka concurred in the agency's determination to initiate withdrawal of the RAXAR NDA and waived its opportunity for a hearing, provided under 21 CFR 314.150(a) and (b).

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(e)), § 314.150(d), and under authority delegated to the Director, Center for Drug Evaluation and Research (21 CFR 5.105(a)), approval of the NDA 20-695, and all amendments and supplements thereto, is withdrawn, effective (see **DATES**). Distribution of this product in interstate commerce without an approved application is illegal and

subject to regulatory action (see sections 505(a) and 301(d) of the act (21 U.S.C. 331(d)).

Dated: May 31, 2007.

Douglas C. Throckmorton,

Deputy Director, Center for Drug Evaluation and Research.

[FR Doc. E7-11427 Filed 6-13-07; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Oncologic Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Oncologic Drugs Advisory Committee.

General Function of the Committee:

To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on July 24, 2007, from 8 a.m. to 5 p.m.

Location: Advisors and Consultants Staff Conference Room, 5630 Fishers Lane, rm. 1066, Rockville, MD 20857.

Contact Person: Johanna Clifford, Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane (for express delivery, 5630 Fishers Lane, rm. 1093), Rockville, MD 20857, 301-827-6761, FAX: 301-827-6776, e-mail: Johanna.Clifford@fda.hhs.gov, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 3014512542. Please call the Information Line for up-to-date information on this

Tab 30

Federal Register of July 9, 2007
(72 FR 37244)

5100 Paint Branch Pkwy., College Park, MD 20740-3835, 301-436-1278.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379e(d)(1)), notice is given that a color additive petition (CAP 7C0283) has been filed by Nippon Oil Corp., c/o Beckloff Assoc., 7400 West 110th St., suite 300, Overland Park, KS 66210. The petition proposes to amend the color additive regulations in 21 CFR part 73 to provide for the safe use of *Paracoccus carotinifaciens* granules as a color additive in the feed of salmonid fish to enhance the color of their flesh.

The agency has determined under 21 CFR 25.32(r) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Dated: June 28, 2007.

Laura M. Tarantino,
Director, Office of Food Additive Safety,
Center for Food Safety and Applied Nutrition.
[FR Doc. E7-13161 Filed 7-6-07; 8:45 am]
BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2007N-0221]

Otsuka Pharmaceutical Co., Ltd.; Withdrawal of Approval of a New Drug Application; Correction

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; correction.

SUMMARY: The Food and Drug Administration (FDA) is correcting a notice that appeared in the **Federal Register** of June 14, 2007 (72 FR 32852). The agency issued a withdrawal of a new drug application (NDA) for RAXAR (grepafloxacin hydrochloride (HCl)) Tablets held by Otsuka Pharmaceutical Co., Ltd. (Otsuka), c/o Otsuka Pharmaceutical Development & Commercialization, Inc., 2440 Research Blvd., Rockville, MD 20850. The document published with typographical errors and cited a section of the Code of Federal Regulations that no longer exists. This document corrects those errors. The agency is also announcing the removal of RAXAR Tablets from the list of approved drug products in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the Orange Book).

DATES: Effective July 9, 2007.

FOR FURTHER INFORMATION CONTACT: Joyce Strong, Office of Policy and Planning (HF-27), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7010.

SUPPLEMENTARY INFORMATION: In FR Doc. E7-11427, appearing on page 32852 in the **Federal Register** of Thursday, June 14, 2007, the following correction is made:

1. On page 32852, in the second and third columns, the **SUPPLEMENTARY INFORMATION** section is corrected to read:

SUPPLEMENTARY INFORMATION: In a letter dated March 5, 2003, Otsuka requested that FDA withdraw approval of NDA 20-695 for RAXAR (grepafloxacin HCl) Tablets, stating that the product was no longer being marketed. In FDA's acknowledgment letter of June 20, 2003, the agency informed Otsuka that RAXAR (grepafloxacin HCl) Tablets, indicated for the treatment of a variety of infections, had been removed from the market because of safety concerns; in its followup letter of January 12, 2007, the agency also informed Otsuka that it had determined that the RAXAR NDA should be withdrawn under § 314.150(d) (21 CFR 314.150(d)) because of its effect on cardiac repolarization, manifested as QTc interval prolongation on the electrocardiogram, which could put patients at risk of Torsade de Pointes. In its letter of March 20, 2007, Otsuka concurred in the agency's determination to initiate withdrawal of the RAXAR NDA and waived its opportunity for a hearing, provided under § 314.150(a) and (b).

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(e)), § 314.150(d), and under authority delegated to the Director, Center for Drug Evaluation and Research, by the Commissioner of Food and Drugs, approval of the NDA 20-695, and all amendments and supplements thereto, is withdrawn effective (see **DATES**). Distribution of this product in interstate commerce without an approved application is illegal and subject to regulatory action (see sections 505(a) and 301(d) of the act (21 U.S.C. 331(d)). Also, on the basis of the circumstances described in this document that led to the withdrawal of the approval of NDA 20-695, the agency will remove RAXAR (grepafloxacin HCl) Tablets from the list of drug products with effective approvals published in the Orange Book.

Dated: June 28, 2007.

Jeffrey Shuren,
Assistant Commissioner for Policy.
[FR Doc. E7-13160 Filed 7-6-07; 8:45 am]
BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2004D-0524]

Guidance for Industry on ANDAs: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls Information; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled "ANDAs: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls Information." The guidance is intended to assist applicants with the submission of abbreviated new drug applications (ANDAs) when a drug substance exists in polymorphic forms.

DATES: Submit written or electronic comments on agency guidance documents at any time.

ADDRESSES: Submit written requests for single copies of this guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Andre Raw, Center for Drug Evaluation and Research (HFD-600), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 240-276-9310.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "ANDAs: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls

Tab 31

Federal Register of August 16, 2001
(66 FR 43017)

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration**

[Docket No. 01N-0336]

Schering Corp. et al.; Withdrawal of Approval of 51 New Drug Applications and 25 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of 51 new drug applications (NDAs) and 25 abbreviated new drug applications (ANDAs). The holders of the applications notified the agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

DATES: Effective September 17, 2001.**FOR FURTHER INFORMATION CONTACT:** Florine P. Purdie, Center for Drug

Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: The holders of the applications listed in the table in this document have informed FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications. The applicants have also, by their requests, waived their opportunity for a hearing.

Application No.	Drug	Applicant
NDA 3-158	Oreton Methyl (methyltestosterone) Tablets, 10 milligrams (mg) and 25 mg.	Schering Corp., 2000 Galloping Hill Rd., Kenilworth, NJ 07033.
NDA 5-963	Sodium Sulamyd (sulfacetamide sodium) Ophthalmic Solution and Ointment.	Do.
NDA 6-325	Tubocurarine Chloride Injection.	Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285.
NDA 6-632	Metubine Iodide (metocurine iodide) Injection.	Do.
NDA 6-772	Vasoxyl (methoxamine hydrochloride (HCl)) Injection.	GlaxoSmithKline (GSK), P.O. Box 13398, Five Moore Dr., Research Triangle Park, NC 27709.
NDA 6-925	Nisentil (alphaprodine HCl) Injection.	Hoffman-LaRoche, Inc., 340 Kingsland St., Nutley, NJ 07110-1199.
NDA 7-600	Surital (thiamylal sodium).	Parkdale Pharmaceuticals, 2800 Plymouth Rd., Ann Arbor, MI 48105.
NDA 8-200	Sodium Iodide I-131 Capsules, Solution, and Injection.	Syncor International Corp., 6464 Canoga Ave., Woodland Hills, CA 91367.
NDA 8-592	Ravocaine HCl (propoxycaine HCl and procaine HCl, with nordefrin or norepinephrine bitartrate).	Eastman Kodak Co., Health Imaging, 343 State St., Rochester, NY 14612-1122.
NDA 9-127	Cortril (hydrocortisone) Tablets.	Pfizer, Inc., 235 East 42d St., New York, NY 10017.
NDA 9-130	Cortril (hydrocortisone acetate) Ophthalmic Ointment.	Do.
NDA 9-238	Progesterone Injection.	Eli Lilly and Co., Lilly Corporate Center, Indianapolis, IN 46285.
NDA 9-458	Cortisone Acetate Tablets, 25 mg.	Impax Laboratories, Inc., 30831 Huntwood Ave., Hayward, CA 94544.
NDA 9-996	Sterane (prednisolone) Tablets.	Pfizer, Inc.
NDA 10-423	Lorfan (levallorphan tartrate) Injection.	Hoffman-LaRoche, Inc.
NDA 10-554	Magnacort (hydrocortamate HCl) Topical Ointment.	Pfizer Pharmaceuticals, 235 East 42d St., New York, NY 10017.
NDA 11-539	Ultra-Feminine (Topical Liquid).	Coscelebre, Inc., 415 Madison Ave., New York, NY 10017.
NDA 11-557	Trilafon (perphenazine) Concentrate, 16 mg/5 mL (milliliters).	Schering Corp.
NDA 11-679	Pentothal Sodium (thiopental sodium) Suspension.	Abbott Laboratories, D-389, Bldg. AP30, 200 Abbott Park Rd., Abbott Park, IL 60064-6157.
NDA 12-148	Oreticyl Tablets and Oreticyl Forte (hydrochlorothiazide and deserpidine) Tablets.	Do.
NDA 12-715	Gantanol (sulfamethoxazole) Tablets.	Hoffman-LaRoche, Inc.

Application No.	Drug	Applicant
NDA 13-056	Penthane (methoxyflurane) Inhalation Liquid.	Abbott Laboratories.
NDA 13-934	Stoxil (idoxuridine) Ophthalmic Solution, 0.1%.	SmithKline Beecham Pharmaceuticals, One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101.
NDA 14-083	Apodol (anileridine HCl) Tablets.	Bristol-Myers Squibb, P.O. Box 4000, Princeton, NJ 08543-4000.
NDA 14-087	Apodol (anileridine) Injection.	Do.
NDA 15-868	Stoxil (idoxuridine) Ophthalmic Ointment, 0.5%.	SmithKline Beecham Pharmaceuticals.
NDA 17-255	DTPA (chelate) Multidose (kit for the preparation of Tc-99m pentetate injection).	Nycomed Amersham Imaging, 101 Carnegie Center, Princeton, NJ 08540.
NDA 17-256	Xenon Xe-133.	Do.
NDA 17-257	Selenomethionine Se-75 Injection.	Do.
NDA 17-266	Technetium Tc-99m Sulfur Colloid Injection.	Do.
NDA 17-267	Sodium Pertechnetate Tc-99m Injection.	Do.
NDA 17-383	Methosarb (calusterone) Tablets.	The Upjohn Co., 7000 Portage Rd., Kalamazoo, MI 49001.
NDA 17-456	Technetium Tc-99m Sulfur Colloid.	Do.
NDA 17-483	Methadone HCl Bulk (methadone HCl).	Penick Corp., 158 Mount Olivet Ave., Newark, NJ 07114.
NDA 17-562	Technetium Tc-99m Diphosphonate Injection (Tin Kit).	Nycomed Amersham Imaging.
NDA 17-664	Sodium Polyphosphate Injection (Tin Kit).	Do.
NDA 17-667	Stannous Diphosphonate Injection.	Do.
NDA 18-228	Hypnomidate (etomidate) Injection.	Janssen Research Foundation, 1125 Trenton-Harbourton Rd., P.O. Box 200, Titusville, NJ 08560.
NDA 18-289	Iodohippurate Sodium I-123.	Nycomed Amersham Imaging.
NDA 18-871	Protostat (metronidazole) Tablets.	R. W. Johnson Pharmaceutical Research Institute, Route 202 South, P.O. Box 300, Raritan, NJ 08869-0602.
NDA 19-450	Velosulin BR Human (semisynthetic purified human insulin) Injection.	Novo Nordisk Pharmaceuticals, Inc., 100 College Rd. West, Princeton, NJ 08540.
NDA 20-420	GenESA (arbutamine HCl) Injection.	Gensia Automedics, Inc., 9360 Towne Centre Dr., San Diego, CA 92121.
NDA 20-689	Posicor (miobefradil dihydrochloride) Oral Tablets, 50 mg and 100 mg.	Hoffmann-LaRoche, Inc.
ANDA 40-059	Fluocinolone Acetonide Topical Solution USP, 0.01%.	Bausch & Lomb Pharmaceuticals, Inc., 8500 Hidden River Pkwy., Tampa, FL 33637.
NDA 50-311	Randomycin (methacycline HCl) Capsules.	Pfizer, Inc.
NDA 50-448	Grifulvin (griseofulvin) Oral Suspension.	Johnson & Johnson Consumer Products Co., 199 Grandview Rd., Skillman, NJ 8558-9418.
NDA 50-637	Zefazone (cefmetazole sodium) Sterile Powder.	Pharmacia & Upjohn Co., 7000 Portage Rd., Kalamazoo, MI 49001.
NDA 50-683	Zefazone (cefmetazole sodium) Intravenous Solution.	Do.
ANDA 60-760	Oxytetracycline HCl Capsules, 250 mg.	Impax Laboratories, Inc.
ANDA 62-223	Totacillin (Ampicillin Trihydrate for Oral Suspension USP).	SmithKline Beecham Pharmaceuticals.
ANDA 62-736	Bactocill (oxacillin sodium) Injection.	GlaxoSmithKline (GSK).
ANDA 64-055	Neomycin Sulfate and Dexamethosone Sodium Phosphate Ophthalmic Solution	Bausch & Lomb Pharmaceuticals, Inc.

Application No.	Drug	Applicant
ANDA 74-813	Etoposide Injection 20 mg/mL.	Pierre Fabre Medicament, c/o Guidelines Integrated Service, 10320 USA Today Way, Miramar, FL 33062.
ANDA 80-079	Trisulfapyrimidines Tablets USP.	Impax Laboratories, Inc.
ANDA 80-151	Thyroglobulin Tablets USP.	Do.
ANDA 80-153	Isoniazid Tablets USP.	Do.
ANDA 80-281	Oreton Methyl Buccal Tablets (Methyltestosterone Tablets USP).	Schering Corp.
ANDA 80-780	Prednisolone Tablets USP, 5 mg.	Impax Laboratories, Inc.
ANDA 80-807	Diphenhydramine HCl Capsules USP, 25 mg and 50 mg.	Do.
ANDA 80-951	Ergocalciferol Capsules USP.	Do.
ANDA 80-952	Vitamin A Capsules USP.	Do.
ANDA 80-953	Vitamin A Capsules USP.	Do.
ANDA 80-955	Vitamin A Capsules USP.	Do.
ANDA 83-011	Hydrocortisone Cream USP, 1%.	Solvay Pharmaceuticals, Inc., 901 Sawyer Rd., Marietta, GA 30062.
ANDA 83-347	Quinidine Sulfate Tablets USP, 200 mg.	Impax Laboratories, Inc.
ANDA 84-214	Promethazine HCl Tablets USP, 25 mg.	Do.
ANDA 84-340	Triamcinolone Tablets USP, 4 mg.	Do.
ANDA 84-575	Aminophylline Tablets USP, 200 mg.	Do.
ANDA 84-577	Aminophylline Tablets USP, 100 mg.	Do.
ANDA 85-098	Hydrochlorothiazide Tablets USP, 100 mg.	Do.
ANDA 85-563	Glycopyrrolate Tablets, 2 mg.	Circa, 130 Lincoln St., Copiague, NY 11726.
ANDA 86-639	Levsin PB (hyoscyamine sulfate and phenobarbital) Oral Solution.	Schwarz Pharma, Inc., P.O. Box 2038, Milwaukee, WI 53201.

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) and under authority delegated to the Director, Center for Drug Evaluation and Research (21 CFR 5.82), approval of the applications listed in the table in this document, and all amendments and supplements thereto, is hereby withdrawn, effective September 17, 2001.

Dated: August 1, 2001.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 01-20605 Filed 8-15-01; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Center for Research Resources; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Center for Research Resources Special Emphasis Panel, Biomedical Research Technology.

Date: October 22-23, 2001.

Time: October 22, 2001, 8:00 am to adjournment.

Agenda: To review and evaluate grant applications.

Place: Gaithersburg Marriott, Washingtonian Center, 9751 Washingtonian Boulevard, Gaithersburg, MD 20878.

Contact Person: Mohan Viswanathan, PhD, Scientific Review Administrator, National Center for Research Resources, National Institutes of Health, Office of Review, 6705 Rockledge Drive, MSC 7965, One Rockledge Centre, Room 6018, Bethesda, MD 20892, (301) 435-0829, viswanathanm@ncrr.nih.gov

(Catalogue of Federal Domestic Assistance Program Nos. 93.306, Comparative Medicine, 93.306; 93.333, Clinical Research, 93.333; 93.371, Biomedical Technology; 93.389, Research Infrastructure, National Institutes of Health, HHS)

Tab 32

Federal Register of September 6, 2005
(70 FR 53019)

ways to minimize the burden of the collection of information on respondents, including the use of automated collection techniques or other forms of information technology.

Comments submitted in response to this notice will be summarized and included in the request for OMB approval of the proposed information collection. All comments will become a matter of public record.

Dated: August 12, 2005.

Carolyn M. Clancy,
Director.

[FR Doc. 05-17617 Filed 9-2-05; 8:45 am]

BILLING CODE 4160-90-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2004P-0379]

Determination That Penthrane (Methoxyflurane) Inhalation Liquid, 99.9 Percent, Was Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, was withdrawn from sale for reasons of safety or effectiveness. The agency will not accept or approve abbreviated new drug applications (ANDAs) for methoxyflurane inhalation liquid, 99.9 percent.

FOR FURTHER INFORMATION CONTACT: Mary Catchings, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved. Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new

drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book." Under FDA regulations, drugs are removed from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (§ 314.162 (21 CFR 314.162)).

Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, was the subject of NDA 13-056, held by Abbott Laboratories (Abbott). Penthrane is a potent inhalation anesthetic indicated to provide anesthesia for surgical procedures in which total duration of administration is anticipated to be 4 hours or less (not to be used at concentrations that provide skeletal muscle relaxation). Penthrane was also indicated to provide analgesia in obstetrics and in minor surgical procedures and for use by self-administration using hand held inhalers. In the **Federal Register** of August 16, 2001 (66 FR 43017), FDA withdrew approval of NDA 13-056 for Penthrane after Abbott notified the agency that Penthrane was no longer being marketed under NDA 13-056 and requested withdrawal of that application. Penthrane was then moved to the "Discontinued Drug Product List" section of the Orange Book.

In a citizen petition dated August 25, 2004 (Docket No. 2004P-0379/CP1), submitted under § 10.30 (21 CFR 10.30), and in accordance with § 314.161, AAC Consulting Group requested that the agency determine whether Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, was withdrawn from sale for reasons of safety or effectiveness.

We have carefully reviewed our files for records concerning the withdrawal of Penthrane (methoxyflurane)

Inhalation Liquid, 99.9 percent, including the NDA file for this drug product. We have also independently evaluated relevant literature and data for possible postmarketing adverse event reports. FDA has determined under §§ 314.161 and 314.162(a)(2) that Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, was withdrawn from sale for reasons of safety. FDA's review shows that methoxyflurane, a volatile anesthetic agent, is associated with serious, irreversible, and even fatal nephrotoxicity and hepatotoxicity in humans. FDA has also reviewed the latest approved labeling for Penthrane and has determined that this labeling is inadequate. FDA believes that the risks of toxicity outweigh any potential benefits if methoxyflurane is used according to the latest approved labeling. Since the initial approval of Penthrane in 1962, with a subsequent finding of efficacy in the **Federal Register** of December 11, 1981 (46 FR 60652), alternative safe and effective anesthetics have been approved by FDA and entered the market. FDA has determined that new clinical studies are necessary before methoxyflurane could be considered for reintroduction to the market. The agency has determined, under § 314.161, that Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent was withdrawn from sale for reasons of safety. Therefore, Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, will be removed from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to this drug product.

Dated: August 29, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 05-17559 Filed 9-2-05; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. 2005M-0158, 2005M-0159, 2005M-0129, 2005M-0160, 2005M-0130, 2005M-0151, 2005M-0117, 2005M-0118, 2005M-0241, 2005M-0191, 2005M-0192, 2005M-0193, 2005M-0270]

Medical Devices; Availability of Safety and Effectiveness Summaries for Premarket Approval Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a

Tab 33

Federal Register of February 11, 2009
(74 FR 6896)

more accurately describe the information collection content.

Section 2(c) of The Medical Device User Fee Stabilization Act of 2005 (Public Law 109-43) amends section 502(u) of the act by limiting the provision to reprocessed single-use devices (SUDs) and the manufacturers who reprocess them. Under the amended provision, if the original SUD or an attachment to it prominently and conspicuously bears the name of the manufacturer, then the reprocessor of the SUD is required to identify itself by name, abbreviation, or symbol, in a prominent and conspicuous manner on the device or attachment to the device. If the original SUD does not

prominently and conspicuously bear the name of the manufacturer, the manufacturer who reprocesses the SUD for reuse, may identify itself using a detachable label that is intended to be affixed to the patient record.

The requirements of section 502(u) of the act impose a minimal burden on industry. This section of the act only requires the manufacturer, packer, or distributor of a device to include their name and address on the labeling of a device. This information is readily available to the establishment and easily supplied. From its registration and premarket submission database, FDA estimates that there are 10 establishments that distribute

approximately 1,000 reprocessed SUDs. Each response is anticipated to take 0.1 hours resulting in a total burden to industry of 100 hours.

In the **Federal Register** of November 17, 2008 (73 FR 67873), FDA published a 60-day notice requesting public comment on the information collection provisions. The agency received one comment in support of the collection of information stating that it is necessary to help reproducers of SUDs comply with section 502(u) of the act. The comment further stated that the estimated reporting burden did not appear excessive.

FDA estimates the burden of this collection of information as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN¹

Section of the Act	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
502(u)	10	100	1,000	.1	100

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: January 26, 2009.
Jeffrey Shuren,
Associate Commissioner for Policy and Planning.
 [FR Doc. E9-2902 Filed 2-10-09; 8:45 am]
BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
 [Docket No. FDA-2009-N-0026]

Apothecon et al.; Withdrawal of Approval of 103 New Drug Applications and 35 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of 103 new drug applications (NDAs) and 35 abbreviated new drug applications (ANDAs) from multiple applicants. The holders of the applications notified the agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

DATES: Effective March 13, 2009.

FOR FURTHER INFORMATION CONTACT: Florine P. Purdie, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6366,

Silver Spring, MD 20993-0002, 301-796-3601.

SUPPLEMENTARY INFORMATION: The holders of the applications listed in the table in this document have informed FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications. The applicants have also, by their requests, waived their opportunity for a hearing.

Application No.	Drug	Applicant
NDA 7-335	Pronestyl (procainamide hydrochloride (HCl)) Capsules and Injection	Apothecon, c/o Bristol-Myers Squibb Co., P.O. Box 4000, Princeton, NJ 08543-4000
NDA 7-935	Phenergan (promethazine HCl) Tablets	Wyeth Pharmaceuticals, Inc., P.O. Box 8299, Philadelphia, PA 19101-8299
NDA 9-193	Cogentin (benztropine mesylate) Tablets	Merck & Co., Inc., Sunneytown Pike, P.O. Box 4, BLA-20, West Point, PA 19486
NDA 9-986	Deltasone (prednisone) Tablets	Pharmacia & Upjohn Co., c/o Pfizer, Inc., 235 East 42d St., New York, NY 10017
NDA 10-374	Medihaler-Epi (epinephrine bitartrate)	3M Pharmaceuticals, 3M Center, Bldg. 0275-05-W-12, St. Paul, MN 55144-1000
NDA 10-375	Medihaler-ISO (isoproterenol)	Do.
NDA 10-598	Bendectin (doxylamine succinate and pyridoxine HCl) Tablets	Sanofi-Aventis, 300 Somerset Corporate Blvd., Bridgewater, NJ 08807-0977

Application No.	Drug	Applicant
NDA 10-796	Harmony (deserpidine) Tablets	Abbott Laboratories, 200 Abbott Park Rd., Abbott Park, IL 60064-6154
NDA 10-800	Tralgon (acetaminophen) Elixir	Bristol-Myers Squibb Co., P.O. Box 4000, Princeton, NJ 08543-4000
NDA 10-927	Phosphotope (sodium phosphates solution USP) Oral Solution	Bracco Diagnostics, P.O. Box 5225, Princeton, NJ 08543-5225
NDA 10-928	Aureotope (gold injection)	Do.
NDA 11-161	Aristocort (triamcinolone) Tablets	Astellas Pharma US, Inc., Three Parkway North, Deerfield, IL 60015-2537
NDA 11-467	Trancopal (chlormezanone) Tablets	Sanofi-Aventis
NDA 11-721	Neptazane (methazolamide) Tablets	Lederle Laboratories, c/o Wyeth Pharmaceuticals, Inc., P.O. Box 8299, Philadelphia, PA 19101-8299
NDA 11-751	Prolixin (fluphenazine HCl) Injection and Tablets	Apothecon, c/o Bristol-Myers Squibb Co.
NDA 11-832	Vasodilan (isoxsuprine HCl)	Do.
NDA 12-097	Kenalog in Orabase (triamcinolone acetonide dental paste USP)	Do.
NDA 12-164	Naturetin (bendroflumethiazide USP), 2.5 milligrams (mg), 5 mg, and 10 mg	Do.
NDA 12-515	Kenacort (triamcinolone diacetate) Syrup	Bristol-Meyers Squibb Co.
NDA 13-296	Duo-Medihaler (phenyleprine bitartrate and isoproterenol HCl)	3M Pharmaceuticals
NDA 13-601	Mucumyst (acetylcysteine solution USP)	Apothecon, c/o Bristol-Myers Squibb Co.
NDA 14-715	Triavil (perphenazine and amitriptyline HCl) Tablets	New River Pharmaceuticals, Inc., 2200 Kraft Dr., suite 2050, Blacksburg, VA 24060
NDA 15-419	Hippotope (iodohippurate sodium I-131 injection USP)	Bracco Diagnostics
NDA 16-033	Vontrol (diphenidol HCl) Tablets, 25 mg	GlaxoSmithKline, Five Moore Dr., P.O. Box 13398, Research Triangle Park, NC 27709
NDA 16-090	Rubratope-60 (cyanocobalamin CO-60)	Bracco Diagnostics
NDA 16-224	Robengatope (rose bengal sodium I-131 injection USP)	Do.
NDA 16-727	Prolixin Decanoate (fluphenazine decanoate) Injection	Bristol-Myers Squibb Co.
NDA 16-783	Vascoray (iothalamate meglumine, 52% and iothalamate sodium, 26% injection)	Tyco Healthcare/Mallinckrodt Inc., P.O. Box 5840, St. Louis, MO 63134-0840
NDA 16-906	Technetope II (technetium Tc-99m sodium pertechnetate sterile generator)	Bracco Diagnostics
NDA 16-923	Tesuloid (technetium Tc-99m sulfur colloid kit)	Do.
NDA 16-929	FUDR (floxuridine) Injection, 500 mg/5 milliliters (mL)	Hospira, Inc., 275 North Field Dr., Lake Forest, IL 60045-5046
NDA 16-996	Hyperstat (diazoxide) Injection	Schering Corp., 2000 Galloping Hill Rd., Kenilworth, NJ 07033
NDA 17-024	Strotope (strontium nitrate Sr-85) Injection	Bracco Diagnostics
NDA 17-045	Renotec (technetium Tc-99m ferpenetate kit)	Do.
NDA 17-047	Sethotope (selenomethionine Se-75) Injection	Do.
NDA 17-269	Chlormerodrin Hg-197 Injection	Do.
NDA 17-339	Minitec (technetium Tc-99m sodium pertechnetate generator)	Do.

Application No.	Drug	Applicant
NDA 17-371	Pronestyl (procainamide HCl) Tablets	Apothecon, c/o Bristol-Myers Squibb Co.
NDA 17-395	Intropin (dopamine HCl) Injection, 40 mg/mL, 80 mg/mL, and 160 mg/mL	Hospira, Inc.
NDA 17-598	Septra (trimethoprim and sulfamethoxazole) Oral Suspension	Monarch Pharmaceuticals, Inc., 501 5th St., Bristol, TN 37620
NDA 17-685	Conray 325 (iothalamate sodium)	Mallinckrodt Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
NDA 17-787	Radionuclide-Labeled (I-125) Fibrinogen Sensor	Abbott Laboratories
NDA 17-834	Albumotope-LS (albumin aggregated iodinated I-131-serum)	Bracco Diagnostics
NDA 17-902	Renovue-65 (iodamide meglumine) Injection, 65%	Do.
NDA 17-903	Renovue-Dip (iodamide meglumine) Injection	Do.
NDA 17-931	Iletin I (insulin pork)	Eli Lilly & Co., Lilly Corporate Center, Indianapolis, IN 46285
NDA 17-932	Protamine Zinc and Iletin I (insulin suspension protamine zinc beef/pork)	Do.
NDA 17-935	Ultralente Iletin I (insulin zinc suspension extended beef/pork)	Do.
NDA 17-936	NPH Iletin I (insulin suspension isophane beef/pork)	Do.
NDA 17-943	Proloprin (trimethoprim) Tablets, 100 mg and 200 mg	Monarch Pharmaceuticals, Inc.
NDA 17-970	Nolvadex (tamoxifen citrate) Tablets	AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, P.O. Box 8355, Wilmington, DE 19803-8355
NDA 17-979	Heparin Sodium Injection USP	Abraxis Pharmaceutical Products, Riverway One, 6133 North River Rd., suite 500, Rosemont, IL 60018
NDA 18-017	Blocadren (timolol maleate) Tablets	Merck & Co., Inc., UG2C-50, P.O. Box 1000, North Wales, PA 19454-1099
NDA 18-061	Timolide (timolol maleate and hydrochlorothiazide) Tablets, 10 mg/25mg	Do.
NDA 18-076	Cholovue (iodoxamate meglumine) Injection, 40.3%	Bracco Diagnostics
NDA 18-077	Cholovue (iodoxamate meglumine) for Infusion	Do.
NDA 18-116	Cyclocort (amcinonide) Cream, 0.1%	Astellas Pharma US, Inc.
NDA 18-211	Ditropan (oxybutynin chloride) Syrup, 5 mg	Ortho-McNeil-Janssen Pharmaceuticals, Inc., 1000 U.S. Highway 202, P.O. Box 3000, Raritan, NJ 08869-0602
NDA 18-344	Iletin II (insulin purified pork)	Eli Lilly & Co.
NDA 18-345	NPH Iletin II (insulin suspension isophane purified pork)	Do.
NDA 18-346	Protamine, Zinc, and Iletin II (insulin suspension protamine zinc purified pork)	Do.
NDA 18-347	Lente Iletin II (insulin zinc suspension purified pork)	Do.
NDA 18-354	Ortho-Novum 10/11-21 and 10/11-28 (norethindrone and ethinyl estradiol) Tablets	Ortho-McNeil Pharmaceutical, Inc., c/o Johnson & Johnson Pharmaceutical Research & Development, LLC, 920 Rt. 202 South, P.O. Box 300, Raritan, NJ 08869
NDA 18-452	Septra (sulfamethoxazole and trimethoprim) Injection	Monarch Pharmaceuticals, Inc.

Application No.	Drug	Applicant
NDA 18-476	Protamine, Zinc, and Iletin II (insulin suspension protamine zinc purified beef)	Eli Lilly & Co.
NDA 18-477	Lente Iletin II (insulin zinc suspension purified beef)	Do.
NDA 18-478	Regular Iletin II (insulin purified beef)	Do.
NDA 18-479	NPH Iletin II (insulin suspension isophane purified beef)	Do.
NDA 18-498	Cyclocort (amcinonide) Ointment, 0.1%	Astellas Pharma US, Inc.
NDA 18-537	Tridil (nitroglycerin) Injection	Hospira, Inc.
NDA 18-831	Tracrium (atracurium besylate) Injection	Hospira, Inc.
NDA 18-873	Mexitil (mexiletine HCl) Capsules, 150 mg, 200 mg, and 250 mg	Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Rd., P.O. Box 368, Ridgefield, CT 06877-0368
NDA 18-922	Lodine (etodolac) Capsules and Tablets	Wyeth Pharmaceuticals, Inc.
NDA 19-085	Atrovent (ipratropium bromide) Aerosol	Boehringer Ingelheim Pharmaceuticals, Inc.
NDA 19-166	Regular Insulin (insulin zinc suspension beef) Injection	Eli Lilly & Co.
NDA 19-167	NPH Insulin Beef (insulin zinc suspension beef)	Do.
NDA 19-529	Humulin BR (insulin recombinant human)	Do.
NDA 19-729	Cyclocort (amcinonide) Lotion, 0.1%	Astellas Pharma US, Inc.
NDA 19-816	Oruvail (ketoprofen) Extended-Release Capsules	Wyeth Pharmaceuticals, Inc.
NDA 19-890	Stadol (butorphanol tartrate) Nasal Spray	Bristol-Myers Squibb Co.
NDA 19-965	Novolin L (insulin zinc suspension recombinant human)	Novo Nordisk, Inc., 100 College Road West, Princeton, NJ 08540
NDA 20-152	Serzone (nefazodone HCl) Tablets	Bristol-Myers Squibb Co.
NDA 20-219	Livostin (levocabastine HCl) Ophthalmic Suspension, 0.05%	Novartis Pharmaceuticals Corp., One Health Plaza, East Hanover, NJ 07936-1080
NDA 20-225	Indur (isosorbide mononitrate) Extended-Release Tablets, 30 mg, 60 mg, and 120 mg	Schering Corp.
NDA 20-326	Neutrexin (trimetrexate glucuronate) Injection, 25 mg and 200 mg vials	MedImmune Oncology, Inc., One MedImmune Way, Gaithersburg, MD 20878
NDA 20-377	Cordarone (amiodarone HCl), Injection, 50 mg/mL	Wyeth Pharmaceuticals, Inc.
NDA 20-429	Orudis KT (ketoprofen) Tablets, 12.5 mg	Wyeth Consumer Healthcare, Five Giralda Farms, Madison, NJ 07940
NDA 20-584	Lodine XL (etodolac) Extended-Release Tablets	Wyeth Pharmaceuticals, Inc.
NDA 20-698	MiraLax (polyethylene glycol 3350) Powder for Solution	Braintree Laboratories, Inc., 60 Columbian Street West, P.O. Box 850929, Braintree, MA 02185-0929
NDA 20-784	Nasacort HFA (triamcinolone acetonide) Nasal Spray	Sanofi-Aventis
NDA 20-974	Prozac (fluoxetine HCl) Tablets	Eli Lilly & Co.
NDA 21-028	Velosulin BR (insulin recombinant injection)	Novo Nordisk, Inc.
NDA 21-369	Codeprex (codeine polistirex and chlorpheniramine polistirex) Extended-Release Suspension	UCB, Inc., 1950 Lake Park Dr., Smyrna, GA 30080
NDA 21-387	Pravigard Pak (copackaged) (pravastatin sodium and aspirin) Tablets	Bristol-Meyers Squibb Co.

Application No.	Drug	Applicant
ANDA 40-305	Meperidien HCl Injection USP, 10 mg/mL	Hospira, Inc.
NDA 50-155	Chloromycetin Sodium Succinate (chloramphenicol sodium succinate for injection USP)	Parkedale Pharmaceuticals, Inc., c/o King Pharmaceuticals, Inc., 501 5th St., Bristol, TN 37620
NDA 50-205	Chloromycetin (chloramphenicol) Otic Solution	Do.
NDA 50-285	Mycifradin (neomycin sulfate) Oral Suspension	Pharmacia & Upjohn Co., c/o Pfizer, Inc.
NDA 50-339	Albamycin (novobiocin sodium) Capsules	Do.
NDA 50-435	Geocillin (carbenicillin indanyl sodium) Tablets, 382 mg	Pfizer, Inc., 235 East 42d St., New York, NY 10017
NDA 50-504	Mandol (cefamandole nafate) Injection	Eli Lilly & Co.
NDA 50-589	Cefizox (ceftizoxime sodium)	Astellas Pharma US, Inc.
NDA 50-621	Suprax (cefixime) Tablets, 200 mg and 400 mg	Lederle Laboratories, c/o Wyeth Pharmaceuticals, Inc.
NDA 50-622	Suprax (cefixime) Powder for Suspension	Do.
ANDA 60-591	Chloromycetin (chloramphenicol capsules USP), 50 mg, 100 mg, and 250 mg	Parkedale Pharmaceuticals, Inc., c/o King Pharmaceuticals, Inc.
ANDA 61-922	Vidarabine Monohydrate Micronized Powder, Sterile	Do.
ANDA 62-655	Tazidime (ceftazidime for injection USP)	Eli Lilly & Co.
ANDA 63-350	Amikacin Sulfate Injection USP, 50 mg base/mL and 250 mg base/mL	Hospira, Inc.
ANDA 70-847	Metoclopramide Injection USP, 5 mg base/mL	Hospira, Inc.
ANDA 71-291	Metoclopramide Injection USP, 5 mg base/mL	Do.
ANDA 71-364	Acetylcysteine Solution USP	Do.
ANDA 71-365	Acetylcysteine Solution USP	Do.
ANDA 71-645	Droperidol Injection USP, 2.5 mg/mL	Do.
ANDA 73-272	Albuterol Inhalation Aerosol	IVAX Pharmaceuticals Ireland, c/o IVAX Pharmaceuticals, Inc., Two University Plaza, suite 220, Hackensack, NJ 07601
ANDA 74-966	Fluphenazine Decanoate Injection, 25 mg/mL	Hospira, Inc.
ANDA 75-106	Diltiazem HCl Injection, 5 mg/mL	Do.
ANDA 75-242	Labetalol HCL Injection, 5 mg/mL	Do.
ANDA 75-342	Butorphanol Tartrate Injection USP, 1 mg/mL and 2mg/mL	Do.
ANDA 75-396	Midazolam HCl Injection	Do.
ANDA 75-484	Midazolam HCl Injection, 5 mg base/mL	Do.
ANDA 75-571	Enalaprilat Injection, 1.25 mg/mL	Do.
ANDA 75-669	Famotidine Injection, 10 mg/mL	Do.
ANDA 75-705	Famotidine Injection, 10 mg/mL	Do.
ANDA 75-816	Calcitriol Injection	Do.
ANDA 75-830	Milrinone Lactate Injection, 1 mg base/mL	Do.
ANDA 75-108	Amiodarone HCl Injection, 50 mg/mL	Do.
ANDA 76-233	Paclitaxel Injection	Do.
ANDA 76-473	Carboplatin for Injection USP	Do.

Application No.	Drug	Applicant
ANDA 76-978	Ondansetron HCl and Dextrose Injection	Do.
ANDA 77-362	Amlodipine Besylate Tablets	King and Spalding, U.S. Agent for Genpharm Inc., 1700 Pennsylvania Ave., NW., Washington, DC 20006-4706
ANDA 77-925	Meloxicam Tablets, 7.5 mg and 15 mg	Roxane Laboratories, Inc., 1809 Wilson Rd., Columbus, OH 43228
ANDA 85-153	Alkergot (ergoloid mesylates) Sublingual Tablets, 0.5 mg	Sandoz, Inc., 227-15 North Conduit Ave., Laurelton, NY 11413
ANDA 85-916	Diethylpropion HCl Tablets, 25 mg	Do.
ANDA 86-172	Meclizine HCl Tablets, 12.5 mg	Do.
ANDA 86-174	Meclizine HCl Tablets, 25 mg	Do.
ANDA 86-184	Sulfasalazine Tablets, 500 mg	Do.
ANDA 87-417	Alkergot (ergoloid mesylates) Sublingual Tablets, 1 mg	Do.
ANDA 89-565	Vinblastine Sulfate Injection, 10 mg/vial	Hospira, Inc.

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) and under authority delegated to the Director, Center for Drug Evaluation and Research, by the Commissioner of Food and Drugs, approval of the applications listed in the table in this document, and all amendments and supplements thereto, is hereby withdrawn, effective March 13, 2009.

Dated: January 12, 2009.

Douglas C. Throckmorton,

Deputy Director, Center for Drug Evaluation and Research.

[FR Doc. E9-2901 Filed 2-10-09; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA2008E0091; Docket No. FDA2008E0099; Docket No. FDA2008E0204]

Determination of Regulatory Review Period for Purposes of Patent Extension; MACROPLASTIQUE IMPLANTS

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for MACROPLASTIQUE IMPLANTS and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of applications to the Director of Patents and Trademarks, Department of Commerce, for the

extension of patents which claim that medical device.

ADDRESSES: Submit written comments and petitions to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6222, Silver Spring, MD 20993-0002, 301-796-3602.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100-670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For medical devices, the testing phase begins with a clinical investigation of the device and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the device and continues until permission to market the device is granted. Although only a portion of a regulatory review period may count

toward the actual amount of extension that the Director of Patents and Trademarks may award (half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a medical device will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(3)(B).

FDA recently approved for marketing the medical device MACROPLASTIQUE IMPLANTS. MACROPLASTIQUE IMPLANTS are indicated for transurethral injection in the treatment of adult women diagnosed with stress urinary incontinence (SUI) primarily due to intrinsic sphincter deficiency (ISD). Subsequent to this approval, the Patent and Trademark Office received patent term restoration applications for MACROPLASTIQUE IMPLANTS (U.S. Patent Nos. 5,258,028; 5,336,263; and 5,571,182) from Uroplasty, Inc., and the Patent and Trademark Office requested FDA's assistance in determining these patents' eligibilities for patent term restoration. In a letter dated May 6, 2008, FDA advised the Patent and Trademark Office that this medical device had undergone a regulatory review period and that the approval of MACROPLASTIQUE IMPLANTS represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for MACROPLASTIQUE IMPLANTS is 2,651 days. Of this time, 1,973 days occurred during the testing phase of the

Tab 34

Federal Register of January 19, 2011
(76 FR 3143)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

Office of Child Care; Delegation of Authority

Notice is hereby given that I have delegated to the Director, Office of Child Care, Administration for Children and Families, the authorities vested in me by the Secretary of Health and Human Services in the memorandum dated August 20, 1991, pertaining to the Head Start Program and the Child Development Associate Scholarship Assistance Grants Program; in the memorandum dated August 20, 1991, pertaining to the Omnibus Budget Reconciliation Act of 1981; in the memorandum dated August 20, 1991, pertaining to the Omnibus Budget Reconciliation Act of 1990 (OBRA 1990, Pub. L. 101–508); and in the memorandum dated September 16, 1997, pertaining to the Personal Responsibility and Work Opportunity Reconciliation Act of 1996 (PRWORA, Pub. L. 104–193), as amended, as they pertain to the functions assigned to the Office of Child Care.

(a) Authorities Delegated

1. Authority to administer the provisions of the Child Development Associate Scholarship Assistance Act, 42 U.S.C. 10901–10905, and as amended now and hereafter.

2. Authority to administer the provisions of Subchapter D—Grants for Planning and Development of Dependent Care Programs and for other purposes (Chapter 8, Title VI of the Omnibus Budget Reconciliation Act of 1981, Pub. L. 97–35, 42 U.S.C. 9871 *et seq.*) and as amended now and hereafter.

3. Authority for the Child Care and Development Block Grants, under Section 5082 of OBRA 1990, (42 U.S.C. 9858 *et seq.*), and as amended now and hereafter.

4. Authority to administer the provisions of the Child Care and Development Block Grant Amendments of 1996, 42 U.S.C. 9801 note, under Sections 601–615 of the Personal Responsibility and Work Opportunity Reconciliation Act of 1996, 42 U.S.C. 1305 note, 42 U.S.C. 601 *et seq.*, and as amended now and hereafter.

(b) Limitations

1. These authorities shall be exercised under the Department's policy on regulations and the existing delegation of authority to approve and issue regulations.

2. This delegation does not include the authority to submit reports to Congress and shall be exercised under financial and administrative requirements applicable to all Administration for Children and Families authorities.

3. The approval or disapproval of grant applications and the making of grant awards require concurrence of the appropriate Grants Officer. The approval or disapproval of contract proposals and awards are subject to the requirements of the Federal Acquisition Regulations and requires the concurrence of the Contracting Officer.

4. This delegation of authority does not include the authority to sign and issue notices of grant awards.

5. This delegation of authority does not include the authority to appoint Action Officials for Audit Resolution.

6. This delegation of authority does not include the authority to appoint Central Office or Regional Office Grant Officers for the administration of the child care related programs.

7. This delegation of authority does not include the authority to hold hearings.

8. This delegation of authority does not include the authority to approve or disapprove awards for grants or contracts for research, demonstration, or evaluations relating to child care.

9. Any re-delegation shall be in writing and prompt notification must be provided to all affected managers, supervisors, and other personnel, and requires the concurrence of the Deputy Assistant Secretary for Administration.

(c) Effect on Existing Delegations

This delegation supersedes all existing delegations of these authorities.

(d) Effective Date

This delegation is effective immediately. I hereby affirm and ratify any actions taken by the Director, Office of Child Care, or his or her subordinates, which involved the exercise of the authorities delegated herein prior to the effective date of this delegation.

Dated: January 10, 2011.

David A. Hansell,

Acting Assistant Secretary for Children and Families.

[FR Doc. 2011–1067 Filed 1–18–11; 8:45 am]

BILLING CODE 4184–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–P–0431]

Determination That ALBAMYCIN (Novobiocin Sodium) Capsule, 250 Milligrams, Was Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that ALBAMYCIN (novobiocin sodium) capsule, 250 milligrams (mg) was withdrawn from sale for reasons of safety or effectiveness. The Agency will not accept or approve abbreviated new drug applications (ANDAs) for ALBAMYCIN (novobiocin sodium) capsule, 250 mg.

FOR FURTHER INFORMATION CONTACT:

Nancy Hayes, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6244, Silver Spring, MD 20993–0002, 301–796–3601.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the “listed drug,” which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is known generally as the “Orange Book.” Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or

ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162). Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the Agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

ALBAMYCIN (novobiocin sodium) capsule, 250 mg, is the subject of NDA 50-339, held by Pfizer, Inc. (Pfizer), and initially approved on September 4, 1964. ALBAMYCIN is indicated for the treatment of serious infections due to susceptible strains of *Staphylococcus aureus* when other less toxic antibiotics such as the penicillins, cephalosporins, vancomycin, lincomycin, erythromycin, and the tetracyclines cannot be used.

Novobiocin antibiotic drug products were reviewed for efficacy under the Drug Efficacy Study Implementation (DESI) program. Under this program, implemented in response to the 1962 amendments to the FD&C Act requiring demonstration of effectiveness (The Kefauver-Harris Amendments, Public Law 87-781 (1962)), the National Academy of Sciences-National Research Council (NAS-NRC) undertook a study of some 4,000 drug formulations to assess the efficacy of the products. Upon consideration of the findings and recommendations of the NAS-NRC, FDA set forth in the **Federal Register** its conclusions and assessment of whether and under what circumstances the reviewed drug products are considered "effective" for use as required by the FD&C Act.

In the **Federal Register** of May 2, 1969 (34 FR 7252), FDA announced its conclusions following consideration of the findings and recommendations of the NAS-NRC regarding oral and parenteral forms of novobiocin including ALBAMYCIN (novobiocin sodium) capsule, 250 mg. The announcement stated that FDA had concluded that novobiocin is effective for certain indications and provided labeling guidelines in accordance with this conclusion. We note, however, that the initial panel review of a syrup form of novobiocin raised questions, even at that time, concerning the safety and effectiveness of this antibiotic. The panel report included the following statement: "The development of safer and more effective drugs has virtually eliminated the need for novobiocin. The majority of the Panel believes that orally administered novobiocin should be taken off the market." Report of the

Anti-Infectives Panel, National Academy of Sciences-National Research Council, Albamycin Syrup.

In an annual report received on June 9, 1999, Pharmacia & Upjohn (now Pfizer, Inc.) notified FDA that ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was no longer being manufactured. In a letter dated June 27, 2007, Pfizer, then the current holder of NDA 50-339, notified FDA that ALBAMYCIN (novobiocin sodium) capsule, 250 mg, had been discontinued. In the **Federal Register** of February 11, 2009 (74 FR 6896), FDA announced that it was withdrawing approval of NDA 50-339 in response to Pfizer's withdrawal request. As a result, ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was moved to the "Discontinued Drug Product List" section of the Orange Book.

Crixmore LLC submitted a citizen petition dated July 9, 2008 (Docket No. FDA-2008-P-0431), under 21 CFR 10.30, requesting that the Agency determine whether ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was withdrawn from sale for reasons of safety or effectiveness.

After considering the citizen petition and reviewing Agency records, FDA has determined under § 314.161 that ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was withdrawn for reasons of safety or effectiveness. The petitioner stated that it had identified no data or other information suggesting that ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was withdrawn for reasons of safety or effectiveness and speculated that the discontinuation of this product was an economic/strategic decision totally unrelated to safety and/or efficacy. We have carefully reviewed our files for records concerning the withdrawal of ALBAMYCIN (novobiocin sodium) capsule, 250 mg, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. The literature and adverse event reports reveal several significant safety concerns. Reported adverse reactions include relatively common skin reactions, jaundice, hepatic failure, and blood dyscrasias (neutropenia, anemia, and thrombocytopenia). The literature also reveals concern about the development of novobiocin-resistant *Staphylococci* during treatment, and a potential for drug interactions. In light of the significant safety concerns with this product, we conclude that the withdrawal of this product from the market was on the basis of safety or effectiveness.

Accordingly, the Agency will remove ALBAMYCIN (novobiocin sodium)

capsule, 250 mg, from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to this drug product.

Dated: January 13, 2011.

David Dorsey,

Acting Deputy Commissioner for Policy, Planning and Budget.

[FR Doc. 2011-1000 Filed 1-18-11; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-D-0024]

Draft Guidance for Industry on Size of Beads in Drug Products Labeled for Sprinkle; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Size of Beads in Drug Products Labeled for Sprinkle." This draft guidance provides sponsors of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics licensing applications (BLAs) the Center for Drug Evaluation and Research's (CDER's) current thinking on appropriate size ranges for beads in drug products that are labeled to be administered via sprinkling (*e.g.*, capsules or packets containing beads).

DATES: Although you can comment on any guidance at any time (*see* 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by April 19, 2011.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Tab 35

Federal Register of April 18, 2013
(78 FR 23273)

states that “The public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public

is not included * * *” within the definition of “collection of information.”

FDA requests public comments on the information collection provisions described in this document and set forth in the following table:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN ¹

Activity	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Submission to Docket Number FDA–2008–D–0150	1	1	1	10	10
Cardiovascular Outcome Claim Supplement Submission ...	8	2.5	20	20	400
Total					410

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: April 12, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013–09093 Filed 4–17–13; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA–2001–P–0238, FDA–2010–P–0526, FDA–2010–P–0540, FDA–2011–P–0473]

Determination That the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20–553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that OXYCONTIN (oxycodone hydrochloride) extended-release tablets (10 milligrams (mg), 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg) approved under new drug application (NDA) 20–553 were withdrawn from sale for reasons of safety or effectiveness. The Agency will not accept or approve abbreviated new drug applications (ANDAs) for products that reference NDA 20–553.

FOR FURTHER INFORMATION CONTACT: Patrick Raulerson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6368, Silver Spring, MD 20993–0002, 301–796–3522.

SUPPLEMENTARY INFORMATION:

I. Background

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417)

(the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the “listed drug,” which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is known generally as the “Orange Book.” Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 U.S.C. 355(j)(7)(C); 21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made before approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

OXYCONTIN (oxycodone hydrochloride) extended-release tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg (original OxyContin), are the subject of NDA 20–553, held by Purdue Pharma LP (Purdue) and initially approved on

December 12, 1995. A reformulated version of these products, OXYCONTIN (oxycodone hydrochloride) extended-release tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg (reformulated OxyContin), are the subject of NDA 22–272, also held by Purdue and initially approved on April 5, 2010. Reformulated OxyContin was developed with physicochemical properties that are intended to make the tablet more difficult to manipulate for purposes of abuse or misuse. Both original and reformulated OxyContin are opioid agonist products indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

In correspondence dated August 10, 2010, Purdue notified FDA that it had ceased shipment of original OxyContin, and FDA subsequently moved original OxyContin to the “Discontinued Drug Product List” section of the Orange Book. On April 16, 2013, FDA approved a supplemental application for reformulated OxyContin, approving changes to the product labeling that describe certain abuse-deterrent properties of the reformulated product.

Several parties have submitted citizen petitions under 21 CFR 10.30, requesting that the Agency determine whether original OXYCONTIN (oxycodone hydrochloride) extended-release tablets were voluntarily withdrawn from sale for reasons other than safety or effectiveness.¹

Based on the information available at this time, FDA has determined under § 314.161 that original OxyContin was

¹ Varam, Inc., Docket No. 2011–P–0473 (June 9, 2011) (10, 15, 20, 30, 40, 50, 80, and 160 mg); Sheppard, Mullin, Richter & Hampton LLP, Docket No. 2010–P–0540 (Oct. 8, 2010) (10, 15, 20, 30, 40, 60, and 80 mg); Lachman Consultant Services, Inc., Docket No. FDA–2010–P–0526 (Sept. 30, 2010) (10, 15, 20, 30, 40, 60, 80, and 160 mg). Lachman also submitted a petition in 2001 concerning just Purdue’s 2001 withdrawal of the 160 mg strength. Docket No. FDA–2001–P–0473 (formerly Docket No. 2001P–0426) (Sept. 18, 2001).

withdrawn from sale for reasons of safety or effectiveness. FDA has reached this determination following a careful review and analysis of the following information: (1) The citizen petitions described previously; (2) the comments submitted to the dockets associated with these petitions; (3) the Agency records and other information concerning original and reformulated OxyContin and the withdrawal of original OxyContin; and (d) data, literature, and other information concerning postmarketing adverse events associated with original OxyContin, reformulated OxyContin, and other extended-release oxycodone products.

II. Initiatives To Address Abuse of Opioid Analgesics

Opioid analgesics are an important component of modern pain management. Abuse and misuse of these products, however, has grown into a public health epidemic. According to the Centers for Disease Control and Prevention, sales of prescription opioids in the United States increased over 300 percent from 1999 to 2008 (Ref. 1). Overdose deaths involving these products increased commensurately over the same period, from 4,000 to 14,800 (Refs. 1 and 2). In 2008 prescription opioids were involved in more overdose deaths than heroin and cocaine combined (Ref. 3). In 2010 the number of overdose deaths in which prescription opioids were involved rose to 16,651, which represented more than 75 percent of all overdose deaths involving prescription drugs (Ref. 4).

FDA, together with other Federal agencies, is working to address this large and growing problem while ensuring that patients in pain have appropriate access to opioid analgesics. FDA has worked to improve the labeling of OxyContin and other opioid analgesics to better warn prescribers and patients of the serious risks associated with abuse and misuse. FDA also has worked extensively with the sponsors of OxyContin and other extended-release or long-acting prescription (ER/LA) opioid analgesics to address these risks through a classwide risk evaluation and mitigation strategy (REMS) <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf>.

This REMS, approved on July 9, 2012, requires sponsors of ER/LA opioids to make available training for health care professionals on proper prescribing practices and also to distribute educational materials to prescribers and patients on the safe use of these medications.

FDA considers the development of opioid analgesics that can deter abuse and misuse to be a public health priority. Opioid analgesics can be abused orally or by injection, snorting, or smoking and also may be misused in therapeutic contexts. Products may be designed to deter one or more of these methods of abuse or misuse. Following mandates in the 2011 White House prescription drug abuse prevention plan (Ref. 5) and section 1122(c) of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144) (126 Stat. 1075), FDA recently issued a draft guidance to industry on the evaluation and labeling of potentially abuse-deterrent opioid analgesics (Ref. 6).

III. Assessment of Abuse-Deterrent Properties of Reformulated OxyContin

All forms of opioid analgesic abuse are dangerous, and non-oral routes of abuse are particularly dangerous. Intranasal and intravenous opioid abuse is associated with serious adverse events including addiction, overdose, and death (Refs. 7, 8, and 9). Intravenous opioid abuse is associated with HIV and hepatitis B and C infection risk (Ref. 10). Further, as stated in the OxyContin labeling (see section 9.2), injection of OxyContin excipients “can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.” The label is available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272s016lbl.pdf. Intranasal opioid abuse is associated with nasal, palatal, and pharyngeal necrosis (Refs. 7 and 11).

Original OxyContin was often abused by manipulating the product to defeat its extended-release mechanism, causing the oxycodone to be released more rapidly. Original OxyContin also was manipulated for therapeutic purposes, for example, by crushing the product to sprinkle it onto food or to administer it through a gastric tube. As noted in the boxed warning of the labeling, disruption of the tablet and controlled-release mechanism for abuse or misuse “can lead to rapid release and absorption of a potentially fatal dose of oxycodone.”

FDA has conducted an extensive review of data available to the Agency regarding reformulated OxyContin, including in vitro, pharmacokinetic, clinical abuse potential, and postmarketing study data. The data show that, when compared to original OxyContin, reformulated OxyContin has an increased ability to resist crushing, breaking, and dissolution using a variety of tools and solvents. The data also

demonstrate that, when subjected to an aqueous environment, reformulated OxyContin gradually forms a viscous hydrogel. The data also indicate that insufflation of finely crushed reformulated OxyContin was associated with lower “liking” compared to finely crushed original OxyContin in recreational opioid users with a history of intranasal drug abuse. FDA concludes, based on these data and our review of all data and information available to the Agency at this time, that the physicochemical properties of reformulated OxyContin are expected to make abuse via injection difficult and are expected to reduce abuse via the intranasal route. In addition, reformulated OxyContin also may deter certain types of misuse in therapeutic contexts.

Additional postmarketing studies intended to assess the impact of reformulated OxyContin on abuse and misuse in the community also have been conducted; some of these are still ongoing. FDA has reviewed the available data from these studies and has concluded that they suggest, but do not confirm, a reduction in non-oral abuse. The Agency will continue to review data from these studies as they become available, as well as any other relevant data that may be developed in the future.

FDA has long considered the abuse potential of a drug in numerous regulatory contexts. Where appropriate, FDA may take into account abuse potential as part of the safety profile of a drug when weighing its benefits and risks. In this case, FDA has considered the abuse potential as part of the Agency’s determination of whether the original formulation of OxyContin was withdrawn from sale for reasons of safety or effectiveness. This approach is particularly appropriate here in light of the extensive and well-documented history of OxyContin abuse.

Original OxyContin has the same therapeutic benefits as reformulated OxyContin. Original OxyContin, however, poses an increased potential for abuse by certain routes of administration, when compared to reformulated OxyContin. Based on the totality of the data and information available to the Agency at this time, FDA concludes that the benefits of original OxyContin no longer outweigh its risks. FDA has determined that OXYCONTIN (oxycodone hydrochloride) extended release tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg (approved under new drug application 20–553), were withdrawn from sale for reasons of safety or effectiveness. Accordingly, the

Agency will remove OXYCONTIN (oxycodone hydrochloride) extended-release tablets (10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg) approved under NDA 20–553 from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to these drug products.

IV. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site addresses in this reference section, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

1. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (CDC), “Policy Impact: Prescription Painkiller Overdoses” (www.cdc.gov/HomeandRecreationalSafety/pdf/PolicyImpact-PrescriptionPainkillerOD.pdf).
2. CDC, “Vital Signs: Overdoses of Prescription Opioid Pain Relievers—United States, 1999–2008,” *Morbidity and Mortality Weekly Report*, vol. 60, No. 43, pp. 1487–1492, 2011 (www.cdc.gov/mmwr/pdf/wk/mm6043.pdf).
3. National Center for Injury Prevention and Control, CDC, “Unintentional Drug Poisoning in the United States” (www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf).
4. Jones, C.M., K.A. Mack, and L.J. Paulozzi, “Pharmaceutical Overdose Deaths, United States, 2010,” *Journal of the American Medical Association*, vol. 309, pp. 657–659, 2013.
5. FDA, “FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics” (<http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf>).
6. FDA, “Draft Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling,” (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf).
7. Katz, N., R.C. Dart, E. Bailey, et al., “Tampering With Prescription Opioids: Nature and Extent of the Problem, Health Consequences, and Solutions,” *The American Journal of Drug and Alcohol Abuse*, vol. 37, pp. 205–217, 2011.
8. Silva, K., S.M. Schrager, A. Kecojevic, et al., “Factors Associated With History of Non-Fatal Overdose Among Young Nonmedical Users of Prescription

Drugs,” *Drug and Alcohol Dependence*, vol. 128, pp. 104–110, 2013.

9. Degenhardt, L., C. Bucello, B. Mathers, et al., “Mortality Among Regular or Dependent Users of Heroin and Other Opioids: A Systematic Review and Meta-Analysis of Cohort Studies,” *Addiction*, vol. 106, pp. 32–51, 2011.
10. CDC, “Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance From the CDC and the U.S. Department of Health and Human Services,” *Morbidity and Mortality Weekly Report*, vol. 61, pp. 1–40, 2012.
11. Alexander, D., K. Alexander, and J. Valentino, “Intranasal Hydrocodone-Acetaminophen Abuse-Induced Necrosis of the Nasal Cavity and Pharynx,” *The Laryngoscope*, vol. 122, pp. 2378–2381, 2012.

Dated: April 12, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013–09092 Filed 4–16–13; 4:15 pm]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Service Administration

Advisory Committee on Interdisciplinary, Community-Based Linkages; Notice of Meeting

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), notice is hereby given of the following meeting:

Name: Advisory Committee on Interdisciplinary, Community-Based Linkages (ACICBL).

Dates and Times: April 22, 2013, 8:30 a.m.–5:00 p.m., April 23, 2013, 9:00 a.m.–5:00 p.m.

Place: Health Resources and Services Administration, U.S. Department of Health and Human Services, 5600 Fishers Lane, Rockville, Maryland 20852, Room 18–57.

Status: The meeting will be open to the public.

Purpose: The members of the ACICBL will begin discussions to develop the legislatively mandated 13th Annual Report to the Secretary of Health and Human Services and Congress. The Committee members will focus on the working topic: Optimizing the Interprofessional Team Member’s Contributions to Population Health. The Committee has invited Dr. John Gilbert, former Principal and Professor Emeritus at the University of British Columbia, Canada; Ms. Rachel Watman, Senior Program Officer, The John A. Hartford

Foundation; Dr. John Bulger, Chief Quality Officer, Geisinger Health System; Dr. Paul McGann, Deputy Chief Medical Officer for Innovation Grants, Centers for Medicare & Medicaid Services; Dr. Thomas Edes, Director of Home and Community-Based Care, U.S. Department of Veterans Affairs; and Dr. Alex Camacho, Deputy Director, Office of Performance Measurement, Health Resources and Services Administration. The meeting will afford committee members with the opportunity to identify and discuss population health; interprofessional education, care and competencies; and best practices and the like in an effort to formulate appropriate recommendations for the Secretary and the Congress.

Agenda: The ACICBL agenda includes an overview of the Committee’s general business activities, presentations by and dialogue with experts, and discussion sessions specifically for the development of recommendations to be addressed in the 13th Annual ACICBL Report. The agenda will be available 2 days prior to the meeting on the HRSA Web site (<http://www.hrsa.gov/advisorycommittees/bhpradvisory/acicbl/acicbl.html>). Agenda items are subject to change as priorities dictate.

SUPPLEMENTARY INFORMATION: Members of the public and interested parties may request to provide comments or register to attend the meeting by emailing their first name, last name, and full email address to BHPRAdvisoryCommittee@hrsa.gov or by contacting Ms. Crystal Straughn at 301–443–3594. Registration is first come, first served as space is limited.

FOR FURTHER INFORMATION CONTACT: Anyone requesting information regarding the ACICBL should contact Dr. Joan Weiss, Designated Federal Official within the Bureau of Health Professions, Health Resources and Services Administration, in one of three ways: (1) Send a request to the following address: Dr. Joan Weiss, Designated Federal Official, Bureau of Health Professions, Health Resources and Services Administration, Parklawn Building, Room 9C–05, 5600 Fishers Lane, Rockville, Maryland 20857; (2) call (301) 443–6950; or (3) send an email to jweiss@hrsa.gov.

Dated: April 11, 2013.

Bahar Niakan,

Director, Division of Policy and Information Coordination.

[FR Doc. 2013–09135 Filed 4–17–13; 8:45 am]

BILLING CODE 4165–15–P

Tab 36

Reference 1: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (CDC), “Policy Impact: Prescription Painkiller Overdoses”

POLICY
IMPACT

PRESCRIPTION PAINKILLER OVERDOSES

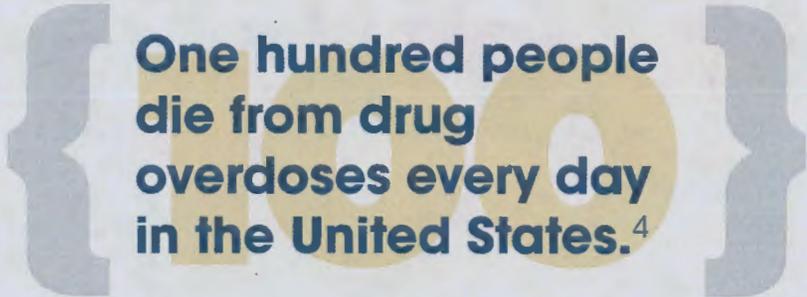
National Center for Injury Prevention and Control
Division of Unintentional Injury Prevention



WHAT'S THE ISSUE?

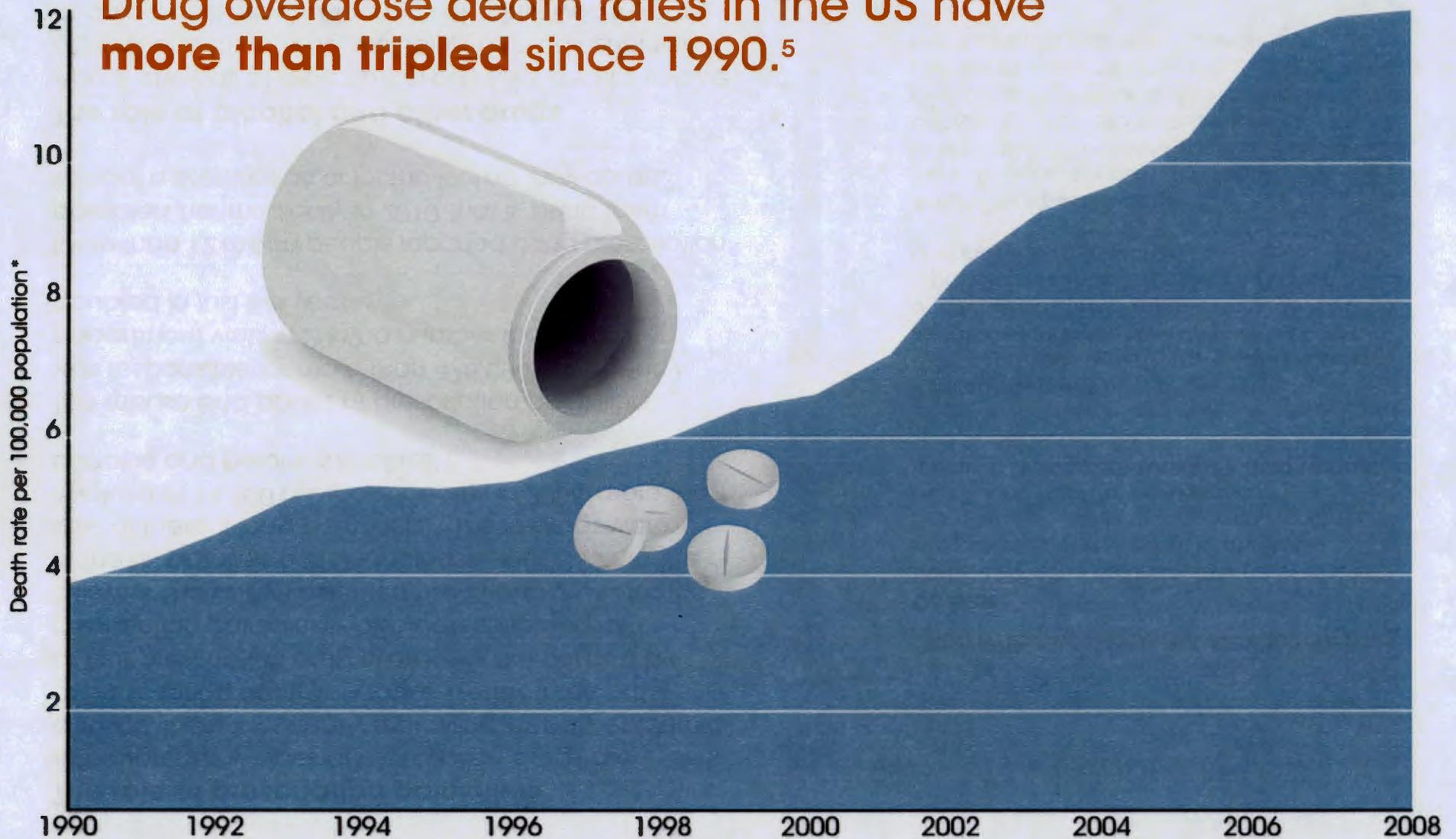
In a period of nine months, a tiny Kentucky county of fewer than 12,000 people sees a 53-year-old mother, her 35-year-old son, and seven others die by overdosing on pain medications obtained from pain clinics in Florida.¹ In Utah, a 13-year-old fatally overdoses on oxycodone pills taken from a friend's grandmother.² A 20-year-old Boston man dies from an overdose of methadone, only a year after his friend also died from a prescription drug overdose.³

These are not isolated events. Drug overdose death rates in the United States have more than tripled since 1990 and have never been higher. In 2008, more than 36,000 people died from drug overdoses, and most of these deaths were caused by prescription drugs.⁴



**One hundred people
die from drug
overdoses every day
in the United States.⁴**

Drug overdose death rates in the US have more than tripled since 1990.⁵



*Deaths are those for which poisoning by drugs (illicit, prescription, and over-the-counter) was the underlying cause.

WHAT DO WE KNOW?

The role of prescription painkillers

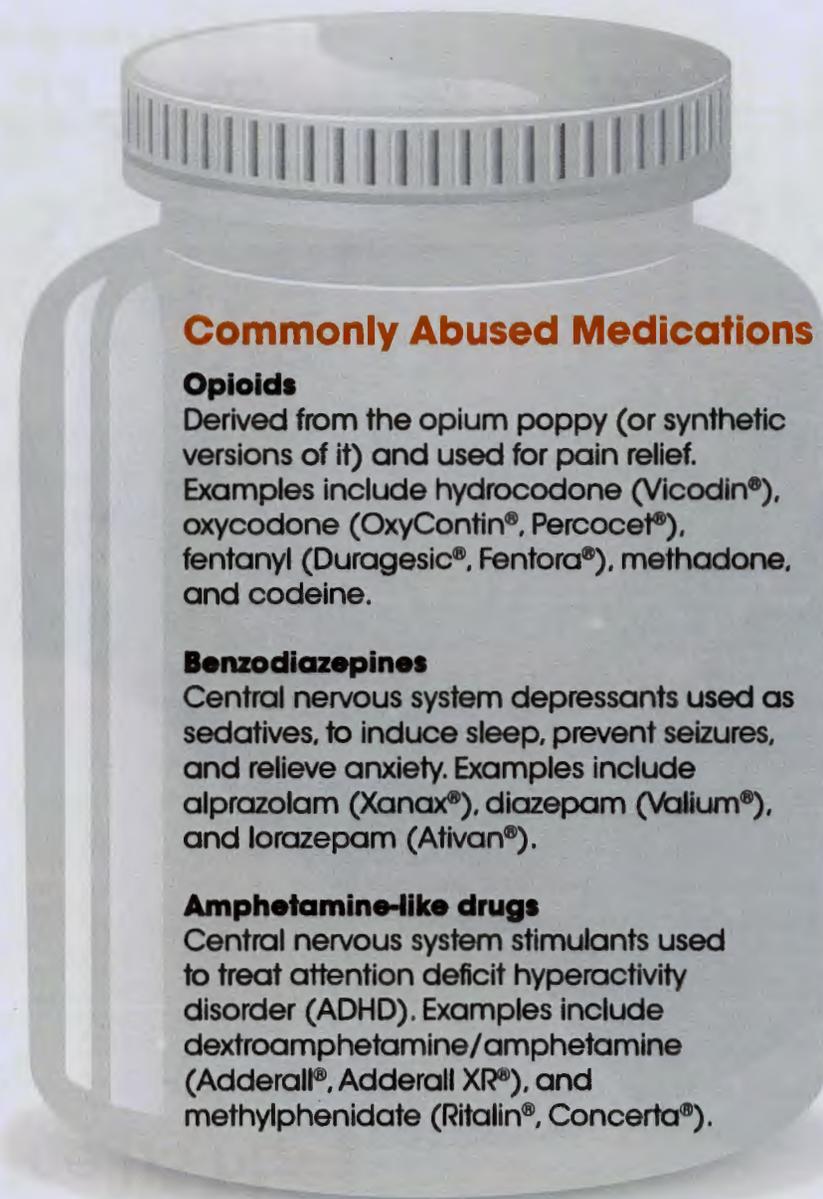
Although many types of prescription drugs are abused, there is currently a growing, deadly epidemic of prescription painkiller abuse. Nearly three out of four prescription drug overdoses are caused by prescription painkillers—also called opioid pain relievers. The unprecedented rise in overdose deaths in the US parallels a 300% increase since 1999 in the sale of these strong painkillers.⁴ These drugs were involved in 14,800 overdose deaths in 2008, more than cocaine and heroin combined.⁴

The misuse and abuse of prescription painkillers was responsible for more than 475,000 emergency department visits in 2009, a number that nearly doubled in just five years.⁶

More than 12 million people reported using prescription painkillers nonmedically in 2010, that is, using them without a prescription or for the feeling they cause.⁷

The role of alcohol and other drugs

About one-half of prescription painkiller deaths involve at least one other drug, including benzodiazepines, cocaine, and heroin. Alcohol is also involved in many overdose deaths.⁸



Commonly Abused Medications

Opioids

Derived from the opium poppy (or synthetic versions of it) and used for pain relief. Examples include hydrocodone (Vicodin[®]), oxycodone (OxyContin[®], Percocet[®]), fentanyl (Duragesic[®], Fentora[®]), methadone, and codeine.

Benzodiazepines

Central nervous system depressants used as sedatives, to induce sleep, prevent seizures, and relieve anxiety. Examples include alprazolam (Xanax[®]), diazepam (Valium[®]), and lorazepam (Ativan[®]).

Amphetamine-like drugs

Central nervous system stimulants used to treat attention deficit hyperactivity disorder (ADHD). Examples include dextroamphetamine/amphetamine (Adderall[®], Adderall XR[®]), and methylphenidate (Ritalin[®], Concerta[®]).

In 2008, there were **14,800** prescription painkiller deaths.⁴

For every **1** death there are...



10 treatment admissions for abuse⁹

32 emergency dept visits for misuse or abuse⁶

130 people who abuse or are dependent⁷

825 nonmedical users⁷

How prescription painkiller deaths occur

Prescription painkillers work by binding to receptors in the brain to decrease the perception of pain. These powerful drugs can create a feeling of euphoria, cause physical dependence, and, in some people, lead to addiction. Prescription painkillers also cause sedation and slow down a person's breathing.

A person who is abusing prescription painkillers might take larger doses to achieve a euphoric effect and reduce withdrawal symptoms. These larger doses can cause breathing to slow down so much that breathing stops, resulting in a fatal overdose.

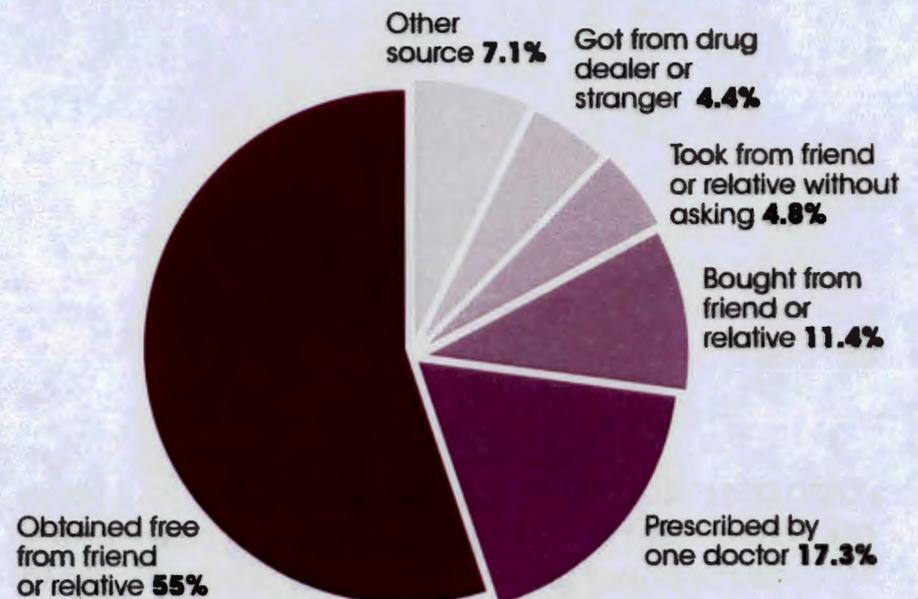
In 2010, 2 million people reported using prescription painkillers nonmedically for the first time within the last year—nearly 5,500 a day.⁷

Where the drugs come from

Almost all prescription drugs involved in overdoses come from prescriptions originally; very few come from pharmacy theft. However, once they are prescribed and dispensed, prescription drugs are frequently diverted to people using them without prescriptions. More than three out of four people who misuse prescription painkillers use drugs prescribed to someone else.⁷

Most prescription painkillers are prescribed by primary care and internal medicine doctors and dentists, not specialists.¹⁰ Roughly 20% of prescribers prescribe 80% of all prescription painkillers.^{11, 12, 13}

People who abuse prescription painkillers get drugs from a variety of sources⁷



Who is most at risk

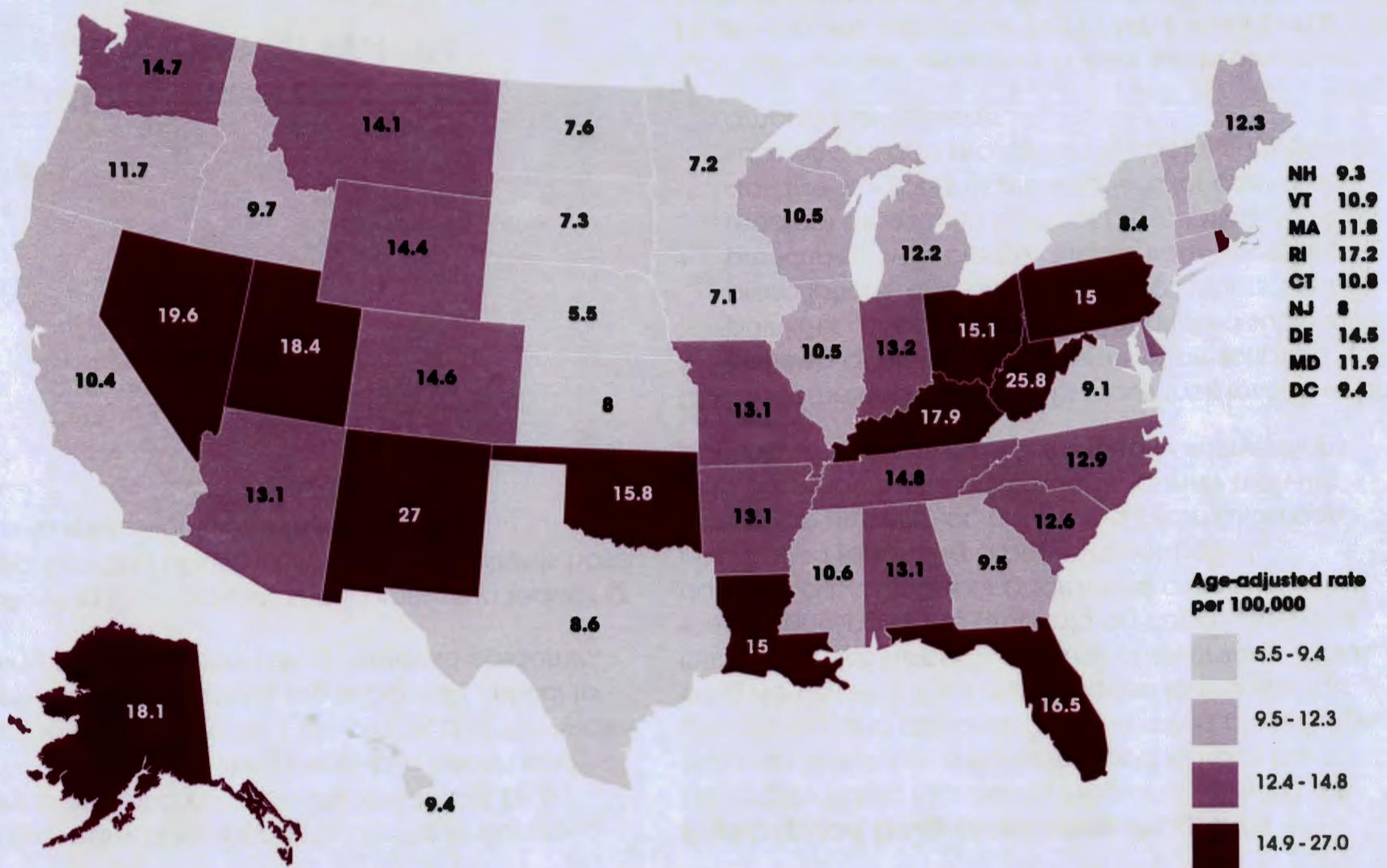
Understanding the groups at highest risk for overdose can help states target interventions. Research shows that some groups are particularly vulnerable to prescription painkiller overdose:

- People who obtain multiple controlled substance prescriptions from multiple providers—a practice known as “doctor shopping.”^{14,15}
- People who take high daily dosages of prescription painkillers and those who misuse multiple abuse-prone prescription drugs.^{15,16,17,18,19}
- Low-income people and those living in rural areas.
 - People on Medicaid are prescribed painkillers at twice the rate of non-Medicaid patients and are at six times the risk of prescription painkillers overdose.^{20,21} One Washington State study found that 45% of people who died from prescription painkiller overdoses were Medicaid enrollees.²⁰
- People with mental illness and those with a history of substance abuse.¹⁹

Where overdose deaths are the highest

The drug overdose epidemic is most severe in the Southwest and Appalachian region, and rates vary substantially between states. The highest drug overdose death rates in 2008 were found in New Mexico and West Virginia, which had rates nearly five times that of the state with the lowest rate, Nebraska.⁴

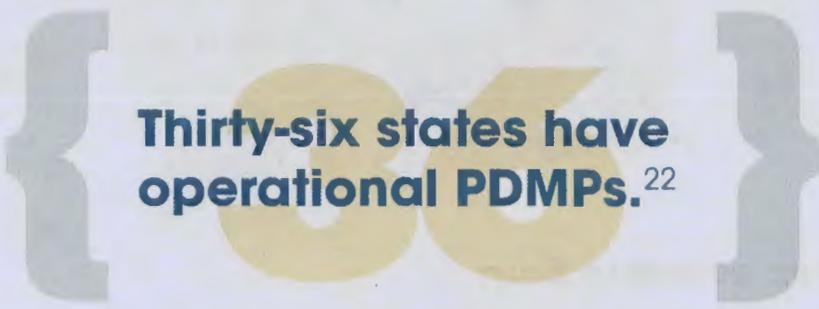
Drug overdose death rates by state, 2008⁴



WHAT CAN WE DO?

There are many different points of intervention to prevent prescription drug overdoses. States play a central role in protecting the public health and regulating health care and the practice of the health professions. As such, states are especially critical to reversing the prescription drug overdose epidemic.

The following state policies show promise in reducing prescription drug abuse while ensuring patients have access to safe, effective pain treatment.



Thirty-six states have operational PDMPs.²²

CDC RECOMMENDATIONS

Prescription Drug Monitoring Programs

Prescription Drug Monitoring Programs (PDMPs) are state-run electronic databases used to track the prescribing and dispensing of controlled prescription drugs to patients. They are designed to monitor this information for suspected abuse or diversion—that is, the channeling of the drug into an illegal use—and can give a prescriber or pharmacist critical information regarding a patient's controlled substance prescription history. This information can help prescribers and pharmacists identify high-risk patients who would benefit from early interventions.

CDC recommends that PDMPs focus their resources on

- **patients** at highest risk in terms of prescription painkiller dosage, numbers of controlled substance prescriptions, and numbers of prescribers; and
- **prescribers** who clearly deviate from accepted medical practice in terms of prescription painkiller dosage, numbers of prescriptions for controlled substances, and proportion of doctor shoppers among their patients.

CDC also recommends that PDMPs link to electronic health records systems so that PDMP information is better integrated into health care providers' day-to-day practices.

Patient review and restriction programs

State benefits programs (like Medicaid) and workers' compensation programs should consider monitoring prescription claims information and PDMP data (where applicable) for signs of inappropriate use of controlled prescription drugs. For patients whose use of multiple providers cannot be justified on medical grounds, such programs should consider reimbursing claims for controlled prescription drugs from a single designated physician and a single designated pharmacy. This can improve the coordination of care and use of medical services, as well as ensure appropriate access, for patients who are at high risk for overdose.

Health care provider accountability

States should ensure that providers follow evidence-based guidelines for the safe and effective use of prescription painkillers. Swift regulatory action taken against health care providers acting outside the limits of accepted medical practice can decrease provider behaviors that contribute to prescription painkiller abuse, diversion, and overdose.

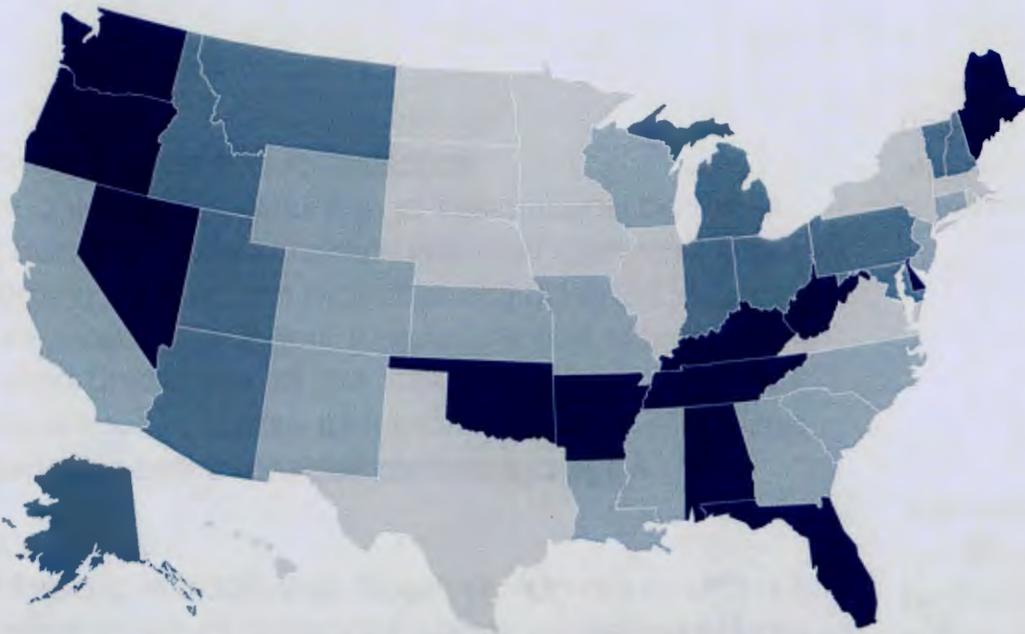
Laws to prevent prescription drug abuse and diversion

States can enact and enforce laws to prevent doctor shopping, the operation of rogue pain clinics or "pill mills," and other laws to reduce prescription painkiller diversion and abuse while safeguarding legitimate access to pain management services. These laws should also be rigorously evaluated for their effectiveness.

Better access to substance abuse treatment

Effective, accessible substance abuse treatment programs could reduce overdose among people struggling with dependence and addiction. States should increase access to these important programs.

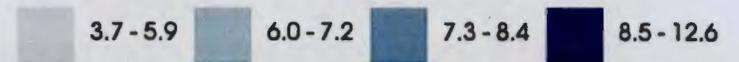
These recommendations are based on promising interventions and expert opinion. Additional research is needed to understand the impact of these interventions on reducing prescription drug overdose deaths.



The amount of prescription painkillers sold in states varies⁴

The quantity of prescription painkillers sold to pharmacies, hospitals, and doctors' offices was 4 times larger in 2010 than in 1999. Enough prescription painkillers were prescribed in 2010 to medicate every American adult around-the-clock for one month.

Kilograms of prescription painkillers sold, rates per 10,000 people



POLICY IMPACT

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For references, visit: www.cdc.gov/homeandrecreationalafety/rxbrief

November 2011

Tab 37

Reference 2: CDC, “Vital Signs: Overdoses of Prescription Opioid Pain Relievers—United States, 1999–2008,” *Morbidity and Mortality Weekly Report*, vol. 60, No. 43, pp. 1487–1492, 2011

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Weekly / Vol. 60 / No. 43

November 4, 2011

World Pneumonia Day — November 12, 2011

Pneumonia kills more children than any other illness; among approximately 9 million children aged <5 years who die each year worldwide, 1.6 million die from pneumonia (1). At the 2010 World Health Assembly, a resolution on the prevention and control of childhood pneumonia was passed (2). The resolution stated that leaders in each country should implement comprehensive plans to reduce pneumonia deaths. This effort will support United Nations Millennium Development Goal 4, which states that childhood mortality should be reduced by two thirds from 1990 to 2015 (3).

Illness and deaths from pneumonia can be reduced with the use of *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae* type b (Hib), influenza, and measles vaccines; antimicrobial treatments; and supportive health care, among other strategies.

To raise awareness of the effects of pneumonia globally, the third annual World Pneumonia Day, November 12, 2011, is being promoted by a coalition of approximately 120 major health, humanitarian relief, advocacy, faith-based, government, and other organizations; CDC and United Nations Children's Fund (UNICEF) are providing technical assistance. Events are scheduled around the world. More information is available at <http://worldpneumoniaday.org>.

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Invasive Pneumococcal Disease and 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Coverage Among Children Aged ≤59 Months — Selected U.S. Regions, 2010–2011

On March 12, 2010, the Advisory Committee on Immunization Practices (ACIP) published recommendations for use of a newly licensed, 13-valent pneumococcal conjugate vaccine (PCV13) to replace the 7-valent vaccine (PCV7) for all children and for a supplemental dose for those aged 14 through 59 months (1). PCV is given routinely to children at ages 2, 4, and 6 months, and a booster dose is given at 12–15 months (1). PCV13 includes antigens of six pneumococcal serotypes in addition to those in PCV7 (1). Children only vaccinated with PCV7 are susceptible to those six serotypes, which can cause invasive pneumococcal disease (IPD) and death. During 2010 and 2011, CDC evaluated available data to assess the occurrence of PCV13-type IPD cases and PCV13 vaccination coverage among children aged ≤59 months. During May 1, 2010–April 30, 2011, 63 vaccine-eligible children with IPD caused by a serotype that would have been prevented by PCV13 were identified within 12 study regions. Most of those children were aged 24 through 59 months and were vaccinated completely with PCV7 but had not received the recommended supplemental dose of PCV13. Immunization Information System (IIS) sentinel site data from March 2010–June 2011 indicated that the proportion of PCV7-vaccinated children who had received the PCV13 supplemental dose was only

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37%. Similarly, among children aged ≤ 59 months requiring additional primary series doses, PCV13 coverage was only 46%. Given the potential for missed PCV13 vaccination, health-care providers should recommend PCV13 vaccination for all eligible children aged 14 through 59 months during all visits, and continue to ensure receipt of the full PCV13 primary series for younger children.

In June 2011, a girl in California, aged 2 years, died of IPD caused by serotype 19A, one of six serotypes included in PCV13 but not in PCV7. The child had received 3 doses of PCV7 but had not received PCV13. The California Department of Public Health identified an additional 30 PCV13-eligible children who had developed nonfatal IPD caused by the pneumococcal serotypes not covered by PCV7 and who became ill after PCV13 was recommended by ACIP. In August 2011, a health advisory was sent to California health-care providers to remind them of ACIP's recommendation for PCV13 use (2). To determine if other areas of the country were identifying cases of PCV13-type IPD among children eligible to receive PCV13 and to assess PCV13 vaccination coverage among children aged ≤ 59 months, CDC assessed data from 12 geographic regions participating in its ongoing PCV13 Vaccine Effectiveness Evaluation (3) and from eight IIS sentinel sites (4).

The PCV13 Vaccine Effectiveness Evaluation used data from Active Bacterial Core surveillance (ABCs), an active, population-based and laboratory-based surveillance system for monitoring invasive bacterial pathogens, and the Epidemiology

and Laboratory Capacity for Infectious Diseases (ELC) network, a group of U.S. sites supported by CDC to strengthen their capacity to address infectious disease threats (3). Children aged 2 months through 59 months who 1) were identified as having IPD by routine surveillance at ABCs and ELC sites, 2) were recommended by ACIP to receive PCV13, and 3) had a pneumococcal isolate available for serotyping were eligible for inclusion in the PCV13 Vaccine Effectiveness Evaluation. The catchment area for the evaluation comprised the 10 ABCs sites, (Connecticut, Minnesota, and New Mexico, and selected counties in California, Colorado, Georgia, Maryland, New York, Oregon, and Tennessee), plus Utah and Los Angeles County from the ELC sites, with a total population of 3.2 million children aged ≤ 59 months (5). Cases included in this analysis occurred in children enrolled in the PCV13 Vaccine Effectiveness Evaluation who had IPD caused by one of six serotypes included in PCV13 but not PCV7 and a complete vaccination history available at the time of analysis, and who were eligible to receive PCV13 at least 2 weeks before diagnosis of IPD.

During May 1, 2010–April 30, 2011, 135 cases of IPD caused by serotypes unique to PCV13 were identified among children aged 2 through 59 months. Among those, 81 (58%) had a complete vaccination history; of these, 66 (81%) had no previous PCV13 dose recorded. Three of the 66 cases involved children who were ineligible to receive PCV13 because of dates of PCV7 receipt and timing of disease diagnosis. Of the 63 remaining cases, 43 (68%) involved children aged 24–48

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months. Nearly all of these children (94%) had no underlying medical conditions. Among the 63 children, 48 (76%) were hospitalized; no deaths were reported. Thirty-nine of the children (62%) had received a full, 4-dose PCV7 series but had not received a supplemental PCV13 dose, and 11 others (18%) had received 3 doses of PCV7 but had not received a fourth pneumococcal vaccine dose, which should have been PCV13 (Figure 1) (1).

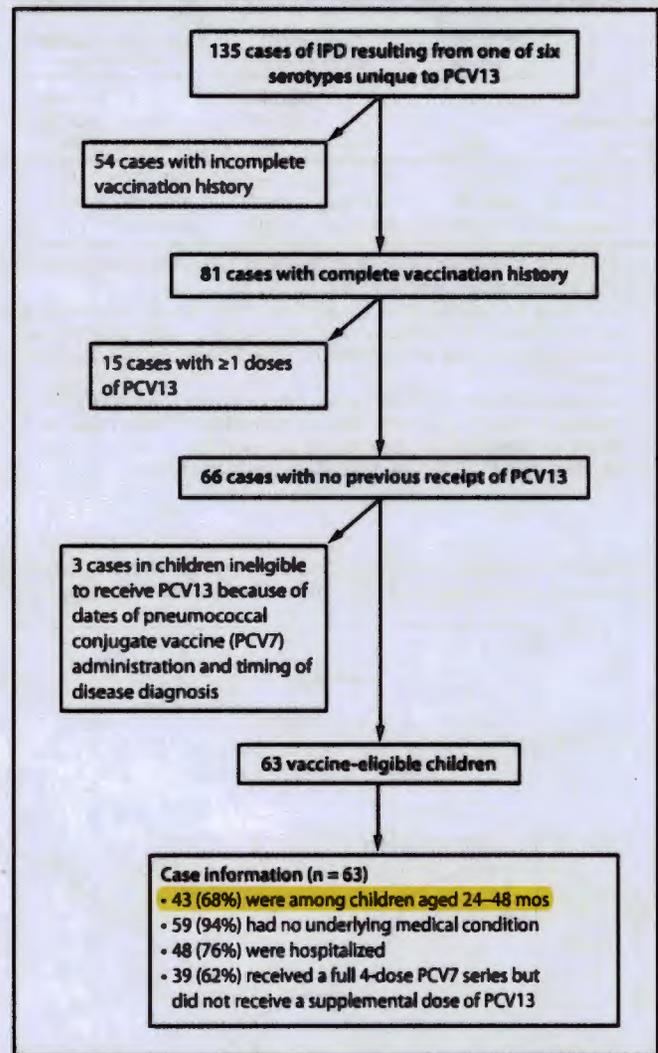
To assess coverage with PCV13, CDC collected data from the eight state and city-based IIS sentinel sites (4). Those collaborating sites include parts of Arizona, Colorado, Michigan, Minnesota, Oregon, and Wisconsin, all of North Dakota, and New York City, and include nearly 2 million children aged <6 years. Data on receipt of PCV13 were collected from March 2010, when PCV13 was first recommended, through June 2011 on children aged 0 through 11 months, 12 through 23 months, and 24 through 59 months as of March 2010, by primary PCV7 series completion status. A complete primary PCV7 series was defined as ≥ 4 doses, if the fourth dose was administered at age ≥ 12 months; 3 doses, if the third dose was administered at age ≥ 12 months; 2 doses, if both doses were administered at age ≥ 12 months; or 1 dose, if administered at age 24 to <60 months. Overall estimates were calculated by averaging unweighted site-specific estimates. Additionally, to evaluate the overall transition from PCV7 to PCV13, all sites reported the total number of doses administered weekly, by PCV type, during March 7–August 21, 2010.

Among approximately 850,000 children aged 12 through 59 months with a complete PCV7 series as of March 2010, 37% subsequently received the supplemental PCV13 dose as of June 30, 2011. The proportion of children receiving the dose was lower among children aged 24 through 59 months (32%) compared with children aged 12 through 23 months (58%) (Table). Among nearly 700,000 children aged 0 through 59 months with an incomplete primary PCV7 series as of March 2010, PCV13 coverage reached 46% by June 30, 2011. Similarly, children aged 24 through 59 months were less likely (14%) than younger children to receive a PCV13 dose (0 through 11 months: 71%; 12 through 23 months: 45%). Initial coverage with PCV13 occurred quickly after vaccine recommendation (Figure 2). By the week of April 18, the number of weekly PCV13 doses administered exceeded the number of weekly PCV7 doses administered. However, PCV7 continued to be used for a small proportion of children through August 2010.

Reported by

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FIGURE 1. Invasive pneumococcal disease (IPD) resulting from pneumococcal serotypes unique to 13-valent pneumococcal conjugate vaccine (PCV13), exclusion criteria applied, and characteristics of affected children aged ≤ 59 months — CDC's PCV13 Vaccine Effectiveness Evaluation,* United States, May 2010–April 2011



* Twelve areas across the United States participate in CDC's ongoing PCV13 Vaccine Effectiveness Evaluation, representing a population of 3.2 million children aged ≤ 59 months.

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Editorial Note

Within 2 months of the ACIP recommendation, PCV13 accounted for more than half of the weekly PCV doses administered. In spite of this rapid transition, not all children eligible for a supplemental dose are receiving it, leaving them more likely to develop IPD secondary to one of six serotypes

TABLE. Percentage of children aged ≤ 59 months who received an age-appropriate 13-valent pneumococcal conjugate vaccine (PCV13) dose, by primary 7-valent pneumococcal conjugate vaccine (PCV7) series completion status and age group — Immunization Information System (IIS) sentinel sites, United States, March 12, 2010–June 30, 2011

Age group (mos)*	Enrolled in IIS in birth range	Completed [†] PCV7 series*		Did not complete [‡] PCV7 series*	
	No.	No.	Received PCV13 [§] (%)	No.	Received PCV13 [§] (%)
0 through 11	288,671	—	—	288,671	(71)
12 through 23	297,285	160,565	(58)	136,720	(45)
24 through 59	953,295	694,135	(32)	259,160	(14)

* As of March 12, 2010, when the Advisory Committee on Immunization Practices (ACIP) published recommendations for use of PCV13.

[†] Defined as ≥ 4 doses if fourth dose was administered at age ≥ 12 months, 3 doses if third dose administered at age ≥ 12 months, 2 doses if both doses were administered at age ≥ 12 months, or 1 dose if administered at age 24 to < 60 months.

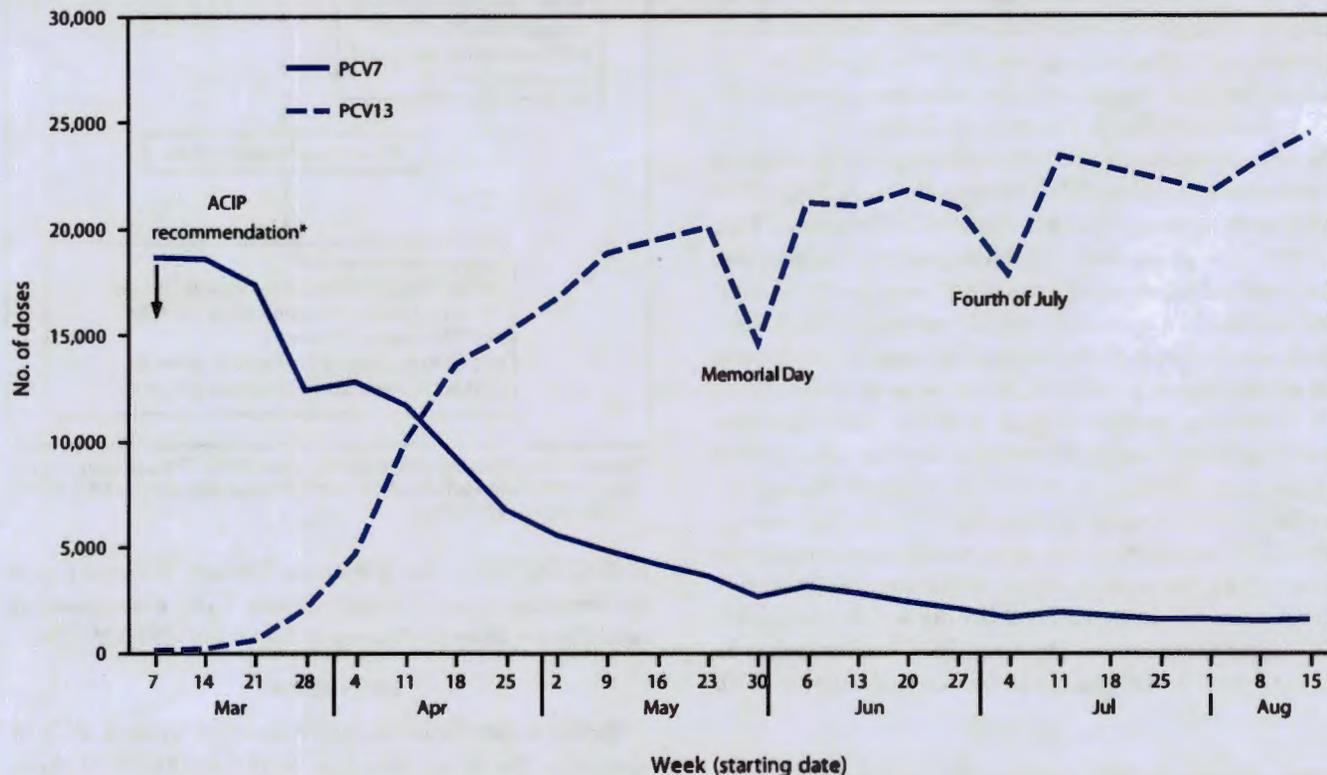
[‡] Incomplete as of March 12, 2010; includes children who received no PCV doses. All children 0 through 11 months have an incomplete PCV series because a complete series requires at least 1 dose at ≥ 12 months.

[§] On or after March 12, 2010. Unweighted average across sites.

uniquely covered by PCV13. Current PCV13 vaccination trends suggest that the majority of children not receiving the supplemental dose are aged 24 through 59 months rather than 12 through 23 months.

Health-care providers rapidly transitioned from PCV 7 to PCV13 administration. To facilitate the rapid transition from PCV7 to PCV13, the manufacturer accepted returns of PCV7 from public and private providers. In the public sector, PCV13 was available as of March 18, 2010, and all unused PCV7 had to be returned by May 10, 2010, to receive credit from the manufacturer. By July 2010, Pfizer reported that $>90\%$ of its private shipments of pneumococcal conjugate vaccines were for PCV13 (P.L. Alexa, Pfizer Inc., personal communication, July 2010). The underlying factors contributing to PCV13 coverage differences across age groups could not be determined with certainty. Lower coverage among the oldest age group might be related to fewer preventive care visits and vaccination opportunities compared with younger children (6), decreased perceived risk for invasive disease among the older children (7),

FIGURE 2. Pneumococcal conjugate vaccine doses administered to children aged 0 through 59 months, by vaccine type and week — Immunization Information System sentinel sites, United States, March 7–August 21, 2010



Abbreviations: ACIP = Advisory Committee on Immunization Practices; PCV7 = 7-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine.

* CDC. Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010. MMWR 2010;59:258–61.

What is already known on this topic?

On February 24, 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) was licensed and in March 2010, the Advisory Committee for Immunization Practices (ACIP) published recommendations to use PCV13 exclusively in place of the 7-valent vaccine (PCV7) and to administer a single supplemental dose of PCV13 to all children aged 14 through 59 months who have received an age-appropriate series of PCV7.

What is added by this report?

Children are developing invasive pneumococcal disease (IPD) caused by serotypes that could be prevented by PCV13 but not PCV7. In June 2011, a child, who had received 3 doses of PCV7 died of IPD caused by one of six serotypes to which PCV13 uniquely provides protection. In an evaluation of data from CDC's ongoing PCV13 Vaccine Effectiveness Evaluation, 63 children eligible but not vaccinated with PCV13 developed IPD caused by one those six serotypes. Vaccination trends at eight Immunization Information System sentinel sites indicated that receipt of the supplemental PCV13 dose is <40% among PCV7-vaccinated children.

What are the implications for public health practice?

Immunization programs and vaccination providers should encourage parents of all children aged 14 through 59 months who have received an age-appropriate PCV7 series to have their child receive a single supplemental dose of PCV13. Providers should take advantage of all office visits to vaccinate all eligible children with PCV13 to increase vaccination coverage.

and health-care provider lack of awareness of or inconsistency in implementing PCV recommendations for older children (8).

Estimates from the National Immunization Survey show coverage with ≥ 4 doses of PCV increased from 80% in 2009 to 83% in 2010 and remained high at 93% for ≥ 3 doses of PCV among children aged 19–35 months. Although coverage levels for PCV continue to increase, careful monitoring of coverage levels overall and across subpopulations (i.e., older children) will be important to ensure that all children are protected adequately (9).

The findings in this report are subject to at least three limitations. First, although the ABCs, ELC, and IIS systems are important sources of U.S. population-based data for surveillance of invasive bacterial disease incidence and patterns of vaccine coverage, they represent a select sample of U.S. regions and the findings might not be nationally representative. Second, although IIS sentinel site data are monitored for accuracy, some PCV13 doses might have been misclassified as PCV7 in IIS, thereby underestimating PCV13 coverage. Finally, although no reports of difficulty in obtaining PCV13 have occurred, some vaccination providers might have experienced a delay in receipt of vaccine.

To prevent IPD among children, health-care providers should administer a single supplemental dose of PCV13 to all children aged 14 through 59 months who have received an age-appropriate number of PCV7 doses to provide additional protection against the six serotypes unique to PCV13 (1). Additionally, health-care providers should complete the PCV7 series with PCV13, and continue to ensure that all children receive timely receipt of the full primary series as recommended by ACIP. No PCV7 should be used at this time. To increase PCV13 coverage, health-care providers should take advantage of opportunities to provide the supplemental dose of PCV13 to age-eligible patients during any health-care visit.

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Progress Toward Poliomyelitis Eradication — India, January 2010–September 2011

The Global Polio Eradication Initiative was launched in 1988 (1). In 1995, when eradication activities were initiated in India, an estimated 50,000 polio cases were occurring each year (2). By 2006, transmission of indigenous wild poliovirus (WPV) had been interrupted in all countries except India, Afghanistan, Pakistan, and Nigeria (1). During 2006–2009, India annually reported 559 to 874 cases of confirmed WPV, with cases centered in the northern states of Uttar Pradesh and Bihar (3). These cases accounted for 43% of confirmed cases of WPV reported worldwide during this period. However, in 2010, only 42 WPV cases were reported in India, and in 2011, only one WPV case had been confirmed as of October 31. This report updates previous reports (2,3) and summarizes progress toward polio eradication in India during January 2010–September 2011. Throughout India, the most recent confirmed WPV type 3 (WPV3) case occurred on October 22, 2010, in Jharkhand, and the most recent confirmed WPV type 1 (WPV1) case occurred on January 13, 2011, in West Bengal; WPV2 has not been reported in India since 1999. Importation of WPV into India is a risk, and undetected low-level WPV transmission is a possibility, requiring high vaccination coverage in all states, continued focus on children in migrant and underserved populations, sensitive surveillance for prompt detection of any WPV, and preparedness to mount a robust emergency vaccination campaign in response to any WPV cases.

Immunization Activities

The most recent population-based survey from 2009 found that nationwide routine vaccination coverage with 3 doses of trivalent oral polio vaccine (tOPV) was 70% among children aged 12–23 months (4). This percentage is similar to the reported estimates of nationwide routine vaccination coverage in 2010 with 3 doses of tOPV by age 12 months (5). The survey estimates for coverage in Bihar (62%; increased from 51% in 2006) and Uttar Pradesh (54%; increased from 50% in 2006) were among the lowest in the country, whereas coverage was higher in Jharkhand (70%) and West Bengal (74%) (4).

For the past several years, increased attention in India during supplementary immunization activities (SIAs)* has

focused on vaccinating 1) populations at high risk for polio in areas where polio has been endemic and 2) large populations of migrants, who contributed to the persistence and spread of WPV transmission (3). In January 2010, bivalent OPV (bOPV) types 1 and 3 was introduced for use in SIAs, largely replacing monovalent OPVs (mOPVs) (3).

SIAs conducted in India during 2010–2011 included two national immunization days each year. In addition, six sub-national immunization days (SNIDs) and four large-scale (multidistrict) mop-up† activities were conducted during 2010, and six SNIDs and one large-scale mop-up were conducted during January–September 2011 (Figure 1). The response to the WPV case in West Bengal in 2011 included three SIAs, using a combination of mOPV type 1 and bOPV conducted within 7 weeks of notification of the case (the first SIA was held 7 days after detection), followed by monthly SIAs using bOPV for 6 months (Figure 2).

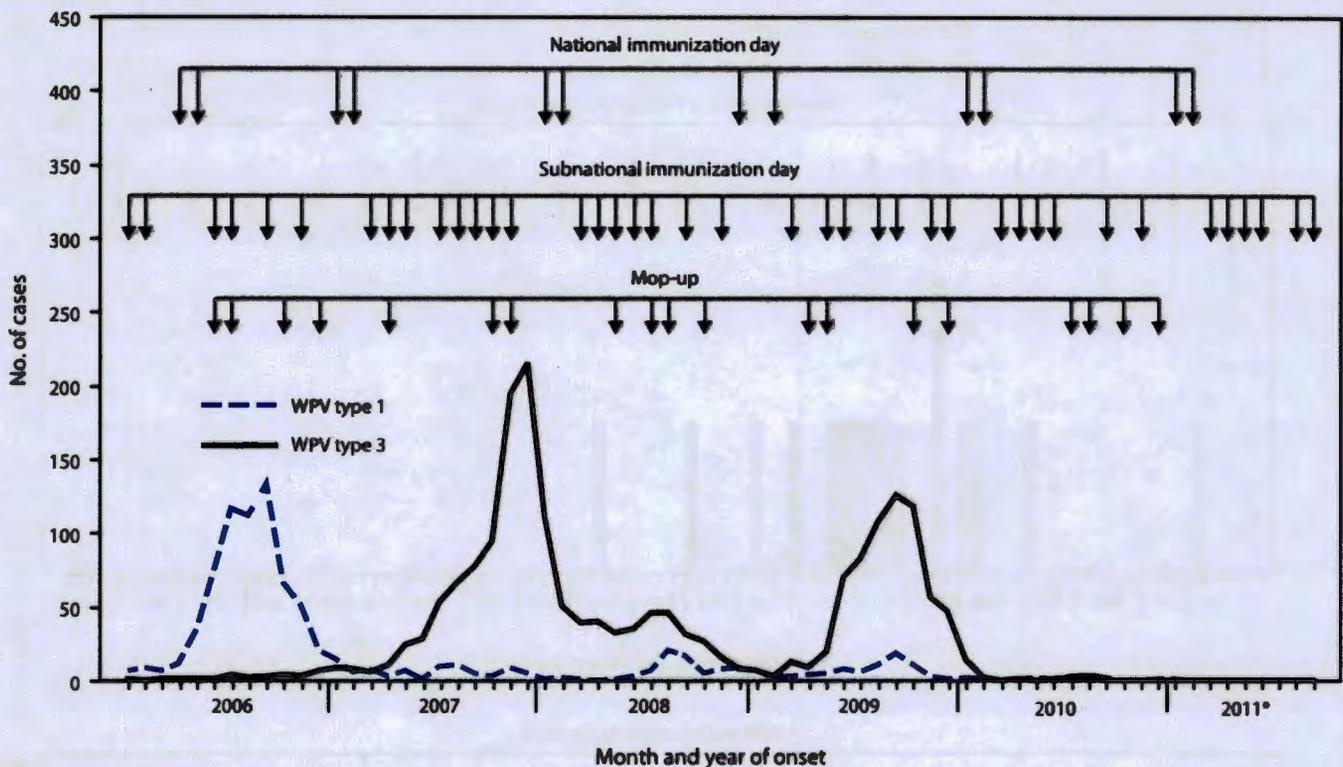
Monitoring data§ are used to estimate the proportion of children missed in each SIA. In 2011, the mean percentage of missed children in the general population aged <2 years based on these SIA surveys was 0.3% in Bihar, 1.8% in Uttar Pradesh, 3.7% in Jharkhand, and 6.1% in West Bengal. Efforts to identify and vaccinate urban slum dwellers and specific migrant populations (e.g., construction laborers, nomads, and brick kiln workers) were enhanced further during 2010–2011. The percentage of missed children per SIA in the migrant population aged <2 years, based on surveys conducted after SIA rounds in 2011 in nine states with large numbers of these populations, was 0.4%–12.3% (mean: 2.3%). In Uttar Pradesh, the mean percentage of children missed in migrant populations (1.3%) was comparable to the mean percentage of children missed in the general population aged <2 years (1.8%). In West Bengal, the mean percentage of children missed in migrant populations aged <2 years (7.3%) was higher than the overall mean among migrant populations in eight other states (2.0%) and remains higher than the mean percentage of children missed in the general population in that state (6.1%).

† Mop-up rounds are intensive house-to-house SIAs conducted in a limited area (groups of districts) with evidence of recent transmission.

§ SIA monitoring data are obtained from systematic surveys conducted after every SIA in high-risk areas to identify children aged <2 years who were missed with vaccination.

* SIAs are mass campaigns conducted over a period of days in which 1 dose of OPV is administered to all children aged <5 years, regardless of vaccination history. Surveillance data analysis determines the geographic extent of campaigns (i.e., national or subnational).

FIGURE 1. Number of wild poliovirus (WPV) cases, by type, month of onset, and type of supplementary immunization activity — India, January 2006–September 2011



* Data as of October 31, 2011.

WPV Surveillance

Acute flaccid paralysis (AFP) surveillance. In India, the national nonpolio AFP (NPAFP) rate,[§] a proxy measure of polio surveillance system sensitivity, was 12.7 per 100,000 children aged <15 years in 2010 and 12.1 per 100,000 (annualized) during January–September 2011. During that period, the highest state-level NPAFP rates were in Bihar (37.9) and Uttar Pradesh (23.9); three of 35 states and union territories had NPAFP rates <2 per 100,000. Adequate stool specimen collection** in India was 83% in 2010 and 84.1% during January–September 2011; in five states, adequate specimen collection was <80% during January–September 2011.^{††}

Environmental surveillance. Weekly testing of wastewater for poliovirus began in Mumbai in June 2001 and in Delhi in May 2010, and biweekly testing began in Patna, Bihar, in

[§] The NPAFP rate is the number of AFP cases not associated with WPV per 100,000 children aged <15 years. India's operational target for each district is two or more AFP cases per 100,000.

** The percentage of reported AFP cases with two stool specimens collected within 14 days of paralysis onset with at least 24 hours between the two specimens (target: ≥80%).

^{††} The eight polio laboratories in India processed 109,057 stool specimens during 2010 and 85,161 stool specimens during January–September 2011.

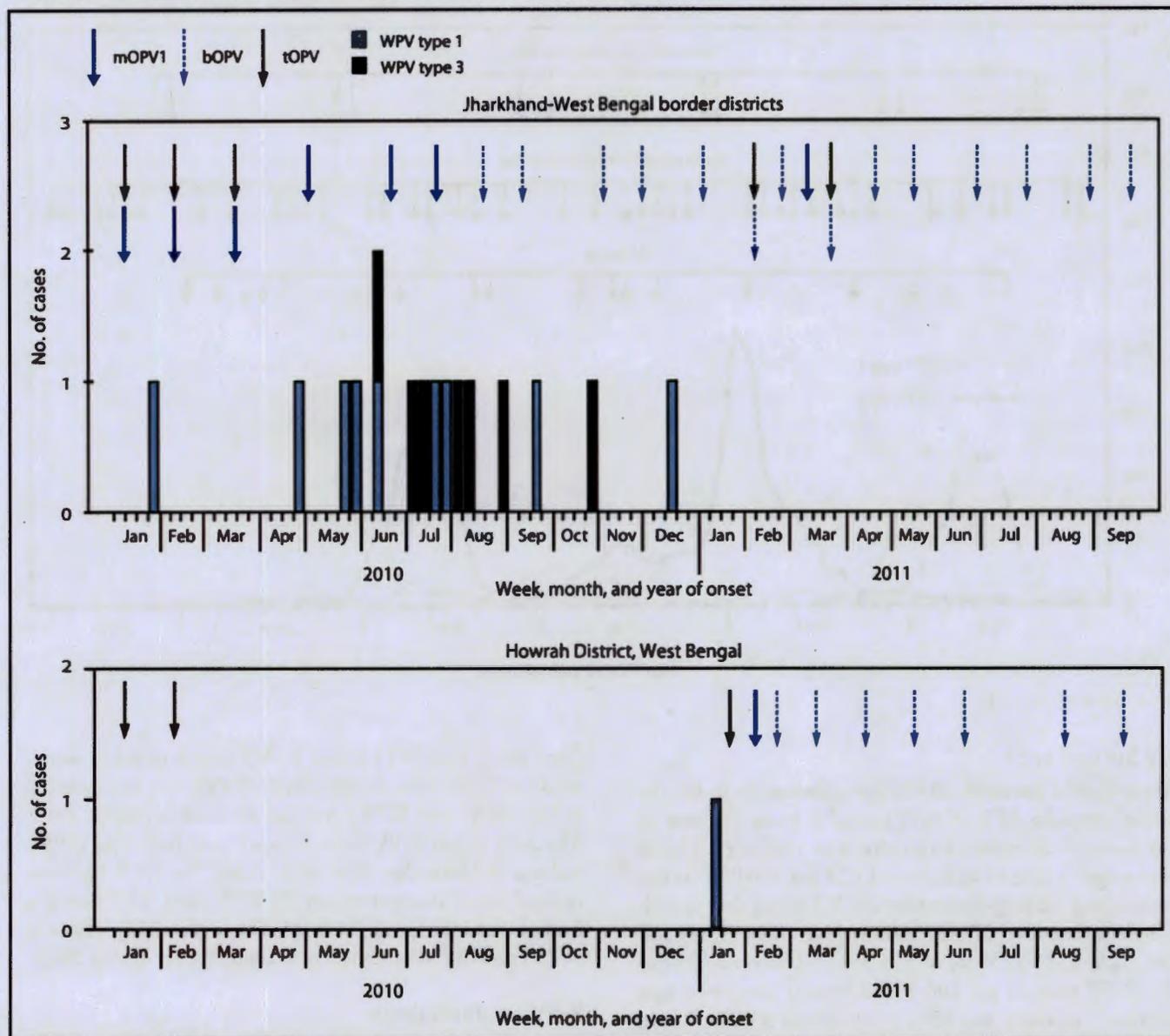
April 2011. Both WPV1 and WPV3 were detected in wastewater at Delhi sites during 2010; WPV3 was last detected in July 2010, and WPV1 was last detected in August 2010. The most recent WPV from wastewater in India was WPV1 isolated in November 2010 in Mumbai. No WPV has been isolated from Patna wastewater. All WPV1 and WPV3 isolates from wastewater during 2010–2011 were genetically related to WPV1 and WPV3 circulating in central Bihar during 2009.

WPV Epidemiology

During 2010, a total of 42 WPV cases (18 WPV1 and 24 WPV3) were reported in India in 17 districts in seven states (Figure 3). During January–September 2011, only one WPV case (WPV1) was reported in India, in West Bengal, compared with 40 WPV cases (17 WPV1 and 23 WPV3) from 17 districts in seven states during the same period during 2010. All WPV1 isolates from patients during 2010–2011 were related genetically to WPV circulating in central Bihar during 2009.

The most recent confirmed WPV1 case in India occurred on January 13, 2011, in a child from a community in which the rate of vaccine refusal was high during previous SIAs in Howrah District, West Bengal. The most recent confirmed

FIGURE 2. Number of wild poliovirus (WPV) cases (n = 17), by type, week of onset, and vaccine used in supplementary immunization activities — selected districts, India, January 2010—September 2011

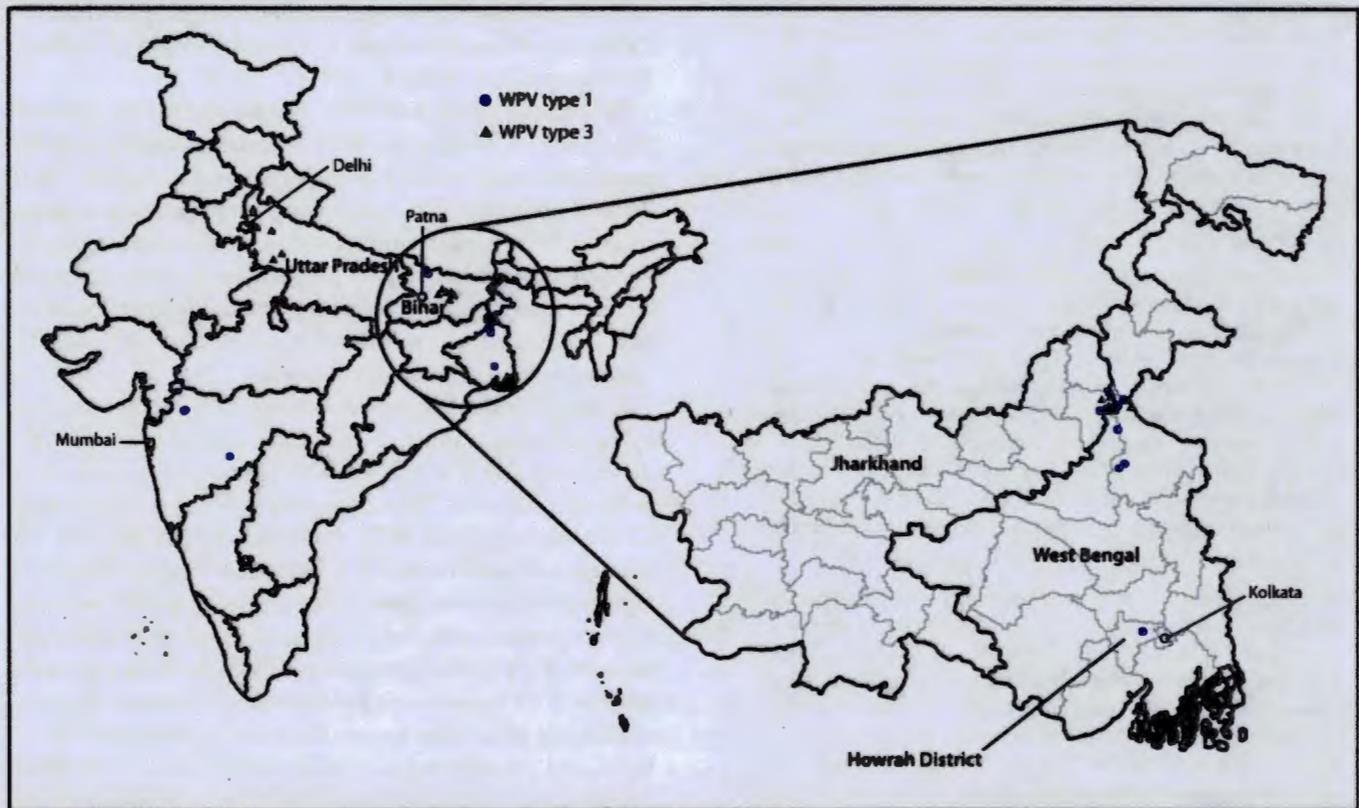


Abbreviations: mOPV1 = monovalent oral poliovirus vaccine type 1; bOPV = bivalent oral poliovirus vaccine; tOPV = trivalent oral poliovirus vaccine.

WPV3 case occurred on October 22, 2010, in Jharkhand. During 2010, simultaneous transmission of WPV1 and WPV3 occurred in Jharkhand and West Bengal around their common border (Figures 2 and 3). However, the WPV1 isolated from the patient in Howrah was not directly related genetically to WPV1 circulating at the border in Jharkhand and West Bengal during 2010, but was related genetically to WPV circulating in Bihar in September 2009 and also isolated from wastewater in Delhi in August 2010.

Among the 43 WPV cases reported during 2010–2011, 30 (70%) occurred among children aged <2 years. Of these children, six (14%) had received 1–3 OPV doses, 11 (26%) had received 4–7 doses, 24 (56%) had received >7 doses, one (2%) had unknown vaccination status, and one (2%) had not received any OPV doses (the child with WPV1 in West Bengal in January 2011).

FIGURE 3. Wild poliovirus (WPV) cases (N = 43), by type — India and selected states, 2010 and 2011*



* Data as of October 31, 2011.

Reported by

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Editorial Note

During 2010 and 2011, India made substantial progress toward polio eradication. A year has passed since the last confirmed WPV3 case, and >9 months have passed since the last confirmed WPV1 case. The absence of any reported WPV cases since January, including during much of the June–November high-transmission season, is unprecedented. WPV was last detected in sewage in Delhi in August 2010 and in

Mumbai in November 2010. The subsequent lack of detection of WPV in any samples from any site is further indication that WPV transmission might have been interrupted. No WPV cases have been reported for >17 months and >12 months in the previously polio-endemic states of Uttar Pradesh and Bihar, respectively. If no WPV is identified throughout the high-transmission season in 2012, India will be regarded as polio-free. This would put the World Health Organization South-East Asia Region, of which India is a member, on track to be certified polio-free as early as 2014.

The introduction of bOPV in SIAs beginning in January 2010 likely contributed substantially to the simultaneous reduction in WPV1 and WPV3 cases in India. Previous SIAs were conducted predominantly using mOPV type 1 and occasionally using mOPV type 3; a clinical trial demonstrated the superiority of bOPV compared with tOPV and noninferiority compared with mOPV types 1 and 3 (6). The special attention focused on vaccination coverage of children in high-risk endemic areas and migrant populations during the last several years likely increased and sustained the levels of immunity needed to stop WPV transmission. Rapid response SIAs

What is already known on this topic?

India is one of four countries (the others are Afghanistan, Nigeria, and Pakistan) where wild poliovirus (WPV) remains endemic. Until 2010, most polio cases in India were reported in Uttar Pradesh and Bihar, two states with low routine vaccination coverage, lower vaccine effectiveness than elsewhere, and large migrant populations that require frequent supplementary immunization activities (SIAs) to control WPV transmission.

What is added by this report?

As of October 31, only one confirmed WPV case had been reported in India during January–September 2011, compared with 40 WPV cases during the same 9-month period in 2010. A year has passed since the most recent WPV3 case in India and more than 9 months since the last case of WPV1. This unprecedented finding is corroborated by the lack of any WPV isolation from wastewater samples since November 2010, and likely resulted from a combination of factors, including introduction of bivalent oral poliovirus vaccine types 1 and 3 in SIAs in 2010, targeting of migrant populations, and rapid outbreak response.

What are the implications for public health practice?

In India, the risk for importation or undetected WPV transmission remains, particularly in migrant populations. To ensure interruption of all WPV transmission, strong surveillance and high population immunity are needed in all states (with specific focus on migrant populations), as well as rapid response SIAs after any detected WPV cases. Elimination of WPV in India will establish that WPV transmission can be interrupted even in the most challenging of settings, remove the threat of importation from India, and provide impetus to the Global Polio Eradication Initiative goal of interrupting all WPV transmission.

contributed to successfully stopping WPV transmission after report of the case in Howrah, West Bengal. This response, led by the government and partners,⁵⁵ included massive mobilization of human and financial resources, revision of detailed subdistrict SIA operational plans, retraining of vaccinators and supervisors, increased community outreach and mobilization, and enhanced monitoring in the outbreak areas. Of note is that routine vaccination coverage improved in both Bihar and Uttar Pradesh over the last several years at the same time the two states conducted almost monthly SIAs and frequent large-scale mop-ups.

AFP surveillance indicators have reached or greatly exceeded targets in the majority of states and territories since 2005. Continued vigilance is needed to ensure that all states and union territories reach targets for surveillance indicators and that high-risk populations are adequately included to achieve the highest sensitivity required for detecting any WPV circulation. Appropriately targeted environmental surveillance can

be more sensitive in detecting low-level WPV circulation than AFP surveillance (7). Sewage sampling is ongoing in Mumbai, Delhi, and Patna, Bihar, and is planned to begin in Kolkata, West Bengal, late in 2011.

Despite the absence of WPV cases in India since January 2011, the risk remains for WPV circulation among migrant populations and residents of high-risk areas in western Uttar Pradesh and central Bihar and in migrant populations in other states. In West Bengal, families within certain migrant populations continue to have higher proportions of undervaccinated children than families in migrant populations and the general population aged <2 years in other states, according to 2011 directed surveys of these populations.

Although India has served as a reservoir for importation to neighboring countries and some distant countries (8), the country also is at risk for WPV importations from other polio-affected areas. The recent polio outbreak in neighboring China resulting from WPV importation from Pakistan (9) is a reminder of the need for continued vigilance to ensure high population immunity in all states (with specific focus on migrant populations) along with rapid response SIAs after any detected WPV cases. Elimination of WPV in India will establish that WPV transmission can be interrupted even in the most challenging of settings, remove the threat of importation from India, and provide impetus to the Global Polio Eradication Initiative goal of interrupting all WPV transmission globally by the end of 2012.

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Vital Signs: Overdoses of Prescription Opioid Pain Relievers — United States, 1999–2008

On November 1, 2011, this report was posted as an MMWR Early Release on the MMWR website (<http://www.cdc.gov/mmwr>).

Abstract

Background: Overdose deaths involving opioid pain relievers (OPR), also known as opioid analgesics, have increased and now exceed deaths involving heroin and cocaine combined. This report describes the use and abuse of OPR by state.

Methods: CDC analyzed rates of fatal OPR overdoses, nonmedical use, sales, and treatment admissions.

Results: In 2008, drug overdoses in the United States caused 36,450 deaths. OPR were involved in 14,800 deaths (73.8%) of the 20,044 prescription drug overdose deaths. Death rates varied fivefold by state. States with lower death rates had lower rates of nonmedical use of OPR and OPR sales. During 1999–2008, overdose death rates, sales, and substance abuse treatment admissions related to OPR all increased substantially.

Conclusions: The epidemic of overdoses of OPR has continued to worsen. Wide variation among states in the nonmedical use of OPR and overdose rates cannot be explained by underlying demographic differences in state populations but is related to wide variations in OPR prescribing.

Implications for Public Health Practice: Health-care providers should only use OPRs in carefully screened and monitored patients when non-OPR treatments are insufficient to manage pain. Insurers and prescription drug monitoring programs can identify and take action to reduce both inappropriate and illegal prescribing. Third-party payers can limit reimbursement in ways that reduce inappropriate prescribing, discourage efforts to obtain OPR from multiple health-care providers, and improve clinical care. Changes in state laws that focus on the prescribing practices of health-care providers might reduce prescription drug abuse and overdoses while still allowing safe and effective pain treatment.

Introduction

In 2007, nearly 100 persons per day died of drug overdoses in the United States (1). The death rate of 11.8 per 100,000 population in 2007 was roughly three times the rate in 1991. Prescription drugs have accounted for most of the increase in those death rates since 1999 (2). In 2009, 1.2 million emergency department (ED) visits (an increase of 98.4% since 2004) were related to misuse or abuse of pharmaceuticals, compared with 1.0 million ED visits related to use of illicit drugs such as heroin and cocaine (3). Prominent among these prescription drug-related deaths and ED visits are opioid pain relievers (OPR), also known as narcotic or opioid analgesics, a class of drugs that includes oxycodone, methadone, and hydrocodone, among others. OPR now account for more overdose deaths than heroin and cocaine combined. OPR frequently are diverted for nonmedical use by patients or their friends or sold on the street. In 2010, 4.8% of the U.S. population aged ≥ 12 years used OPR nonmedically (4). Nonmedical use of OPR costs insurance companies up to \$72.5 billion annually in health-care costs (5).

States regulate the use of prescription drugs, such as OPR, and the practices of prescribers and pharmacists. States also finance and regulate health care for Medicaid populations, which are at greater risk for overdose (6). States therefore have a central role in ensuring that OPR are used legally and safely.

Comparisons among jurisdictions in drug overdose mortality, nonmedical use of OPR, and OPR sales can help identify risk factors and effective prevention measures. Among the states, OPR sales varied fourfold in 2002 (7), and death rates for overdoses involving OPR varied from 1.8 to 15.6 per 100,000 population in 2006 (2). More rural and more impoverished counties tend to have higher prescription drug overdose death rates (8,9).

Methods

For this report, death rates are based on the National Vital Statistics System multiple cause of death files (10). Rates were age-adjusted to the 2000 U.S. Census population using bridged-race* population figures. Drug poisoning deaths, referred to as

* Information about bridged-race categories is available at http://www.cdc.gov/nchs/nvss/bridged_race.htm.

drug overdose deaths in this report, were defined as those with an underlying cause of death classified by the *International Classification of Diseases, 10th Revision (ICD-10)* external cause of injury codes as X40–X44, X60–X64, X85, or Y10–Y14. Rates include injury deaths of any intent (unintentional, suicide, homicide, or undetermined) for U.S. residents. Among deaths with drug overdose as the underlying cause, CDC identified the type of drug involved using ICD-10 codes: prescription drugs (T36–T39, T40.2–T40.4, T41–T43.5, and T43.7–T50.8), including prescription opioid pain relievers (T40.2–T40.4); illicit drugs (T40.1, T40.5, T40.7–T40.9, and T43.6); or only unspecified drugs (T50.9 alone). The prescription drug category includes some over-the-counter medications. Some deaths involved prescription and illicit drugs and are counted in both drug categories. Years of potential life lost (YPLL) before age 65 years were calculated by subtracting age at death from 65 years and summing to get the total YPLL.

Rates of nonmedical OPR use in the past year by state were obtained from the 2008–2009 National Surveys on Drug Use and Health (NSDUH) (11). Nonmedical use was defined as use of a prescription pain reliever without a prescription belonging to the respondent or use for the experience or feeling the drug causes. The prescription pain reliever category includes OPR and selected barbiturate combination products used for headaches.

Annual drug sales for 1999–2010 were determined from the Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA) (12). For this report, ARCOS sales data were used as a surrogate for OPR use. DEA provided data on sales to pharmacies, hospitals, and practitioners for codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, and oxycodone (Kyle Wright, personal communication, April 11, 2011). Sales of drugs to substance abuse treatment programs were not included. Amounts of drugs were standardized to morphine milligram equivalents (13).

The percentage of the state population below the federal poverty level by race and ethnicity during 2007–2008 was provided by the Kaiser Family Foundation (Rachel Licata, personal communication, August 10, 2011). Trends in substance abuse treatment admission rates were based on the Treatment Episode Data Set (14). Rates were calculated for admissions for treatment of substance abuse where the primary substance was an OPR.

Spearman's correlation coefficient was used to correlate the absolute increase in the non-Hispanic white overdose death rate during 1999–2008 with poverty level by state. Fisher's exact test was used to compare the proportions of states above and below national rates. Test results are statistically significant at $p < 0.05$.

Results

In 2008, a total of 36,450 deaths were attributed to drug overdose, a rate of 11.9 per 100,000 population (Table 1), among which a drug was specified in 27,153 (74.5%) deaths. One or more prescription drugs were involved in 20,044 (73.8%) of the 27,153 deaths, and OPR were involved in 14,800 (73.8%) of the 20,044 prescription drug overdose deaths. Rates varied by sex, race/ethnicity, and age. For deaths involving OPR, the rate among non-Hispanic whites and American Indians/Alaska Natives was three times higher than the rates in blacks and Hispanic whites. All death rates were highest among persons aged 35–54 years. Overdose resulted in 830,652 YPLL before age 65 years, a number comparable to the YPLL from motor vehicle crashes.

Rates for all outcomes studied varied widely by state (Table 2, Figure 1)[†] Overdose death rates ranged from 5.5 per 100,000 population in Nebraska to 27.0 in New Mexico. The prevalence of nonmedical use of OPR during 2008–2009 ranged from 3.6% in Nebraska to 8.1% in Oklahoma. The rate of OPR sales ranged from 3.7 kg per 10,000 population in Illinois to 12.6 kg in Florida. The highest sales rates were clustered in the Southeast and the Northwest. Among the 27 states with overdose death rates above the national rate, 21 (77.8%) had rates of nonmedical use above the national rate. Among the 24 states with death rates at or below the national rate, six (25.0%) had rates of nonmedical use above the national rate ($p < 0.001$). Among the 27 states with death rates above the national rate, 21 (77.8%) had rates of OPR sales above the national rate. Among the 24 states with death rates at or below the national rate, five (20.8%) had rates of OPR sales above the national rate ($p < 0.001$).

During 1999–2008, overdose death rates, sales, and substance abuse treatment admissions related to OPR increased in parallel (Figure 2). The overdose death rate in 2008 was nearly four times the rate in 1999. Sales of OPR in 2010 were four times those in 1999. The substance abuse treatment admission rate in 2009 was almost six times the rate in 1999. The rate of sales of OPR in 2010, 7.1 kg per 10,000 population, was equivalent to 710 mg per person in the United States. The percentage of the non-Hispanic white population below the poverty level during 2007–2008 correlated positively with the increase in overdose death rates among non-Hispanic whites from 1999 to 2008 by state ($r = 0.54$; $p < 0.001$). Louisiana, Mississippi, Kentucky, and West Virginia had some of the largest mortality increases and some of the highest poverty levels among non-Hispanic whites.

[†] For this report, District of Columbia is grouped with the states.

TABLE 1. Drug overdose death rates by selected characteristics — National Vital Statistics System, United States, 2008

Characteristic	Age-adjusted rate*			
	All drugs [†]	Prescription drugs [‡]	Opioid pain relievers [§]	Illicit drugs [¶]
Overall	11.9	6.5	4.8	2.8
Sex				
Men	14.8	7.7	5.9	4.3
Women	9.0	5.3	3.7	1.4
Race/Ethnicity				
White	13.2	7.4	5.6	2.8
Hispanic ^{††}	6.1	3.0	2.1	2.5
Non-Hispanic	14.7	8.4	6.3	2.9
Black	8.3	3.0	1.9	4.0
Asian/Native Hawaiian or Pacific Islander	1.8	1.0	0.5	0.6
American Indian/Alaska Native	13.0	8.4	6.2	2.7
Age group (yrs)				
0–14	0.2	0.2	0.1	— ^{§§}
15–24	8.2	4.5	3.7	2.2
25–34	16.5	8.8	7.1	4.4
35–44	20.9	11.0	8.3	5.3
45–54	25.3	13.8	10.4	6.0
55–64	13.0	7.3	5.0	2.5
≥65	4.1	3.0	1.0	0.3
Intent				
Unintentional	9.2	4.8	3.9	2.6
Undetermined	1.1	0.6	0.5	0.2
Suicide	1.6	1.1	0.5	0.1

* Rate per 100,000 population age-adjusted to the 2000 U.S. standard population using the vintage 2008 population. Because deaths might involve both prescription and illicit drugs, some deaths are included in both categories.

[†] Deaths with underlying causes of unintentional drug poisoning (X40–44), suicide drug poisoning (X60–64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the *International Classification of Diseases, 10th Revision*.

[‡] Drug overdose deaths, as defined, that have prescription drugs (T36–T39, T40.2–T40.4, T41–T43.5, and T43.7–T50.8) as contributing causes.

[§] Drug overdose deaths, as defined, that had other opioids (T40.2), methadone (T40.3), and other synthetic narcotics (T40.4) as contributing causes.

[¶] Drug overdose deaths, as defined, that have heroin (T40.1), cocaine (T40.5), hallucinogens (T40.7–T40.9), or stimulants (T43.6) as contributing causes.

^{††} Non-white Hispanics are included in the other racial groups.

^{§§} Rate is not presented when the estimate is unstable because the number of deaths is less than 20.

Conclusions and Comment

The epidemic of prescription drug overdoses in the United States has worsened over the last decade, and by 2008, drug overdose deaths (36,450) were approaching the number of deaths from motor vehicle crashes (39,973), the leading cause of injury death in the United States. Parallel trends in deaths and OPR sales between 1999 and 2008, combined with continuing upward trends in ED visits (4), OPR abuse treatment admissions (14), and OPR sales after 2008 suggest that the death rate also has increased since 2008. Preliminary 2009 death data are consistent with such an increase (15). These

Key Points

- Death from opioid pain relievers (OPR) is an epidemic in the United States.
- Sales of OPR quadrupled between 1999 and 2010. Enough OPR were prescribed last year to medicate every American adult with a standard pain treatment dose of 5 mg of hydrocodone (Vicodin and others) taken every 4 hours for a month.
- Abuse of OPR costs health insurers approximately \$72.5 billion annually in health-care costs.
- State-based prescription drug monitoring program records and insurance claims information can identify and address inappropriate prescribing and use by patients. State laws and regulations based on these data need to be enacted, enforced, and rigorously evaluated.
- Additional information is available at <http://www.cdc.gov/vitalsigns>.

increases occurred despite numerous warnings and recommendations over the past decade for voluntary education of providers about more cautious use of OPR (16).

Differences in OPR overdose mortality by race/ethnicity match the pattern for medical and nonmedical use of OPR, with the lowest rates for medical and nonmedical use among Asians and blacks and the highest rates among American Indians/Alaska Natives and non-Hispanic whites (4,17). Differences in OPR overdose mortality by race and ethnicity cannot explain the wide variation in death rates among states, given the equally large differences in non-Hispanic white mortality between states. Nor can demographic differences fully explain the wide variations among states in the nonmedical use and sales of OPR. Montana and Iowa, for example, have largely non-Hispanic white populations but widely varying rates of nonmedical use and sales of OPR.

By 2010, enough OPR were sold to medicate every American adult with a typical dose of 5 mg of hydrocodone every 4 hours for 1 month. Increased use of OPR has contributed to the overall increases in rates of overdose death and nonmedical use, and variation among states in OPR sales probably contributes to state variation in these outcomes. Given that 3% of physicians accounted for 62% of the OPR prescribed in one study (18), the proliferation of high-volume prescribers can have a large impact on state use of OPR and overdose death rates. Large increases in overdoses involving the types of drugs sold by illegitimate pain clinics (i.e., "pill mills") have been reported in Florida (19) and Texas (20). Such clinics provide OPR to large volumes of patients

TABLE 2. Rates of drug overdose death, nonmedical use of opioid pain relievers (OPR), and OPR sales, by state — United States

State	Drug overdose deaths*				OPR			
	Overall		Non-Hispanic whites		Nonmedical use†		Sales‡	
	Rate	(SE)	Rate	(SE)	%	(SE)	Rate	(SE)
National	11.9	(0.1)	14.7	(0.1)	4.8	(0.1)	7.1	(0.0)
New Mexico	27.0	(1.2)	25.1	(1.7)	5.7 [¶]	(0.6)	6.7	(0.2)
West Virginia	25.8	(1.2)	26.6	(1.3)	5.9 [¶]	(0.6)	9.4	(0.2)
Nevada	19.6	(0.9)	27.5	(1.3)	5.9 [¶]	(0.4)	11.8	(0.2)
Utah	18.4	(0.9)	20.4	(1.0)	5.3 [¶]	(0.4)	7.4 [¶]	(0.2)
Alaska	18.1	(1.6)	18.1 [¶]	(2.1)	5.2 [¶]	(0.8)	8.2	(0.3)
Kentucky	17.9	(0.7)	19.6	(0.7)	6.0	(0.3)	9.0	(0.1)
Rhode Island	17.2	(1.3)	19.5	(1.5)	6.1	(0.6)	5.9	(0.2)
Florida	16.5	(0.3)	23.9	(0.5)	4.1	(0.2)	12.6	(0.1)
Oklahoma	15.8	(0.7)	17.5	(0.8)	8.1	(0.3)	9.2	(0.2)
Ohio	15.1	(0.4)	16.0	(0.4)	5.5	(0.2)	7.9	(0.1)
Louisiana	15.0	(0.6)	19.2	(0.8)	5.3 [¶]	(0.3)	6.8	(0.1)
Pennsylvania	15.1	(0.4)	15.6	(0.4)	4.1	(0.2)	8.0	(0.1)
Tennessee	14.8	(0.5)	17.2	(0.6)	4.9 [¶]	(0.2)	11.8	(0.1)
Washington	14.7	(0.5)	16.1	(0.6)	6.1	(0.2)	9.2	(0.1)
Colorado	14.6	(0.5)	15.0 [¶]	(0.6)	5.7 [¶]	(0.3)	6.3	(0.1)
Delaware	14.5	(1.3)	18.7	(1.8)	5.6 [¶]	(0.7)	10.2	(0.3)
Wyoming	14.4 [¶]	(1.8)	14.6 [¶]	(2.0)	3.9 [¶]	(0.9)	6.0	(0.3)
Montana	14.1 [¶]	(1.2)	13.7 [¶]	(1.3)	5.3 [¶]	(0.6)	8.4	(0.3)
Indiana	13.2	(0.5)	14.4 [¶]	(0.5)	5.7 [¶]	(0.2)	8.1	(0.1)
Alabama	13.1	(0.5)	17.6	(0.7)	5.1 [¶]	(0.3)	9.7	(0.1)
Arizona	13.1	(0.5)	17.1	(0.7)	6.0 [¶]	(0.2)	8.4	(0.1)
Arkansas	13.1 [¶]	(0.7)	15.6 [¶]	(0.9)	5.1 [¶]	(0.4)	8.7	(0.2)
Missouri	13.1	(0.5)	14.2 [¶]	(0.5)	4.4 [¶]	(0.2)	7.2 [¶]	(0.1)
North Carolina	12.9	(0.4)	17.1	(0.5)	5.0 [¶]	(0.2)	6.9	(0.1)
South Carolina	12.6 [¶]	(0.5)	16.7	(0.8)	4.7 [¶]	(0.3)	7.2 [¶]	(0.1)
Maine	12.3 [¶]	(1.0)	12.2	(1.0)	4.7 [¶]	(0.5)	9.8	(0.3)
Michigan	12.2 [¶]	(0.4)	13.0	(0.4)	5.7	(0.2)	8.1	(0.1)
Maryland	11.9 [¶]	(0.5)	15.3 [¶]	(0.7)	3.8	(0.2)	7.3 [¶]	(0.1)
Massachusetts	11.8 [¶]	(0.4)	12.9	(0.5)	5.3 [¶]	(0.2)	5.8	(0.1)
Oregon	11.7 [¶]	(0.6)	12.8	(0.6)	6.8	(0.3)	11.6	(0.2)
Vermont	10.9 [¶]	(1.4)	10.9	(1.4)	4.6 [¶]	(0.7)	8.1	(0.4)
Connecticut	10.8 [¶]	(0.6)	12.5	(0.7)	3.8	(0.3)	6.7	(0.1)
Mississippi	10.6	(0.6)	16.1 [¶]	(1.0)	4.7 [¶]	(0.3)	6.1	(0.1)
Illinois	10.5	(0.3)	11.7	(0.4)	4.1	(0.1)	3.7	(0.1)
Wisconsin	10.5	(0.4)	10.4	(0.5)	4.8 [¶]	(0.2)	6.5	(0.1)
California	10.4	(0.2)	16.1	(0.3)	4.8 [¶]	(0.1)	6.2	(0.0)
Idaho	9.7	(0.8)	10.7	(0.9)	5.8 [¶]	(0.4)	7.5 [¶]	(0.2)
Georgia	9.5 ^{**}	(0.3)	13.4 ^{**}	(0.5)	4.6 [¶]	(0.2)	6.5	(0.1)
District of Columbia	9.4 [¶]	(1.4)	—††	—	3.7	(0.7)	3.9	(0.3)
Hawaii	9.4	(0.9)	16.4 [¶]	(2.3)	5.1 [¶]	(0.4)	5.9	(0.2)
New Hampshire	9.3	(0.8)	9.5	(0.9)	5.9	(0.4)	8.1	(0.3)
Virginia	9.1	(0.3)	11.9	(0.5)	4.6 [¶]	(0.2)	5.6	(0.1)
Texas	8.6	(0.2)	13.2	(0.3)	4.6 [¶]	(0.1)	4.2	(0.0)
New York	8.4	(0.2)	10.0	(0.3)	4.4 [¶]	(0.1)	5.3	(0.1)
Kansas	8.0	(0.5)	8.6	(0.6)	5.0 [¶]	(0.3)	6.8 [¶]	(0.2)
New Jersey	8.0	(0.3)	10.5	(0.5)	3.8	(0.2)	6.0	(0.1)
North Dakota	7.6	(1.3)	7.5	(1.4)	3.9 [¶]	(0.6)	5.0	(0.3)
South Dakota	7.3	(1.1)	6.2	(1.1)	3.8	(0.6)	5.5	(0.3)
Minnesota	7.2	(0.4)	7.2	(0.4)	4.4 [¶]	(0.2)	4.2	(0.1)
Iowa	7.1	(0.5)	7.5	(0.5)	3.6	(0.3)	4.6	(0.1)
Nebraska	5.5	(0.6)	5.8	(0.7)	3.6	(0.3)	4.2	(0.2)

Abbreviation: SE = standard error.

* Deaths per 100,000 population in 2008; age-adjusted to the 2000 U.S. standard population using the vintage 2008 population.

† Percentage of persons aged ≥12 years using OPR nonmedically during 2008–2009.

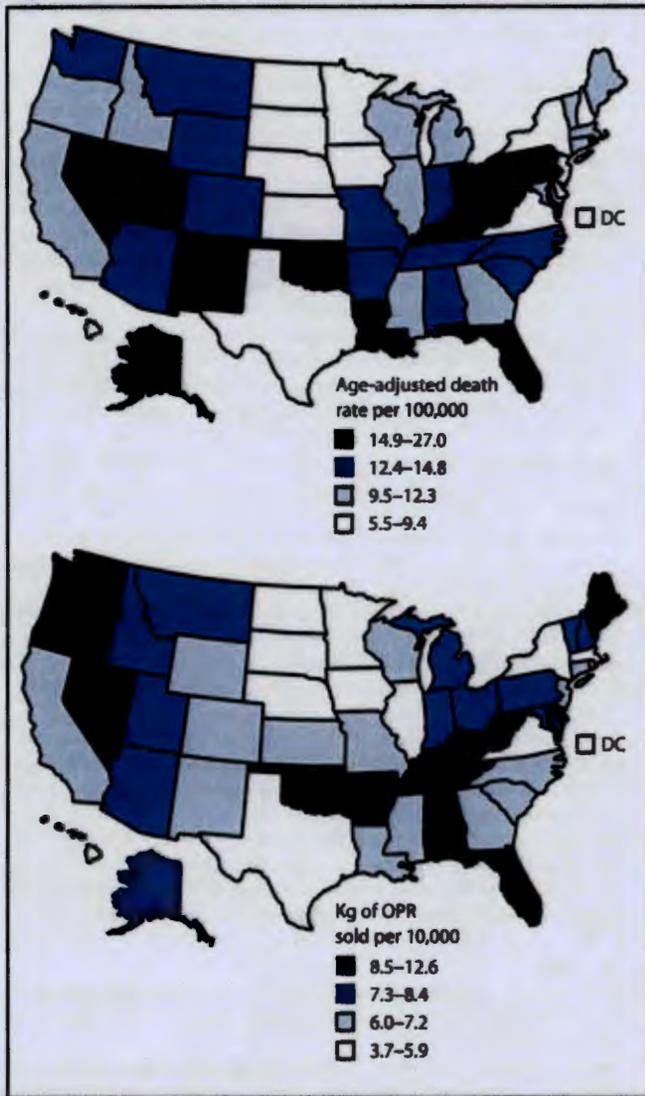
‡ Kilograms of OPR sold per 10,000 population in morphine equivalents in 2010.

¶ Rate is not significantly different from the national rate.

** Death rates from Georgia are based on preliminary numbers of deaths and might be underestimates.

†† The rate is not presented when the estimate is unstable because the number of deaths is less than 20.

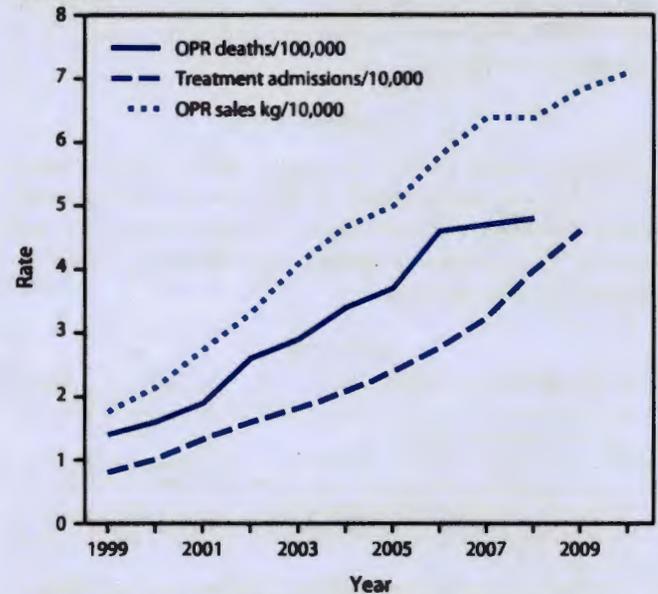
FIGURE 1. Drug overdose death rate in 2008 and rate of kilograms (kg) of opioid pain relievers (OPR) sold in 2010 — United States



without adequate evaluation or follow-up. Another possible contributor to state disparities is poverty, which was associated with greater increases in state death rates during 1999–2008. Medicaid populations are at greater risk of OPR overdose than non-Medicaid populations (6).

The findings in this report are subject to at least four limitations. First, vital statistics underestimate the rates of prescription and illicit drugs because the type of drug is not specified on many death certificates. Second, respondents might underreport nonmedical use of OPR in surveys such as the NSDUH. Third, ARCOS data reflect sales to retail outlets by state, but some drugs might have been used by nonstate residents or sent to other states by mail-order pharmacies or

FIGURE 2. Rates* of opioid pain reliever (OPR) overdose death, OPR treatment admissions, and kilograms of OPR sold — United States, 1999–2010



* Age-adjusted rates per 100,000 population for OPR deaths, crude rates per 10,000 population for OPR abuse treatment admissions, and crude rates per 10,000 population for kilograms of OPR sold.

otherwise not used by state residents. Finally, sales data did not include buprenorphine, an opioid primarily used for substance abuse treatment, though sometimes prescribed for pain. Its inclusion with drugs primarily used to treat pain would have inappropriately increased sales rates.

Public health interventions to reduce prescription drug overdose must strike a balance between reducing misuse and abuse and safeguarding legitimate access to treatment. To find this balance, health-care providers should only use OPR in carefully screened and monitored patients when non-OPR treatments have not been sufficient to treat pain, as recommended in evidence-based guidelines (21). States, as regulators of health-care practice, have the responsibility and authority to monitor and correct inappropriate and illegal prescribing. Data from state prescription drug monitoring programs, which collect records of prescription drugs prone to abuse from pharmacies, and Medicaid claims data can be used to identify and address OPR misuse and abuse. State Medicaid programs and other public insurers can use economic measures to hold providers accountable for their prescribing of OPR and other controlled prescription drugs. State professional licensing boards can take action against prescribers misusing their licenses, and law enforcement agencies can take action against illegal activities. State policies that focus on providers operating outside of normal medical practice, such as laws prohibiting so-called “pill mills,”

are a promising approach (19). All interventions need to be evaluated further and new interventions developed. Concerted attempts to address this problem, especially in states with high rates of OPR sales, nonmedical use, or overdose mortality, might help control the epidemic.

Reported by

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Announcements

National Epilepsy Awareness Month — November 2011

November is National Epilepsy Awareness Month. Epilepsy, which affects approximately 2 million persons in the United States, is characterized by recurrent, unprovoked seizures (1). Although epilepsy can occur at any age, the condition is more likely to begin among children aged <2 years and adults aged ≥65 years (1). Delayed recognition of seizures and subsequent inadequate treatment increases the risk for additional seizures, disability, decreased health-related quality of life, and, in rare instances, death (2–4). Analysis of Behavioral Risk Factor Surveillance System data from 19 states indicated that approximately 1% of adults have active epilepsy, and many might not be receiving the best available medical care (5). As do many persons who live with other chronic disorders, those with epilepsy often face challenges related to medication schedules, management of symptoms, disability, lifestyle limitations, emotional stress, and stigma (6).

The Managing Epilepsy Well (MEW) Network, established in 2007, is composed of persons interested in improving the care for persons with epilepsy (7). MEW Network members, including representatives from U.S. universities, community-based organizations, and CDC, are working together to develop and test self-management programs and tools that promote self-management and improve quality of life for persons with epilepsy.

MEW Network programs available to communities include Web Epilepsy Awareness Support and Education (WebEase), Using Practice and Learning to Increase Favorable Thoughts (UPLIFT), and the Program to Encourage Active Rewarding Lives (PEARLS). WebEase is an Internet self-management program to improve medication adherence, stress management, and sleep (7). UPLIFT is an Internet and telephone program that combines cognitive behavioral therapy with mindfulness to treat depression in persons with epilepsy (8). PEARLS is a home-based, collaborative-care depression treatment program for persons with epilepsy (9).

Interventions currently under development or evaluation by the MEW Network include a self management program that integrates self-management and social support for adults with refractory epilepsy, a decision-support system for clinics to enhance self-management behavior, a consumer-driven self-management program, and a telephone-based depression prevention program. Additional information about the MEW Network is available at <http://www.sph.emory.edu/managingepilepsywell> and <http://www.cdc.gov/epilepsy>.

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National Chronic Obstructive Pulmonary Disease (COPD) Awareness Month — November 2011

Chronic obstructive pulmonary disease (COPD) characterizes a group of diseases that cause airflow obstruction, including emphysema and chronic bronchitis. In 2008, chronic lower respiratory diseases (primarily COPD) became the third leading cause of death in the United States (1).

November is National COPD Awareness Month. Sponsored by the U.S. COPD Coalition, the observance is an opportunity for health professionals, health-care providers, and COPD patient groups to collaborate and improve awareness and treatment of COPD by participating in the National Heart, Lung, and Blood Institute's COPD Learn More, Breathe Better campaign. In addition, CDC and its partners recently have released a set of goals to define the unique role and contributions of public health in the prevention and control of COPD (2).

The most significant cause of COPD is tobacco smoke. Smokers should be encouraged to quit, and persons should be protected from exposure to secondhand smoke. Smoking cessation information is available at <http://www.smokefree.gov> and http://www.cdc.gov/tobacco/quit_smoking. Exposures to certain chemicals, fumes or vapors, or air pollution also are risks factors, as are asthma and respiratory infections.

Although no cure for COPD is available, it is treatable, and early detection is essential. Persons at risk for COPD who experience chronic cough, shortness of breath, and sputum

Announcements

production are encouraged to talk to their health-care provider and request a simple breathing test called spirometry to assess lung function. Additional information is available from CDC (<http://www.cdc.gov/copd>), the National Heart, Lung, and Blood Institute (<http://www.nhlbi.nih.gov/health/public/lung/copd/lmbb-campaign>), and the U.S. COPD Coalition (<http://www.uscopdcoalition.org>).

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Reinstatement of Notification Requirements for Emergency Response Employees Potentially Exposed to Life-Threatening Infectious Diseases

In October 2009, Congress reauthorized the Ryan White HIV/AIDS Treatment Extension Act of 2009 and included Part G, which reinstated notification requirements for emergency response employees potentially exposed to life-threatening infectious diseases.* On July 7, 2010, the Secretary of the U.S. Department of Health and Human Services delegated to CDC responsibility for compiling a list of such diseases, including emerging infectious diseases, and specifying those diseases usually transmitted through airborne or aerosolized means. The Secretary further delegated the updating of guidelines for determining circumstances under which emergency response employees might be exposed to such diseases while attending to or transporting victims of emergencies and guidelines for medical facilities making determinations whether such exposures have occurred.

CDC staff members developed the required list and guidelines, incorporating input received via a public comment process† during December 2010–February 2011. On November 2, 2011, CDC published a final notice in the Federal Register, detailing responses to the public comments and setting forth the final list of diseases and the final guidelines, which will become effective 30 days after publication.§

* Additional information available at <http://edocket.access.gpo.gov/2010/2010-31149.htm>.

† Additional information available at <http://edocket.access.gpo.gov/2010/pdf/C1-2010-31110.pdf>.

§ Available at <http://www.gpo.gov/fdsys/pkg/FR-2011-11-02/pdf/2011-28234.pdf>.

Epi Info 7 Software Released

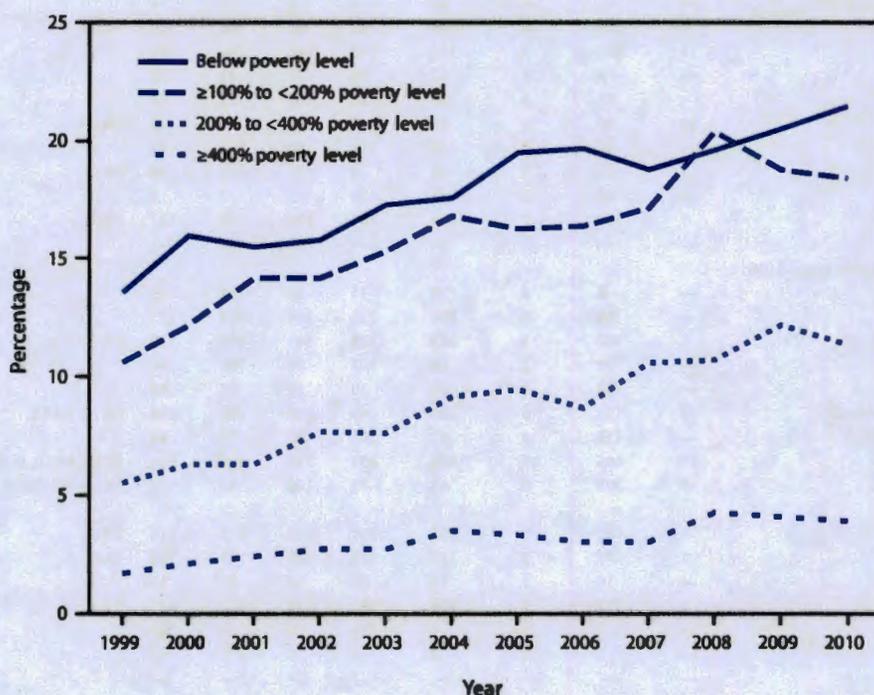
CDC has released Epi Info 7 (available at <http://www.cdc.gov/epiinfo>), the latest version of its public-domain software designed to enable epidemiologists to create complex forms rapidly, collect large amounts of data, and quickly analyze information to assess situations. With Epi Info 7, users will be able to 1) distribute, deploy, and use Epi Info 7 during emergencies without requiring administrative privileges; 2) rapidly create complex questionnaires by dragging and dropping templates; 3) store data either on a server, when network infrastructure is available, or in local database files when disasters disrupt network connectivity; 4) link records together to assess relationships; and 5) visualize data on case-based cluster maps, social network analysis graphs, and a new visual dashboard.

Epi Info 7 also will enable future additions of web-based and mobile device-based extensions to the Epi Info platform.

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage of Adults Aged 18–64 Years Who Did Not Get Needed Prescription Drugs Because of Cost,* by Poverty Status[†] — National Health Interview Survey, United States, 1999–2010[‡]



* Based on response to the question, "During the past 12 months, was there any time when you needed prescription medicine but didn't get it because you couldn't afford it?"

[†] Poverty status is based on family income and family size using the U.S. Census Bureau poverty thresholds. Family income was imputed when information was missing, using multiple imputation methodology.

[‡] Estimates are based on household interviews of a sample of the U.S. civilian, noninstitutionalized adult population.

During 1999–2010, the percentage of working-age adults who reported that in the past 12 months they needed prescription drugs but did not obtain them because of cost was higher among those in families with low income than in families with higher income. The percentage that reported not getting needed prescription drugs increased for all income groups during the period 1999–2010. In 2010, 21.5% of those below the poverty level did not obtain needed prescription drugs compared with 3.9% among those at or exceeding 400% of the poverty level.

Source: National Health Interview Survey data, 1999–2010. Available at <http://www.cdc.gov/nchs/nhis.htm>.

Notifiable Diseases and Mortality Tables

TABLE I. Provisional cases of infrequently reported notifiable diseases (<1,000 cases reported during the preceding year) — United States, week ending October 29, 2011 (43rd week)*

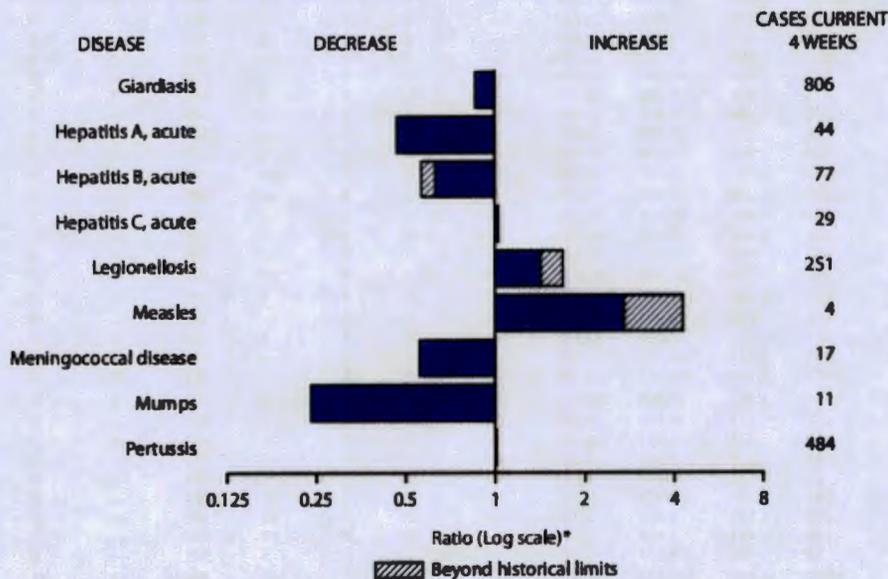
Disease	Current week	Cum 2011	5-year weekly average†	Total cases reported for previous years					States reporting cases during current week (No.)
				2010	2009	2008	2007	2006	
Anthrax	—	—	—	—	1	—	1	1	
Arboviral diseases ^{§, ¶} :									
California serogroup virus disease	—	106	1	75	55	62	55	67	
Eastern equine encephalitis virus disease	—	3	—	10	4	4	4	8	
Powassan virus disease	—	13	0	8	6	2	7	1	
St. Louis encephalitis virus disease	—	3	0	10	12	13	9	10	
Western equine encephalitis virus disease	—	—	—	—	—	—	—	—	
Babesiosis	3	579	0	NN	NN	NN	NN	NN	NY (3)
Botulism, total	19	101	2	112	118	145	144	165	
foodborne	—	8	0	7	10	17	32	20	
infant	—	65	1	80	83	109	85	97	
other (wound and unspecified)	19	28	0	25	25	19	27	48	CA (19)
Brucellosis	—	65	2	115	115	80	131	121	
Chancroid	1	27	1	24	28	25	23	33	VA (1)
Cholera	—	28	0	13	10	5	7	9	
Cyclosporiasis [§]	1	140	2	179	141	139	93	137	FL (1)
Diphtheria	—	—	—	—	—	—	—	—	
<i>Haemophilus influenzae</i> , ^{¶¶} invasive disease (age <5 yrs):									
serotype b	—	6	0	23	35	30	22	29	
nonsertotype b	—	88	3	200	236	244	199	175	
unknown serotype	1	192	3	223	178	163	180	179	OK (1)
Hansen disease [§]	—	39	2	98	103	80	101	66	
Hantavirus pulmonary syndrome [§]	—	18	0	20	20	18	32	40	
Hemolytic uremic syndrome, postdiarrheal [§]	3	150	6	266	242	330	292	288	OR (1), CA (2)
Influenza-associated pediatric mortality ^{§, ††}	—	112	4	61	358	90	77	43	
Listeriosis	11	606	17	821	851	759	808	884	NY (4), MI (1), WA (1), OR (1), CA (4)
Measles ^{§§}	3	205	0	63	71	140	43	55	NC (1), AZ (1), OR (1)
Meningococcal disease, invasive ^{¶¶} :									
A, C, Y, and W-135	1	152	5	280	301	330	325	318	OK (1)
serogroup B	1	77	2	135	174	188	167	193	VA (1)
other serogroup	—	10	1	12	23	38	35	32	
unknown serogroup	1	327	8	406	482	616	550	651	OR (1)
Novel influenza A virus infections ^{¶¶¶}	—	7	0	4	43,774	2	4	NN	
Plague	—	2	0	2	8	3	7	17	
Polio myelitis, paralytic	—	—	—	—	1	—	—	—	
Polio virus infection, nonparalytic [§]	—	—	—	—	—	—	—	NN	
Psittacosis [§]	—	2	0	4	9	8	12	21	
Q fever, total [§]	1	88	3	131	113	120	171	169	
acute	—	65	1	106	93	106	—	—	
chronic	1	23	0	25	20	14	—	—	ME (1)
Rabies, human	—	1	0	2	4	2	1	3	
Rubella ^{†††}	—	3	0	5	3	16	12	11	
Rubella, congenital syndrome	—	—	—	—	2	—	—	1	
SARS-CoV [§]	—	—	—	—	—	—	—	—	
Smallpox [§]	—	—	—	—	—	—	—	—	
Streptococcal toxic-shock syndrome [§]	—	92	2	142	161	157	132	125	
Syphilis, congenital (age <1 yr) ^{§§§}	—	182	7	377	423	431	430	349	
Tetanus	—	7	1	26	18	19	28	41	
Toxic-shock syndrome (staphylococcal) [§]	1	63	2	82	74	71	92	101	NC (1)
Trichinellosis	—	9	—	7	13	39	5	15	
Tularemia	2	117	1	124	93	123	137	95	WA (2)
Typhoid fever	2	298	7	467	397	449	434	353	CA (2)
Vancomycin-intermediate <i>Staphylococcus aureus</i> [§]	1	52	1	91	78	63	37	6	MO (1)
Vancomycin-resistant <i>Staphylococcus aureus</i> [§]	—	—	0	2	1	—	2	1	
Vibriosis (noncholera <i>Vibrio</i> species infections) [§]	13	598	12	846	789	588	549	NN	PA (1), OH (1), MD (2), FL (3), AL (1), AZ (2), NV (1), CA (2)
Viral hemorrhagic fever ^{¶¶¶}	—	—	—	1	NN	NN	NN	NN	
Yellow fever	—	—	—	—	—	—	—	—	

See Table 1 footnotes on next page.

TABLE I. (Continued) Provisional cases of infrequently reported notifiable diseases (<1,000 cases reported during the preceding year) — United States, week ending October 29, 2011 (43rd week)*

—: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts.
 * Case counts for reporting year 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf.
 † Calculated by summing the incidence counts for the current week, the 2 weeks preceding the current week, and the 2 weeks following the current week, for a total of 5 preceding years. Additional information is available at http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/5yearweeklyaverage.pdf.
 ‡ Not reportable in all states. Data from states where the condition is not reportable are excluded from this table except starting in 2007 for the arboviral diseases, STD data, TB data, and influenza-associated pediatric mortality, and in 2003 for SARS-CoV. Reporting exceptions are available at http://www.cdc.gov/osels/ph_surveillance/nndss/phs/infdis.htm.
 § Includes both neuroinvasive and nonneuroinvasive. Updated weekly from reports to the Division of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases (ArboNET Surveillance). Data for West Nile virus are available in Table II.
 ¶ Data for H. influenzae (all ages, all serotypes) are available in Table II.
 †† Updated weekly from reports to the Influenza Division, National Center for Immunization and Respiratory Diseases. Since October 2, 2011, no influenza-associated pediatric deaths occurring during the 2011-12 influenza season have been reported.
 ††† The three measles cases reported for the current week were imported.
 †††† Data for meningococcal disease (all serogroups) are available in Table II.
 ††††† CDC discontinued reporting of individual confirmed and probable cases of 2009 pandemic influenza A (H1N1) virus infections on July 24, 2009. During 2009, four cases of human infection with novel influenza A viruses, different from the 2009 pandemic influenza A (H1N1) strain, were reported to CDC. The four cases of novel influenza A virus infection reported to CDC during 2010, and the seven cases reported during 2011, were identified as swine influenza A (H3N2) virus and are unrelated to the 2009 pandemic influenza A (H1N1) virus. Total case counts are provided by the Influenza Division, National Center for Immunization and Respiratory Diseases (NCIRD).
 †††††† No rubella cases were reported for the current week.
 ††††††† Updated weekly from reports to the Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention.
 †††††††† There was one case of viral hemorrhagic fever reported during week 12 of 2010. The one case report was confirmed as lassa fever. See Table II for dengue hemorrhagic fever.

FIGURE I. Selected notifiable disease reports, United States, comparison of provisional 4-week totals October 29, 2011, with historical data



* Ratio of current 4-week total to mean of 15 4-week totals (from previous, comparable, and subsequent 4-week periods for the past 5 years). The point where the hatched area begins is based on the mean and two standard deviations of these 4-week totals.

Notifiable Disease Data Team and 122 Cities Mortality Data Team

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Morbidity and Mortality Weekly Report

TABLE II. Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)*

Reporting area	Chlamydia trachomatis infection					Coccidioidomycosis					Cryptosporidiosis				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	11,158	26,513	31,142	1,102,585	1,072,235	146	368	568	15,714	NN	112	131	359	7,030	7,878
New England	773	862	2,043	36,773	34,448	—	0	1	1	NN	—	7	22	339	446
Connecticut	219	219	1,557	8,842	9,391	—	0	0	—	NN	—	1	9	63	77
Maine†	80	58	100	2,572	2,101	—	0	0	—	NN	—	1	4	41	90
Massachusetts	458	423	860	18,657	17,035	—	0	0	—	NN	—	3	7	140	147
New Hampshire	1	53	87	2,215	1,997	—	0	1	1	NN	—	1	5	55	52
Rhode Island†	15	78	154	3,324	2,863	—	0	0	—	NN	—	0	1	1	15
Vermont†	—	26	84	1,163	1,061	—	0	0	—	NN	—	1	4	39	65
Mid. Atlantic	1,996	3,417	5,069	142,157	140,956	—	0	1	3	NN	4	16	40	752	746
New Jersey	173	542	1,069	24,900	21,795	—	0	0	—	NN	—	0	4	21	46
New York (Upstate)	810	716	2,099	29,935	28,219	—	0	0	—	NN	2	4	15	190	187
New York City	204	1,117	2,468	44,493	51,713	—	0	0	—	NN	—	2	6	70	80
Pennsylvania	809	980	1,240	42,829	39,229	—	0	1	3	NN	2	9	26	471	433
E.N. Central	1,027	4,018	7,039	163,027	170,034	—	0	5	42	NN	54	31	140	2,161	2,199
Illinois	22	1,076	1,320	42,051	50,216	—	0	0	—	NN	—	3	26	174	307
Indiana	160	496	3,376	22,073	16,694	—	0	0	—	NN	—	4	14	180	253
Michigan	487	919	1,414	39,370	41,184	—	0	3	26	NN	3	6	13	280	293
Ohio	185	1,002	1,134	41,209	42,634	—	0	3	16	NN	49	9	95	998	422
Wisconsin	173	460	559	18,324	19,306	—	0	0	—	NN	2	8	58	529	924
W.N. Central	124	1,466	1,667	59,546	60,226	—	0	2	6	NN	3	18	84	1,138	1,732
Iowa	26	211	253	8,837	8,798	—	0	0	—	NN	—	6	18	313	363
Kansas	9	200	288	8,530	8,080	—	0	0	—	NN	—	0	8	30	98
Minnesota	—	277	368	10,706	12,895	—	0	0	—	NN	—	0	9	—	375
Missouri	—	529	759	22,030	21,692	—	0	0	—	NN	3	4	63	471	525
Nebraska†	82	112	218	5,038	4,153	—	0	2	6	NN	—	4	12	166	241
North Dakota	7	42	77	1,739	1,967	—	0	0	—	NN	—	0	12	28	29
South Dakota	—	63	93	2,666	2,641	—	0	0	—	NN	—	2	13	130	101
S. Atlantic	2,968	5,293	6,685	229,790	215,252	—	0	2	3	NN	15	21	37	956	903
Delaware	113	85	128	3,590	3,681	—	0	0	—	NN	1	0	1	8	7
District of Columbia	107	109	191	4,681	4,647	—	0	0	—	NN	—	0	1	5	7
Florida	897	1,492	1,698	63,421	63,079	—	0	0	—	NN	11	8	17	380	334
Georgia	441	987	2,384	42,081	36,414	—	0	0	—	NN	1	5	11	237	230
Maryland†	—	475	1,125	19,536	20,254	—	0	2	3	NN	1	1	6	55	33
North Carolina	—	878	1,688	41,491	35,968	—	0	0	—	NN	—	0	13	36	82
South Carolina†	401	526	946	23,827	22,071	—	0	0	—	NN	—	3	8	112	103
Virginia†	930	654	965	27,656	25,948	—	0	0	—	NN	1	2	8	107	90
West Virginia	79	79	121	3,507	3,190	—	0	0	—	NN	—	0	5	16	17
E.S. Central	1,011	1,894	3,314	80,341	76,200	—	0	0	—	NN	—	6	13	271	307
Alabama†	439	544	1,566	24,268	22,476	—	0	0	—	NN	—	2	7	116	161
Kentucky	313	280	2,352	13,329	12,280	—	0	0	—	NN	—	1	5	37	75
Mississippi	—	407	696	17,441	17,809	—	0	0	—	NN	—	1	4	41	22
Tennessee†	259	595	795	25,303	23,635	—	0	0	—	NN	—	1	6	77	49
W.S. Central	409	3,663	4,560	151,265	146,644	—	0	1	4	NN	21	7	62	440	438
Arkansas†	330	305	440	13,295	13,069	—	0	0	—	NN	—	0	2	23	31
Louisiana	—	477	1,052	18,089	22,508	—	0	1	4	NN	—	0	9	40	63
Oklahoma	79	349	1,324	16,239	11,821	—	0	0	—	NN	—	1	34	72	78
Texas†	—	2,452	3,107	103,642	99,246	—	0	0	—	NN	21	5	37	305	266
Mountain	703	1,741	2,155	74,054	69,457	89	284	457	12,410	NN	3	11	30	513	533
Arizona	—	537	717	23,470	22,565	88	280	454	12,272	NN	—	1	4	36	35
Colorado	368	415	848	19,685	16,404	—	0	0	—	NN	—	3	12	138	121
Idaho†	10	81	235	3,512	3,343	—	0	0	—	NN	—	2	9	95	92
Montana†	73	61	88	2,808	2,574	—	0	2	4	NN	3	1	6	65	44
Nevada†	173	201	380	8,878	8,302	1	1	5	78	NN	—	0	2	9	37
New Mexico†	66	200	1,183	8,701	9,044	—	0	4	43	NN	—	3	8	109	116
Utah	—	130	181	5,429	5,526	—	0	2	10	NN	—	1	5	38	65
Wyoming†	13	38	90	1,571	1,699	—	0	2	3	NN	—	0	5	23	23
Pacific	2,147	3,950	6,559	165,632	159,018	57	68	143	3,245	NN	12	11	29	460	574
Alaska	—	116	157	4,817	5,077	—	0	0	—	NN	—	0	3	13	5
California	1,510	2,971	5,763	126,371	121,890	57	68	143	3,238	NN	7	6	19	273	298
Hawaii	—	105	135	3,896	5,080	—	0	0	—	NN	—	0	0	—	1
Oregon	284	278	524	11,611	9,305	—	0	1	7	NN	3	2	8	108	196
Washington	353	437	672	18,937	17,666	—	0	0	—	NN	2	1	9	66	74
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	NN	N	0	0	N	N
C.N.M.I.	—	—	—	—	—	—	—	—	—	NN	—	—	—	—	—
Guam	—	10	81	189	757	—	0	0	—	NN	—	0	0	—	—
Puerto Rico	—	104	349	4,341	5,050	—	0	0	—	NN	N	0	0	N	N
U.S. Virgin Islands	—	16	27	642	479	—	0	0	—	NN	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

† Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

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TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)*

Reporting area	Dengue Virus Infection†									
	Dengue Fever‡				Dengue Hemorrhagic Fever§					
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max			
United States	—	3	16	162	646	—	0	1	1	9
New England	—	0	1	1	9	—	0	0	—	—
Connecticut	—	0	0	—	—	—	0	0	—	—
Maine**	—	0	1	—	5	—	0	0	—	—
Massachusetts	—	0	0	—	—	—	0	0	—	—
New Hampshire	—	0	0	—	—	—	0	0	—	—
Rhode Island**	—	0	0	—	1	—	0	0	—	—
Vermont**	—	0	1	1	3	—	0	0	—	—
Mid. Atlantic	—	1	6	50	214	—	0	0	—	5
New Jersey	—	0	1	—	28	—	0	0	—	—
New York (Upstate)	—	0	1	—	30	—	0	0	—	2
New York City	—	1	4	36	135	—	0	0	—	3
Pennsylvania	—	0	2	14	21	—	0	0	—	—
E.N. Central	—	0	4	9	65	—	0	0	—	1
Illinois	—	0	2	1	20	—	0	0	—	—
Indiana	—	0	1	2	14	—	0	0	—	—
Michigan	—	0	1	2	9	—	0	0	—	—
Ohio	—	0	1	2	16	—	0	0	—	—
Wisconsin	—	0	2	2	6	—	0	0	—	1
W.N. Central	—	0	2	6	31	—	0	1	—	—
Iowa	—	0	1	3	2	—	0	0	—	—
Kansas	—	0	1	1	4	—	0	0	—	—
Minnesota	—	0	1	—	13	—	0	0	—	—
Missouri	—	0	1	1	4	—	0	0	—	—
Nebraska**	—	0	0	—	7	—	0	0	—	—
North Dakota	—	0	1	1	1	—	0	0	—	—
South Dakota	—	0	0	—	—	—	0	1	—	—
S. Atlantic	—	1	8	67	226	—	0	1	1	2
Delaware	—	0	2	2	—	—	0	0	—	—
District of Columbia	—	0	0	—	—	—	0	0	—	—
Florida	—	1	7	49	178	—	0	0	—	2
Georgia	—	0	1	3	11	—	0	0	—	—
Maryland**	—	0	2	4	—	—	0	0	—	—
North Carolina	—	0	1	2	8	—	0	0	—	—
South Carolina**	—	0	0	—	13	—	0	0	—	—
Virginia**	—	0	1	7	14	—	0	1	1	—
West Virginia	—	0	0	—	2	—	0	0	—	—
E.S. Central	—	0	3	4	6	—	0	0	—	—
Alabama**	—	0	1	2	3	—	0	0	—	—
Kentucky	—	0	0	—	2	—	0	0	—	—
Mississippi	—	0	0	—	—	—	0	0	—	—
Tennessee**	—	0	2	2	1	—	0	0	—	—
W.S. Central	—	0	2	6	25	—	0	0	—	1
Arkansas**	—	0	0	—	—	—	0	0	—	1
Louisiana	—	0	1	3	4	—	0	0	—	—
Oklahoma	—	0	1	—	4	—	0	0	—	—
Texas**	—	0	1	3	17	—	0	0	—	—
Mountain	—	0	2	4	20	—	0	0	—	—
Arizona	—	0	2	2	10	—	0	0	—	—
Colorado	—	0	0	—	—	—	0	0	—	—
Idaho**	—	0	1	—	2	—	0	0	—	—
Montana**	—	0	1	—	3	—	0	0	—	—
Nevada**	—	0	1	1	4	—	0	0	—	—
New Mexico**	—	0	0	—	1	—	0	0	—	—
Utah	—	0	1	1	—	—	0	0	—	—
Wyoming**	—	0	0	—	—	—	0	0	—	—
Pacific	—	0	4	15	50	—	0	0	—	—
Alaska	—	0	0	—	1	—	0	0	—	—
California	—	0	2	5	34	—	0	0	—	—
Hawaii	—	0	4	5	—	—	0	0	—	—
Oregon	—	0	0	—	—	—	0	0	—	—
Washington	—	0	1	5	15	—	0	0	—	—
Territories										
American Samoa	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	29	192	1,060	10,029	—	0	3	17	227
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—

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U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

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† Updated weekly from reports to the Division of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases (ArboNET Surveillance).

‡ Dengue Fever includes cases that meet criteria for Dengue Fever with hemorrhage, other clinical and unknown case classifications.

§ DHF includes cases that meet criteria for dengue shock syndrome (DSS), a more severe form of DHF.

** Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)*

Reporting area	Ehrlichiosis/Anaplasmosis [†]														
	<i>Ehrlichia chaffeensis</i>				<i>Anaplasma phagocytophilum</i>				Undetermined						
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	6	6	109	619	591	7	15	53	609	1,572	—	2	13	93	82
New England	—	0	2	4	5	1	2	24	208	94	—	0	1	1	2
Connecticut	—	0	0	—	—	—	0	5	—	32	—	0	0	—	—
Maine [§]	—	0	1	1	3	—	0	2	15	15	—	0	0	—	—
Massachusetts	—	0	0	—	—	—	0	17	135	—	—	0	0	—	—
New Hampshire	—	0	1	2	2	—	0	4	14	16	—	0	1	1	2
Rhode Island [§]	—	0	1	1	—	—	0	15	40	29	—	0	0	—	—
Vermont [§]	—	0	0	—	—	1	0	1	4	2	—	0	0	—	—
Mid. Atlantic	1	1	7	56	80	2	5	29	274	230	—	0	2	11	11
New Jersey	—	0	1	—	48	—	0	3	—	64	—	0	0	—	1
New York (Upstate)	1	0	7	47	25	2	3	25	234	154	—	0	2	11	7
New York City	—	0	1	9	5	—	0	5	36	11	—	0	0	—	—
Pennsylvania	—	0	0	—	2	—	0	1	4	1	—	0	0	—	3
E.N. Central	—	0	3	24	41	—	0	8	15	480	—	1	5	41	42
Illinois	—	0	2	14	15	—	0	2	6	8	—	0	1	2	3
Indiana	—	0	0	—	—	—	0	0	—	—	—	0	3	32	15
Michigan	—	0	2	4	2	—	0	1	—	4	—	0	2	5	—
Ohio	—	0	1	6	6	—	0	1	6	2	—	0	1	1	—
Wisconsin	—	0	1	—	18	—	0	7	3	466	—	0	1	1	24
W.N. Central	—	1	19	152	119	—	0	20	33	689	—	0	11	15	10
Iowa	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
Kansas	—	0	1	3	6	—	0	1	2	1	—	0	0	—	—
Minnesota	—	0	12	—	—	—	0	20	1	676	—	0	11	—	—
Missouri	—	1	19	147	111	—	0	7	27	12	—	0	7	14	10
Nebraska [§]	—	0	1	1	2	—	0	1	1	—	—	0	1	1	—
North Dakota	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
South Dakota	—	0	1	1	—	—	0	1	2	—	—	0	0	—	—
S. Atlantic	4	2	33	215	237	3	1	8	54	57	—	0	1	7	6
Delaware	—	0	2	15	17	—	0	1	1	4	—	0	0	—	—
District of Columbia	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
Florida	1	0	3	14	8	—	0	3	9	3	—	0	0	—	—
Georgia	—	0	3	16	20	—	0	2	7	1	—	0	1	1	1
Maryland [§]	1	0	3	25	21	—	0	2	6	14	—	0	0	—	2
North Carolina	2	0	17	57	94	—	0	6	17	23	—	0	0	—	—
South Carolina [§]	—	0	1	1	4	—	0	0	—	1	—	0	1	1	—
Virginia [§]	—	1	13	87	71	3	0	3	14	11	—	0	1	4	3
West Virginia	—	0	1	—	2	—	0	0	—	—	—	0	1	1	—
E.S. Central	1	0	8	67	86	—	0	2	15	19	—	0	3	12	8
Alabama [§]	—	0	2	4	10	—	0	1	4	7	N	0	0	N	N
Kentucky	—	0	3	10	16	—	0	0	—	—	—	0	0	—	1
Mississippi	—	0	1	3	3	—	0	1	1	2	—	0	0	—	1
Tennessee [§]	1	0	5	50	57	—	0	2	10	10	—	0	3	12	6
W.S. Central	—	0	87	101	22	1	0	9	7	3	—	0	0	—	1
Arkansas [§]	—	0	12	43	4	—	0	2	5	—	—	0	0	—	—
Louisiana	—	0	0	—	1	—	0	0	—	—	—	0	0	—	—
Oklahoma	—	0	82	57	14	1	0	7	2	2	—	0	0	—	—
Texas [§]	—	0	1	1	3	—	0	1	—	1	—	0	0	—	1
Mountain	—	0	0	—	—	—	0	0	—	—	—	0	1	4	—
Arizona	—	0	0	—	—	—	0	0	—	—	—	0	1	3	—
Colorado	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
Idaho [§]	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
Montana [§]	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
Nevada [§]	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
New Mexico [§]	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
Utah	—	0	0	—	—	—	0	0	—	—	—	0	1	1	—
Wyoming [§]	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Pacific	—	0	1	—	1	—	0	1	3	—	—	0	1	2	2
Alaska	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
California	—	0	1	—	1	—	0	0	—	—	—	0	1	2	2
Hawaii	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
Oregon	—	0	0	—	—	—	0	1	3	—	—	0	0	—	—
Washington	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Territories															
American Samoa	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
Puerto Rico	N	0	0	N	N	N	0	0	N	N	N	0	0	N	N
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

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[†] Cumulative total *E. ewingii* cases reported for year 2011 = 13.

[§] Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)^a

Reporting area	Giardiasis				Gonorrhea				Haemophilus influenzae, invasive ^b All ages, all serotypes						
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	183	290	445	12,446	16,674	2,368	6,022	7,484	250,992	253,640	26	65	141	2,581	2,471
New England	8	26	61	1,227	1,428	122	105	206	4,493	4,604	2	4	12	172	146
Connecticut	—	4	9	176	253	46	45	150	1,918	2,056	—	1	6	43	30
Maine ^c	3	3	10	153	180	8	4	17	198	140	—	0	2	21	11
Massachusetts	—	12	27	566	618	53	47	80	1,942	1,979	—	2	6	80	77
New Hampshire	—	2	8	101	143	2	2	7	107	127	1	0	2	13	10
Rhode Island ^c	—	1	10	57	67	13	6	16	285	254	—	0	2	9	11
Vermont ^c	5	3	17	174	167	—	0	8	43	48	1	0	3	6	7
Mid. Atlantic	33	58	103	2,469	2,807	399	783	1,074	32,733	29,793	5	14	32	590	465
New Jersey	—	4	14	134	415	51	148	258	6,747	4,778	—	2	7	87	87
New York (Upstate)	18	24	72	963	954	113	115	271	4,786	4,643	3	3	18	152	124
New York City	8	16	29	710	781	45	244	469	10,140	9,949	1	3	7	141	75
Pennsylvania	7	16	27	662	657	190	257	365	11,060	10,423	1	5	11	210	179
E.N. Central	19	48	69	1,973	2,818	299	1,014	2,091	42,788	46,975	1	11	22	452	405
Illinois	—	9	19	379	611	9	270	362	10,691	12,991	—	3	10	131	141
Indiana	—	5	11	189	345	50	117	1,018	5,366	4,722	—	2	7	81	85
Michigan	7	10	19	408	608	127	237	494	10,070	11,373	—	1	4	57	26
Ohio	12	16	30	674	717	61	312	395	13,013	13,741	1	2	7	129	99
Wisconsin	—	8	17	323	537	52	92	126	3,648	4,148	—	1	5	54	54
W.N. Central	13	23	50	948	1,834	29	302	363	12,369	12,271	3	3	10	129	180
Iowa	2	4	15	236	253	3	37	53	1,569	1,470	—	0	1	1	1
Kansas	—	2	7	76	188	4	42	57	1,693	1,707	—	0	2	18	18
Minnesota	—	0	16	—	737	1	36	53	1,465	1,811	—	0	5	—	65
Missouri	8	8	23	359	361	—	149	186	6,025	5,797	3	1	5	72	68
Nebraska ^c	3	4	11	159	182	21	25	45	1,013	942	—	0	3	26	18
North Dakota	—	0	12	36	26	—	4	8	174	164	—	0	6	11	10
South Dakota	—	1	8	82	87	—	10	20	430	380	—	0	1	1	—
S. Atlantic	31	52	98	2,246	3,357	750	1,474	1,862	61,817	63,886	9	15	31	618	633
Delaware	—	0	3	27	29	28	16	31	667	840	—	0	2	4	5
District of Columbia	—	1	3	29	50	31	39	68	1,671	1,761	—	0	1	—	4
Florida	22	23	50	1,017	1,802	255	377	465	16,393	17,031	7	4	12	199	155
Georgia	—	13	51	608	678	121	313	874	12,753	12,645	1	3	7	112	137
Maryland ^c	4	4	13	229	224	—	119	246	4,666	5,946	1	2	5	79	56
North Carolina	N	0	0	N	N	—	304	548	13,386	12,066	—	1	7	63	109
South Carolina ^c	2	2	8	99	125	117	145	257	6,780	6,736	—	1	5	63	72
Virginia ^c	3	5	32	215	410	190	111	176	4,836	6,416	—	1	8	81	73
West Virginia	—	0	8	22	39	8	16	29	665	445	—	0	9	17	22
E.S. Central	3	3	11	144	182	264	518	1,007	21,964	20,677	2	3	11	159	147
Alabama ^c	3	3	11	144	182	135	165	409	7,418	6,486	—	1	4	45	23
Kentucky	N	0	0	N	N	65	76	712	3,644	3,209	1	0	4	23	32
Mississippi	N	0	0	N	N	—	120	197	4,786	5,051	—	0	3	14	11
Tennessee ^c	N	0	0	N	N	64	144	224	6,116	5,931	1	2	5	77	81
W.S. Central	6	5	15	218	346	116	953	1,319	39,387	40,640	2	2	26	109	116
Arkansas ^c	5	2	9	107	112	92	89	138	3,958	3,965	1	0	3	28	16
Louisiana	1	2	10	111	172	—	132	372	5,170	6,866	—	0	4	38	27
Oklahoma	—	0	0	—	62	24	100	375	4,681	3,576	1	1	19	42	65
Texas ^c	N	0	0	N	N	—	603	867	25,578	26,233	—	0	4	1	8
Mountain	24	26	47	1,112	1,516	78	203	273	8,899	7,899	2	5	12	210	256
Arizona	3	3	6	110	137	—	76	131	3,546	2,641	—	2	6	75	94
Colorado	16	12	25	541	606	31	44	89	1,854	2,298	1	1	5	51	71
Idaho ^c	4	3	9	120	185	—	3	15	120	96	—	0	2	17	15
Montana ^c	1	2	5	67	93	2	1	4	68	89	—	0	1	3	2
Nevada ^c	—	1	7	57	90	45	38	103	1,688	1,497	—	0	2	15	7
New Mexico ^c	—	1	6	75	93	—	29	98	1,382	970	1	1	4	33	34
Utah	—	3	9	121	267	—	4	10	205	278	—	0	3	15	27
Wyoming ^c	—	0	5	21	45	—	1	3	36	30	—	0	1	1	6
Pacific	46	49	128	2,109	2,386	311	624	791	26,542	26,895	—	3	8	142	123
Alaska	—	2	7	83	88	—	20	34	826	1,087	—	0	3	21	22
California	33	32	67	1,411	1,454	258	506	695	21,768	21,925	—	0	4	35	22
Hawaii	—	0	4	27	50	—	13	24	511	634	—	0	3	21	19
Oregon	1	7	20	289	419	9	27	52	1,177	866	—	1	6	62	55
Washington	12	7	57	299	375	44	52	79	2,260	2,383	—	0	2	3	5
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	3	—	0	10	6	80	—	0	0	—	—
Puerto Rico	—	1	4	37	81	—	6	14	265	263	—	0	0	—	1
U.S. Virgin Islands	—	0	0	—	—	—	2	10	113	119	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

^a Case counts for reporting year 2011 are provisional and subject to change. For further information on interpretation of these data, see <http://www.cdc.gov/od/ohph/surveillance/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf>. Data for TB are displayed in Table IV, which appears quarterly.

^b Data for H. influenzae (age <5 yrs for serotype b, nonserotype b, and unknown serotype) are available in Table I.

^c Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

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TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)*

Reporting area	Hepatitis (viral, acute), by type														
	A					B					C				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	10	22	74	950	1,349	23	47	167	1,996	2,721	4	18	39	821	677
New England	—	1	5	56	85	—	1	8	62	49	—	1	5	44	48
Connecticut	—	0	3	16	24	—	0	4	10	20	—	0	3	25	33
Maine†	—	0	2	6	7	—	0	2	8	13	—	0	2	4	2
Massachusetts	—	0	3	25	44	—	1	6	42	9	—	0	2	11	12
New Hampshire	—	0	1	—	1	—	0	1	2	5	N	0	0	N	N
Rhode Island†	—	0	1	3	9	U	0	0	U	U	U	0	0	U	U
Vermont†	—	0	2	6	—	—	0	0	—	2	—	0	1	4	1
Mid. Atlantic	1	4	10	176	232	2	5	12	230	241	1	1	6	74	84
New Jersey	—	1	4	28	68	—	1	4	52	67	—	0	4	1	18
New York (Upstate)	1	1	4	42	51	—	1	9	41	39	1	1	4	42	40
New York City	—	1	6	58	68	—	1	5	65	72	—	0	2	2	3
Pennsylvania	—	1	3	48	45	2	2	4	72	63	—	0	4	29	23
E.N. Central	—	4	8	159	180	1	6	37	279	412	—	3	12	157	77
Illinois	—	1	4	48	44	—	1	6	54	108	—	0	2	6	1
Indiana	—	0	3	12	11	—	1	3	48	63	—	1	5	53	24
Michigan	—	1	6	60	65	—	1	6	69	106	—	2	7	92	36
Ohio	—	1	3	34	42	1	1	30	85	87	—	0	1	5	8
Wisconsin	—	0	2	5	18	—	0	3	23	48	—	0	1	1	8
W.N. Central	—	1	25	34	66	1	2	16	110	100	—	0	6	8	15
Iowa	—	0	1	5	10	—	0	1	9	13	—	0	0	—	—
Kansas	—	0	2	3	10	—	0	2	10	8	—	0	1	3	2
Minnesota	—	0	22	9	14	—	0	15	9	7	—	0	6	2	6
Missouri	—	0	1	10	17	1	2	5	69	59	—	0	1	—	5
Nebraska†	—	0	1	5	14	—	0	3	12	11	—	0	1	3	2
North Dakota	—	0	3	—	—	—	0	0	—	—	—	0	0	—	—
South Dakota	—	0	2	2	1	—	0	1	1	2	—	0	0	—	—
S. Atlantic	3	5	13	190	283	6	12	55	541	748	2	4	11	198	154
Delaware	—	0	1	2	7	—	0	2	11	24	U	0	0	U	U
District of Columbia	—	0	0	—	1	—	0	0	—	3	—	0	0	—	2
Florida	1	1	6	66	114	5	4	8	171	246	1	1	4	51	46
Georgia	—	1	4	38	34	—	2	8	78	140	—	1	3	31	24
Maryland†	2	0	4	23	18	—	1	4	44	57	—	0	3	29	20
North Carolina	—	0	3	23	43	1	2	12	94	87	1	1	7	48	33
South Carolina†	—	0	2	9	22	—	1	4	27	53	—	0	1	1	1
Virginia†	—	1	3	21	42	—	1	7	50	78	—	0	3	16	11
West Virginia	—	0	5	8	2	—	0	43	66	60	—	0	6	22	17
E.S. Central	—	1	6	42	33	4	9	14	351	305	—	3	8	149	132
Alabama†	—	0	2	6	6	1	2	5	92	59	—	0	3	16	6
Kentucky	—	0	6	9	13	2	2	6	84	109	—	1	7	64	89
Mississippi	—	0	1	7	2	—	1	3	37	29	U	0	0	U	U
Tennessee†	—	0	5	20	12	1	4	8	138	108	—	1	5	69	37
W.S. Central	4	3	15	108	121	6	7	67	255	484	—	2	11	75	59
Arkansas†	—	0	0	—	2	—	1	4	41	51	—	0	0	—	1
Louisiana	—	0	1	2	10	—	1	4	27	45	—	0	2	5	2
Oklahoma	—	0	4	3	2	2	1	16	69	82	—	1	10	40	25
Texas†	4	2	11	103	107	4	3	45	118	306	—	0	3	30	31
Mountain	—	1	5	52	130	—	1	4	61	117	1	1	4	49	53
Arizona	—	0	2	14	57	—	0	3	13	22	U	0	0	U	U
Colorado	—	0	2	17	34	—	0	2	15	39	1	0	3	15	14
Idaho†	—	0	1	6	6	—	0	1	2	6	—	0	2	8	9
Montana†	—	0	1	2	4	—	0	0	—	—	—	0	1	2	2
Nevada†	—	0	3	5	13	—	0	3	20	35	—	0	2	9	5
New Mexico†	—	0	1	5	4	—	0	2	6	5	—	0	1	12	13
Utah	—	0	2	1	9	—	0	1	5	8	—	0	1	1	10
Wyoming†	—	0	1	2	3	—	0	1	—	2	—	0	1	2	—
Pacific	2	3	13	133	219	3	3	25	107	265	—	1	12	67	55
Alaska	—	0	1	2	1	—	0	1	4	3	U	0	0	U	U
California	1	2	12	95	179	—	1	22	49	182	—	1	4	29	23
Hawaii	—	0	2	7	7	—	0	1	6	6	U	0	0	U	U
Oregon	—	0	2	8	16	1	0	4	28	35	—	0	3	11	14
Washington	1	0	4	21	16	2	0	4	20	39	—	0	5	27	18
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	5	8	4	—	1	8	28	68	—	0	4	10	56
Puerto Rico	—	0	2	6	15	—	0	2	8	24	N	0	0	N	N
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

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U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

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† Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

Morbidity and Mortality Weekly Report

TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)*

Reporting area	Legionellosis					Lyme disease					Malaria				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	51	54	167	3,066	2,835	358	361	1,904	26,464	27,427	17	26	114	1,115	1,441
New England	—	4	42	303	235	3	73	447	5,492	8,228	2	2	20	78	93
Connecticut	—	1	10	64	41	1	29	223	2,282	2,792	—	0	20	10	2
Maine†	—	0	2	15	11	—	13	66	775	621	2	0	1	6	5
Massachusetts	—	2	27	181	116	—	21	72	1,082	3,118	—	1	5	51	67
New Hampshire	—	0	3	18	22	—	9	65	705	1,205	—	0	1	2	4
Rhode Island†	—	0	2	14	36	—	1	31	113	169	—	0	4	3	12
Vermont†	—	0	2	11	9	2	5	66	535	323	—	0	1	6	3
Mid. Atlantic	18	15	79	1,044	803	304	154	1,201	16,608	9,788	2	7	17	253	438
New Jersey	—	2	14	155	128	86	58	586	7,111	3,370	—	0	6	8	90
New York (Upstate)	11	5	27	317	250	102	35	214	3,183	2,291	2	1	4	43	66
New York City	—	3	13	170	145	—	1	17	100	648	—	3	10	153	231
Pennsylvania	7	5	35	402	280	116	65	500	6,214	3,479	—	1	4	49	51
E.N. Central	14	10	51	651	610	—	17	106	1,163	3,657	2	3	8	131	143
Illinois	—	1	11	96	137	—	1	18	144	134	—	1	4	50	53
Indiana	3	1	5	82	54	—	0	15	89	78	—	0	2	9	13
Michigan	2	3	15	163	159	—	1	14	102	92	—	0	4	29	28
Ohio	9	4	34	309	202	—	1	9	43	26	2	1	4	37	37
Wisconsin	—	0	2	1	58	—	13	66	785	3,327	—	0	2	6	12
W.N. Central	—	1	9	71	105	1	2	15	120	2,024	—	1	45	28	62
Iowa	—	0	2	10	14	—	0	11	76	84	—	0	3	18	12
Kansas	—	0	2	9	11	—	0	2	12	10	—	0	2	6	10
Minnesota	—	0	8	—	27	—	0	15	—	1,899	—	0	45	—	3
Missouri	—	1	5	43	32	—	0	0	—	4	—	0	1	—	19
Nebraska†	—	0	1	5	9	—	0	2	8	8	—	0	1	3	15
North Dakota	—	0	1	2	4	1	0	10	21	18	—	0	1	—	—
South Dakota	—	0	1	2	8	—	0	1	3	1	—	0	1	1	3
S. Atlantic	15	9	29	447	459	43	52	169	2,882	3,401	5	8	23	374	383
Delaware	—	0	4	19	15	3	12	47	723	574	—	0	3	7	2
District of Columbia	—	0	3	9	16	—	0	2	13	38	—	0	1	5	11
Florida	4	3	9	144	140	6	2	7	98	75	—	2	7	88	109
Georgia	—	1	3	31	56	—	0	5	23	10	1	1	5	68	62
Maryland†	11	1	14	101	100	12	17	112	1,051	1,496	4	2	13	103	86
North Carolina	—	1	7	57	53	—	0	8	54	71	—	0	6	34	47
South Carolina†	—	0	5	17	12	—	0	6	29	27	—	0	1	4	5
Virginia†	—	1	9	63	56	22	15	76	818	999	—	1	8	65	58
West Virginia	—	0	2	6	11	—	0	14	73	111	—	0	0	—	3
E.S. Central	1	2	10	134	120	—	1	5	47	42	2	0	4	29	28
Alabama†	—	0	2	22	17	—	0	2	14	2	—	0	3	6	8
Kentucky	—	0	3	31	26	—	0	1	1	5	—	0	1	7	6
Mississippi	—	0	3	13	12	—	0	1	3	—	—	0	1	1	2
Tennessee†	1	1	8	68	65	—	0	3	29	35	2	0	3	15	12
W.S. Central	—	3	13	110	145	—	1	29	33	97	—	1	18	28	87
Arkansas†	—	0	2	12	16	—	0	0	—	—	—	0	1	5	4
Louisiana	—	0	3	14	9	—	0	1	1	3	—	0	1	1	5
Oklahoma	—	0	3	9	12	—	0	0	—	—	—	0	1	5	5
Texas†	—	2	11	75	108	—	1	29	32	94	—	0	17	17	73
Mountain	—	2	5	82	149	1	0	4	35	26	—	1	4	54	58
Arizona	—	1	3	28	55	—	0	2	11	2	—	0	4	22	23
Colorado	—	0	2	5	29	—	0	1	1	3	—	0	3	18	20
Idaho†	—	0	1	6	5	1	0	2	4	8	—	0	1	2	3
Montana†	—	0	1	1	4	—	0	3	9	4	—	0	1	1	2
Nevada†	—	0	2	13	19	—	0	1	3	1	—	0	2	7	6
New Mexico†	—	0	2	10	7	—	0	2	5	5	—	0	1	3	1
Utah	—	0	2	15	23	—	0	1	1	3	—	0	1	1	3
Wyoming†	—	0	2	4	7	—	0	1	1	—	—	0	0	—	—
Pacific	3	5	21	224	209	6	2	11	84	164	4	3	11	140	149
Alaska	—	0	0	—	2	—	0	2	7	6	—	0	2	5	3
California	3	4	15	188	175	—	1	9	54	107	3	2	8	96	99
Hawaii	—	0	1	1	1	N	0	0	N	N	—	0	1	6	3
Oregon	—	0	3	16	12	—	0	2	11	38	—	0	4	14	13
Washington	—	0	6	19	19	6	0	4	12	13	1	0	3	19	31
Territories															
American Samoa	N	0	0	N	N	N	0	0	N	N	—	0	1	1	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	1	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	0	1	—	1	N	0	0	N	N	—	0	0	—	5
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

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TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)*

Reporting area	Meningococcal disease, invasive [†]					Mumps					Pertussis				
	All serogroups														
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	3	13	53	566	656	7	7	47	271	2,455	162	283	2,925	11,389	19,107
New England	—	0	3	24	16	2	0	1	9	24	1	11	25	494	439
Connecticut	—	0	1	3	2	—	0	0	—	11	—	1	4	47	100
Maine [§]	—	0	1	4	3	2	0	1	2	1	—	2	19	147	39
Massachusetts	—	0	2	11	6	—	0	1	4	9	—	4	10	177	235
New Hampshire	—	0	1	1	—	—	0	0	—	3	—	1	7	78	16
Rhode Island [§]	—	0	1	—	—	—	0	1	2	—	—	0	4	23	36
Vermont [§]	—	0	3	5	5	—	0	1	1	—	1	0	4	22	13
Mid. Atlantic	—	1	6	63	66	1	1	23	31	2,073	16	31	125	1,310	1,274
New Jersey	—	0	1	5	19	—	0	2	10	346	—	3	7	127	143
New York (Upstate)	—	0	4	19	11	1	0	3	9	661	13	13	81	573	432
New York City	—	0	3	24	17	—	0	22	10	1,038	—	0	36	74	73
Pennsylvania	—	0	2	15	19	—	0	16	2	28	3	13	70	536	626
E.N. Central	—	2	6	81	111	1	2	7	74	60	25	61	198	2,400	4,339
Illinois	—	0	3	23	20	1	1	5	49	22	—	17	50	659	762
Indiana	—	0	2	15	24	—	0	0	—	4	—	4	26	165	601
Michigan	—	0	2	11	21	—	0	2	10	17	2	13	53	565	1,227
Ohio	—	0	2	22	28	—	0	5	12	14	21	13	80	616	1,345
Wisconsin	—	0	2	10	18	—	0	1	3	3	2	10	25	395	404
W.N. Central	—	1	4	40	45	—	0	4	31	80	5	22	501	943	1,939
Iowa	—	0	1	9	9	—	0	1	5	38	—	4	36	157	531
Kansas	—	0	1	2	6	—	0	1	4	4	—	2	10	80	149
Minnesota	—	0	2	—	5	—	0	4	1	4	—	0	469	326	639
Missouri	—	0	3	16	18	—	0	3	12	9	5	6	43	265	376
Nebraska [§]	—	0	2	10	5	—	0	1	5	23	—	1	11	46	176
North Dakota	—	0	1	1	2	—	0	3	4	—	—	0	10	41	41
South Dakota	—	0	1	2	—	—	0	0	—	2	—	0	7	28	27
S. Atlantic	1	2	8	117	116	—	0	4	24	49	15	27	106	1,101	1,467
Delaware	—	0	1	1	1	—	0	0	—	—	—	0	5	21	11
District of Columbia	—	0	1	1	1	—	0	0	—	3	—	0	2	3	8
Florida	—	1	5	45	51	—	0	2	7	8	5	6	17	274	266
Georgia	—	0	1	14	10	—	0	2	5	2	1	3	13	141	203
Maryland [§]	—	0	1	11	9	—	0	1	1	11	—	1	6	65	117
North Carolina	—	0	3	13	12	—	0	2	7	9	5	3	35	152	270
South Carolina [§]	—	0	1	9	11	—	0	0	—	4	—	3	25	122	305
Virginia [§]	1	0	2	16	19	—	0	2	4	10	4	6	41	265	203
West Virginia	—	0	3	7	2	—	0	0	—	2	—	0	41	58	84
E.S. Central	—	0	3	21	39	—	0	1	4	9	3	8	28	305	662
Alabama [§]	—	0	2	9	6	—	0	1	1	6	—	2	11	116	175
Kentucky	—	0	2	2	17	—	0	0	—	1	2	1	16	71	227
Mississippi	—	0	1	3	5	—	0	1	3	—	—	0	10	29	70
Tennessee [§]	—	0	2	7	11	—	0	1	—	2	1	2	10	89	190
W.S. Central	1	1	12	49	73	1	1	15	59	104	20	21	297	784	2,497
Arkansas [§]	—	0	2	10	5	—	0	2	3	5	—	2	16	53	184
Louisiana	—	0	2	10	12	—	0	2	—	6	—	0	3	17	37
Oklahoma	1	0	2	10	15	—	0	2	4	—	3	0	92	41	54
Texas [§]	—	0	10	19	41	1	1	14	52	93	17	19	187	673	2,222
Mountain	—	1	4	41	49	1	0	2	8	18	25	39	100	1,523	1,308
Arizona	—	0	1	10	13	1	0	0	1	5	1	14	29	576	392
Colorado	—	0	1	9	18	—	0	1	3	7	7	9	63	340	220
Idaho [§]	—	0	1	5	5	—	0	1	1	1	4	2	11	111	175
Montana [§]	—	0	2	4	1	—	0	0	—	—	13	1	16	89	69
Nevada [§]	—	0	1	3	8	—	0	0	—	1	—	0	5	28	30
New Mexico [§]	—	0	1	2	3	—	0	2	2	—	—	3	16	159	124
Utah	—	0	2	8	1	—	0	0	—	3	—	5	16	211	286
Wyoming [§]	—	0	1	—	—	—	0	1	1	1	—	0	1	9	12
Pacific	1	3	26	130	141	1	0	9	31	38	52	62	1,710	2,529	5,182
Alaska	—	0	1	2	1	—	0	1	1	1	—	0	4	23	37
California	—	2	17	92	92	—	0	9	23	24	—	46	1,569	1,711	4,490
Hawaii	—	0	1	4	1	—	0	1	2	4	—	1	9	73	59
Oregon	1	0	3	19	27	—	0	1	4	3	—	5	18	249	244
Washington	—	0	8	13	20	1	0	1	1	6	52	8	131	473	352
Territories															
American Samoa	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	1	4	12	474	—	0	14	31	3
Puerto Rico	—	0	0	—	2	—	0	1	1	1	—	0	1	2	2
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

† Data for meningococcal disease, invasive caused by serogroups A, C, Y, and W-135; serogroup B; other serogroup; and unknown serogroup are available in Table I.

§ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

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TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)*

Reporting area	Rabies, animal					Salmonellosis					Shiga toxin-producing <i>E. coli</i> (STEC) [†]				
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
		Med	Max				Med	Max				Med	Max		
United States	25	60	119	2,529	3,777	555	880	1,828	38,852	45,257	69	95	264	4,202	4,418
New England	1	4	16	202	258	1	34	107	1,743	2,110	—	3	12	180	192
Connecticut	—	2	10	94	112	—	8	28	400	491	—	0	4	47	60
Maine [‡]	—	1	6	56	55	—	2	8	114	112	—	0	3	27	17
Massachusetts	—	0	0	—	—	—	19	45	886	1,141	—	1	9	67	75
New Hampshire	—	0	3	17	15	—	3	8	143	155	—	0	3	22	20
Rhode Island [‡]	—	0	4	15	28	—	0	62	135	145	—	0	2	4	3
Vermont [‡]	1	0	2	20	48	1	1	7	65	66	—	0	3	13	17
Mid. Atlantic	5	16	35	731	930	44	90	205	4,576	5,116	5	11	35	512	485
New Jersey	—	0	0	—	—	—	16	48	797	1,045	—	2	6	92	104
New York (Upstate)	5	7	20	321	439	27	25	67	1,210	1,250	2	4	12	182	168
New York City	—	0	3	9	142	—	19	42	968	1,164	—	2	6	77	62
Pennsylvania	—	8	21	401	349	17	30	111	1,601	1,657	3	3	18	161	151
E.N. Central	1	2	17	162	224	24	86	150	3,739	5,130	4	12	48	748	717
Illinois	—	0	6	46	113	—	28	74	1,301	1,731	—	3	13	169	138
Indiana	—	0	7	23	—	—	9	19	350	664	—	2	8	86	121
Michigan	—	1	6	52	66	7	14	41	711	829	1	2	19	146	136
Ohio	1	0	5	41	45	17	21	46	1,058	1,154	3	3	10	165	121
Wisconsin	N	0	0	N	N	—	7	45	319	752	—	2	20	182	201
W.N. Central	4	2	40	72	225	16	41	102	2,004	2,605	24	12	39	647	799
Iowa	—	0	1	—	25	2	9	19	386	474	—	2	15	172	161
Kansas	—	0	4	28	56	—	6	25	378	388	—	2	8	89	66
Minnesota	—	0	34	—	25	—	0	16	—	648	—	0	7	—	252
Missouri	—	0	1	—	61	9	17	45	845	702	23	4	14	239	206
Nebraska [‡]	2	0	3	31	44	5	4	13	221	216	1	1	7	91	65
North Dakota	2	0	6	13	14	—	0	15	37	46	—	0	4	12	17
South Dakota	—	0	0	—	—	—	3	17	137	131	—	1	4	44	32
S. Atlantic	11	18	93	930	996	249	279	721	11,948	12,804	8	13	27	537	590
Delaware	—	0	0	—	—	2	3	11	153	157	—	0	2	14	6
District of Columbia	—	0	0	—	—	—	1	5	47	82	—	0	1	3	9
Florida	—	0	84	97	121	158	107	203	4,762	5,203	7	3	15	127	188
Georgia	—	0	0	—	—	33	42	127	2,093	2,477	—	2	8	95	93
Maryland [‡]	—	5	13	247	330	14	18	41	796	928	—	1	8	39	79
North Carolina	—	0	0	—	—	9	33	251	1,780	1,438	—	2	11	99	63
South Carolina [‡]	N	0	0	N	N	14	30	68	1,294	1,394	—	0	4	15	20
Virginia [‡]	11	11	27	511	480	19	21	68	978	978	1	3	9	142	116
West Virginia	—	0	30	75	65	—	0	14	45	147	—	0	4	3	16
E.S. Central	—	3	11	156	156	27	58	187	3,389	3,402	3	4	22	224	221
Alabama [‡]	—	1	7	73	65	15	18	70	1,007	874	—	1	15	70	42
Kentucky	—	0	2	14	19	—	9	20	372	498	1	1	5	42	60
Mississippi	—	0	1	1	—	—	20	66	1,152	1,090	—	0	12	19	17
Tennessee [‡]	—	1	6	68	72	12	16	51	858	940	2	1	11	93	102
W.S. Central	2	1	31	80	744	85	118	515	5,077	6,016	4	7	151	305	276
Arkansas [‡]	2	0	10	49	26	21	14	53	752	688	1	1	6	47	45
Louisiana	—	0	0	—	—	2	14	44	731	1,180	—	0	2	9	18
Oklahoma	—	0	20	31	41	16	11	95	577	562	3	1	55	60	26
Texas [‡]	—	0	17	—	677	46	78	381	3,017	3,586	—	5	95	189	187
Mountain	—	0	4	36	65	22	45	91	2,064	2,505	3	11	30	487	575
Arizona	N	0	0	N	N	—	14	33	625	866	—	2	14	76	70
Colorado	—	0	0	—	—	12	10	24	471	492	—	2	11	95	203
Idaho [‡]	—	0	1	6	11	3	3	8	131	141	3	2	7	106	86
Montana [‡]	N	0	0	N	N	2	2	10	116	85	—	0	5	35	38
Nevada [‡]	—	0	2	13	8	5	3	8	138	268	—	0	7	32	31
New Mexico [‡]	—	0	2	10	12	—	6	22	273	294	—	1	3	40	43
Utah	—	0	2	7	10	—	6	15	259	305	—	1	7	78	85
Wyoming [‡]	—	0	0	—	24	—	1	9	51	54	—	0	7	25	19
Pacific	1	3	15	160	179	87	101	288	4,312	5,569	18	14	46	562	563
Alaska	—	0	2	11	12	—	1	6	45	73	—	0	1	3	2
California	—	3	11	136	152	61	74	232	3,303	4,118	5	8	36	342	245
Hawaii	—	0	0	—	—	—	6	14	285	293	—	0	1	6	28
Oregon	1	0	2	13	15	2	5	12	217	456	2	1	11	83	100
Washington	—	0	14	—	—	24	12	42	462	629	11	2	13	128	188
Territories															
American Samoa	N	0	0	N	N	—	0	0	—	2	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	3	6	11	—	0	0	—	—
Puerto Rico	1	0	6	30	38	—	5	17	188	526	—	0	0	—	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

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U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/pls/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

[†] Includes *E. coli* O157:H7; Shiga toxin-positive, serogroup non-O157; and Shiga toxin-positive, not serogrouped.

[‡] Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

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TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)*

Reporting area	Spotted Fever Rickettsiosis (including RMSF) [†]														
	Shigellosis				Confirmed					Probable					
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	203	238	742	9,209	11,757	—	3	15	174	132	9	25	245	1,652	1,416
New England	—	4	19	205	302	—	0	1	1	—	—	0	1	6	4
Connecticut	—	0	3	36	69	—	0	0	—	—	—	0	0	—	—
Maine [‡]	—	0	4	20	6	—	0	0	—	—	—	0	0	—	2
Massachusetts	—	2	18	136	201	—	0	0	—	—	—	0	1	4	—
New Hampshire	—	0	1	3	14	—	0	1	1	—	—	0	1	1	1
Rhode Island [‡]	—	0	4	6	11	—	0	0	—	—	—	0	1	1	1
Vermont [‡]	—	0	1	4	1	—	0	0	—	—	—	0	0	—	—
Mid. Atlantic	7	15	74	721	1,448	—	0	2	13	2	—	1	4	43	93
New Jersey	—	3	9	125	338	—	0	0	—	1	—	0	2	—	56
New York (Upstate)	7	3	18	236	204	—	0	1	3	1	—	0	1	7	14
New York City	—	5	20	254	268	—	0	0	—	—	—	0	3	20	11
Pennsylvania	—	3	56	106	638	—	0	2	10	—	—	0	3	16	12
E.N. Central	6	16	40	643	1,378	—	0	2	8	3	1	1	8	97	75
Illinois	—	5	16	192	773	—	0	1	2	2	—	0	4	38	34
Indiana [‡]	—	1	4	43	53	—	0	1	2	1	1	0	4	42	20
Michigan	1	3	10	141	222	—	0	1	1	—	—	0	1	1	1
Ohio	5	5	27	267	265	—	0	2	3	—	—	0	2	16	14
Wisconsin	—	0	4	—	65	—	0	0	—	—	—	0	1	—	6
W.N. Central	1	6	27	254	1,909	—	0	6	27	13	—	4	29	330	266
Iowa	—	0	4	17	47	—	0	0	—	—	—	0	2	5	5
Kansas [‡]	—	1	12	50	242	—	0	0	—	—	—	0	0	—	—
Minnesota	—	0	4	—	55	—	0	0	—	—	—	0	2	—	—
Missouri	1	4	18	169	1,506	—	0	3	20	10	—	4	29	319	258
Nebraska [‡]	—	0	7	14	52	—	0	3	5	3	—	0	1	5	2
North Dakota	—	0	0	—	—	—	0	1	2	—	—	0	0	—	1
South Dakota	—	0	2	4	7	—	0	0	—	—	—	0	1	1	—
S. Atlantic	81	68	134	3,090	2,132	—	1	8	92	79	4	6	54	433	440
Delaware [‡]	2	0	1	6	38	—	0	1	1	1	—	0	4	18	19
District of Columbia	—	0	2	12	27	—	0	1	1	1	—	0	1	1	—
Florida [‡]	60	43	98	2,188	918	—	0	1	3	3	1	0	2	11	8
Georgia	11	11	24	485	672	—	0	6	59	56	—	0	0	—	—
Maryland [‡]	—	2	7	84	114	—	0	1	2	—	—	0	3	28	45
North Carolina	6	3	36	179	158	—	0	4	12	13	—	0	49	202	226
South Carolina [‡]	2	1	4	49	60	—	0	2	11	1	—	0	2	20	18
Virginia [‡]	—	2	8	83	119	—	0	1	3	4	3	2	13	149	124
West Virginia	—	0	66	4	26	—	0	0	—	—	—	0	1	4	—
E.S. Central	16	15	26	553	643	—	0	2	9	20	2	4	24	307	383
Alabama [‡]	12	4	13	196	167	—	0	1	4	5	—	1	8	62	76
Kentucky	1	1	6	43	205	—	0	1	1	6	—	0	0	—	—
Mississippi	2	3	10	160	44	—	0	0	—	1	—	0	2	12	21
Tennessee [‡]	1	4	11	154	227	—	0	2	4	8	2	4	18	233	286
W.S. Central	56	54	503	2,169	2,259	—	0	8	9	6	2	1	235	403	141
Arkansas [‡]	2	2	7	67	59	—	0	2	5	2	2	0	51	351	93
Louisiana	2	4	21	201	246	—	0	0	—	—	—	0	2	7	2
Oklahoma	10	2	161	129	237	—	0	5	3	3	—	0	202	41	22
Texas [‡]	42	42	338	1,772	1,717	—	0	1	1	1	—	0	5	4	24
Mountain	4	16	42	689	707	—	0	5	14	3	—	0	6	33	13
Arizona	4	5	27	305	386	—	0	4	13	1	—	0	6	18	1
Colorado [‡]	—	1	8	82	86	—	0	1	—	—	—	0	1	2	1
Idaho [‡]	—	0	3	16	23	—	0	1	1	—	—	0	1	1	5
Montana [‡]	—	1	15	121	7	—	0	0	—	2	—	0	1	1	1
Nevada [‡]	—	0	4	30	44	—	0	0	—	—	—	0	1	1	—
New Mexico [‡]	—	3	9	89	120	—	0	0	—	—	—	0	1	1	1
Utah	—	1	4	44	41	—	0	0	—	—	—	0	1	1	3
Wyoming [‡]	—	0	1	2	—	—	0	0	—	—	—	0	2	8	1
Pacific	32	21	63	885	979	—	0	2	1	6	—	0	0	—	1
Alaska	—	0	2	5	1	N	0	0	N	N	N	0	0	N	N
California	28	16	59	727	786	—	0	2	1	6	—	0	0	—	—
Hawaii	—	1	3	42	41	N	0	0	N	N	N	0	0	N	N
Oregon	—	1	4	38	53	—	0	0	—	—	—	0	0	—	1
Washington	4	1	6	73	98	—	0	1	—	—	—	0	0	—	—
Territories															
American Samoa	—	0	1	1	4	N	0	0	N	N	N	0	0	N	N
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	1	1	5	N	0	0	N	N	N	0	0	N	N
Puerto Rico	—	0	1	—	4	N	0	0	N	N	N	0	0	N	N
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

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 * Case counts for reporting year 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nnds/phs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.
 † Illnesses with similar clinical presentation that result from Spotted fever group rickettsia infections are reported as Spotted fever rickettsioses. Rocky Mountain spotted fever (RMSF) caused by Rickettsia rickettsii, is the most common and well-known spotted fever.
 ‡ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

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TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)*

Reporting area	Streptococcus pneumoniae, [†] invasive disease										Syphilis, primary and secondary				
	All ages				Age <5										
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	111	298	937	10,962	12,465	6	27	118	988	1,742	55	259	363	10,538	11,424
New England	5	16	79	610	687	1	1	5	40	87	1	7	16	300	403
Connecticut	—	6	49	258	273	—	0	3	9	23	—	1	5	39	81
Maine [‡]	2	2	13	105	99	—	0	1	4	8	—	0	2	11	26
Massachusetts	—	0	3	28	59	—	0	2	14	41	—	5	9	189	247
New Hampshire	1	2	8	86	97	—	0	1	5	5	1	0	3	17	19
Rhode Island [‡]	—	2	8	73	94	—	0	1	2	6	—	0	7	36	28
Vermont [‡]	2	1	6	60	65	1	0	2	6	4	—	0	2	8	2
Mid. Atlantic	2	30	81	1,081	1,310	—	2	27	90	195	4	29	52	1,232	1,418
New Jersey	—	13	35	498	584	—	0	4	30	50	—	4	13	164	203
New York (Upstate)	1	1	10	66	122	—	1	9	36	91	1	3	20	152	108
New York City	1	12	42	517	604	—	0	14	24	54	1	15	31	632	804
Pennsylvania	N	0	0	N	N	N	0	0	N	N	2	6	13	284	303
E.N. Central	36	65	114	2,404	2,562	—	5	13	198	311	6	30	48	1,261	1,621
Illinois	N	0	0	N	N	—	1	6	65	79	5	12	24	512	773
Indiana	—	16	33	544	587	—	0	4	25	48	—	3	8	131	151
Michigan	3	14	29	529	593	—	1	3	28	73	—	5	12	220	206
Ohio	30	25	45	989	969	—	2	7	67	82	1	8	21	352	448
Wisconsin	3	8	24	342	413	—	0	3	13	29	—	1	5	46	43
W.N. Central	—	3	33	140	706	—	1	6	51	135	2	6	13	230	302
Iowa	N	0	0	N	N	N	0	0	N	N	—	0	2	14	18
Kansas	N	0	0	N	N	N	0	0	N	N	2	0	3	20	18
Minnesota	—	0	18	—	540	—	0	3	—	77	—	2	8	96	120
Missouri	N	0	0	N	N	—	0	4	28	32	—	2	6	94	133
Nebraska [‡]	—	2	9	96	109	—	0	2	10	14	—	0	2	5	9
North Dakota	—	0	25	44	57	—	0	1	1	2	—	0	1	1	—
South Dakota	N	0	0	N	N	—	0	2	12	10	—	0	0	—	4
S. Atlantic	31	72	170	3,039	3,337	4	7	25	259	465	22	67	178	2,781	2,637
Delaware	—	1	6	39	31	—	0	1	—	—	—	0	4	17	4
District of Columbia	—	1	3	29	63	—	0	1	4	8	2	3	8	129	114
Florida	18	23	68	1,105	1,212	3	2	13	102	166	1	23	36	969	980
Georgia	4	22	54	808	1,082	—	2	7	59	131	11	15	130	616	564
Maryland [‡]	7	9	32	438	434	1	0	4	31	46	—	9	20	364	264
North Carolina	N	0	0	N	N	N	0	0	N	N	—	8	21	316	340
South Carolina [‡]	2	8	25	365	415	—	0	3	23	47	5	4	11	190	127
Virginia [‡]	N	0	0	N	N	—	0	3	26	48	3	4	16	178	238
West Virginia	—	0	48	255	100	—	0	6	14	19	—	0	1	2	6
E.S. Central	8	18	36	725	840	—	2	4	57	94	5	16	34	645	747
Alabama [‡]	N	0	0	N	N	N	0	0	N	N	—	4	11	187	210
Kentucky	N	0	0	N	N	N	0	0	N	N	4	2	16	98	110
Mississippi	N	0	0	N	N	—	0	2	9	14	—	3	14	163	183
Tennessee [‡]	8	18	36	725	840	—	1	4	48	80	1	5	11	197	244
W.S. Central	12	31	368	1,463	1,512	—	4	38	167	247	1	36	50	1,479	1,784
Arkansas [‡]	5	3	26	183	141	—	0	3	11	15	1	3	10	160	185
Louisiana	—	3	11	128	99	—	0	2	12	23	—	6	25	306	481
Oklahoma	N	0	0	N	N	—	1	8	30	40	—	2	8	84	82
Texas [‡]	7	25	333	1,152	1,272	—	3	27	114	169	—	23	30	929	1,036
Mountain	17	30	72	1,365	1,416	1	3	8	113	192	—	12	20	454	513
Arizona	5	12	45	639	658	—	1	5	52	83	—	4	10	183	189
Colorado	9	9	23	434	441	1	0	4	30	57	—	2	6	88	119
Idaho [‡]	N	0	0	N	N	—	0	1	4	6	—	0	4	11	2
Montana [‡]	N	0	0	N	N	N	0	0	N	N	—	0	1	4	3
Nevada [‡]	N	0	0	N	N	N	0	0	N	N	—	2	9	109	99
New Mexico [‡]	3	4	13	198	130	—	0	2	15	16	—	1	4	50	44
Utah	—	1	8	74	174	—	0	3	12	27	—	0	2	9	57
Wyoming [‡]	—	0	15	20	13	—	0	1	—	3	—	0	0	—	—
Pacific	—	3	11	135	95	—	0	2	13	16	14	53	68	2,156	1,999
Alaska	—	3	11	130	95	—	0	1	10	16	—	0	1	1	3
California	N	0	0	N	N	N	0	0	N	N	8	42	58	1,740	1,697
Hawaii	—	0	3	5	—	—	0	1	3	—	—	0	5	10	29
Oregon	N	0	0	N	N	N	0	0	N	N	2	3	12	152	55
Washington	N	0	0	N	N	N	0	0	N	N	4	6	13	253	215
Territories															
American Samoa	N	0	0	N	N	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—
Puerto Rico	—	0	0	—	—	—	0	0	—	—	—	4	14	193	193
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/pfs/files/ProvisionalNationalNotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

† Includes drug resistant and susceptible cases of invasive Streptococcus pneumoniae disease among children <5 years and among all ages. Case definition: Isolation of S. pneumoniae from a normally sterile body site (e.g., blood or cerebrospinal fluid).

‡ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

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TABLE II. (Continued) Provisional cases of selected notifiable diseases, United States, weeks ending October 29, 2011, and October 30, 2010 (43rd week)*

Reporting area	West Nile virus disease [†]														
	Varicella (chickenpox)					Neuroinvasive				Nonneuroinvasive [‡]					
	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010	Current week	Previous 52 weeks		Cum 2011	Cum 2010
	Med	Max				Med	Max				Med	Max			
United States	208	271	367	10,506	12,787	—	0	54	392	622	—	0	24	187	391
New England	10	21	50	971	979	—	0	3	14	14	—	0	1	2	5
Connecticut	9	5	16	225	288	—	0	2	8	7	—	0	1	1	4
Maine [§]	—	4	10	170	201	—	0	0	—	—	—	0	0	—	—
Massachusetts	—	7	18	355	231	—	0	2	4	6	—	0	1	1	1
New Hampshire	—	2	9	102	131	—	0	0	—	1	—	0	0	—	—
Rhode Island [¶]	—	0	6	33	39	—	0	1	1	—	—	0	0	—	—
Vermont [¶]	1	2	10	86	89	—	0	1	1	—	—	0	0	—	—
Mid. Atlantic	32	44	76	2,007	1,415	—	0	11	32	123	—	0	6	20	63
New Jersey	7	15	68	1,194	496	—	0	1	2	15	—	0	1	3	15
New York (Upstate)	N	0	0	N	N	—	0	5	17	56	—	0	4	14	30
New York City	—	0	0	—	—	—	0	4	9	33	—	0	1	2	9
Pennsylvania	25	19	41	813	919	—	0	1	4	19	—	0	1	1	9
E.N. Central	55	65	118	2,376	4,092	—	0	13	68	80	—	0	6	26	30
Illinois	—	15	31	605	1,041	—	0	6	20	45	—	0	3	10	16
Indiana [¶]	14	5	18	214	308	—	0	2	6	6	—	0	1	3	7
Michigan	15	18	38	742	1,199	—	0	7	32	25	—	0	1	1	4
Ohio	26	21	58	814	1,118	—	0	3	9	4	—	0	3	11	1
Wisconsin	—	0	22	1	426	—	0	1	1	—	—	0	1	1	2
W.N. Central	—	7	42	323	792	—	0	8	28	32	—	0	6	27	75
Iowa	N	0	0	N	N	—	0	2	5	5	—	0	2	4	4
Kansas [¶]	—	2	15	85	316	—	0	1	4	4	—	0	0	—	15
Minnesota	—	0	0	—	—	—	0	1	1	4	—	0	1	1	4
Missouri	—	4	24	167	371	—	0	1	4	3	—	0	1	3	—
Nebraska [¶]	—	0	4	5	21	—	0	4	13	10	—	0	3	14	29
North Dakota	—	0	10	36	39	—	0	1	1	2	—	0	1	3	7
South Dakota	—	1	4	30	45	—	0	0	—	4	—	0	1	2	16
S. Atlantic	21	31	64	1,422	1,840	—	0	9	49	38	—	0	4	17	22
Delaware [¶]	—	0	3	6	32	—	0	1	1	—	—	0	0	—	—
District of Columbia	—	0	2	12	18	—	0	1	1	3	—	0	0	—	3
Florida [¶]	16	16	38	721	856	—	0	5	19	9	—	0	2	2	3
Georgia	N	0	0	N	N	—	0	2	7	4	—	0	1	5	9
Maryland [¶]	N	0	0	N	N	—	0	5	10	17	—	0	3	10	6
North Carolina	N	0	0	N	N	—	0	1	2	—	—	0	0	—	—
South Carolina [¶]	—	0	9	12	75	—	0	0	—	1	—	0	0	—	—
Virginia [¶]	5	7	25	359	476	—	0	2	8	4	—	0	0	—	1
West Virginia	—	5	32	312	383	—	0	1	1	—	—	0	0	—	—
E.S. Central	4	5	15	222	261	—	0	8	45	8	—	0	5	25	10
Alabama [¶]	4	4	14	210	253	—	0	1	3	1	—	0	0	—	2
Kentucky	N	0	0	N	N	—	0	1	2	2	—	0	1	1	1
Mississippi	—	0	3	12	8	—	0	4	26	3	—	0	4	22	5
Tennessee [¶]	N	0	0	N	N	—	0	3	14	2	—	0	1	2	2
W.S. Central	54	44	258	2,148	2,408	—	0	3	13	101	—	0	2	7	19
Arkansas [¶]	—	4	20	245	164	—	0	1	1	6	—	0	0	—	1
Louisiana	—	1	6	68	72	—	0	2	6	18	—	0	2	4	7
Oklahoma	N	0	0	N	N	—	0	1	—	—	—	0	0	—	—
Texas [¶]	54	41	247	1,835	2,172	—	0	2	6	77	—	0	1	3	11
Mountain	32	18	65	944	902	—	0	9	53	155	—	0	4	24	127
Arizona	4	4	50	409	—	—	0	6	31	105	—	0	2	10	60
Colorado [¶]	27	4	31	211	347	—	0	2	2	26	—	0	2	5	55
Idaho [¶]	N	0	0	N	N	—	0	1	1	—	—	0	1	1	1
Montana [¶]	—	2	28	123	172	—	0	1	1	—	—	0	0	—	—
Nevada [¶]	N	0	0	N	N	—	0	4	12	—	—	0	2	4	2
New Mexico [¶]	1	1	4	37	89	—	0	1	4	21	—	0	0	—	4
Utah	—	3	26	156	278	—	0	1	1	1	—	0	1	2	1
Wyoming [¶]	—	0	3	8	16	—	0	1	1	2	—	0	1	2	4
Pacific	—	2	6	93	98	—	0	16	90	71	—	0	6	39	40
Alaska	—	1	4	48	38	—	0	0	—	—	—	0	0	—	—
California	—	0	2	9	30	—	0	16	90	70	—	0	6	39	39
Hawaii	—	1	4	36	30	—	0	0	—	—	—	0	0	—	—
Oregon	N	0	0	N	N	—	0	0	—	—	—	0	0	—	—
Washington	N	0	0	N	N	—	0	0	—	1	—	0	0	—	1
Territories															
American Samoa	N	0	0	N	N	—	0	0	—	—	—	0	0	—	—
C.N.M.I.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Guam	—	0	4	16	25	—	0	0	—	—	—	0	0	—	—
Puerto Rico	5	4	17	166	550	—	0	0	—	—	—	0	0	—	—
U.S. Virgin Islands	—	0	0	—	—	—	0	0	—	—	—	0	0	—	—

C.N.M.I.: Commonwealth of Northern Mariana Islands.

U: Unavailable. —: No reported cases. N: Not reportable. NN: Not Nationally Notifiable. Cum: Cumulative year-to-date counts. Med: Median. Max: Maximum.

* Case counts for reporting year 2011 are provisional and subject to change. For further information on interpretation of these data, see http://www.cdc.gov/osels/ph_surveillance/nndss/phs/files/ProvisionalNational%20NotifiableDiseasesSurveillanceData20100927.pdf. Data for TB are displayed in Table IV, which appears quarterly.

† Updated weekly from reports to the Division of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases (ArboNET Surveillance). Data for California serogroup, eastern equine, Powassan, St. Louis, and western equine diseases are available in Table I.

‡ Not reportable in all states. Data from states where the condition is not reportable are excluded from this table, except starting in 2007 for the domestic arboviral diseases and influenza-associated pediatric mortality, and in 2003 for SARS-CoV. Reporting exceptions are available at http://www.cdc.gov/osels/ph_surveillance/nndss/phs/infdis.htm.

¶ Contains data reported through the National Electronic Disease Surveillance System (NEDSS).

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TABLE III. Deaths in 122 U.S. cities,* week ending October 29, 2011 (43rd week)

Reporting area	All causes, by age (years)						P&I [†] Total	Reporting area (Continued)	All causes, by age (years)						P&I [†] Total
	All Ages	≥65	45-64	25-44	1-24	<1			All Ages	≥65	45-64	25-44	1-24	<1	
New England	522	355	117	31	11	8	42	S. Atlantic	1,064	681	256	65	38	24	64
Boston, MA	143	87	37	12	5	2	15	Atlanta, GA	113	57	34	8	9	5	3
Bridgeport, CT	30	25	3	1	1	—	2	Baltimore, MD	160	93	44	15	5	3	15
Cambridge, MA	12	8	4	—	—	—	1	Charlotte, NC	118	82	26	6	1	3	7
Fall River, MA	21	16	4	1	—	—	3	Jacksonville, FL	94	65	20	8	1	—	8
Hartford, CT	43	26	13	2	—	2	4	Miami, FL	97	65	18	6	8	—	2
Lowell, MA	26	21	4	1	—	—	2	Norfolk, VA	59	36	12	5	1	5	1
Lynn, MA	11	8	3	—	—	—	1	Richmond, VA	63	37	18	4	4	—	5
New Bedford, MA	22	17	5	—	—	—	2	Savannah, GA	40	29	8	1	1	1	2
New Haven, CT	35	20	10	4	1	—	1	St. Petersburg, FL	44	26	13	1	2	2	2
Providence, RI	70	51	14	1	2	2	—	Tampa, FL	179	130	39	7	3	—	10
Somerville, MA	4	2	1	1	—	—	—	Washington, D.C.	88	56	22	2	3	5	9
Springfield, MA	34	22	5	3	2	2	4	Wilmington, DE	9	5	2	2	—	—	—
Waterbury, CT	33	22	10	1	—	—	2	E.S. Central	840	550	197	67	14	12	55
Worcester, MA	38	30	4	4	—	—	5	Birmingham, AL	204	125	52	18	4	5	11
Mid. Atlantic	1,892	1,341	388	109	32	22	88	Chattanooga, TN	60	40	12	8	—	—	1
Albany, NY	59	42	12	—	2	3	7	Knoxville, TN	102	64	25	9	2	2	4
Allentown, PA	36	30	5	—	1	—	—	Lexington, KY	45	29	13	2	—	1	1
Buffalo, NY	76	53	17	4	—	2	1	Memphis, TN	148	102	32	10	3	1	16
Camden, NJ	23	13	6	2	—	2	3	Mobile, AL	98	64	24	7	1	2	2
Elizabeth, NJ	14	9	3	2	—	—	—	Montgomery, AL	49	40	8	—	1	—	11
Erie, PA	62	49	7	5	—	1	4	Nashville, TN	134	86	31	13	3	1	9
Jersey City, NJ	16	11	4	—	1	—	2	W.S. Central	1,088	710	241	80	31	26	65
New York City, NY	1,091	783	224	57	18	9	49	Austin, TX	94	61	24	5	1	3	3
Newark, NJ	54	28	15	5	5	1	3	Baton Rouge, LA	64	35	14	11	4	—	—
Paterson, NJ	21	16	1	3	—	1	—	Corpus Christi, TX	60	48	9	—	1	2	9
Philadelphia, PA	143	82	41	16	2	2	6	Dallas, TX	205	123	58	10	8	6	20
Pittsburgh, PA [‡]	39	26	9	3	1	—	1	El Paso, TX	81	60	15	5	1	—	4
Reading, PA	28	25	2	—	1	—	1	Fort Worth, TX	U	U	U	U	U	U	U
Rochester, NY	62	46	12	3	—	1	2	Houston, TX	127	71	31	12	7	6	6
Schenectady, NY	34	27	6	1	—	—	3	Little Rock, AR	80	63	8	3	2	4	1
Scranton, PA	26	18	8	—	—	—	—	New Orleans, LA	U	U	U	U	U	U	U
Syracuse, NY	57	42	10	5	—	—	4	San Antonio, TX	220	140	51	23	3	3	12
Trenton, NJ	23	17	5	1	—	—	—	Shreveport, LA	46	29	8	6	2	1	5
Utica, NY	16	15	1	—	—	—	1	Tulsa, OK	111	80	23	5	2	1	5
Yonkers, NY	12	9	—	2	1	—	1	Mountain	930	658	179	56	21	15	54
E.N. Central	1,828	1,222	407	114	53	32	124	Albuquerque, NM	117	86	20	10	1	—	9
Alkon, OH	67	48	10	7	1	1	4	Boise, ID	50	35	13	1	1	—	—
Canton, OH	46	29	13	2	1	1	3	Colorado Springs, CO	63	45	8	6	—	4	1
Chicago, IL	230	151	51	17	7	4	14	Denver, CO	98	61	26	6	1	4	5
Cincinnati, OH	87	55	18	9	1	4	5	Las Vegas, NV	261	189	48	17	5	2	19
Cleveland, OH	180	120	48	9	—	3	11	Ogden, UT	36	22	10	—	3	1	3
Columbus, OH	215	141	52	15	4	3	13	Phoenix, AZ	U	U	U	U	U	U	U
Dayton, OH	137	94	36	4	2	1	11	Pueblo, CO	16	12	4	—	—	—	—
Detroit, MI	81	33	27	11	8	2	8	Salt Lake City, UT	122	83	22	7	5	4	11
Evansville, IN	33	27	5	1	—	—	3	Tucson, AZ	167	125	28	9	5	—	6
Fort Wayne, IN	74	57	13	1	1	2	2	Pacific	1,590	1,067	355	93	46	29	139
Gary, IN	11	6	4	1	—	—	—	Berkeley, CA	11	8	3	—	—	—	—
Grand Rapids, MI	58	45	8	3	1	1	6	Fresno, CA	128	89	20	5	3	11	12
Indianapolis, IN	191	122	36	14	13	6	15	Glendale, CA	44	30	11	2	1	—	11
Lansing, MI	63	45	15	1	2	—	7	Honolulu, HI	68	50	14	2	1	1	14
Milwaukee, WI	81	45	24	6	5	1	4	Long Beach, CA	61	36	16	8	1	—	5
Peoria, IL	29	25	3	1	—	—	3	Los Angeles, CA	234	129	65	24	14	2	17
Rockford, IL	51	36	10	2	2	1	2	Pasadena, CA	24	17	5	1	1	—	3
South Bend, IN	42	30	8	3	1	—	7	Portland, OR	110	76	24	7	3	—	5
Toledo, OH	85	54	18	7	4	2	2	Sacramento, CA	172	123	31	11	4	3	12
Youngstown, OH	67	59	8	—	—	—	4	San Diego, CA	163	115	28	10	5	5	15
W.N. Central	671	460	152	33	7	19	44	San Francisco, CA	102	70	26	4	—	2	12
Des Moines, IA	86	68	14	—	1	3	8	San Jose, CA	179	122	37	10	7	3	15
Duluth, MN	14	14	—	—	—	—	—	Santa Cruz, CA	26	19	7	—	—	—	1
Kansas City, KS	21	13	5	2	1	—	2	Seattle, WA	107	74	25	3	3	2	5
Kansas City, MO	101	67	22	9	1	2	4	Spokane, WA	49	36	10	3	—	—	2
Lincoln, NE	43	34	8	—	—	1	1	Tacoma, WA	112	73	33	3	3	—	10
Minneapolis, MN	71	45	19	4	1	2	2	Total[§]	10,425	7,044	2,292	648	253	187	675
Omaha, NE	87	57	19	6	—	5	5								
St. Louis, MO	112	57	41	9	1	4	10								
St. Paul, MN	58	48	7	1	2	—	6								
Wichita, KS	78	57	17	2	—	2	6								

U: Unavailable. —: No reported cases.

* Mortality data in this table are voluntarily reported from 122 cities in the United States, most of which have populations of >100,000. A death is reported by the place of its occurrence and by the week that the death certificate was filed. Fetal deaths are not included.

[†] Pneumonia and influenza.

[‡] Because of changes in reporting methods in this Pennsylvania city, these numbers are partial counts for the current week. Complete counts will be available in 4 to 6 weeks.

[§] Total includes unknown ages.

Morbidity and Mortality Weekly Report

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Data presented by the Notifiable Disease Data Team and 122 Cities Mortality Data Team in the weekly *MMWR* are provisional, based on weekly reports to CDC by state health departments. Address all inquiries about the *MMWR* Series, including material to be considered for publication, to Editor, *MMWR* Series, Mailstop E-90, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30333 or to mmwrq@cdc.gov.

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Tab 38

Reference 3: National Center for Injury
Prevention and Control, CDC,
“Unintentional Drug Poisoning in the
United States”

Unintentional Drug Poisoning in the United States

July 2010



Background

A poisoning occurs when a person's exposure to a natural or manmade substance has an undesirable effect. A drug poisoning occurs when that substance is an illegal, prescription, or over-the-counter drug. Most fatal poisonings in the United States result from drug poisoning.

Poisoning can be classified as:

- self-harm or suicide when the person wants to harm himself;
- assault or homicide when the person wants to harm another; and
- unintentional, also known as "accidental," when no harm is intended. Unintentional drug poisoning includes drug overdoses resulting from drug misuse, drug abuse, and taking too much of a drug for medical reasons.

This document summarizes the most recent information about deaths and emergency department (ED) visits resulting from drug poisoning. Information about deaths comes from death certificates for deaths in 2007. Information about emergency department visits comes from a national surveillance system, the Drug Abuse Warning Network (DAWN), operated by the Substance Abuse and Mental Health Services Administration (SAMHSA).

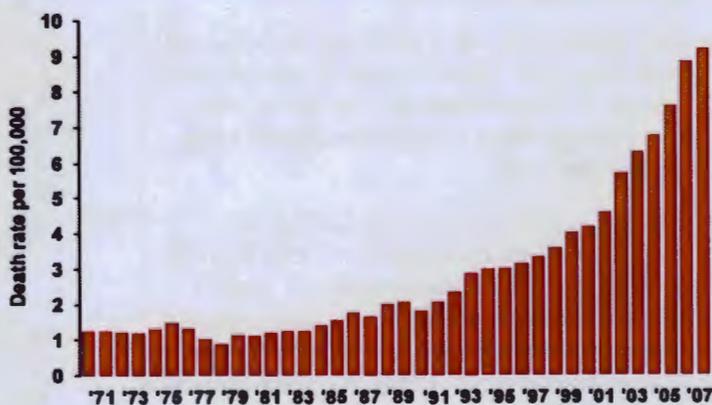
Drug overdose death rates in the United States have never been higher

- Drug overdose death rates have risen steadily in the United States since 1970. (See Figure 1)
- In 2007, 27,658 unintentional drug overdose deaths occurred in the United States.
- Drug overdose deaths were second only to motor vehicle crash deaths among leading causes of unintentional injury death in 2007 in the United States.

Rates have increased roughly five-fold since 1990.

- Age-adjusted rates of drug overdose death for whites have exceeded those among African Americans since 2003.

Figure 1: Rate of unintentional drug overdose death in the United States, 1970-2007



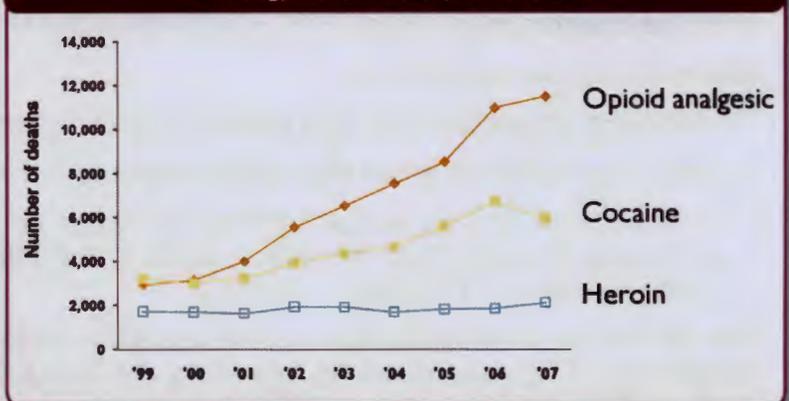
Source: National Vital Statistics System

The increase in drug overdose death rates is largely because of prescription opioid painkillers

- Among deaths attributed to drugs, the most common drug categories are cocaine, heroin, and a type of prescription drug called opioid painkillers.
- "Opioids" are synthetic versions of opium. They have the ability to reduce pain but can also suppress breathing to a fatal degree when taken in excess. Examples of opioids are oxycodone (OxyContin®), hydrocodone (Vicodin®), and methadone.
- There has been at least a 10-fold increase in the medical use of opioid painkillers during the last 20 years because of a movement toward more aggressive management of pain.
- Because opioids cause euphoria, they have been associated increasingly with misuse and abuse. Opioids are now widely available in illicit markets in the United States.

In 2007, the number of deaths involving opioid analgesics was 1.93 times the number involving cocaine and 5.38 times the number involving heroin.

Figure 2: Unintentional drug overdose deaths by major type of drug, United States, 1999-2007



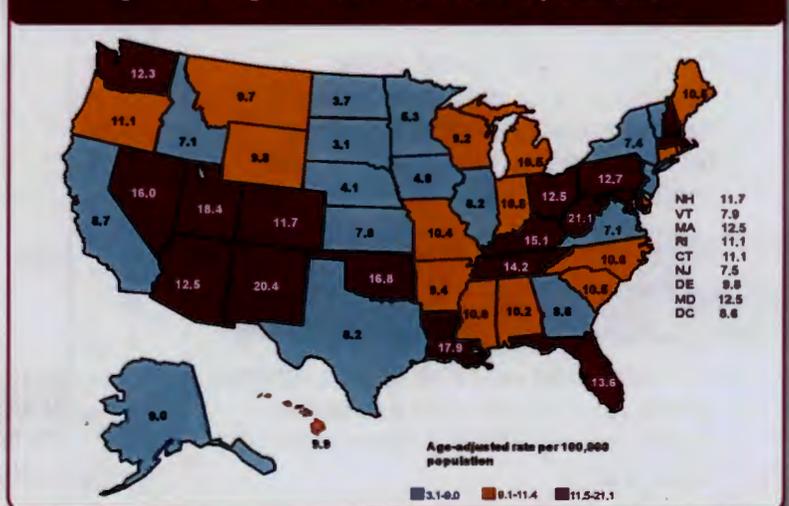
Source: National Vital Statistics System

In 2007, opioids were involved in more overdose deaths than heroin and cocaine combined. (See Figure 2)

Overall drug overdose death rates in the United States vary by state and region

- States in the Appalachian region and the Southwest have the highest death rates. (See Figure 3)
- The highest drug overdose death rate was found in West Virginia, which was nearly 7 times that of the state with the lowest drug overdose death rate, South Dakota.
- In 2007, states such as California and New York had some of the lowest overall death rates among all states because of low opioid overdose rates. In contrast, in the early 1990s these states had some of the highest overall rates, largely because of high heroin and cocaine overdose rates.

Figure 3: Drug Overdose Death Rates by State, 2007

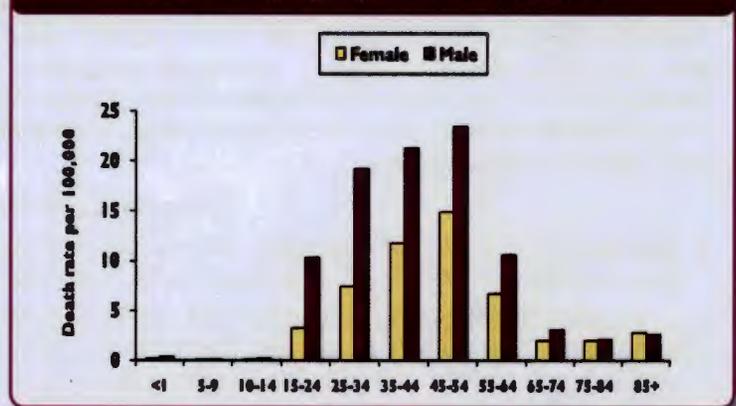


Source: National Vital Statistics System

Men and middle-aged people are more likely to die from drug overdose

- In 2007, 18,029 drug overdose deaths occurred among males and 9,626 among females. Male rates exceeded female rates in almost every age group. Men have historically had higher rates of substance abuse than women. (See Figure 4)
- Male rates have doubled and female rates have tripled since 1999.
- For both sexes, the highest rates were in the 45-54 years old age group. Rates declined dramatically after the age of 54.
- After age 64, the male and female rates become comparable, probably as a result of the reduction in rates of substance abuse with age.

Figure 4: Unintentional drug overdose death rates by sex and age group, United States, 2007



Source: National Vital Statistics System

Among emergency department visits for the misuse or abuse of drugs, legal drugs have caught up with illegal drugs

- The Drug Abuse Warning Network (DAWN) estimates ED visits caused by illicit drugs or the nonmedical use of legal drugs, which includes taking more than the prescribed amount, taking drugs prescribed for someone else, or substance abuse. Nonmedical use by this definition does not include use of drugs to harm oneself, e.g., suicide attempts, or unintentional ingestions.

ED visits for the nonmedical use of prescription and over-the-counter drugs are now comparable to ED visits for use of illicit drugs like heroin and cocaine.

Figure 5: Estimated numbers of ED visits involving legal drugs used nonmedically and illegal drugs, United States, 2008



Source: Drug Abuse Warning Network

- In 2008, DAWN estimates show that prescription or over-the-counter drugs used nonmedically were involved in 1.0 million ED visits, and illicit drugs were involved in 1.0 million visits (See Figure 5). Among the legal drugs, the most common drug categories involved were drugs acting on the central nervous system, especially opioid painkillers, and psychotherapeutic drugs, especially sedatives and antidepressants. Opioid painkillers were associated with approximately 306,000 visits and benzodiazepines (a type of sedative) with 272,000 visits.
- Among illicit drugs, cocaine was involved in 482,000 visits, and heroin was involved in 201,000 visits.
- People who abuse opioids have direct health care costs more than eight times those of nonabusers. A conservative estimate of the costs to society of prescription opioid abuse in the United States was \$8.6 billion in 2001 (\$9.5 billion in 2005 dollars).

Recommendations

The following recommendations are not founded in evidence-based research but are based on promising interventions and expert opinion. Additional research is needed to understand the impact of these interventions on decreasing unintentional drug poisoning and on health care costs. All of the following recommendations should be implemented in concert and collaboration with public health entities and other relevant stakeholders.

Health Care Providers

- Use opioid medications for acute or chronic pain only after determining that alternative therapies do not deliver adequate pain relief. The lowest effective dose of opioids should be used.
- In addition to behavioral screening and use of patient contracts, consider random, periodic, targeted urine testing for opioids and other drugs for any patient less than 65 years old with noncancer pain who is being treated with opioids for more than six weeks.
- If a patient's dosage has increased to ≥ 120 morphine milligram equivalents per day without substantial improvement in pain and function, seek a consult from a pain specialist.
- Do not prescribe long-acting or controlled-release opioids (e.g., OxyContin®, fentanyl patches, and methadone) for acute pain.
- Periodically request a report from your state prescription drug monitoring program on the prescribing of opioids to your patients by other providers.

Private Insurance Providers and Pharmacy Benefit Managers (PBMs)

- Identify patients using opioids for noncancer pain who 1) receive a total of 120 or more morphine milligram equivalents of opioids per day from two or more sources; 2) show inappropriate patterns of usage such as multiple prescriptions for the same medication from different providers; or 3) also use a sedative-hypnotic. Notify the prescribing providers about such patients.
- For patients whose use of multiple providers cannot be justified on medical grounds, insurers and PBMs should only reimburse opioid prescription claims from a single designated physician and a single designated pharmacy.

State and Federal Agencies

- To the extent permitted by applicable law, state prescription drug monitoring programs should routinely send reports to providers on patients less than 65 years old if they are being treated with opioids for more than 6 weeks by two or more providers or if there are signs of inappropriate use of controlled substances. (If legal authority to do so does not exist, work toward obtaining that authority.)
- To the extent permitted by applicable law, state and federal benefits programs should consider monitoring prescription claims information for signs of inappropriate use of controlled substances by patients. For patients whose use of multiple providers cannot be justified on medical grounds, such programs should consider reimbursing opioid prescription claims from a single designated physician and a single designated pharmacy.
- State and federal agencies should work to improve the availability of substance abuse treatment services.

For More Information on Unintentional Drug Poisonings in the United States, go to:

Centers for Disease Control and Prevention www.cdc.gov

National Center for Injury Prevention and Control
www.cdc.gov/HomeandRecreationalSafety/Poisoning

Call: 1-800-CDC-INFO (232-4636) | TTY: 1-888-232-6348



Tab 39

Reference 5: FDA, “FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics”

Introduction for the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

In April 2011, FDA announced the elements of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of extended-release and long-acting (ER/LA) opioid analgesics outweigh the risks. The REMS supports national efforts to address the prescription drug abuse epidemic.

As part of the REMS, all ER/LA opioid analgesic companies must provide:

- ! Education for prescribers of these medications, which will be provided through accredited continuing education (CE) activities supported by independent educational grants from ER/LA opioid analgesic companies.
- ! Information that prescribers can use when counseling patients about the risks and benefits of ER/LA opioid analgesic use.

FDA developed core messages to be communicated to prescribers in the Blueprint for Prescriber Education (FDA Blueprint), published the draft FDA Blueprint for public comment, and considered the public comments when finalizing the FDA Blueprint. This final FDA Blueprint contains the core educational messages. It is approved as part of the ER/LA Opioid Analgesic REMS and will remain posted on the FDA website for use by CE providers to develop the actual CE activity. A list of all REMS-compliant CE activities that are supported by independent educational grants from the ER/LA opioid analgesic companies to accredited CE providers will be posted at www.ER-LA-opioidREMS.com as that information becomes available.

The CE activities provided under the FDA Blueprint will focus on the safe prescribing of ER/LA opioid analgesics and consist of a core content of about three hours. The content is directed to prescribers of ER/LA opioid analgesics, but also may be relevant for other healthcare professionals (e.g., pharmacists). The course work is not intended to be exhaustive nor a substitute for a more comprehensive pain management course.

Accrediting bodies and CE providers will ensure that the CE activities developed under this REMS will be in compliance with the standards for CE of the Accreditation Council for Continuing Medical Education (ACCME)^{1,2} or another CE accrediting body as appropriate to the prescribers' medical specialty or healthcare profession.

For additional information from FDA, including more detailed Questions and Answers about the REMS for ER/LA Opioid Analgesics, see <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>.

¹Accreditation Council for Continuing Medical Education. 2012 *Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria*. Accessed on March 30, 2012.

²Accreditation Council for Continuing Medical Education. 2012. *Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support*. Accessed on March 30, 2012.

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

Why Prescriber Education is Important

Health care professionals who prescribe extended-release (ER) and long-acting (LA) opioid analgesics (hereafter referred to as ER/LA opioid analgesics) are in a key position to balance the benefits of prescribing ER/LA opioid analgesics to treat pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death. Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem.

- ! Based on the 2010 National Survey on Drug Use and Health, public health experts estimate more than 35 million Americans age 12 and older used an opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.³
- ! In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.⁴
- ! In 2008, nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.⁵
- ! Improper use of any opioid can result in serious side effects including overdose and death, and this risk can be greater with ER/LA opioid analgesics.

Appropriate prescribing practices and patient education are important steps to help address this public health problem. Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of these drug products.

The expected results of the prescriber education in this REMS are that the prescribers will:

- a. Understand how to assess patients for treatment with ER/LA opioid analgesics.
- b. Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- c. Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
- d. Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- e. Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

- a. Prescribers should consider risks involved with ER/LA opioid analgesics and balance these against potential benefits. Risks include:
 - i. Overdose with ER/LA formulations, as most dosage units contain more opioid than immediate-release formulations.

³ Substance Abuse and Mental Health Services Administration. 2011. *Results from the 2010 National Survey on Drug Use and Health: Detailed Table*, Table 7.1.a. Rockville, MD. <http://www.samhsa.gov/data/NSDUH/2k10NSDUH/tabs/Sect7peTabs1to45.htm#Tab7.1A>. Accessed on March 30, 2012.

⁴ Substance Abuse and Mental Health Services Administration. 2011. *Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits*, Table 19. Rockville, MD. <http://www.samhsa.gov/data/2k11/DAWN/2k9DAWNED/HTML/DAWN2k9ED.htm#Tab19>. Accessed on March 30, 2012.

⁵ Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief, No 81*. December 2011. Hyattsville, MD. <http://www.cdc.gov/nchs/data/databriefs/db81.pdf>. Accessed on March 30, 2012.

- ii. Abuse by patient or household contacts.
 - iii. Misuse and addiction.
 - iv. Physical dependence and tolerance.
 - v. Interactions with other medications and substances (See table in Section VI for specific information).
 - vi. Inadvertent exposure by household contacts, especially children.
- b. Prescribers should assess each patient's risk of abuse, including substance use and psychiatric history. Prescribers should:
- i. Obtain a complete history and conduct a complete physical examination, including assessment of family history of substance abuse and psychiatric disorders, as well as special considerations for the elderly and children.
 - A history of substance abuse does not prohibit treatment with ER/LA opioid analgesics but may require additional monitoring and expert consultation.
 - ii. Be knowledgeable about risk factors for opioid abuse.
 - iii. Understand and appropriately use screening tools for addiction or abuse to help assess potential risks associated with chronic opioid therapy and to help manage patients using ER/LA opioid analgesics (e.g., structured interview tools).
 - iv. Adequately document all patient interactions and treatment plans.
- c. Prescribers should understand when to appropriately refer high risk patients to pain management specialists.
- d. Prescribers should understand opioid tolerance criteria as defined in the product labeling.
- Prescribers should know which products and which doses are indicated for use only in opioid tolerant patients. (See table in Section VI for specific information).

II. Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics

- a. Prescribers should have awareness of federal and state regulations on opioid prescribing.
- b. Prescribers should be aware that:
 - i. Dose selection is critical, particularly when initiating therapy in opioid non-tolerant patients.
 - ii. Some ER/LA opioid analgesics are only appropriate for opioid-tolerant patients.
 - iii. Dosage should be individualized in every case.
 - iv. Titration should be based on efficacy and tolerability.
- c. Prescribers should be knowledgeable about when and how to supplement pain management with immediate-release analgesics, opioids and non-opioids.
- d. Prescribers should be knowledgeable about converting patients from immediate-release to ER/LA opioid products and from one ER/LA opioid product to another ER/LA opioid product.
- e. Prescribers should understand the concept of incomplete cross-tolerance when converting patients from one opioid to another.
- f. Prescribers should understand the concepts and limitations of equianalgesic dosing and follow patients closely during all periods of dose adjustments.
- g. Prescribers should understand the warning signs and symptoms of significant respiratory depression from opioids.
- h. Prescribers should understand that tapering the opioid dose is necessary to safely discontinue treatment with ER/LA opioid analgesics when therapy is no longer needed.

III. Managing Therapy with ER/LA Opioid Analgesics

- a. Prescribers should establish analgesic and functional goals for therapy and periodically

- evaluate pain control, functional outcomes, side-effect frequency and intensity, and health-related quality of life.
- b. Prescribers should be aware of the existence of Patient Prescriber Agreements (PPAs).
 - i. PPAs are documents signed by both prescriber and patient at the time an opioid is prescribed.
 - ii. PPAs can help ensure patients and caregivers understand the goals of treatment, the risks, and how to use the medications safely.
 - iii. PPAs can include commitments to return for follow-up visits, to comply with appropriate monitoring (such as random drug testing), and to safeguard the medication.
 - c. Prescribers should monitor patient adherence to the treatment plan, especially with regard to misuse and abuse by:
 - i. Recognizing, documenting, and addressing aberrant drug-related behavior.
 - ii. Utilizing state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
 - iii. Understanding the utility and interpretation of drug testing (e.g., screening and confirmatory tests), and using it as indicated.
 - iv. Screening and referring for substance abuse treatment as indicated.
 - v. Performing medication reconciliation as indicated.
 - d. Prescribers should understand how to anticipate and manage adverse events associated with ER/LA opioid analgesics.
 - e. Prescribers treating patients with ER/LA opioid analgesics should periodically assess benefits and side effects of these drugs, and the continued need for opioid analgesics.
 - f. Prescribers should understand the need for reevaluation of patient's underlying medical condition if the clinical presentation changes over time.
 - g. Prescribers should be familiar with referral sources for the treatment of abuse or addiction that may arise from the use of ER/LA opioid analgesics.

IV. Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

- a. Prescribers should use the Patient Counseling Document as part of the discussion when prescribing opioid analgesics.
- b. Prescribers should explain product-specific information about the prescribed ER/LA opioid analgesic.
- c. Prescribers should explain how to take the ER/LA opioid analgesic as prescribed.
- d. Prescribers should explain the importance of adherence to dosing regimen, how to handle missed doses, and to contact their prescriber should pain not be controlled.
- e. Prescribers should inform patients and caregivers to read the specific ER/LA opioid analgesic Medication Guide they receive from the pharmacy.
- f. Prescribers should warn patients that under no circumstances should an oral ER/LA opioid analgesic be broken, chewed or crushed, and patches should not be cut or torn prior to use, as this may lead to rapid release of the ER/LA opioid analgesic causing overdose and death. When a patient cannot swallow a capsule whole, prescribers should refer to the product labeling to determine if it is appropriate to sprinkle the contents of a capsule on applesauce or administer via a feeding tube.
- g. Prescribers should caution patients that the use of other CNS depressants such as sedative-hypnotics and anxiolytics, alcohol, or illegal drugs with ER/LA opioid analgesics can cause overdose and death. Patients should be instructed to only use other CNS depressants, including other opioids, under the instruction of their prescriber.

- h. Prescribers should instruct patients to tell all of their doctors about all medications they are taking.
- i. Prescribers should warn patients not to abruptly discontinue or reduce their ER/LA opioid analgesic and discuss how to safely taper the dose when discontinuing.
- j. Prescribers should caution patients that ER/LA opioid analgesics can cause serious side effects that can lead to death. Prescribers should counsel patients and caregivers on the risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions.
- k. Prescribers should counsel patients and caregivers on the most common side effects of ER/LA opioid analgesics, and about the risk of falls, working with heavy machinery, and driving.
- l. Patients should call their prescriber for information about managing side effects.
- m. Prescribers should explain that sharing ER/LA opioid analgesics with others may cause them to have serious side effects including death, and that selling or giving away ER/LA opioid analgesics is against the law.
- n. Prescribers should counsel patients to store their ER/LA opioid analgesic in a safe and secure place away from children, family members, household visitors, and pets.
- o. Prescribers should warn patients that ER/LA opioid analgesics must be protected from theft.
- p. Prescribers should counsel patients to dispose of any ER/LA opioid analgesics when no longer needed and to read the product-specific disposal information included with the ER/LA opioid analgesic product.
- q. Prescribers should counsel patients and caregivers to inform them about side effects.
- r. Adverse events should be reported to the FDA at 1-800-FDA-1088 or via <http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082725.pdf>.

V. General Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about general characteristics, toxicities, and drug interactions for ER/LA opioid analgesic products. For example,

- a. ER/LA opioid analgesic products are scheduled under the Controlled Substances Act and can be misused and abused.
- b. Respiratory depression is the most important serious adverse effect of opioids as it can be immediately life-threatening.
- c. Constipation is the most common long-term side effect and should be anticipated.
- d. Drug-drug interaction profiles vary among the products. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for the safer administration of opioid analgesics.
 - i. Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
 - ii. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. Some drug levels may increase without dose dumping when exposed to alcohol. See individual product labeling.
 - iii. Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase in respiratory depression. Using certain opioids with MAOIs may cause serotonin syndrome.
 - iv. Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic

- hormone (ADH).
 - v. Some opioids (methadone, buprenorphine) can prolong the QTc interval.
 - vi. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. (See table in Section VI for specific information).
- e. Tolerance to sedating and respiratory-depressant effects of opioids is critical to the safe use of certain products, certain dosage unit strengths, or certain doses of some products.
- i. Patients must be opioid tolerant before using any strength of
 - Transdermal fentanyl, or
 - ER hydromorphone.
 - ii. For other ER products, patients must be opioid tolerant before using
 - Certain strengths, or
 - Certain daily doses.
 - iii. See table in Section VI for specific information.
- f. ER/LA opioid analgesic tablets must be swallowed whole. ER/LA opioid analgesic capsules should be swallowed intact or when necessary, the pellets from some capsules can be sprinkled on applesauce and swallowed without chewing.
- g. For transdermal products, external heat, fever, and exertion can increase absorption of the opioid, leading to fatal overdose. Transdermal products with metal foil backings are not safe for use in MRIs.

VI. Specific Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about specific characteristics of the ER/LA opioid analgesic products they prescribe, including the drug substance, formulation, strength, dosing interval, key instructions, specific information about conversion between products where available, specific drug interactions, use in opioid-tolerant patients, product-specific safety concerns, and relative potency to morphine. The attached table is a reference. For detailed information, prescribers can refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
<p>Avinza (morphine sulfate ER capsules) Dolophine (methadone HCl tablets) Embeda (morphine sulfate ER-naltrexone capsules) Kadian (morphine sulfate ER capsules) Nucynta ER (tapentadol HCl ER tablets) OxyContin (oxycodone HCl CR tablets)</p>	<p>Butrans (buprenorphine transdermal system) Duragesic (fentanyl transdermal system) Exalgo (hydromorphone HCl ER tablets) MS Contin (morphine sulfate CR tablets) Opana ER (oxymorphone HCl ER tablets)</p>
Dosing Interval	<ul style="list-style-type: none"> ▪ Refer to individual product information.
Key Instructions	<ul style="list-style-type: none"> ▪ Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. ▪ The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval. ▪ Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions. ▪ During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids. ▪ If pain increases, attempt to identify the source, while adjusting the dose. ▪ When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue these products. ▪ Limitations of usage: <ul style="list-style-type: none"> ! Not for use as an as-needed analgesic. ! Not for mild pain or pain not expected to persist for an extended duration. ! Not for use in treating acute pain. ▪ Solid oral dosage forms: <ul style="list-style-type: none"> ! Swallow tablets and capsules whole: crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of a potentially fatal dose of opioid. ! Some capsules can be opened and pellets sprinkled on applesauce for patients who can reliably swallow without chewing and used immediately. See individual product information. ! Exposure of some products to alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of opioid. ! Dispose of unused product by flushing down the toilet. ▪ Transdermal dosage forms: <ul style="list-style-type: none"> ! Avoid exposure to external heat. Patients with fever must be monitored for signs or symptoms of increased opioid exposure. ! Location of application must be rotated. ! Prepare skin by clipping, not shaving hair, and washing area only with water. ▪ See individual product information for the following: <ul style="list-style-type: none"> ! Dosage reduction for hepatic or renal impairment.
Drug Interactions Common to the Class	<ul style="list-style-type: none"> ▪ Concurrent use with other central nervous system depressants (sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, profound sedation, or coma. Reduce the initial dose of one or both agents. ▪ Partial agonists and mixed agonist/antagonist analgesics (i.e., buprenorphine, pentazocine, nalbuphine and butorphanol) may reduce the analgesic effect or precipitate withdrawal symptoms. Avoid concurrent use.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> ▪ Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. ▪ Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ See individual product information for which products: <ul style="list-style-type: none"> ! Have strengths or total daily doses only for use in opioid-tolerant patients. ! Are only for use in opioid-tolerant patients at all strengths.
Contraindications	<ul style="list-style-type: none"> ▪ Significant respiratory depression ▪ Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment ▪ Known or suspected paralytic ileus ▪ Hypersensitivity (e.g., anaphylaxis) <p>See individual product information for additional contraindications.</p>
Relative Potency To Oral Morphine	<ul style="list-style-type: none"> ▪ These are intended as general guides. ▪ Follow conversion instructions in individual product information. ▪ Incomplete cross-tolerance and inter-patient variability require the use of conservative dosing when converting from one opioid to another - halve the calculated comparable dose and titrate the new opioid as needed.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza	Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients is 30 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsule whole (do not chew, crush, or dissolve). ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately. ▪ Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	90 mg and 120 mg capsules are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 10 mcg/hr, 20 mcg/hr
Dosing Interval	One transdermal system every 7 days
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients when converting from less than 30 mg morphine equivalents, and in mild to moderate hepatic impairment - 5 mcg/hr dose. ▪ When converting from 30 mg to 80 mg morphine equivalents - first taper to 30 mg morphine equivalent, then initiate with 10 mcg/hr dose. ▪ Titrate after a minimum of 72 hours prior to dose adjustment. ▪ Maximum dose: 20 mcg/hr due to risk of QTc prolongation. ▪ Application <ul style="list-style-type: none"> ! Apply only to sites indicated in the Full Prescribing Information. ! Apply to intact/non-irritated skin. ! Skin may be prepped by clipping hair, washing site with water only ! Rotate site of application a minimum of 3 weeks before reapplying to the same site. ! Do not cut. ▪ Avoid exposure to heat. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 Inhibitors may increase buprenorphine levels. ▪ CYP3A4 Inducers may decrease buprenorphine levels. ▪ Benzodiazepines may increase respiratory depression. ▪ Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
Use in Opioid-Tolerant Patients	Butrans 10 mcg/hr and 20 mcg/hr transdermal systems are for use in opioid-tolerant patients only.
Drug-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointe. ▪ Hepatotoxicity ▪ Application site skin reactions
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Dosing Interval	Every 8 to 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients: 2.5 to 10 mg ▪ Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information. ▪ High inter-patient variability in absorption, metabolism, and relative analgesic potency. ▪ Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of Federal Regulations, Title 42, Sec 8).
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Pharmacokinetic drug-drug interactions with methadone are complex. <ul style="list-style-type: none"> ▪ CYP 450 inducers may decrease methadone levels. ▪ CYP 450 inhibitors may increase methadone levels. ▪ Anti-retroviral agents have mixed effects on methadone levels. ▪ Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe. ▪ Benzodiazepines may increase respiratory depression
Use in Opioid-Tolerant Patients	Refer to full prescribing information.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointe. ▪ Peak respiratory depression occurs later and persists longer than analgesic effect. ▪ Clearance may increase during pregnancy. ▪ False positive urine drug screens possible.
Relative Potency To Oral Morphine	Varies depending on patient's prior opioid experience.
Duragesic	Fentanyl Transdermal System, 12, 25, 50, 75, and 100 mcg/hr
Dosing Interval	Every 72 hours (3 days)
Key Instructions	<ul style="list-style-type: none"> ▪ Use product specific information for dose conversion from prior opioid ▪ Use 50% of the dose in mild or moderate hepatic or renal impairment, avoid use in severe hepatic or renal impairment ▪ Application <ul style="list-style-type: none"> ! Apply to intact/non-irritated/non-irradiated skin on a flat surface. ! Skin may be prepped by clipping hair, washing site with water only ! Rotate site of application. ! Titrate using no less than 72 hour intervals. ! Do not cut. ▪ Avoid exposure to heat. ▪ Avoid accidental contact when holding or caring for children. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet. ▪ Specific contraindications: <ul style="list-style-type: none"> ▪ Patients who are not opioid-tolerant. ▪ Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time. ▪ Management of post-operative pain, including use after out-patient or day surgery. ▪ Management of mild pain.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure.
Use in Opioid-Tolerant	All doses of Duragesic are indicated for use in opioid-tolerant patients only.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Patients	
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Accidental exposure due to secondary exposure to unwashed/unclothed application site. ▪ Increased drug exposure with increased core body temperature or fever. ▪ Bradycardia ▪ Application site skin reactions
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid
Embeda	Morphine Sulfate ER-Naltrexone Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose as first opioid: 20 mg/0.8 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve) ▪ Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms. ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Exalgo	Hydromorphone Hydrochloride Extended-Release Tablets, 8 mg, 12 mg, 16 mg, and 32 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> ▪ Use the conversion ratios in the individual product information. ▪ Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal hepatic function. ▪ Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function. ▪ Titrate using a minimum of 3 to 4 day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Do not use in patients with sulfite allergy—contains sodium metabisulfite.
Specific Drug Interactions	None
Use in Opioid-Tolerant Patients	All doses of Exalgo are indicated for opioid-tolerant patients only.
Drug-Specific Adverse Reactions	Allergic manifestations to sulfite component.
Relative Potency To Oral Morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.
Kadian	Morphine Sulfate Extended-Release Capsules, 10 mg, 20mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 2-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve).

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Kadian 100 mg and 200 mg capsules are for use in opioid-tolerant patients.
Product-Specific Safety Concerns	None
MS Contin	Morphine Sulfate Controlled-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	<ul style="list-style-type: none"> Product information recommends not using as first opioid. Titrate using a minimum of 2-day intervals. Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MS Contin 100 mg and 200 mg tablet strengths are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg
Dosing Interval	Every 12 hours
Key Instructions	<ul style="list-style-type: none"> Use 50 mg every 12 hours as initial dose in opioid nontolerant patients Titrate by 50 mg increments using a minimum of 3-day intervals. Maximum total daily dose is 500 mg Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth. Dose once daily in moderate hepatic impairment with 100 mg per day maximum Avoid use in severe hepatic and renal impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of tapentadol. Contraindicated in patients taking MAOIs.
Use in Opioid-Tolerant Patients	No product-specific considerations.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> Risk of serotonin syndrome Angioedema
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Opana ER	Oxymorphone Hydrochloride ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg
Dosing Interval	Every 12h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.
Key Instructions	<ul style="list-style-type: none"> Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance < 50 mL/min) and patients over 65 years of age Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> ▪ Titrate using a minimum of 2-day intervals. ▪ Contraindicated in moderate and severe hepatic impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.
Use in Opioid-Tolerant Patients	No product specific considerations.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	<ul style="list-style-type: none"> ▪ Oxycodone Hydrochloride ▪ Controlled-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	<ul style="list-style-type: none"> ▪ Every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Opioid-naïve patients: initiate treatment with 10 mg every 12 hours. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Hepatic impairment: start with one third to one half the usual dosage ▪ Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage. ▪ Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase oxycodone exposure. ▪ CYP3A4 inducers may decrease oxycodone exposure.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet. ▪ Contraindicated in patients with gastrointestinal obstruction.
Relative Potency To Oral Morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio.
For detailed information, refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda .	

Tab 40

Reference 6: FDA, “Draft Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling”

Guidance for Industry Abuse-Deterrent Opioids — Evaluation and Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Matthew Sullivan at (301) 796-1245.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**January 2013
Clinical Medical**

Guidance for Industry Abuse-Deterrent Opioids — Evaluation and Labeling

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<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

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Guidance for Industry¹

Abuse-Deterrent Opioids — Evaluation and Labeling

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors who wish to develop formulations of opioid drug products with potentially abuse-deterrent properties (abuse-deterrent formulations). Specifically, the guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, how those studies will be evaluated, and what labeling claims may be approved based on the results of those studies.

The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Therefore, FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. FDA welcomes comments and suggestions on this guidance, and encourages additional scientific and clinical research that will advance the development and assessment of abuse-deterrent technologies.

This guidance document is not intended to set forth FDA's views on the approvability of opioid drug products in general, whether formulated to deter abuse or otherwise, nor its views on abuse-deterrent formulations of other classes of drug products with potential for abuse. This guidance also does not address the manufacture, quality assurance, or stability evaluation of products designed to have abuse-deterrent properties.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

¹ This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Regulatory Policy, the Office of Surveillance and Epidemiology, the Office of Biostatistics, and the Controlled Substance Staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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41 cited. The use of the word *should* in Agency guidances means that something is suggested or
42 recommended, but not required.

43

44

45 II. BACKGROUND

46

47 Prescription opioid analgesics are an important component of modern pain management. Abuse
48 and misuse of these products, however, have created a serious and growing public health
49 problem. FDA has worked to address this problem while ensuring that patients in pain have
50 appropriate access to opioid analgesics.

51

52 One potentially important step towards the goal of creating safer opioid analgesics has been the
53 development of opioids that are formulated to deter abuse. FDA considers the development of
54 these products a high public health priority.

55

56 Opioid analgesics are often manipulated for purposes of abuse. Most abuse-deterrent
57 technologies developed to date are designed to make product manipulation more difficult or to
58 make abuse of the manipulated product less attractive or rewarding. However, these
59 technologies have not yet proven successful at deterring the most common form of abuse –
60 swallowing a number of intact pills or tablets to achieve a feeling of euphoria. Because opioid
61 analgesics must be able to deliver the opioid to patients for the management of pain, the extent to
62 which an abuse-deterrent product is able to reduce abuse will never be absolute. Therefore, the
63 extent of abuse deterrence can only be understood when studied relative to a comparator. The
64 following sections describe the categories of abuse-deterrent formulations, discuss premarketing
65 studies of the product's potentially abuse-deterrent properties, discuss the postmarketing studies
66 that should be used to assess the real-world impact of a potentially abuse-deterrent formulation,
67 and discuss possible labeling claims for abuse-deterrent formulations.

68

69

70 III. OPIOID ABUSE-DETERRENT FORMULATIONS

71

72 Opioid analgesics can be abused in a number of ways. For example, they can be swallowed
73 whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved
74 and injected. Abuse-deterrent formulations should target known or expected routes of abuse for
75 the opioid drug substance for that formulation. As a general framework, abuse-deterrent
76 formulations can be categorized as follows:

77

- 78 1. *Physical/Chemical barriers* – Physical barriers can prevent chewing, crushing, cutting,
79 grating, or grinding. Chemical barriers can resist extraction of the opioid using common
80 solvents like water, alcohol, or other organic solvents. Physical and chemical barriers can
81 change the physical form of an oral drug rendering it less amenable to abuse.
- 82 2. *Agonist/Antagonist combinations* – An opioid antagonist can be added to interfere with,
83 reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered
84 and released only upon manipulation of the product. For example, a drug product may be
85 formulated such that the substance that acts as an antagonist is not clinically active when

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86 the product is swallowed but becomes active if the product is crushed and injected or
87 snorted.

88 3. *Aversion* – Substances can be combined to produce an unpleasant effect if the dosage
89 form is manipulated prior to ingestion or a higher dosage than directed is used.

90 4. *Delivery System* (including depot injectable formulations and implants) – Certain drug
91 release designs or the method of drug delivery can offer resistance to abuse. For
92 example, a sustained-release depot injectable formulation that is administered
93 intramuscularly or a subcutaneous implant can be more difficult to manipulate.

94 5. *Prodrug* – A prodrug that lacks opioid activity until transformed in the gastrointestinal
95 tract can be unattractive for intravenous injection or intranasal routes of abuse.

96 6. *Combination* – Two or more of the above methods can be combined to deter abuse.

97

98

99 **IV. PREMARKETING STUDIES**

100

101 First and foremost, studies designed to evaluate the abuse-deterrent characteristics of an opioid
102 formulation should be scientifically rigorous. Important general considerations for the design of
103 these studies include the use of appropriate positive controls and comparator drugs, appropriate
104 outcome measures, appropriate data analyses to permit a meaningful statistical analysis, and the
105 selection of appropriate subjects for the study.

106

107 The evaluation of an abuse-deterrent formulation should take into consideration the most
108 common routes of abuse for the opioid. For example, studies evaluating abuse by the intranasal
109 route would not be particularly relevant if the drug is not known to be abused by that route.
110 Overall, the oral route is the most common route of abuse of prescription opioids, followed by
111 snorting and injection.

112

113 FDA is committed to retaining a flexible, adaptive approach to evaluating potentially abuse-
114 deterrent opioid drug products. In some cases, data from all three categories or “tiers” of studies
115 noted below may not be necessary. In most cases, however, in order to obtain a full and
116 scientifically rigorous understanding of the impact of a technology or technologies on a
117 product’s abuse potential, data from each of the following three categories of premarketing
118 studies are appropriate:

119

120 1. Laboratory-based in vitro manipulation and extraction studies (Category 1)

121 2. Pharmacokinetic studies (Category 2)

122 3. Clinical abuse potential studies (Category 3)

123

124 The results of Category 1 studies influence the design of Category 2 pharmacokinetic studies,
125 and the results of Category 2 studies influence the need for Category 3 studies of human abuse
126 potential and the designs and goals of these studies.

127

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128 **Category 4 studies analyze postmarketing data to assess the impact of an abuse-deterrent**
129 **formulation on actual abuse. These studies are addressed in Section V of this guidance.**

130

131 **A. Laboratory Manipulation and Extraction Studies (Category 1)**

132

133 **The goal of the laboratory-based studies, Category 1, should be to evaluate the ease with which**
134 **the potentially abuse-deterrent properties of a formulation can be defeated or compromised.**
135 **These studies are critical to the understanding of formulation characteristics and performance.²**
136 **Methodologically, these studies should be designed with knowledge of the physicochemical**
137 **properties of the formulation and the methods available to abusers, and should be conducted on**
138 **the to-be-marketed formulation. Sponsors should consider both the mechanisms by which**
139 **abusers can be expected to attempt to deliberately overcome the abuse-deterrent properties of the**
140 **product as well as the ways that patients may alter the formulation (unintentionally or**
141 **intentionally) that change the rate or amount of drug released (for example, dose dumping may**
142 **occur when taking the product with alcohol or when the product is cut, chewed, or crushed).**
143 **Testing should provide information sufficient to fully characterize the product's abuse-deterrent**
144 **properties, including the degree of effort required to bypass or defeat those properties.**

145

146 **The in vitro studies should assess various simple and sophisticated mechanical and chemical**
147 **ways a drug can be manipulated, such as: (1) defeating or compromising the controlled release of**
148 **an opioid from extended-release formulations for purposes of abuse by different routes of**
149 **administration; (2) preparing an immediate-release formulation for alternative routes of**
150 **administration; or (3) separating the opioid antagonist, if present, from the opioid agonist, thus**
151 **compromising the product's abuse-deterrent properties.**

152

153 **The test product should be compared to appropriate comparator products for ease of mechanical**
154 **manipulation. The ability to crush, cut, grate, or grind the product formulation using readily**
155 **available items such as spoons, cutters, and coffee grinders should be assessed. Particular**
156 **attention should be given to particle size distribution following each mode of physical**
157 **manipulation, as particle size may influence the rate of opioid extraction from manipulated**
158 **product. The effect of heat and cold on mechanical manipulation should also be studied.**

159

160 **Extractability and solubility studies should be designed to determine whether any of the**
161 **formulation components might be differentially solubilized and extracted, allowing an abuser to**
162 **bypass the drug's abuse-deterrent properties. After establishing how a product could be**
163 **manipulated, chemical extraction of the opioid from the intact and the manipulated product**
164 **should be assessed and compared to opioid extraction from the selected intact and similarly**
165 **manipulated comparator products. The ease of extracting the opioid from the intact and**
166 **manipulated product should be determined using a variety of solvents that are commonly**
167 **available (e.g., water, vinegar, ethanol, isopropanol, acetone, mineral spirits) and those which**
168 **have potentially relevant solvent characteristics (e.g., pH, polarity, protic vs. aprotic). The**

² This topic has been discussed at meetings of the Anesthetic & Life Support Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee (NDA 022272, *OxyContin*, May 5, 2008, and September 24, 2009). Additional information on these meetings is available on FDA's web site at the following location: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM187082.pdf>.

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169 effects of time, temperature, pH, and agitation on solvent extraction should also be determined.
170 For combination products containing more than one drug substance, extractability and solubility
171 studies should be designed to determine whether any of the drugs present in the combination
172 might be differentially solubilized and extracted. The in vitro drug-release characteristics of the
173 intact and manipulated product should also be compared using a discriminatory and robust
174 dissolution method.

175

176 In addition to the general evaluation of the effects of physical and chemical manipulation on the
177 product, there are important route-specific data that should be generated, as follows:

178

- 179 • For a product with potential for snorting, the particle size distribution should be
180 established.
- 181 • For a product with potential for smoking, the vaporization temperature and degradation
182 temperature of the opioid in salt and base form should be determined.
- 183 • For a product with potential for intravenous injection, the opioid concentration in a small
184 injection volume and the viscosity (syringeability and injectability) of the injection fluid
185 should be determined.

186

187 The following examples illustrate the kinds of outcomes that in vitro studies should evaluate:

188

189 1. Limitations to manipulation of the product by crushing, grinding or melting, or by changing
190 the intact formulation through other methods that would limit insufflation of the
191 manipulated product, and/or that would limit dissolution of the manipulated product and
192 incorporation into a solvent that could then be injected by intravenous or subcutaneous
193 routes.

194

195 2. Limitations to the extraction of the opioid of the product that would, therefore, reduce the
196 likelihood of the product being injected by intravenous or subcutaneous routes and/or make
197 the manipulated product difficult to draw up into a syringe.

198

199 3. A formulation that results in noxious effects either upon insufflation or injection when the
200 product is manipulated for administration by those routes, or when the product is
201 administered by oral ingestion and the noxious component is released into systemic
202 circulation.

203

204 4. A formulation that, upon manipulation, would result in the release of pharmacologic
205 antagonists to the opioid, thereby creating a substance that would either decrease the
206 product's pharmacologic effects (e.g., euphoria) or result in a mild to moderate degree of
207 drug withdrawal when the manipulated substance is injected or administered by another
208 route of abuse.

209

210 5. A formulation that limits the user's ability to manipulate it for abuse due to a specific
211 feature of the product, such as an injectable, intramuscular depot formulation or implant.

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213 6. A prodrug that cannot be manipulated *in vitro* to release the abusable opioid and, therefore,
214 the opioid can only be released by metabolism that occurs in the gastrointestinal track or
215 the systemic circulation after ingestion.

216

217 B. Pharmacokinetic Studies (Category 2)

218

219 The goal of the clinical pharmacokinetic studies, Category 2, should be to understand the *in vivo*
220 properties of the formulation by comparing the pharmacokinetic profiles of the manipulated
221 formulation with the intact formulation and with manipulated and intact formulations of the
222 comparator drugs through one or more routes of administration. If food and alcohol alter the
223 pharmacokinetic parameters of the formulation, data should be provided to characterize those
224 effects.³

225

226 Relevant pharmacokinetic parameters for the opioid drug and any psychoactive metabolites that
227 should be measured in these studies include:

228

- maximum concentration (C_{max}),

229

- time to maximum concentration (T_{max}),

230

- area under the curve (AUC_{0-t} and $AUC_{0-\infty}$),

231

- relevant partial AUC, such as AUC_{0-30} minutes or AUC_{0-2} hours, and

232

- terminal elimination half-life ($T_{1/2}$).

233

234 The rate of rise of drug concentration should be assessed when possible, because it is thought to
235 contribute to differential abuse potential among drugs, formulations, and routes of
236 administration.⁴ To support these analyses, it is important to have specimen collection and
237 analysis time points sufficient to cover the onset, peak, and offset of the effects of both
238 immediate-release (IR) and extended-release (ER) formulations, in both the intact and
239 manipulated products. ER formulations typically have a slower onset and lower peak
240 concentration compared to IR formulations. Pharmacokinetic parameters also differ between
241 different routes of administration of a drug substance, such as oral versus intranasal routes.

242

243 If food significantly increases systemic exposure of the intact formulation, the underlying
244 mechanism for the food effect should be established by assessing whether the effect is based on

³ See FDA draft guidance for industry, *Assessment of Abuse Potential of Drugs*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

⁴ References suggesting that drugs associated with a rapid onset of action are associated with greater abuse potential include:

Abreu, M.E., G.E. Bigelow, L. Fleisher, S.L. Walsh, 2001, Effect of Intravenous Injection Speed on Responses to Cocaine and Hydromorphone in Humans, *Psychopharmacology*, 154:76-84.

de Wit, H., B. Bodker, J. Ambre, 1992, Rate of Increase of Plasma Drug Level Influences Subjective Responses in Humans, *Psychopharmacology*, 107:352-358.

de Wit, H., S. Didish, J. Ambre, 1993, Subjective and Behavioral Effects of Diazepam Depend on Its Rate of Onset, *Psychopharmacology*, 112: 324-330.

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245 the drug substance or the formulation and whether the effect is present with intact product as
246 well as with manipulated product. When food is expected to increase exposure, subsequent
247 abuse potential studies by the oral route should be conducted in the fed state to maximize the
248 potential systemic exposure.

249

250 As a part of these studies, adverse events should be collected. For example, if the manipulated
251 formulation is abused by snorting, it would be important to assess adverse events related to
252 intranasal tolerability.

253

254 C. Clinical Abuse Potential Studies (Category 3)

255

256 Clinical studies of abuse potential, Category 3, are also an important methodology for assessing
257 the relative abuse potential of a new drug for purposes of scheduling under the Controlled
258 Substances Act.⁵

259

260 The preferred design is a randomized, double-blind, placebo-controlled and positive comparator-
261 controlled crossover study. These studies generally are conducted in a drug-experienced abuser
262 population. The use of a pre-qualification phase (see section 2 below) to identify subjects who
263 can distinguish active drug from placebo reproducibly is a common enrichment strategy used to
264 improve the power of the study to distinguish difference between treatments.

265

266 For drugs with abuse-deterrent properties, the purpose of a clinical abuse potential study is to
267 assess the impact of the potentially abuse-deterrent formulation on measures that predict how
268 probable it is that the formulation will be attractive to abusers (“liked”). Accordingly, certain
269 methodological aspects of these studies should be adapted to that objective, as discussed below.

270

271 1. Blinding

272

273 Clinical studies of abuse potential should use a randomized, double-blind, placebo-controlled
274 and positive comparator-controlled crossover design. Because study subjects are recreational
275 drug users and familiar with the effects of the drug substances being studied, the double-dummy
276 technique or other techniques should be used to ensure the blinding of all tests when possible.
277 However, alternative designs may be suitable when the blinding of the study drug and the
278 positive control cannot be maintained. For example, a parallel design may be useful when
279 studying the intranasal route of administration, where subjects may be able to see the differences
280 in volume or color between test drug and placebo or positive comparator.

281

282 Options for assisting with blinding include the administration of the crushed study drug in a
283 narrow neck, opaque container with a pre-inserted straw to facilitate snorting of the drug.
284 Though subjects might not be able to see the sample, due to the physical properties of samples
285 and even differences in weight among samples, un-blinding may still occur. When the study
286 involves intranasal administration of a crushed product, every effort should be made to produce

⁵ See FDA draft guidance for industry, *Assessment of Abuse Potential of Drugs*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

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287 samples with similar particle size distribution and the details of the preparation of the samples
288 should be provided in the study protocol.

289
290 2. *Pre-qualification Phase*

291
292 The purpose of the pre-qualification phase is to increase the power of a study to detect
293 differences in the abuse potential of the various formulations of drug and placebo.⁶ In general,
294 the pre-qualification phase should ensure that subjects can distinguish between placebo and an
295 IR version of the same opioid drug as the abuse-deterrent formulation, using the same route of
296 administration as planned for the assessment in the clinical phase. The positive control should
297 include a strength that is lower than or equal to the lowest strength selected for the assessment
298 during the clinical phase. For example, a 15 mg dose of opioid could be used in the pre-
299 qualification phase when a 30 mg dose will be assessed in the clinical phase.

300
301 Qualifying criteria that help identify subjects with an acceptable placebo response and an
302 acceptable response for the positive control should be pre-specified in the study protocol. After a
303 range for an acceptable placebo response is set, an acceptable response for the positive control
304 should be chosen so that there is no overlap of responses. For example, if a difference in drug
305 liking scores between placebo and the positive control of 15 or higher is set and an acceptable
306 placebo E_{max} ⁷ response range is set between scores of 40 and 60 on a bipolar scale,⁸ liking scores
307 for the positive control that successfully define a suitable subject for the treatment phase would
308 be those equal to or higher than 75 on a bipolar drug liking scale.

309
310 3. *Assessment Phase*

311
312 The potentially abuse-deterrent formulation should be compared to a formulation that serves as a
313 positive control,⁹ and the positive control should be compared to placebo to validate the study.
314 For an IR product with potentially abuse-deterrent properties, the positive control should be an
315 IR formulation of the same opioid. For an ER formulation with potentially abuse-deterrent
316 properties, the positive control could be an IR formulation of the same opioid, an ER formulation
317 of the same opioid, or, if unavailable, a manipulated form of another ER opioid known to be
318 abused. Examples of a manipulated opioid include crushed ER tablets administered orally or
319 placed into an oral solution. The study should include at least two strengths of the positive
320 control.

321
322 Pharmacokinetic data should be collected to correlate with the pharmacodynamic outcomes
323 described in section 7.
324

⁶ An additional advantage of a pre-qualification phase is that it helps subjects to be familiarized with and trained in the use of various scales and questionnaires that measure subjective effects.

⁷ E_{max} refers to the maximum pharmacodynamic response.

⁸ On a bipolar drug liking scale, 50 = neutral, 100 = maximum liking, and 0 = maximum dislike).

⁹ A positive control in general is an opioid with a similar pharmacological profile or, in some cases, on a similar adverse event profile.

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325 4. ***Subjects***
326

327 **Studies should be conducted in opioid-experienced abusers who have experience with the**
328 **particular route of abuse being studied. Subjects should not be physically dependent and should**
329 **not be currently seeking or participating in treatment for drug abuse.**
330

331 **Detailed characteristics of the study population with respect to past and current drug use and**
332 **abuse should be captured (e.g., drugs abused, drug of choice, duration of abuse or abstinence).**
333

334 5. ***Dose Selection, Manipulation Mode, Comparators, Route of Administration, and***
335 ***Sample Preparation***
336

337 **The selection of the route(s) of administration should be based on epidemiological data showing**
338 **that a selected route is a relevant route of abuse. For each route of administration, the potentially**
339 **abuse-deterrent formulation and comparator should be manipulated to cause the highest release**
340 **of the opioid and the highest plasma levels. The dose of the opioid selected for the study should**
341 **be known to produce high levels of liking in opioid-experienced abusers.**
342

343 **The intranasal and intravenous routes of administration present additional challenges. For**
344 **studies using the intranasal route of administration, the preparation of the samples is extremely**
345 **important. The potentially abuse-deterrent formulation and comparator study drug should be**
346 **produced with similar particle size distribution based on a detailed protocol for the preparation of**
347 **the samples.¹⁰**
348

349 **For studies using the intravenous route of administration, the oral formulations may not be safe**
350 **for intravenous use. In place of the manipulated oral formulation, a solution for injection should**
351 **be prepared using commercially available products that are safe for intravenous use. The amount**
352 **of the opioid should be based on extrapolation from in vitro extraction studies of manipulated**
353 **solid formulations.**
354

355 6. ***Outcome Measures and Data Interpretation***
356

357 **In abuse potential studies, the primary method for evaluating the subjective effects of drugs**
358 **should be through the use of standardized instruments. A Statistical Analysis Plan should be**
359 **included in the study protocol.**
360

361 7. ***Instruments to Assess Drug Abuse Potential***
362

363 **In typical abuse potential studies, several instruments have been used to measure subjective**
364 **responses predictive of the likelihood of abuse. These instruments include:**
365

¹⁰ Available safety-related information on the use of the various excipients through the intranasal route should be provided. Additionally, some sponsors have conducted intranasal tolerability studies prior to the abuse potential studies to evaluate irritation of the nasal cavity, nasal congestion, and discharge, among other measures.

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366 • Visual Analogue Scales (VAS) – used for drug liking, good effects, bad effects, and other
367 drug abuse-related effects

368 • Profile of Mood States

369

370 Using these instruments, for the evaluation of the abuse potential of a potentially abuse-deterrent
371 formulation, the VAS for drug liking should be the primary measure as it appears to correlate
372 most directly with potential for abuse. Other measures of particular interest include:

373

374 • Assessment of overall drug liking¹¹

375 • Assessment of high

376 • Assessment of likelihood to take the drug again

377 These measures can be assessed using either a unipolar or bipolar scale, and a rationale should be
378 provided for the choice for a particular scale. In general, we recommend use of a bipolar scale
379 for the primary measure of drug liking.

380

381 8. *Data Interpretation*

382

383 For clinical studies of abuse potential conducted on potentially abuse-deterrent opioid drug
384 products, the primary analysis should be the difference in means of the E_{max} .¹²

385

386 Additional pharmacodynamic measures, including positive subjective effects other than drug
387 liking (e.g., take drug again, high, overall drug liking) and other subject-rated assessments, are
388 generally considered secondary endpoints. Other subject-rated assessments of interest include:
389 alertness; drowsiness; nausea; and, when the intranasal route is used, intranasal irritation,
390 burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal
391 congestion.

392

393 Some sponsors provide descriptive statistics including mean, standard error, median, and
394 interquartile range, calculated for all pharmacodynamic endpoints by time and treatment. (See
395 section on Statistical Analysis for further guidance.) What constitutes a clinically significant
396 difference in drug liking, between the manipulated and intact versions of the potentially abuse-
397 deterrent formulation and positive control, is an area requiring further research and will be
398 evaluated on a case-by-case basis. Analysis of postmarketing data on abuse levels associated
399 with the potentially abuse-deterrent formulation being studied will help to support the findings
400 from abuse potential studies.

401

402 In addition, when interpreting results from human abuse potential studies, attention should be
403 given to the profile of subjective effects produced by the manipulated and intact formulation in

¹¹ 'Overall drug liking' measures the user's retrospective assessment of a drug, whereas 'VAS for drug liking' measures the user's immediate assessment.

¹² In general, the primary endpoint of interest is drug liking, and the E_{max} is captured within 8 hours after dosing. However, the timeframe of measuring the maximum response will be determined by the pharmacokinetic and pharmacodynamic parameters of the formulations studied.

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404 terms of onset, peak duration of activity, and offset. The rate of rise of drug onset for the intact
405 and manipulated potentially abuse-deterrent formulation should be given appropriate weight in
406 the overall analysis of the abuse deterrent properties. A more rapid onset of action or a shorter
407 time-to-reach peak effect is generally associated with greater abuse potential.³ Regarding the
408 duration of effect, it may be difficult to interpret the abuse potential of a formulation that
409 produces a sustained liking effect when taken intact or after manipulation, though lower than that
410 produced by the IR comparator formulation.

411
412 The overall assessment of abuse potential should be based on the pattern of findings across all of
413 the measures. In addition, qualitative aspects of the findings, such as the steepness of the drug
414 liking response and duration of the liking effects associated with manipulated formulations,
415 should be taken into consideration, along with other positive effects and negative effects.

416

417 9. Statistical Analysis

418

419 a. Background

420

421 The overall goal of a clinical study of abuse potential is to assess a number of abuse potential
422 outcome measures (e.g., drug liking VAS) in the potentially abuse-deterrent formulation relative
423 to a formulation of the drug without abuse-deterrent properties (positive control). Substantial
424 decreases in the responses for the potentially abuse-deterrent formulation compared to the
425 positive control are evidence of deterrence.

426

427 The positive control (C) would typically be an appropriate opioid analgesic that has history of
428 misuse and abuse. The test drug (T) would be the potentially abuse-deterrent formulation.

429

430 A clinical study of abuse potential should be validated by comparing the responses to C with
431 those of placebo (P). Thereafter, the assessment of the abuse-deterrence properties of T is of
432 primary interest. This can be achieved by comparing the difference in means between C and T
433 with a *margin* for abuse potential measures and comparing the difference between C and T
434 relative to C in drug liking on a bipolar VAS.

435

436 The statistical analysis of the data in a clinical study should begin with descriptive statistics
437 comprising tabulations and graphs, which include tables of the means (or medians), standard
438 error, and other summary statistics: minimum, Q1, median, Q3, and maximum of the responses
439 of interest for each treatment. Useful graphs include mean time course profiles, heat-maps, and
440 continuous responder profiles.

441

442 b. Primary Analyses

443

444 The primary analysis of abuse-deterrent effects should be based on the comparison of means (or
445 medians) between crushed, chewed, or otherwise modified T and C with an abuse-deterrence
446 margin. That is,

447

$$448 H_0: \mu_C - \mu_T \leq \delta_1 \text{ versus } H_a: \mu_C - \mu_T > \delta_1$$

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450 where $\delta_1 > 0$. Because C is an opioid drug, the validation test also needs a margin, say δ_2 .

451 That is,

452
$$H_0 : \mu_C - \mu_P \leq \delta_2 \text{ versus } H_a : \mu_C - \mu_P > \delta_2$$

453 where $\delta_2 > 0$.

454

455 The actual values of δ_1 and δ_2 may vary according to abuse potential measures and the route of
456 drug administration. Before conducting a study, the sponsor should review the literature and
457 consult with appropriate experts, and then propose the values of δ_1 and δ_2 to the FDA for
458 discussion. We also suggest the use of 95% confidence intervals to assess both the differences
459 $\mu_C - \mu_T$ and $\mu_C - \mu_P$.

460

461 c. Secondary Analyses

462

463 In addition to the primary analysis, an analysis of the percent reduction for the potentially abuse-
464 deterrent formulation relative to C from each individual study subject for drug liking VAS on a
465 bipolar scale from 0 to 100, the most important abuse potential measure, is recommended for the
466 clinical abuse potential studies. One definition for percent reduction for individual subjects is as
467 follows:

468
$$\% \text{reduction} = \frac{c_i - t_i}{c_i - p_i} \times 100\%, i = 1, 2, \dots, n,$$

469 where c_i , t_i and p_i are the E_{\max} values for C, T, and P from the i th subject, respectively; n is
470 the sample size.

471

472 Nevertheless, this definition is problematic because for two subjects having the same E_{\max} values
473 for T and C ($t_1 = t_2$ and $c_1 = c_2$), the larger the placebo response, the greater the percent
474 reduction. A more appropriate definition of percent reduction can be derived by replacing p_i by
475 the neutral score 50 on a bipolar scale; that is,

476
$$\% \text{reduction} = \frac{c_i - t_i}{c_i - 50} \times 100\%, i = 1, 2, \dots, n$$

477 Note that even though most abuse potential studies have a pre-qualification phase,
478 approximately 10% of subjects still have placebo responses p_i over 65, with 5% over 77 in
479 the assessment phase. Consequently, it may be necessary to penalize subjects with large
480 values of p_i in computing percent reduction. For example, the percent reduction could be
481 multiplied by an adjustment factor that equals 1 when p_i is around 50 or less and decreases
482 from 1 when p_i is large. Sponsors should discuss with FDA the need for an adjustment
483 factor in computing percent reduction and an appropriate formula for defining the penalty
484 to be applied prior to finalizing the study protocol.

485

486 Two approaches for assessing the deterrent effects using percent reduction are provided below.

487

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489 Responder Analysis

490

491 A *responder* is defined as a subject who had at least a certain prespecified level of reduction, for
492 example, 30% or 40% reduction, in E_{\max} for T relative to C. A proportion test may be used to
493 test the null hypothesis that 50% or fewer subjects are responders. That is,

494

$$495 H_0 : p^* \leq 50\% \text{ versus } H_a : p^* > 50\%$$

496

497 where p^* denotes the percentage of responders. The 95% confidence interval of p^* may also be
498 calculated.

499

500 Analysis of the Median Percent Reduction

501

502 The median of the percent reduction (*ptr*) is a descriptive measure of central tendency of *ptr*. At
503 most 50% of subjects have *ptr* less than the median, and at most 50% of subjects have *ptr* greater
504 than the median. If the median of *ptr* is equal to 30%, for example, it means that approximately
505 50% of subjects have greater than or equal to a 30% reduction.

506

507 For assessing deterrent effects, we may test

508

$$509 H_0 : \text{median}(ptr) \leq DR\% \text{ versus } H_a : \text{median}(ptr) > DR\%$$

510

511 DR denotes deterrent reduction. If the distribution of *ptr* is symmetric, the Wilcoxon-signed
512 rank test can be used to test the null hypothesis that the $\text{median}(ptr) \leq DR\%$, and a 95%
513 confidence interval for the median based on this test may be readily calculated using standard
514 methods.

515

516 Sponsors should pre-specify one of the two analysis methods for the percent reduction in their
517 statistical analysis plan in addition to the primary analysis in their clinical studies, and discuss
518 with FDA the definition of a responder in the responder analysis or the value of DR% used in the
519 analysis of the median percent reduction prior to finalizing the study protocol.

520

521

522 V. POSTMARKETING STUDIES (CATEGORY 4)

523

524 Premarketing studies focus on assessing the potentially abuse-deterrent properties of a product
525 under controlled conditions. The goal of postmarketing studies, Category 4, is to determine
526 whether the marketing of the potentially abuse-deterrent formulation results in a significant
527 decrease in population-based and use-based estimates of abuse compared to estimates of abuse if
528 only formulations without abuse-deterrent properties are marketed.

529

530 Because data on the actual impact of an abuse-deterrent formulation on drug abuse are limited,
531 the optimal design features of postmarketing epidemiologic studies capable of detecting a change
532 in the occurrence of abuse and abuse-related clinical outcomes (addiction, overdoses, poisonings,
533 and death) as a result of the drug product's abuse-deterrent formulation have not yet been
534 established.

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A wide range of interrelated behavioral, clinical, and societal factors contribute to drug abuse, and the impact of drug abuse can be manifested in a variety of ways. As a result, data on drug abuse can come from a variety of sources and measure a wide range of markers of drug abuse. Sponsors may thus choose to conduct multiple formal studies, using a variety of data sources and outcomes, and also to collect other informal or supportive data. Sponsors should submit to FDA proposals for formal studies and proposals intended to provide supportive data that are supportive of the assessment of abuse deterrence.

Formal studies have the following characteristics:

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550

551

1. They use outcomes that provide meaningful measures of abuse deterrence.
2. They produce estimates of abuse deterrence that are nationally representative, or are based on data from a large geographic region.
3. They assess overall and route-specific abuse and abuse deterrence.
4. They are sufficiently powered to assess meaningful changes in drug abuse.

552

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Data that are considered supportive of the evaluation of abuse deterrence can be used to provide additional context on societal, behavioral, and clinical aspects of abuse. Supportive data may rely on sources that capture diversion events, attitudes, and practices (e.g., tampering) of abusers and other information that may not directly be considered abuse (e.g., data concerning the street value of prescription drugs, information about drug use and misuse from social websites). Supportive data can contribute to the totality of evidence relating to abuse deterrence.

559

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564

The epidemiologic methods and data sources that underlie formal postmarketing studies to evaluate the effect of abuse-deterrent formulations are evolving, and best practices have not been established. Based on the current state of this field, we provide below some basic guidelines on recommended study design features that will allow FDA to evaluate the results of formal studies of potentially abuse-deterrent formulations.

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1. The study hypothesis and its relationship to assessing abuse deterrence should be clearly stated. The study hypothesis should also include the route(s) of abuse that will be studied.
2. Drug abuse should be carefully defined in the protocol.
3. An understanding of each data source is important to the design and interpretation of the study. A description of each data source should be provided in the protocol and should include if and how the data source captures drugs, study outcomes, drug formulation, and route of administration of abuse.
4. If a study in a non-U.S. population is pursued, sponsors should describe each country's data sources; health care use; system of health care delivery; and national policies, patterns, and cultural implications for drug abuse and how these differences could affect the study interpretations.

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- 577 5. The choice of population(s) in each study should be carefully considered. The
578 populations included in the study should be described in the protocol. At least one study
579 should include a high-risk population, such as a population of known drug abusers.
- 580 6. The choice of the outcome measure(s) should be justified. Outcomes should include both
581 reported abuse and clinical outcomes that are consequent to abuse. Outcomes of reported
582 abuse should include prevalence and frequency (e.g., days of abuse in past 30 days) of
583 abuse. Clinical outcomes should include prevalence or rates of overdoses, poisonings,
584 addiction, and death; severity of overdoses, poisonings, and addiction; and duration of
585 addiction.
- 586 7. The relevance of the outcome measure(s) should be explained. If cross-study
587 comparisons are planned, the outcome measures in these studies should be as similar as
588 possible.
- 589 8. The choice of comparator is critical for determining if a reduction in drug abuse is the
590 result of a product's abuse-deterrent properties or the result of other factors (e.g.,
591 educational programs, changes in law enforcement policies, or other interventions). If an
592 abuse-deterrent formulation of a previously marketed product is introduced onto the
593 market, a comparison of abuse rates before and after the introduction of the abuse-
594 deterrent formulation can provide important information about abuse deterrence. Use of
595 other opioid products as concurrent comparators can help to clarify whether observed
596 reductions in drug abuse are the result of interventions other than the introduction of an
597 abuse-deterrent formulation. Sponsors should clearly list all proposed opioid
598 comparators and describe the rationale behind their inclusion. When branded and generic
599 versions of a comparator are marketed, they should be included in the study because
600 many data sources used in abuse studies identify only active ingredients and do not
601 distinguish between branded and generic products or among multiple generic products.
- 602 9. Understanding the background rates of drug abuse is important for protocol design and
603 interpretation of study results. A baseline assessment of the prevalence of drug abuse for
604 formulations lacking abuse-deterrent properties should be conducted.
- 605 10. It is important to control for variables that may affect how the product is used and also
606 for confounders. Examples of confounders to consider include geographic variability and
607 demographic characteristics.
- 608 11. Submissions should discuss how the availability of each opioid and the size of the at-risk
609 population will affect the analysis, study design, and interpretation.
- 610 12. Submissions should provide specific information regarding the statistical analyses in the
611 protocol, including pre-specified hypotheses, methodologies, and sample size estimates.
- 612 13. Qualitative assessments should use available instruments that are shown to be valid
613 measures of the type of drug abuse defined in the protocol and appropriate to the targeted
614 study population. If outcome assessment methods must be developed specifically for a
615 study, they should be tested in a pilot study before their use in the main investigation.

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- 616 14. Assessment of the abuse outcome measures should consider both the average level and
617 the trend over time in the measures. Segmented regression¹³ and interrupted time series¹⁴
618 measures can be useful for this purpose.
- 619 15. Outcome measures should be observed for a sufficient time to adequately characterize the
620 trend. If seasonal and other temporal patterns are present, then analysis of the trend may
621 require longer observational periods.
- 622 16. The accuracy of outcome measures will also influence the required observational period.
623 Outcome measures with large uncertainty (due to bias or variability) may require longer
624 observational periods.
- 625 17. Changes in the average level of the outcome measures within a defined period of time
626 can be estimated with only a few observations if the uncertainties of the measures are
627 well characterized and there is sufficient statistical power. A change in the average level
628 observed in a limited time period does not preclude favorable or unfavorable trends.
- 629 18. Interim analyses are encouraged, but results should be considered as tentative in light of
630 their preliminary nature.

631 As is the case for formal studies, best practices for collecting and submitting additional
632 supportive data are still evolving. However, below are some basic recommendations relating to
633 supportive data.

- 634
- 635 1. The goal of the supportive data should be clearly stated, and the rationale for how these
636 data contribute to a sponsor's portfolio of abuse-related studies should be clearly stated.
- 637 2. The sponsor should clearly describe how supportive data are representative of the
638 population from which it is derived or sampled, if such information is available.
- 639 3. The sponsor should clearly describe how the exposure and outcome are measured and
640 describe the evidence that demonstrates the performance of the outcome assessment in
641 measuring drug abuse as defined in the protocol, if such information is available.
- 642 4. Analysis of supportive data based on geographically-diverse settings are strongly
643 encouraged. Analyses with overlapping geographic areas between formal studies and
644 supportive data should be considered.
- 645 5. Sponsors should clearly state in the protocol whether the supportive data are intended to
646 be descriptive or analytic in nature. A description of the statistical power and related
647 sample size should be provided.

648
649
650

¹³ Wagner A.K., S.B. Soumerai, F. Zhang, D. Ross-Degnan, 2002, Segmented regression analysis of interrupted time series studies in medication use research, *Journal of Clinical Pharmacy and Therapeutics* 27:299-309.

¹⁴ Crosbie J., 1993, Interrupted time-series analysis with brief single-subject data, *Journal of Consulting and Clinical Psychology*, 61(6):966-974).

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651 VI. LABELING

652

653 Including information about a product's demonstrated abuse-deterrent properties in labeling is
654 important to inform health care providers, the patient community, and the public about the
655 product's predicted or actual abuse potential. Accordingly, FDA encourages sponsors to seek
656 approval of proposed product labeling that sets forth the results of physiochemical, physiologic,
657 pharmacodynamic, pharmacokinetic, and/or formal postmarketing studies and appropriately
658 characterizes the abuse-deterrent properties of a product.

659

660 To date, FDA has limited data correlating the potentially abuse-deterrent properties of certain
661 opioid drug products with actual reduction in abuse or adverse events associated with abuse.
662 When the data predict or show that a product's potentially abuse-deterrent properties can be
663 expected to, or actually do, result in a significant reduction in that product's abuse potential,
664 these data, together with an accurate characterization of what the data mean, should be included
665 in product labeling.¹⁵ This information should be communicated as clearly and transparently as
666 possible. It is critical that labeling claims regarding abuse-deterrent properties be based on
667 robust, compelling, and accurate data and analysis, and that any characterization of a product's
668 abuse-deterrent properties or potential to reduce abuse be clearly and fairly communicated.

669

670 Labeling language regarding abuse deterrence should describe the product's specific abuse-
671 deterrent properties as well as the specific routes of abuse that the product has been developed to
672 deter. For example, a formulation that limits an abuser's ability to crush a tablet and to extract
673 the opioid may be labeled as limiting manipulation for the purpose of snorting or injection, if the
674 data support such a claim. For this characterization to be accurate and not misleading, however,
675 appropriate caveats are likely to be necessary. For example, it may be necessary for the labeling
676 to explain that the product's abuse-deterrent properties only make abuse more difficult, not
677 impossible, and that these properties provide no deterrence against other forms of abuse (such as
678 swallowing the intact tablet).

679

680 FDA may also require caveats based on the types of studies performed or on the extent to which
681 those studies accurately predict real-world effects. For example, when data supporting a
682 product's potential to reduce abuse derive from premarketing studies that FDA determines are
683 reasonably predictive but not determinative of reduced abuse, the labeling might include a
684 statement such as:

685

686 *This information is based on the above-described laboratory and clinical studies,*
687 *which may not accurately predict the product's actual abuse potential.*

688 *Postmarketing studies of the actual abuse patterns associated with this product*
689 *are ongoing, and this information may be modified based on the results of such*
690 *studies.*

691

692 In the past, FDA has required descriptions of abuse-deterrence studies in labeling to be
693 accompanied by statements that, for example, the clinical significance of the studies is unknown
694 and that there is "no evidence" that the product's potentially abuse-deterrent properties actually

¹⁵ Abuse-deterrence information will be included in subsection 9.2 (Abuse) of the DRUG ABUSE AND DEPENDENCE section.

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695 reduce the product's abuse potential. However, we believe the approach discussed in this section
696 – which focuses on targeted data and a flexible, adaptive approach to labeling - will be beneficial
697 to public health.

698
699 FDA encourages sponsors to develop abuse-deterrent formulations based on advances in the
700 relevant science and technologies. As abuse-deterrence technologies improve, FDA expects that
701 it will allow claims related to abuse deterrence commensurate with those improvements. On the
702 other hand, FDA is concerned that abusers may adapt to abuse-deterrent formulations and
703 discover methods of defeating them. Accordingly, FDA will take a flexible, adaptive approach
704 to the labeling of these products. If and when abusers can overcome a technology such that it no
705 longer has a meaningful effect in deterring abuse, FDA may require labeling revisions.

706
707 There are four general tiers of claims available to describe the potential abuse-deterrent
708 properties of a product.

709
710 Tier 1: The Product is Formulated with Physicochemical Barriers to Abuse

711 Tier 2: The Product is Expected to Reduce or Block Effect of the Opioid When the
712 Product is Manipulated

713 Tier 3: The Product is Expected to Result in a Meaningful Reduction in Abuse

714 Tier 4: The Product has Demonstrated Reduced Abuse in the Community
715

716 These tiers generally correlate with the four categories of study data described above. However,
717 in order to provide as complete a picture as possible of a product's abuse-deterrent properties,
718 FDA generally expects sponsors to provide data from Categories 1, 2, and 3 in order to be
719 eligible for Tier 1, Tier 2, or Tier 3 claims. For example, Category 1 data alone likely will not be
720 sufficient to support a Tier 1 claim; Category 2 or 3 data (or both) may be needed to ensure that a
721 Tier 1 claim is not misleading.

722
723 That said, some products intended to deter abuse will not require data from each of the four study
724 categories in order to be eligible for an abuse-deterrence claim. One example is a prodrug of an
725 opioid for which there are Category 1 and 2 data demonstrating that it cannot be abused because
726 it is not active until it has been metabolized in the gastrointestinal tract or the systemic
727 circulation after oral ingestion. Based on these data, it may not be necessary to perform
728 Category 3 studies to obtain approval for Tier 1 and/or Tier 2 claims related to deterring abuse
729 via injection or insufflation.

730
731 The goal of product labeling for abuse-deterrent opioid formulations is to accurately reflect the
732 available data regarding the expected or known impact of the abuse-deterrent formulation on
733 abuse of the product while also accurately conveying any uncertainty regarding that impact. As
734 discussed below, the nature of the claims available for a particular product will depend on the
735 types of studies performed and the results of those studies. FDA is not able to provide specific
736 guidance on the magnitude of effect that would be sufficient to support each type of claim.
737 Labeling claims therefore will be assessed on a case-by-case basis, depending on the data
738 presented.

739

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Tier 1: Claims that a Product is Formulated with Physicochemical Barriers to Abuse

As discussed in Section IV, various physicochemical barriers to abuse may be initially assessed in Category 1 premarketing studies. The specific properties that resist manipulation and/or that result in the release of components of the formulation that may limit its ability to be abused should be described. In addition, the specific route or routes of administration affected by these abuse deterrence properties should be described.

An example of a Tier 1 claim could be:

These data demonstrate that, when the intact formulation is ground in a coffee grinder, the resulting particle size makes insufflation extremely difficult; and when those particles are heated they form a gelatinous substance that cannot be drawn up into a syringe or insufflated. Therefore, it appears that injection or snorting of the manipulated drug product would be difficult. However, abuse of this product is still possible by the oral route.

This statement would be followed by an appropriate acknowledgment that data from laboratory studies may not fully predict real-world abuse potential, that post-marketing studies are ongoing, and that this information may be modified based on the results of such studies.

Tier 2: Claims that a Product is Expected to Reduce or Block the Effect of the Opioid When the Product is Manipulated

As discussed in Section IV, pharmacokinetic data may also be used to demonstrate a product's abuse deterrence. An example of a Tier 2 claim could be:

These data demonstrate that, when the intact product is heated in a solvent suitable for injection and the resulting solution is injected, the opioid antagonist component is released into the systemic circulation at a pharmacokinetic exposure level that may result in blocking of the opioid's agonist effects, or in a mild to moderate degree of opioid withdrawal in an opioid-tolerant individual. However, abuse of this product is still possible by the oral route.

This statement would be followed by an appropriate acknowledgment that data from laboratory and clinical studies may not fully predict real-world abuse potential, that post-marketing studies are ongoing, and this information may be modified based on the results of such studies.

Tier 3: Claims that a Product is Expected to Result in a Meaningful Reduction in Abuse

As discussed in Section IV, data from appropriately designed, conducted, and analyzed human abuse potential studies may demonstrate a meaningful degree of reduction in abuse potential. If a sponsor seeks a Tier 3 claim that a product can be expected to result in a meaningful reduction in abuse, that claim generally will need to be supported by data from Category 1, 2, and 3 studies.

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786 The Agency believes that reductions in drug “liking” generally are likely to result in meaningful
787 reductions in abuse. However, data from Category 1 and 2 studies should serve as the basis for
788 performing the Category 3 studies and will provide important supportive information in
789 understanding the results of a Category 3 study. If data from Category 3 studies are robust, Tier
790 3 labeling claims and data regarding the design, conduct, and data from Category 3 studies may
791 be included in the product labeling.

792

793 An example of a Tier 3 claim could be:

794

795 *These data demonstrate that the inclusion of the opioid antagonist component in*
796 *the product’s formulation results in a decrease in euphoria and “liking” when a*
797 *solution of the product in a suitable solvent for injection has been heated and the*
798 *resulting solution injected parenterally. Based on these findings, this product’s*
799 *specific formulation may result in reduced abuse by parenteral injection.*
800 *However, abuse of this product is still possible, including by the oral route or by*
801 *snorting when the product is crushed.*

802

803 This statement would be followed by an appropriate acknowledgment that data from laboratory
804 and clinical studies may not fully predict real-world abuse potential, that post-marketing studies
805 are ongoing, and this information may be modified based on the results of such studies.

806

807 *Tier 4: Claims that a Product has Demonstrated Reduced Abuse in the Community*

808

809 As discussed in Section V, post-marketing data from a variety of sources can demonstrate that a
810 product’s abuse-deterrent properties cause persistent and relevant reduction in its abuse. These
811 data include data from appropriately designed, conducted, and analyzed formal post-marketing
812 studies, as well as data from supplemental sources on the abuse of the product (e.g., data
813 concerning the street value of prescription drugs).

814

815 FDA is currently considering formal studies plus a variety of supplemental data as sources that
816 may be acceptable to provide evidence that a product’s formulation has had an actual impact on
817 its abuse. FDA anticipates that data from Category 1, 2, 3, and 4 studies (including both formal
818 studies and supporting data) would be needed to support a Tier 4 claim. The combined results
819 from all of these studies would be described in the product labeling, including specific study
820 designs, conduct, analyses, and study data.

821

822 An example of a Tier 4 claim could be:

823

824 *These data have demonstrated a reduction in abuse of this opioid in the*
825 *community setting compared to the levels of abuse, overdoses, and deaths that*
826 *occurred when only formulations of the same opioid without abuse deterrence*
827 *properties were available. This reduction in abuse appears to be due to the*
828 *product’s particular formulation, which deters parenteral injection and snorting*
829 *of the manipulated product. However, such abuse of this product is still possible,*
830 *and the product’s abuse deterrence properties do not deter abuse associated with*
831 *swallowing the intact formulation.*

832

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833 This statement would be followed by an appropriate acknowledgment, if applicable, that
834 postmarketing studies are ongoing and that this information may be modified based on the results
835 of those studies.

836

837

838 **VII. ADDITIONAL RESEARCH NEEDS**

839

840 As has been discussed above, the science of abuse deterrence is relatively new. Both the
841 technologies involved and the analytical, clinical, and statistical methods for evaluating those
842 technologies are rapidly evolving. This means that FDA will take a flexible, adaptive approach
843 to the evaluation and labeling of potentially abuse-deterrent products. It also means there is
844 considerable room for additional scientific work that could advance the development and
845 assessment of abuse-deterrent formulations. In particular, the agency encourages additional
846 research on the following topics:

847 • Characterization of the quantitative link between changes in the pharmacokinetics of
848 opioids in different formulations and results of a clinical abuse potential study with those
849 same formulations.

850 • Characterization of the best assessment methods to employ when analyzing a clinical
851 study of abuse potential.

852 • Characterization of the quantitative link between the outcomes from a clinical study of
853 abuse potential comparing formulations and the effect on those same formulations on
854 abuse in the community.

855 • Further understanding of the best study methods to employ to assess the effect of an
856 abuse-deterrent formulation on the rates of abuse in the community.

857

858 Progress on these topics could facilitate the ability of sponsors to propose, and FDA to approve,
859 labeling that would give a more complete picture of the anticipated effect of abuse-deterrent
860 formulations. Ultimately, progress in these areas could facilitate product development by
861 reducing the amount of information that is needed to accurately assess an abuse-deterrent
862 formulation and predict its impact on abuse in the community.

Tab 41

Reference 10: CDC, “Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly,” *Morbidity and Mortality Weekly Report*, vol. 61, pp. 1–40, 2012

Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance from CDC and the U.S. Department of Health and Human Services



Continuing Education Examination available at <http://www.cdc.gov/mmwr/cme/conted.html>.



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

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Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance from CDC and the U.S. Department of Health and Human Services

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Summary

This report summarizes current (as of 2011) guidelines or recommendations published by multiple agencies of the U.S. Department of Health and Human Services (DHHS) for prevention and control of human immunodeficiency virus (HIV) infection, viral hepatitis, sexually transmitted diseases (STDs), and tuberculosis (TB) for persons who use drugs illicitly. It also summarizes existing evidence of effectiveness for practices to support delivery of integrated prevention services. Implementing integrated services for prevention of HIV infection, viral hepatitis, STDs, and TB is intended to provide persons who use drugs illicitly with increased access to services, to improve timeliness of service delivery, and to increase effectiveness of efforts to prevent infectious diseases that share common risk factors, behaviors, and social determinants. This guidance is intended for use by decision makers (e.g., local and federal agencies and leaders and managers of prevention and treatment services), health-care providers, social service providers, and prevention and treatment support groups. Consolidated guidance can strengthen efforts of health-care providers and public health providers to prevent and treat infectious diseases and substance use and mental disorders, use resources efficiently, and improve health-care services and outcomes in persons who use drugs illicitly.

An integrated approach to service delivery for persons who use drugs incorporates recommended science-based public health strategies, including 1) prevention and treatment of substance use and mental disorders; 2) outreach programs; 3) risk assessment for illicit use of drugs; 4) risk assessment for infectious diseases; 5) screening, diagnosis, and counseling for infectious diseases; 6) vaccination; 7) prevention of mother-to-child transmission of infectious diseases; 8) interventions for reduction of risk behaviors; 9) partner services and contact follow-up; 10) referrals and linkage to care; 11) medical treatment for infectious diseases; and 12) delivery of integrated prevention services. These strategies are science-based, public health strategies to prevent and treat infectious diseases, substance use

This report originated in the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Kevin Fenton, MD, PhD, Director.

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disorders, and mental disorders. Treatment of infectious diseases and treatment of substance use and mental disorders contribute to prevention of transmission of infectious diseases. Integrating prevention services can increase access to and timeliness of prevention and treatment.

Introduction

This report summarizes current (as of 2011) public health recommendations and guidelines from multiple agencies of the U.S. Department of Health and Human Services (DHHS) for science-based public health strategies for the prevention of human immunodeficiency virus (HIV) infection, viral hepatitis, sexually transmitted diseases (STDs), and tuberculosis (TB) (referred to collectively as infectious diseases) among persons who use drugs illicitly and their contacts (sex and drug-using partners) in the United States. In addition, the report recommends integrated delivery of the public health strategies and includes a review of recent programmatic efforts to integrate prevention services for persons who use drugs illicitly. Integrated prevention services provide multiple prevention services at a single venue, coordinate referrals, and provide linkage to services delivered at multiple venues to improve access to high-quality and comprehensive prevention services. Such integration can offer providers and programs the opportunity to address multiple infectious diseases and related health conditions (e.g., substance use and mental disorders) at one time or at a single facility, thereby increasing the likelihood that clients will receive needed services (1). Without access to integrated prevention services, persons who use drugs illicitly would need to go to different facilities to access prevention and treatment services for HIV infection, viral hepatitis, STDs, or TB and for substance use or mental disorders. Implementing integrated services is intended to increase access to services, improve the timeliness of service delivery, and increase the effectiveness of efforts to prevent infectious diseases and disorders that share common risk factors, behaviors, and social determinants. The guidance does not review the topic of physical integration of all medical treatment services for such diseases, especially as different regulatory, accreditation, and licensing policies govern the delivery of treatment services for these diseases. However, the guidance emphasizes the importance of treatment for infectious diseases as a major strategy in preventing their further transmission. The guidance also emphasizes treatment of substance use and mental disorders, comorbidities that must be treated effectively to optimize prevention outcomes for infectious diseases.

This report is divided into seven sections: 1) an introduction to the scope and purpose of the guidance; 2) a summary of the methods, including steps and procedures followed in development of the guidance; 3) a brief outline of the epidemiology of illicit drug use and of HIV infection, viral

hepatitis, STDs, TB, and their sequelae among persons who use drugs illicitly in the United States; 4) a description of science-based public health strategies for prevention of HIV infection, viral hepatitis, STDs, and TB among persons who use drugs illicitly; 5) a brief summary of special considerations that affect the prevention and control of infectious diseases among persons who use drugs illicitly; 6) a section discussing practical aspects of delivery of integrated prevention services; and 7) a short conclusion stating the rationale and importance of integrated prevention services for infectious diseases among persons who use drugs illicitly.

Illicit Use of Drugs and Infectious Diseases

Rates of HIV infection, viral hepatitis, STDs, and TB are substantially higher among persons who use drugs illicitly than among persons who do not use drugs illicitly (2–5). The term “illicit use of drugs” encompasses all levels of use, abuse, and dependence because each level is associated with behaviors that increase the risk for contracting or transmitting infectious diseases. Persons who use drugs illicitly are defined as those who use, without prescription, prescription drugs (e.g., oxycodone), or as those who use illicit drugs such as opiates (e.g., heroin), stimulants (e.g., powder cocaine, crack cocaine, and methamphetamine), or other so-called “club drugs” (e.g., gamma hydroxybutyrate [GHB], ketamine, flunitrazepam, and ecstasy). Marijuana use and nonmedical use of prescription drugs also are associated with risk for contracting or transmitting infectious diseases. Although alcohol and tobacco use is considered illicit for certain age groups (i.e., age <21 years for alcohol in all states; age <18 years for tobacco in most states and <19 years in some states) (6), this report does not focus in great detail on tobacco use or alcohol use, even though excessive alcohol use and tobacco use are associated with infectious diseases (7–9). Illicit use of drugs includes multiple drug use (i.e., simultaneous use of illicit drugs and legal substances).

In general, the risk for acquiring and transmitting infectious disease in a population is a reflection of the prevalence of a given infection in the population, the efficiency of transmission of the organism, and the burden of infectious diseases and patterns of the risk behaviors in which that population engages. The high rates of HIV infection, viral hepatitis, STDs, and TB among persons who use drugs illicitly reflect behavioral, social, cultural, environmental, and structural factors that facilitate disease transmission (10–12). Behavioral factors include the

use and sharing of contaminated injection equipment (i.e., needles and syringes) and drug preparation equipment (e.g., water, cotton, and a cooker). Bloodborne infections such as HIV infection and viral hepatitis are transmitted efficiently through sharing of contaminated needles. The transmission also can occur through unprotected sex. Illicit use of alcohol by youth, alcohol intoxication, and illicit use of drugs are associated with unsafe sexual behaviors, which are risk factors for HIV infection, viral hepatitis, and STDs. Such social and cultural factors as marginalization, stigma, and lack of social support can contribute to disease transmission; these factors often affect persons who are members of a sexual minority (i.e., lesbian, gay, bisexual, and transgender), persons who use drugs illicitly, or persons who have a mental disorder (9,10). Environmental factors common among persons who use drugs illicitly include unstable living conditions, and limited availability of sterile injection and drug preparation equipment (13). Lack of access to and underenrollment in substance abuse treatment programs are other structural factors contributing to infectious disease transmission. In addition, fear of arrest by law enforcement officers and fear of discrimination by health-care providers can discourage persons who use drugs illicitly from using health-care services adequately (14). Persons who use drugs illicitly often have other complex health and social needs, including treatment for substance abuse and for preexisting or concurrent mental disorders (9,15–17). Throughout the guidance provided in this report, efforts to facilitate treatment of infectious diseases and treatment of substance use and mental disorders also are classified as preventive interventions.

Utility of the Guidance

This guidance is intended for public health officials at all levels, leaders and managers of programs, program providers, health-care providers (e.g., clinicians, providers of mental health services, outreach workers, and social workers), and prevention and treatment support groups for persons who use drugs illicitly (e.g., coalitions). Persons who use this guidance should adapt it to meet the specific prevention needs of their communities, while preserving the core missions of the organizations, programs, and venues that provide these services.

A coordinated approach to service delivery needs to incorporate multiple science-based public health strategies. Staff working in prevention programs for HIV infection, viral hepatitis, STDs, and TB and in programs to prevent and treat substance use and mental disorders need to consider program collaboration and service integration as an approach to improve access to multiple services (18–21). Preventing infectious diseases among persons who use drugs illicitly can also help prevent infections among their sex and drug-using partners and among other members of their communities.

Program Collaboration and Service Integration

Program collaboration and service integration are mechanisms that programs use to organize and combine interrelated health issues, activities, and prevention strategies so as to facilitate comprehensive delivery of services, to foster integrated care, and to increase operational efficiencies (18). Agencies and providers at the federal, state, local, tribal, and service delivery levels can provide leadership and resources to develop and implement programs that enhance program collaboration and service integration (19).

To the extent that programs can collaborate and integrate prevention services, they can save time, money, and effort. Providing multiple prevention services at a single venue or coordinating referrals and linkage to care for services delivered at multiple venues can improve access to quality and comprehensive prevention services. Such coordination can offer the opportunity to address multiple infectious diseases and related health conditions, such as substance use and mental disorders, at one time or at a single facility, thus increasing the likelihood that clients will receive needed services. Program collaboration and integration of prevention services can be expected to maximize opportunities for prevention, reduce delays between infection and diagnosis and between diagnosis and treatment, and improve adherence to risk reduction behaviors and to treatment regimens for infectious diseases, substance use disorders, and mental disorders.

Program collaboration is a mutually beneficial and well-defined relationship entered into by two or more programs, organizations, or organizational units to achieve common goals (18). The collaboration usually includes a commitment to relationships and mutual goals, a jointly developed structure, shared responsibility, mutual authority and accountability for success, and shared resources and benefits for programs that are not necessarily all delivered at the same physical location. Service integration is intended to provide persons with seamless services from multiple programs or areas within programs without repeated registration procedures, waiting periods, or other administrative barriers (18). By providing access to services at a single health-care entry point, service integration is different from system coordination, in which multiple agencies provide services but at multiple locations, possibly requiring persons to visit several locations and register separately for each program to obtain the services (1).

Comprehensive and integrated service delivery, either through provision of multiple services at a single venue or through coordination of referrals for services delivered at multiple venues, requires collaborative planning and a coordinated approach among service providers. Such collaboration and coordination are needed to ensure that provided services

meet the needs of persons who use drugs illicitly and that the methods of service delivery are acceptable both to providers and to clients. However, an integrated approach to service delivery requires that local, state, and federal agencies work together, which is often a difficult process because of different regulatory constraints, including those caused by complying with the Health Insurance Portability and Accountability Act (HIPAA) regulations. Electronic and portable health records are inconsistently available, further complicating delivery of health-care services. In addition, patients frequently are lost to follow-up in transition from the detection and diagnosis to the treatment of disease. Despite these concerns, a coordinated approach to integrated service delivery can improve services offered to persons who use drugs illicitly and can improve their health seeking behaviors.

Guidance Development Methods

This guidance was developed and written by a CDC work group (members are listed alphabetically on page 1). The work group included health-care professionals, public health scientists, and public health analysts with experience and expertise in prevention of HIV infection, viral hepatitis, STDs, and TB in persons who use drugs illicitly. The work group developed and wrote the guidance to support the needs of stakeholders (e.g., policymakers, leaders, managers, providers, and recipients of prevention and treatment services) for one document that summarizes recommendations and guidelines of science-based public health strategies that can be integrated to enhance service delivery and public health outcomes for persons who use drugs illicitly.

The guidance is the result of the efforts of several DHHS agencies and offices to synchronize activities and achieve synergies in areas where their missions for persons who use drugs illicitly overlap. Starting in late 2007, the work group met biweekly to develop and write the guidance. The group used multiple search strategies in preparing the guidance, including searching medical and professional computerized databases (e.g., PubMed, Psycinfo, and National Guideline Clearinghouse) using relevant key terms and search strings, previously published guidelines or guidance, review papers, and reference lists of published papers and documents (Appendix A). During 2008–2010, the work group wrote a draft document for discussion. In late 2010 and throughout 2011, DHHS agencies, including DHHS offices, reviewed a draft of this report to ensure that the recommendations were science-based and consistent with the missions and recommendations of DHHS agencies and offices. They provided questions or comments that were addressed or incorporated in this report.

DHHS operating divisions or institutes that approved this guidance included the Agency for Healthcare Research and Quality (AHRQ), CDC, the Centers for Medicare and Medicaid Services, the Food and Drug Administration, the National Institute on Drug Abuse (NIDA), the National Institutes of Health, and the Substance Abuse and Mental Health Services Administration (SAMHSA). The DHHS offices and staff divisions that approved this guidance included the Office of the Secretary, the Office of the Assistant Secretary for Health, the Office of the Assistant Secretary for Legislation, the Office of the Assistant Secretary for Planning and Evaluation, the Office of the Assistant Secretary for Public Affairs, the Office of the Assistant Secretary for Financial Resources, the Office of the General Counsel, and the Office of Global Affairs. In addition, several experts who are not part of the federal or local government reviewed the draft guidance and provided questions or comments that were addressed in this report (see Acknowledgments). These persons have expertise in prevention and treatment of HIV infection, viral hepatitis, STDs, TB, substance use disorders, and mental disorders; they are affiliated with private organizations that support services provided to persons who use drugs illicitly, or else have experience working with this population. None of these reviewers reported financial or other conflicts of interest that would preclude their involvement in reviewing this guidance.

Prior to this guidance, recommendations and guidelines for public health strategies for preventing and treating HIV infection, viral hepatitis, STDs, TB, substance use disorders, and mental disorders among persons who use drugs illicitly have appeared in different publications (Appendix B). This guidance provides a summary of published scientific and programmatic literature, including current (as of 2011) recommendations and guidelines for 12 science-based public health strategies: 1) prevention and treatment of substance use and mental disorders; 2) outreach programs; 3) risk assessment for illicit use of drugs; 4) risk assessment for HIV infection, viral hepatitis, STDs, and TB; 5) screening, diagnosis, and counseling for HIV infection, viral hepatitis, STDs, and TB; 6) vaccination; 7) prevention of mother-to-child transmission of HIV infection, viral hepatitis, and STDs; 8) interventions for reduction of risk behaviors; 9) partner services and contact follow-up; 10) referrals and linkage to care; 11) medical treatment for HIV infection, viral hepatitis, STDs, and TB; and 12) delivery of integrated prevention services.

The recommendations and guidelines of CDC, NIDA, SAMHSA, AHRQ, and the U.S. Preventive Services Task Force (USPSTF) for these science-based public health strategies are consistent across the agencies for this high-risk population, i.e., persons who use drugs illicitly. CDC's recommendations address prevention and treatment of HIV infection, viral hepatitis, STDs,

and TB. The guidelines of NIDA and SAMHSA are for prevention and treatment of substance use and mental disorders. The Advisory Committee on Immunization Practices and CDC issued the vaccination recommendations. The recommendations for screening or testing of persons who use drugs illicitly for HIV infection, viral hepatitis, STDs, and TB made by AHRQ and the U.S. Preventative Services Task Force are consistent with those of CDC.

The recommendations or guidelines from CDC, NIDA, and SAMHSA are based on reviews of the scientific evidence and programmatic literature, expert opinion, field experience, and lessons learned from and results of projects funded by these agencies. Recommendations of AHRQ and the U.S. Preventive Services Task Force are based on systematic reviews of the scientific literature. Evidence for the effectiveness of the delivery of integrated prevention services for persons who use drugs illicitly, like the evidence supporting the previously published recommendations and guidelines, is based on a combination of a literature review, expert opinion, field experience, and results of and lessons learned from delivery of integrated services in projects funded by DHHS agencies. The evidence supports delivery of integrated prevention services at venues that serve persons who use drugs illicitly. The report includes information on relevant practical steps (e.g., development of a coordinating body, analysis of local data, staff training, evaluation) to support service integration and to plan, deliver, monitor, and evaluate integrated services. Earlier versions of this report were presented at the National HIV Prevention Conference held in August 2009 and at the National STD Prevention Conferences held in March 2010 and in March 2012.

Epidemiology of Illicit Use of Drugs and of HIV Infection, Viral Hepatitis, STDs, TB, and Their Sequelae in the United States

Illicit Use of Drugs and Its Sequelae

In the 2009 National Survey on Drug Use and Health (NSDUH), an estimated 8.7% of the U.S. noninstitutionalized population aged ≥ 12 years reported illicit use of drugs (i.e., marijuana, cocaine, heroin, hallucinogens, inhalants, and prescription drugs used for nonmedical purposes) during the month before data collection (22). In the 2006–2008 NSDUH, an estimated 425,000 persons aged ≥ 12 years (0.17% of the age-group population) had injected heroin, cocaine, or stimulants during the year before data collection (23). Relatively recent publications provide relevant information. Approximately 1.2 million persons in the United States injected drugs in 2002 (24). The prevalence of a history of injection-drug use remained relatively stable at 1.5% (95% confidence interval

[CI] = 1.4%–1.6%; weighted estimate: 3.4 million persons) during 1979–2002 (25). Data from the 2008 NSDUH indicate that an estimated 3.8 million persons in the United States have used heroin at least once in their lives and that an estimated 213,000 persons used heroin during the month before data collection (26). In 1998, the estimated number of persons who injected drugs ranged from 19 to 173 persons per 10,000 population (median: 60) across 96 large U.S. metropolitan areas (27). Monitoring changes in drug use among all age groups remains important for developing and implementing relevant prevention and treatment programs (28–30).

Persons who inject drugs illicitly are a heterogeneous group, and >50% of them use more than one drug illicitly through means other than injection (e.g., inhalation, sniffing, smoking, or ingesting). They tend to drink alcohol in excess and tend to smoke tobacco (31–36). Estimates of the number of users of illicit drugs through means other than injection range from 1 million to 1.5 million (26).

Illicit drug use is associated with a high risk for mortality and comorbidities. Of particular significance, overdosing with injected drugs poses a risk for death (37,38). Persons who inject drugs illicitly can overdose when they inject alone. They often are in settings where peers are not trained in overdose prevention or are reluctant to call for medical help because of fear of legal consequences, or they are in settings where medical help is not available or accessible in a timely manner (39–41). Drug overdose death rates increased nearly fivefold during 1990–2007 (from two deaths per 100,000 population in 1990 to nine per 100,000 in 2007) (42). In 2006, among unintentional injury- and accident-related causes of death, rates of drug overdose were second only to motor-vehicle crash deaths (42). Opioid pain medications account for the highest number of unintentional overdose deaths, followed by cocaine and heroin (43). Drug overdose is a leading cause of mortality among persons who inject drugs illicitly (44–49). Overdose can be prevented by overdose prevention training programs (37,38,50–52).

HIV Infection, Viral Hepatitis, STDs, and TB Among Persons Who Use Drugs Illicitly

Persons who use drugs illicitly are at increased risk for acquiring and transmitting infectious diseases via bloodborne exposure (for those who inject), and they are at increased risk for sexual exposure to HIV and STDs (4,53–55). Some persons who use drugs illicitly might share unsterile drug injection equipment as well as engage in unprotected vaginal or anal intercourse with partners who engage in high-risk behaviors or with partners who have infectious diseases (56). In the United States, approximately 9%–12% of new HIV cases (57,58), 50% of new hepatitis C cases (59), and 2% of hepatitis A cases (59,60) are associated with illicit injection of drugs. Among persons who are at risk

for infectious diseases, men who have sex with men (MSM) are affected disproportionately by HIV. For example, CDC estimates that the rate of new HIV diagnoses among MSM is between 44 and 86 times that among other men, and between 40 and 77 times that among women (61). A 2008 survey of MSM from cities with high AIDS prevalence indicated that 5% of MSM had ever injected drugs (62), compared with 1.5% among the general population (25). The number of new HIV infections is highest among MSM, particularly young MSM, and next highest among persons infected through heterosexual contact, followed by persons who inject drugs (58).

The epidemiology of HIV infection differs by groups and is influenced by demographic factors affecting use of health-care services. For example, persistent racial and ethnic disparities in infectious diseases among persons who use illicit drugs remain a challenge (63–71). Data indicate racial and ethnic disparities in use of health-care services, including entry and retention in substance abuse treatment programs and other programs (72–84). Data also exist on the limited number of gender-sensitive interventions that meet the sex-specific needs of women who use drugs (e.g., negotiation and empowerment for adoption of safer behaviors and providing for needs of children) (85).

A large body of research has demonstrated that illicit drug use, regardless of the route of absorption of the drug, puts users at risk for acquiring HIV infection and STDs. For example, illicit injection of drugs can impair judgment, increasing the likelihood of engaging in risky sexual behaviors (86). Illicit noninjection drug use also puts users at risk for infectious diseases (72,87,88). Fortunately, prevention efforts aimed at reducing drug injection risk can be successful (57). For example, in recent years, a convergence in HIV prevalence and incidence among those who engage illicitly in injection or noninjection drug use suggests that a decrease has occurred in HIV transmission; the decrease is associated with safer use of syringes. There has also been a corresponding increase in HIV transmission associated with risky sexual behaviors (89). Illicit noninjection drug use, particularly use of stimulants, “club drugs,” and, to some extent, poppers (e.g., amyl nitrite or butyl nitrite) and erectile enhancement drugs, plays a substantial role in transmission of infectious diseases although patterns of substance abuse and preferences vary by age group, race, and ethnicity (90). Many studies highlight the role of methamphetamine and other drugs in risky sexual behavior among MSM as well as the effect of crack cocaine use on exchange of sex for illicit drugs, all of which have implications for infection with HIV and STDs (88,91–98).

The prevalence of STDs among persons who use drugs illicitly varies (range: 1%–6% for syphilis, 1%–5% for chlamydia, 1%–3% for gonorrhea, and 38%–61% for herpes simplex virus-2 [HSV-2] infection) (70,99). The moderately high

prevalence of bacterial STDs among persons who inject drugs illicitly is not much different from the prevalence among youth at high risk (100). The high prevalence of HSV-2 among persons who use drugs illicitly contrasts with the 17% prevalence reported for the general population of persons aged 14–49 years (101). In one study of young persons (median age: 24 years) who use drugs illicitly, the seroprevalence of infection with high-risk oncogenic types of human papillomavirus (HPV) was 7% among men and 38% among women for HPV-16 and 7% among men and 42% among women for HPV-18 (68). For comparison, according to 2003–2004 data from CDC’s National Health and Nutrition Examination Survey, the prevalence of infection with these HPV-types among women aged 15–49 years in the general population was 16% and 7% for HPV-16 and HPV-18, respectively; for men in the same age group, the prevalence was 5% and 2%, respectively (102). In the United States, approximately one in five patients with active TB either uses a drug illicitly or drinks alcohol in excess, or both (103). Among U.S.-born TB patients, one in three patients with TB reports substance abuse (103). In 2008, illicit noninjection drug use was reported in 7.3% of U.S. TB patients, and illicit injection drug use was reported in 1.8% (104).

Comorbidities

Persons who use drugs illicitly have moderate-to-high co-infection rates. They often experience more than one infection, disease, or disorder (i.e., substance use or mental disorders) at the same time (17,86,104,105). Epidemiologic synergy, in which co-occurring infections increase the likelihood of infection transmission and progression of infectious diseases, highlights the importance of preventing and treating co-infections, diseases, and disorders.

Increasing awareness of infectious disease comorbidities and of overlapping risks for multiple infections is essential because of the overlapping risk behaviors associated with acquiring these conditions, the synergistic effects of disease progression and treatment needs, and the social determinants for prevention and treatment. Among HIV-infected persons who inject drugs illicitly, 80% also are infected with hepatitis C virus (HCV) (86). In studies of persons who use drugs illicitly in New York City, infection with HSV-2 is associated with HIV infection (106,107). For example, 80% of HIV-positive persons who inject drugs illicitly are HSV-2 positive (106). In a prospective study, newly detected HPV was more common among HIV-infected women than among women who were not infected with HIV (30% and 6%, respectively) (108). Increased awareness of infectious disease comorbidities is especially important for delivery of comprehensive and integrated services.

Science-Based Public Health Strategies for Prevention

Implementing science-based public health strategies in a manner that respects the rights of persons who use drugs illicitly and their partners is vital for preventing HIV infection, viral hepatitis, STDs, and TB in this population (106,109–113). Decision makers can make the most efficient use of public resources by choosing cost-effective, science-based prevention strategies.

Prevention and Treatment of Substance Use and Mental Disorders

In the field of prevention and treatment of substance use disorders, the terms “use,” “abuse,” and “dependence” are defined in ways that reflect their association with risk for infectious diseases, other health conditions, and adverse social consequences (114,115). From an epidemiologic perspective, frequency of use of a substance and total number of times a substance is used in a lifetime are the principal measures of substance use. Abuse refers to a level of use of a substance that has short-term acute personal or social consequences, including sporadic, nondependent patterns of use despite social problems or physical hazards. The clinical definition of dependence includes psychologic as well as physiologic components. Psychiatric diagnosis of dependence requires evidence of consequences during an extended period of time (114). Salient markers of dependence include loss of behavioral control over using drugs, withdrawal symptoms, and an obsessive-compulsive style of use. The criteria commonly used for dependence include 1) more use of a substance than intended, 2) inability to reduce use, 3) amount of time seeking the substance, 4) physical effects of use, 5) use replacing other activities, 6) continued use despite problems, 7) tolerance, 8) withdrawal symptoms, or 9) use to avoid withdrawal symptoms (114). The term “substance abuse” denotes substance abuse or dependence as defined in the diagnostic and statistical manual (DSM) (114), and the term “substance use disorder” sometimes is used in the literature as a synonym for the term “addiction.”

Evidence demonstrates the effectiveness of science-based approaches to prevent and treat substance use and mental disorders (115–117). The evidence base indicates that scaling-up science-based approaches for treating substance use and mental disorders in publicly funded programs would improve health outcomes. Providing persons who use drugs illicitly with increased access to science-based treatment for substance use and mental disorders is one way to improve prevention and control of infectious diseases (116). The national strategy to reduce drug demand focuses on curtailing illicit drug consumption and on improving public health and public safety by reducing the consequences of drug abuse (118,119). The strategy provides a collaborative and

balanced approach that emphasizes community-based prevention, integration of evidence-based treatment into the health-care system, innovations in prevention and treatment strategies in the criminal justice system, and international partnerships to disrupt drug-trafficking organizations (118,119). The priorities of the national strategy to reduce drug demand acknowledge that it is important to prevent drug use, reduce drug use, and treat substance abuse, and that behavioral, social, environmental, and structural factors contribute to illicit use of drugs (119,120).

Evidence points to the efficacy of “screening, brief intervention, referral, and treatment” (SBIRT) approaches in primary care settings to identify problematic use of drugs and to reduce substance abuse (121–123). SBIRT is a comprehensive, integrated, public health approach to the delivery of early intervention and treatment services for persons with substance use disorders and for those at risk for developing them (121). SBIRT can be provided in a range of health facilities, including primary care centers (121). The goals of SBIRT are to 1) encourage health-care providers to screen and provide brief advice or counseling to their patients who misuse alcohol or abuse other drugs so as to reduce hazardous use of substances, 2) reduce vulnerability to the negative consequences of substance use, and 3) improve linkages between general community health care and specialized substance abuse providers to facilitate access to care when needed (121).

The spectrum of science-based treatment for substance use disorders is broad. Medication approaches (often referred to as medication-assisted therapy) are effective for treating nicotine, alcohol, and opioid addiction, as reflected in recommendations of national and international organizations (115). The use of effective medications in conjunction with science-based behavioral treatments remains valuable because combination interventions can be more effective than single interventions. Science-based behavioral treatments include cognitive behavioral therapy (including relapse prevention), motivational interviewing, and community reinforcement approaches (including contingency management as a stand-alone intervention) (124–126).

Outreach Programs

Community-based outreach, in which peer educators or other persons have established trust and rapport with persons who use drugs illicitly, can reduce risky behaviors (127,128). Outreach is particularly useful in reaching and assisting those who use drugs illicitly who are not ready to enter substance abuse treatment or to be involved in other interventions for risk reduction. Outreach has been demonstrated to increase the use of condoms, substance abuse treatment, and other prevention services (127,128). Outreach to persons who use drugs illicitly

can occur at locations where they congregate, on the streets, or in mobile vans (129). It often involves informal leaders, peers (e.g., trained persons who are former drug users), and other volunteers from the community who have existing relationships and access to the target population (130–132). Providing drug- and sex-related risk-reduction information and materials via trusted peers, while not sufficient to reduce the prevalence of behaviors associated with increased risk for infections, can help establish safer peer norms of behavior and common expectations of safer behaviors (4,11,127).

Outreach workers can provide education on drug- and sex-related risks and risk-reduction information to persons who use drugs illicitly. They can provide persons who use drugs illicitly with risk-reduction supplies (e.g., condoms, sterile syringes and needles, and naloxone) and refer them to prevention programs (129). Outreach workers also can refer persons who use drugs illicitly to facilities that offer targeted testing for TB infection; those identified with active TB disease can be treated appropriately, and those identified with TB infection (3) can be given preventive therapy for TB (133,134). Outreach workers also can provide referrals or direct links to counseling, testing, and treatment for HIV infection; to facilities that offer vaccinations for hepatitis A and hepatitis B; to programs that offer screening and treatment for viral hepatitis and STDs; and to substance abuse treatment (135,136). In addition, outreach workers can help in building trust in prevention and treatment services and in health-care providers (106,127,137).

Risk Assessment for Illicit Use of Drugs

The high prevalence of HIV infection, viral hepatitis, STDs, and TB among persons who use drugs illicitly should sensitize prevention and care providers to conduct risk assessment for illicit use of drugs for everyone seeking services for these infectious diseases (138,139). In addition, many users use multiple drugs, as well as alcohol or tobacco, and eliciting information on use of these substances could assist with prevention and treatment services. For multiple reasons, patients might not be forthcoming about illicit use of drugs; the reasons include fear of legal consequences and concerns about confidentiality. Thus, patients need to feel comfortable about their privacy and confidentiality of their data to share their behaviors with providers.

Risk assessment and risk reduction interventions are essential for adoption of safer behaviors and for referral of clients to relevant prevention and treatment programs (32,33,140–142). The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) can be used as a screening instrument for drug use (143,144).

The recommendation to assess persons who seek preventive and medical care for infectious diseases for illicit use of drugs

is consistent with recommendations of the USPSTF (145), CDC's STD treatment guidelines (146), and the American Medical Association (AMA) guidelines for adolescents (147), which recommend that health-care providers screen adolescents for substance abuse during preventive-service visits.

Risk Assessment for Infectious Diseases

Persons who use drugs illicitly should receive appropriate screening for other risk factors for infectious diseases (e.g., risky sexual behaviors or being a known contact of a person with active TB). They also should receive relevant preventive services and risk-reduction counseling. CDC's 2010 STD treatment guidelines support this approach by recommending that health-care providers of STD services routinely obtain sexual histories from their patients (146). Risk assessments for infectious diseases can be performed by health-care providers at venues that serve persons who use drugs illicitly (5,148).

Screening, Diagnosis, and Counseling for Infectious Diseases

Screening services for infectious diseases are critical components of a comprehensive strategy to reduce and eliminate incident infections among persons who use drugs illicitly (149–159). Such services identify those who are unaware of their infections and provide them with counseling and education and refer and link to treatment those who are infected. Knowledge of one's infection status can help uninfected persons who use drugs illicitly make behavioral changes to reduce the risk for infection (160–164) and can help infected persons reduce the likelihood of medical sequelae and transmission of infection to others (149–164). Screening for illicit use of drugs, including offering brief interventions and providing referrals, and screening for misuse of prescription drugs, can be useful adjuncts to screening for infectious diseases (121). The screening and counseling recommendations for preventing HIV infection, viral hepatitis, STDs, and TB infection in persons who use drugs illicitly have been summarized (Box 1).

Vaccination

Hepatitis A vaccination is recommended for persons who use drugs illicitly. Hepatitis B vaccination is recommended for all adults in certain settings, including STD clinics, HIV testing and treatment facilities, facilities providing substance abuse treatment and prevention services, correctional facilities, and health-care settings serving persons who inject drugs illicitly (100,165).

Prevaccination testing for hepatitis B is recommended for household, sex, and needle-sharing contacts of hepatitis

B surface antigen (HBsAg)-positive persons and for HIV-infected persons (152). In addition, testing might be cost-effective in adult populations with a prevalence of hepatitis B virus (HBV) infection of >20% (e.g., persons who inject drugs illicitly or incarcerated persons). If prevaccination testing for antibody to the hepatitis B surface antigen (anti-HBs) is used to identify immunity after previous HBV infection, HBsAg testing also must be performed to identify persons with chronic HBV infection. Serologic testing should not be a barrier to vaccination of susceptible persons, especially in hard-to-reach populations. The first vaccine dose typically should be administered immediately after collection of the blood sample for serologic testing (166).

Recommendations for the administration of HPV vaccinations are the same for persons who use drugs illicitly as for the general population (167). No vaccines are available for the prevention of infection with HIV, HCV, or any STD other than HPV and HBV. For TB prevention, use of Bacille Calmette-Guérin (BCG) vaccine generally is not recommended in the United States because of the low risk for infection with *Mycobacterium tuberculosis*, the variable effectiveness of the vaccine against adult pulmonary TB, and the vaccine's potential interference with tuberculin skin test reactivity (155,168).

Prevention of Mother-to-Child Transmission of Infectious Diseases

Pregnant women who use drugs illicitly are at elevated risk for transmitting infections (e.g., HIV, HBV, HCV, syphilis, chlamydia, and gonorrhea) to their children during pregnancy or at delivery if they are infected with these pathogens. Women who use drugs illicitly are less likely to use family planning services than other women (169). Pregnant women who use drugs illicitly are more likely than other women to initiate prenatal care later or not at all (170,171). Pregnant women with HIV infection have cited illicit use of drugs as a barrier to prenatal care, because some fear incarceration for illicit use of drugs and possible placement of their newborns in foster care (171). Although the recommendations of the U.S. Public Health Service Task Force to reduce perinatal HIV transmission do not outline special considerations for pregnant women who use drugs illicitly, the recommendations note that discontinuing illicit use of drugs has been associated with a reduced risk for perinatal transmission of HIV (172). HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women (149). All pregnant women, including those who use drugs illicitly, should be screened for HBsAg, and immunoprophylaxis should be administered to infants born to HBsAg-positive women or to women with unknown HBsAg status (152). Previously unvaccinated women at risk for HBV

infection, including persons who use or inject drugs illicitly, should be vaccinated against HBV infection.

Screening pregnant women for HSV-2 at their first prenatal visit is not recommended, but it is important to test pregnant women with symptoms of genital herpes, including those with symptoms at time of delivery, and to provide treatment for pregnant women with newly acquired HSV-2 (146). A summary of current recommendations and guidelines for prevention of mother-to-child transmission of infectious diseases has been provided (Box 2).

Interventions for Reduction of Risk Behaviors

Four broad strategies have been developed to reduce risk behaviors. They are 1) risk-reduction programs and messages, 2) treatment of substance use and mental disorders to prevent infectious diseases, 3) access to sterile injection and drug preparation equipment, and 4) interventions to increase condom availability (173,174).

Risk-Reduction Programs and Messages

Much of the research on HIV prevention programs for persons who inject drugs illicitly has focused on injection-related risk. In recent years, however, multiple studies have concluded that persons who use drugs illicitly, through injection or noninjection routes, are at increased risk for sexual transmission of HIV, HBV, and other STDs, regardless of the means of introducing the drug into the body (70,89,152,166,175,176). Most persons who use drugs illicitly, through injecting or other means (e.g., inhaling, sniffing, or snorting), are sexually active (87,99). Levels of sexual risk are influenced both by the drugs that are used illicitly and by their route of administration (86). Sexual transmission of HIV among persons who use drugs illicitly is associated with several factors, including a history of other STDs, recent initiation of illicit drug injection, and exchange of sex for money or for illicit drugs (87). Male-to-male sex as well as illicit use of drugs through noninjection means, including the use of such stimulants as crack cocaine and methamphetamine, is associated with increased risky sexual behaviors; these drugs increase the libido or reduce inhibitions (70,86).

Although persons who inject drugs illicitly have reduced their injection risk behaviors in response to behavior-change health interventions (177,178), reducing their risky sexual behaviors remains a challenge, similar to the challenge that faces persons who do not use drugs illicitly (179,180). Results of two meta-analyses of studies of HIV prevention interventions for persons who use drugs illicitly indicate that multisession psychosocial behavioral interventions that address sexual risk behaviors have a modest added effect compared with the effect of shorter educational interventions and a larger added effect compared

BOX 1. Summary of recommended screening, counseling, and vaccination services for persons who use drugs illicitly**HIV infection***

Testing (at least annually) of all persons likely to be at high risk for HIV infection, including persons who use drugs illicitly and their sex partners, is recommended.

Hepatitis A virus (HAV) infection†

Hepatitis A vaccination is recommended for persons who inject drugs illicitly and for persons who use drugs illicitly through noninjection routes. Prevacination testing is not indicated for the vaccination of adolescents who use drugs illicitly but might be warranted depending on the type and duration of illicit drug use. Providers should obtain a thorough history to identify patients who use drugs illicitly or are at risk for using them and who might benefit from hepatitis A vaccination. Implementation strategies to overcome barriers and increase coverage, including use of standing orders (i.e., a note in the medical record) should be considered.

Hepatitis B virus (HBV) infection§

All persons seeking protection from HBV infection are recommended to receive hepatitis B vaccination. Hepatitis B vaccination is recommended for all adults in certain settings, including STD clinics, HIV testing and treatment facilities, facilities providing substance abuse treatment and prevention services, health-care settings providing services to persons who inject drugs illicitly, and correctional facilities. Standing orders can be used to administer hepatitis B vaccine as part of routine services to all adults who have not completed a hepatitis B vaccination regimen (e.g., in settings in which high proportions of persons have risk factors for HBV infection).

Persons who inject drugs illicitly, including persons in substance abuse treatment programs, should be offered screening and counseling for chronic HBV infection. Testing should include a serologic assay for hepatitis B surface antigen (HBsAg) offered as a part of routine care, and if the result is positive, be accompanied by appropriate counseling and referral for recommended clinical evaluation and care. Previous and current sex partners and household and needle-sharing contacts of HBsAg-positive persons should be identified. Unvaccinated sex partners and household and needle-sharing contacts should be tested for HBsAg and for antibody to the hepatitis B core antigen (anti-HBc) or antibody to the hepatitis B surface

antigen (anti-HBsAg). All susceptible persons should receive the first dose of hepatitis B vaccine as soon as the blood sample for serologic testing has been collected, unless an established patient-provider relationship can ensure that the patient will return for serologic test results and that vaccination can be initiated at that time if the patient is susceptible. Susceptible persons (i.e., those who have tested negative for HBsAg and anti-HBc) should complete the vaccine series by use of an age-appropriate vaccine dose and schedule. Those who have not been vaccinated fully should complete the vaccine series. Contacts determined to be HBsAg-positive should be referred for medical care.

Medical providers should advise patients identified as HBsAg-positive about measures they can take to prevent transmission to others and protect their health. Providers also should refer patients for counseling if needed.

Susceptible persons should complete a 3-dose hepatitis B vaccine series to prevent infection from ongoing exposure.

Hepatitis C virus (HCV) infection§

All persons who use or inject drugs illicitly should routinely be offered screening and counseling for HCV infection. Persons with a history of risk, even those who have injected illicitly once or many years ago, should be offered screening and counseling for HCV infection. Facilities that provide counseling and testing should include services or referrals for medical evaluation and management of persons identified as infected with HCV.

Tuberculosis (TB)**

Targeted testing programs should be considered for persons at high risk for TB infection, including persons who use drugs illicitly. All persons suspected of having had a recent exposure to someone with active TB should be screened for active TB and TB infection.

Sexually transmitted diseases (STDs)††

Health-care providers should routinely (i.e., at baseline, periodically, and as clinically indicated) obtain sexual histories from their patients and address management of risk reduction. High-intensity behavioral counseling is recommended for all sexually active adolescents and for adults at increased risk for STDs and HIV infection. Questions to identify risk related to illicit use of drugs include questions on whether the patients have ever

See footnotes on page 12.

BOX 1. (Continued) Summary of recommended screening, counseling, and vaccination services for persons who use drugs illicitly

injected drugs illicitly or have partners who have exchanged sex or money for illicit drugs. Persons seeking treatment or screening for a particular STD should be evaluated for all common bacterial and parasitic STDs (e.g., chlamydia, gonorrhea, syphilis, and trichomoniasis) and informed if testing for any common STD has not been performed. Although no comprehensive national guidelines regarding STD care and management have been developed for correctional populations, the utility of expanded STD services in correctional settings has been reported. Universal screening of some populations (e.g., adolescent females) for chlamydia and gonorrhea is recommended at intake in juvenile detention and jail facilities. Universal screening for syphilis should be conducted based on local and institutional prevalence.

Chlamydia⁵⁵

Annual chlamydia screening for all sexually active women aged <25 years and screening of older women with risk factors (e.g., those who have a new sex partner or multiple sex partners) are recommended. Chlamydia-infected women and men should be retested approximately 3 months after treatment. Among persons in correctional facilities, universal screening of adolescent females for chlamydia should be conducted at intake. Universal screening of adult females should be conducted at intake among women up to age 35 years (or on the basis of local institutional prevalence data).

Pregnant women should be screened routinely for chlamydia at the first prenatal visit. Pregnant women at increased risk for chlamydia and women found to have chlamydial infection during the first trimester should be retested during the third trimester to prevent postnatal complications and chlamydial infection in the infant.

Sexually active men who have sex with men (MSM) who have had insertive or receptive anal intercourse or who have had oral sex in the past year should be screened for chlamydia. Testing should be performed on specimens obtained from the pharynx, urethra, or rectum depending on the site of exposure. Screening at 3- to 6-month intervals is recommended for MSM who have multiple or anonymous sex partners, have sex in conjunction with illicit use of drugs, use methamphetamine, or have partners who participate in these activities.

Gonococcal infections⁵⁵

Screening all sexually active women for gonorrhea, including those who are pregnant, if they are at increased risk, is recommended. Women aged <25 years are at highest risk for gonorrhea. Other risk factors for gonorrhea include a previous gonococcal infection, other STDs, new or multiple sex partners, inconsistent condom use, commercial sex work, and illicit drug use. Infected women and men should be retested approximately 3 months after treatment.

Among persons in correctional facilities, universal screening of adolescent females for gonorrhea should be conducted at intake in juvenile detention or jail facilities. Universal screening of adult females should be conducted at intake among females up to age 35 years (or on the basis of local institutional prevalence data).

Pregnant women should be screened at the first prenatal visit. Pregnant women found to have gonococcal infection during the first trimester should be retested in 3–6 months, preferably in the third trimester.

Sexually active MSM who have had insertive, receptive anal or oral intercourse during the previous year should be screened for urethral, rectal, and pharyngeal infection with *Neisseria gonorrhoeae* using specimens obtained from exposed sites. Screening at 3–6 month intervals is recommended for MSM who have multiple or anonymous sex partners, have sex in conjunction with illicit use of drugs, use methamphetamine, or have partners who participate in these activities.

Syphilis^{*}**

Syphilis serology should be performed at least annually for sexually active MSM, including MSM with or without established HIV infection. More frequent screening (at 3–6 month intervals) is indicated for MSM who have multiple or anonymous sex partners, have sex in conjunction with illicit drug use, use methamphetamine, or have sex partners who participate in these activities.

A serologic test for syphilis should be performed for all pregnant women at the first prenatal visit. Women who are at high risk for syphilis, live in areas of high syphilis morbidity, are previously untested, or have positive serology in the first trimester should be screened again early in the third trimester (28 weeks of gestation) and at delivery. Among persons in correctional facilities, universal

See footnotes on page 12.

BOX 1. (Continued) Summary of recommended screening, counseling, and vaccination services for persons who use drugs illicitly

screening should be conducted on the basis of the local area and institutional prevalence of early (primary, secondary, and early latent) infectious syphilis.

Herpes simplex virus-2^{†††}

HSV serologic testing should be considered for persons presenting for an STD evaluation (especially for those persons with multiple sex partners), persons with HIV infection, and MSM at increased risk for HIV acquisition.

Human papillomavirus (HPV)^{§§§}

Routine pre-exposure vaccination of those aged 11 or 12 years is recommended to prevent cervical precancer and cancer caused by high-risk HPV types. Catch-up vaccination is recommended for those aged 13–26 years, as indicated and recommended.

* Sources: CDC. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR* 2006;55(No. RR-14); CDC. HIV/AIDS. Available at <http://www.cdc.gov/hiv>; US Preventative Services Task Force. Screening for HIV: recommendation statement. *Ann Intern Med* 2005;143:32–7. (USPSTF does not have a recommendation on frequency of screening.)

† Sources: CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2006;55(No. RR-7); CDC. Viral hepatitis. Available at <http://www.cdc.gov/hepatitis>.

§ Sources: CDC. Viral hepatitis. Available at <http://www.cdc.gov/hepatitis>; Agency for Healthcare Research and Quality. Guide to clinical preventive services, 2010–2011, section 2, infectious diseases. Available at <http://www.ahrq.gov/clinic/pocketgd1011/gcp10s2b.htm>; CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2006;55(No. RR-16).

¶ Sources: Agency for Healthcare Research and Quality. Guide to clinical preventive services, 2010–2011, section 2, Infectious Diseases. Available at <http://www.ahrq.gov/clinic/pocketgd1011/gcp10s2b.htm>; CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2006;55(No. RR-16); CDC. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR* 1998;47(No. RR-19).

** Sources: CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6); CDC. Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR* 2005;54(No. RR-15); CDC. Tuberculosis. Available at <http://www.cdc.gov/tb>.

†† Sources: CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(No. RR-12); CDC. Sexually transmitted diseases. Available at <http://www.cdc.gov/std>.

§§ Sources: Agency for Healthcare Research and Quality. Guide to clinical preventive services, 2010–2011, section 2, infectious diseases. Available at <http://www.ahrq.gov/clinic/pocketgd1011/gcp10s2b.htm>; CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(No. RR-12); US Preventive Services Task Force. Screening for chlamydial infection. Available at <http://www.uspreventiveservicestaskforce.org/uspstf/uspchlmi.htm>; CDC. Sexually transmitted diseases. Available at <http://www.cdc.gov/std>.

¶¶ Sources: Agency for Healthcare Research and Quality. Guide to clinical preventive services, 2010–2011, section 2, infectious diseases. Available at <http://www.ahrq.gov/clinic/pocketgd1011/gcp10s2b.htm>; CDC. Sexually transmitted diseases. Available at <http://www.cdc.gov/std>; US Preventive Services Task Force. Screening for gonorrhea. Available at <http://www.uspreventiveservicestaskforce.org/uspstf/uspsgono.htm>.

*** Sources: Agency for Healthcare Research and Quality. Guide to clinical preventive services, 2010–2011, section 2, infectious diseases. Available at <http://www.ahrq.gov/clinic/pocketgd1011/gcp10s2b.htm>; CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(No. RR-12); CDC. Sexually transmitted diseases. Available at <http://www.cdc.gov/std>.

††† Sources: CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(No. RR-12); CDC. Sexually transmitted diseases. Available at <http://www.cdc.gov/std>.

§§§ Sources: CDC. Sexually transmitted diseases. Available at <http://www.cdc.gov/std>; US Preventive Services Task Force. Screening for cervical cancer. Available at <http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm>; CDC. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR* 2011;60:1705–8.

with minimal interventions (e.g., waitlist or provision of a self-help booklet) (179,181). Those results indicate that such interventions should be implemented on a wider scale to reach all persons who use drugs illicitly with messages about safer sex behaviors (87,179,181). However, participants with modest reductions in sexual risk might return to pre-intervention sexual risk (e.g., no condom use or a higher number of sex partners) more rapidly than they would return to pre-intervention injection-risk (e.g., use of contaminated needles and sharing of needles) (182). Decision makers can consider strengthening risk-reduction programs because data from several cities indicate that a greater proportion of HIV infections are attributable to sexual risk than to injection risk among persons who use drugs illicitly (4,107,183). The brief counseling intervention in project RESPECT that reduced sexual risk among persons seeking

care at STD clinics (184) was also effective in reducing sexual risk and bacterial STDs among those who had ever injected drugs illicitly (183). This result indicates the potential value of offering and evaluating brief counseling for reducing sexual risk (183).

Risk-reduction interventions for sexual risk are important because illicit noninjection use of drugs has been associated with participation in high-risk sexual activity and with acquisition of HIV, HBV, HCV, or other STDs (88,106,185–192). For example, methamphetamine use has been associated with unprotected sex and with higher numbers of sex partners, both among MSM and among persons who engage in heterosexual sex (188,193–195). Crack cocaine use has been associated with higher prevalence of HIV and HCV infection and with higher frequencies of unprotected sex, sex with multiple partners, and exchange of sex for money or for illicit drugs (189,196–202). Persons who use drugs illicitly should

BOX 2. Recommendations to improve prenatal care and prevent mother-to-child transmission of human immunodeficiency virus (HIV), sexually transmitted diseases (STDs), hepatitis B virus (HBV), and hepatitis C virus (HCV)

- All pregnant women, including those who use drugs illicitly, should be encouraged to seek prenatal care.
- Providers should counsel pregnant women who use drugs illicitly on the risks associated with illicit use of drugs and should encourage them to stop using drugs illicitly. Providing screening, brief interventions, referral, and treatment is a useful and effective strategy.
- All pregnant women, including pregnant women who use drugs illicitly, should be screened for HIV infection, syphilis, chlamydia, and gonorrhea at the first prenatal visit. Women who are at high risk for syphilis, live in areas of high syphilis morbidity, are previously untested, or live in areas of high HIV prevalence should be screened again early in the third trimester (at approximately 28 weeks of gestation) and at delivery. Any woman who delivers a stillborn infant should be tested for syphilis. Pregnant women who use drugs illicitly should be considered for tuberculosis screening.
- For viral hepatitis,
 - All pregnant women should be tested routinely for hepatitis B surface antigen (HBsAg) during an early prenatal visit (e.g., first trimester) in each pregnancy, even if they have been previously vaccinated or tested. Women who were not screened prenatally, those who engage in behaviors that put them at high risk for infection (e.g., illicit drug injection, having had more than one sex partner in the previous 6 months or an HBsAg-positive sex partner, having undergone evaluation or treatment for an STD, or having engaged in recent or current illicit injection of drugs), and those with clinical hepatitis should be tested at the time of admission to the hospital for delivery.
 - Women who have a history of illicit injection drug use and those who have a history of transfusion or organ transplantation before 1992 are considered at high risk for HCV infection and should be tested for hepatitis C antibodies at the first prenatal visit.
 - Women at risk for HBV infection also should be vaccinated. To avoid misinterpreting a transient positive HBsAg result during the 21 days after vaccination, a provider should perform HBsAg testing before the vaccination.
 - HBsAg-positive pregnant women should be advised of the need for their newborns to receive hepatitis B vaccine and hepatitis B immune globulin beginning at birth and to complete the hepatitis B vaccine series according to the recommended immunization schedule.
 - Infants born to women with unknown HBsAg status should receive immunoprophylaxis.

Sources: CDC. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR* 2006;55(No. RR-14); CDC. HIV/AIDS. Available at <http://www.cdc.gov/hiv/>; CDC. Sexually transmitted diseases treatment guidelines 2010. *MMWR* 2010;59(No. RR-12); CDC. Sexually transmitted diseases. Available at <http://www.cdc.gov/std/>; CDC. Hepatitis B vaccine: what you need to know. Available at <http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-hep-b.pdf>; CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part I: immunization of infants, children, and adolescents. *MMWR* 2005;54(No. RR-16); CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. Part II: immunization of adults. *MMWR* 2006;55(No. RR-16).

be provided with or referred to interventions that include some or all of the following prevention components (86,203):

- information on prevention and transmission of infectious diseases and on safer sex and injection practices,
- assessment of personal risk,
- training in how to use condoms correctly and the importance of using condoms consistently,
- counseling to address emotional or practical issues in practicing safe sex,
- training in safer sex negotiation,
- HIV testing,
- STD screening and treatment,
- referral to substance abuse treatment and social services (e.g., housing),

- psychosocial support,
- referrals to relevant mental health and family planning services, and
- training in overdose prevention and provision of naloxone.

CDC has identified several behavioral health interventions for persons who use drugs illicitly. These interventions have been demonstrated to reduce the frequency of high-risk behaviors and ultimately are intended to reduce the risk for acquiring HIV infection or other STDs (204). Other effective interventions can be adapted for use with persons who use drugs illicitly (205). The compendium of science-based HIV prevention interventions includes information on 70 effective interventions, including at least 15 for persons who use drugs illicitly, at least 12 for persons who inject drugs illicitly, and

eight that were evaluated with racial and ethnic minority persons who use drugs illicitly (206). Safety Counts and Community Promise are two evidence-based HIV prevention interventions for persons who use drugs illicitly that were developed based on work with persons who were recruited from settings other than substance abuse treatment. These interventions, which use goal-oriented counseling and peer-support approaches while drawing on several behavior-change principles, have been associated with reductions in high-risk behaviors (207–210). Previously published recommended messages for use by health and social service professionals and by other persons who have clients or client partners who use drugs illicitly have been summarized (Boxes 3 and 4).

Treatment of Substance Use and Mental Disorders to Prevent Infectious Diseases

In general, a short detoxification program from opioids has limited success in leading persons who use drugs illicitly to abstain from such use (211,212). For persons who use drugs illicitly, a longer program for substance abuse treatment that includes medication-assisted therapy (e.g., methadone or buprenorphine) and behavioral interventions is helpful for treating illicit drug use as well as for preventing HIV infection, viral hepatitis, STDs, and TB (116,204–210,213–217). Reducing or eliminating illicit drug use through substance abuse treatment promotes an overall healthy lifestyle and reduces other negative consequences of illicit drug use, including overdose (218).

An estimated 15%–25% of persons addicted to opiates in the United States during 1998–2004 were in methadone maintenance programs (219). Estimates of the percentage of persons who inject drugs illicitly and who are in substance abuse treatment programs have varied greatly (range: 1%–39%) across large U.S. metropolitan areas (27). For persons who use drugs illicitly, both lack of motivation to enter substance abuse treatment and the moderately long waiting periods that face them can be barriers to enrollment (220). Other factors affecting access to substance abuse treatment programs include poverty, lack of health insurance, and fear of being stigmatized as persons who use drugs illicitly (138).

Substance abuse treatment can reduce such risk behaviors as needle-sharing and exchange of sex for money or for illicit drugs (221–227). In addition, substance abuse treatment can serve as an entry point to medical care, and it can improve adherence to medical treatment regimens for infectious diseases (116,228–230). Substance abuse treatment includes nonpharmacologic, psychosocial approaches as well as pharmacologic therapies (174). Often, a combination of the two approaches is employed (215). For example, cognitive and behavioral therapies are effective treatments for abuse of amphetamine-type stimulants; the use of such therapies has

BOX 3. Summary of recommended messages for persons who use drugs illicitly to reduce drug use and infectious disease–related risks

- Get tested for human immunodeficiency virus, hepatitis B, and hepatitis C.
- Get vaccinated against hepatitis A and hepatitis B.
- Stop injection drug use to eliminate the risk for bloodborne infections.
- Get counseling and treatment to stop or reduce drug use.
- Never reuse or share syringes or drug-preparation equipment.
- Use a new, sterile syringe from a reliable source (e.g., a pharmacy or syringe exchange program).
- Use sterile water to prepare drugs, if possible; otherwise, use clean water from a reliable source, such as fresh tap water.
- Use a new container (i.e., cooker) and a new filter (i.e., cotton) to prepare drugs.
- Clean the injection site with a new alcohol swab before injection.
- Dispose of syringes safely after using them.
- Participate in risk-reduction programs.
- Obtain medical treatment for infectious diseases.
- Obtain treatment for substance use and mental disorders.

Sources: CDC. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR* 2006;55(No. RR-14); CDC. HIV/AIDS. Available at <http://www.cdc.gov/hiv>; CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2006;55(No. RR-7); CDC. Viral hepatitis. Available at <http://www.cdc.gov/hepatitis>; CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. Part II: immunization of adults. *MMWR* 2006;55(No. RR-16); National Institute on Drug Abuse. Drug facts: nationwide trends. Available at <http://www.drugabuse.gov/publications/drugfacts/nationwide-trends>; CDC. Persons who use drugs. Available at <http://www.cdc.gov/pwud>; National Institute on Drug Abuse. Principles of HIV prevention in drug-using populations: a research-based guide. Available at <http://archives.drugabuse.gov/POHP>; CDC. Questions and answers: HIV prevention. Available at <http://www.cdc.gov/hiv/resources/qa/prevention.htm>; CDC. How can HIV be prevented? Available at <http://www.cdc.gov/hiv/topics/basic/index.htm#prevention>; CDC. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR* 1998;47(No. RR-19); CDC. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. *MMWR* 2012;61(No. RR-4).

demonstrated reductions in illicit drug use and in high-risk behaviors (125,231). Nonpharmacologic psychotherapies (i.e., behavioral interventions) are valuable when medications are not available or allowable (117,125,126). Adherence interventions might greatly enhance the effects of nonpharmacologic psychotherapies and medications and reduce high-risk behaviors associated with acquisition or transmission of infectious diseases (232,233).

BOX 4. Summary of recommended messages for persons with a history of high-risk sexual practices

- Abstain from sex to avoid infection with sexually transmitted diseases (STDs) or human immunodeficiency virus (HIV).
- Engage in a long-term mutually monogamous relationship with an uninfected partner.
- Limit the number of sex partners.
- Use condoms correctly and consistently.
- Seek counseling to reduce risky sexual behavior.
- Be tested at least once a year for HIV infection.
- Be tested and treated for STDs and insist that your partners do too.
- Assist partner services, if you are told that you have HIV infection or another STD, by voluntarily providing contact information so that partners can be tested and, if appropriate, receive care and treatment.
- Consider encouraging sex partners to get vaccinated against hepatitis A and B or human papillomavirus.

Sources: CDC. Recommendations for partner services programs for HIV infection, syphilis, gonorrhea, and chlamydia infection. *MMWR* 2008;57(No. RR-9); National Institute on Drug Abuse. Drug facts: nationwide trends. Available at <http://www.drugabuse.gov/publications/drugfacts/nationwide-trends>; CDC. How can HIV be prevented? Available at <http://www.cdc.gov/hiv/topics/basic/index.htm#prevention>. CDC. Sexually transmitted diseases. Available at <http://www.cdc.gov/std>; CDC. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR* 2011;60:1705–8.

Medication-assisted therapy with methadone or buprenorphine is highly effective for opioid addiction; it can promote adherence to needed medical care (116,234). An extensive body of evidence demonstrates that therapy with methadone or buprenorphine reduces the frequency of heroin injection, increases rates of retention in substance abuse treatment programs (235,236), and markedly decreases criminal activity (11,14,109,112). For example, methadone maintenance therapy has been associated with reductions in the frequency of illicit injection and sharing of injection equipment (212). It also has been associated with reductions in the number of sex partners and in the exchange of sex for money or for illicit drugs (237,238).

Increased condom use (239,240) and increased safer sexual behaviors (132,241) have been reported by persons who have reduced their illicit use of drugs. Substance abuse treatment is also a key step toward successful therapy of infectious diseases (9,242). Substance abuse treatment improves HIV treatment adherence (230,243,244), resulting in lower viral loads and lower likelihood of HIV transmission (245–247). Substance abuse treatment also facilitates the prevention of TB among persons who use drugs illicitly. Treatment of TB infection and of TB disease among persons who use drugs illicitly is more

successful when integrated with substance abuse treatment, incentives (e.g., food coupons), facilitators (e.g., tokens for transportation), and other services (3,98,248,249).

Access to Sterile Injection and Drug Preparation Equipment

Bloodborne pathogens can be transmitted easily through shared injection and drug-preparation equipment (203,250). Evidence suggests that access to sterile injection equipment can reduce transmission of these pathogens among persons who inject drugs illicitly (251). However, access to sterile needles and syringes generally is controlled by federal and state-specific laws and regulations that control their sale, distribution, and possession. In December 2011, the U.S. Congress reinstated a ban on the use of federal funds for carrying out any program that distributes sterile needles or syringes for hypodermic injection of illegal drugs.

Distribution policies for sterile injection equipment (e.g., secondary exchange or conditions and numbers of syringes provided) can allow syringe services programs to overcome operational barriers (e.g., limited locations or hours of operation) (252) and can increase access to sterile equipment for persons who inject drugs illicitly (253,254). The term “syringe services programs” was adopted by DHHS in 2010 (255,256). The term includes all services and interventions that provide sterile needles and syringes, including syringe exchange programs and nonprescription pharmacy sale of sterile needles and syringes, as well as syringe disposal. It also includes referral and linkage to programs for prevention and treatment of infectious diseases and substance use and mental disorders (255,256).

Although most states do not require a prescription to buy syringes, many states and pharmacies require customers to present personal identification or to sign for the purchase of sterile needles and syringes (83). Participation in no-cost syringe exchange programs leads to a decrease in the frequency of needle-sharing without causing an increase in the frequency of illicit use of drugs (177,257–264).

Existing evidence indicates that syringe exchange programs are effective in reducing the incidence of HIV infection (265). Syringe exchange programs reduce the risk for infection with HCV, which is the most common bloodborne pathogen among persons who inject drugs illicitly (153,266–269). Participation in a syringe exchange program was associated with reduced rates of hepatitis B and C in a case-control study in Tacoma, Washington (270). An indirect protective effect of syringe exchange programs on HCV infection through reduced injection risk behaviors was found in a study of young persons (aged 18–30 years) who inject drugs illicitly conducted in several cities (269). However, the prevalence and incidence of HCV infection remain higher among those persons than among the general population (64,271–273).

In addition to providing sterile syringes, most syringe exchange programs provide other health-related supplies and services to their clients (252,274). In 2008, more than 90% of syringe exchange programs provided male condoms, alcohol pads, and education on safer injection practices and on prevention of HIV infection, viral hepatitis, STDs, and abscesses; 87% provided HIV counseling and testing; 65% provided testing and counseling for HCV; 55% provided STD screening; 49% provided vaccination for hepatitis B; 47% provided vaccination for hepatitis A; 24% provided counseling and testing for hepatitis B; 31% provided TB screening; and 18% provided counseling and testing for hepatitis A (275).

Syringe exchange programs often provide referrals to substance abuse treatment and social services (275). Syringe exchange programs also can serve as sites for TB screening and for testing for TB infection (133,276), and they can serve as gateways to treatment for HIV or HCV infection (275,277,278). Innovative strategies and programs should be developed and tested, such as those that prevent the progression of noninjection drug use to injection drug use and those that promote safer and hygienic injection practices and facilities to prevent HIV and HCV transmission among persons who use drugs illicitly (4,37,107,153,272,273).

Interventions to Increase Condom Availability

Increasing the availability of condoms is associated with substantial reductions in HIV risk (274,279). Results of a Louisiana study on the effects of widespread condom distribution indicated that the rates of condom use increased, while the average number of sex partners over a 12-month period did not increase (274). Limited condom availability attributable to high cost, a low concentration of sale outlets in a given area, or limits on free distribution of condoms is often cited as a barrier to condom use (274). Distributing condoms free of charge at clinics, substance abuse treatment centers, jails and prisons, businesses, or other community locations (e.g., outreach and syringe services programs) can serve as a public health intervention or a supplement to existing campaigns and interventions, because prices as low as 25 cents per condom have been demonstrated to deter their use (280). Condom distribution has been demonstrated to reach a substantial segment of the population and to be cost-effective (280). In addition, condom use can reduce risk for oral and vaginal transmission of HIV, viral hepatitis, and bacterial and viral STDs among persons who use drugs illicitly (57,70,71,106,183,281–286). Because gonorrhea, chlamydia, syphilis, HSV-2, and HIV can be transmitted by oral sex, condom use also can reduce transmission of these infections through oral sex (283).

Partner Services and Contact Follow-up

Partner services begin when persons who have an infection are interviewed to obtain information about their partners in a voluntary and confidential manner. Following this step, partners are notified confidentially of their possible exposure to infection (287). Services that can be offered to infected persons and to their partners include risk-reduction counseling, testing (including partner or couple testing), hepatitis A and B vaccination, treatment or referral to medical care, and referral to other services (e.g., substance abuse treatment, social support, housing assistance, and mental health services) (287). Partner notification services for persons at risk for infections transmitted through illicit injection of drugs (e.g., HIV and HCV) are as effective in reducing transmission of these infections as are the partner notification services for infections transmitted through risky sexual behaviors (e.g., bacterial STDs) (288). Partners can be notified by their infected partners. Alternatively, they can be notified (through the use of information provided confidentially and on a voluntary basis by the infected persons) by trained health department personnel or by health-care providers. This can be done without identifying the names of the infected persons (287–289). State and local health departments provide partner notification services according to state and local regulations. Protocols for partner services include services for patients who inject drugs illicitly, engage in risky sexual behaviors, or have signs or symptoms of infections. All patients should receive treatment as well as risk-reduction counseling or be referred for counseling or other prevention interventions (287).

Venues where drugs are used illicitly (e.g., bars and crack houses) have been identified as sites of TB transmission because of factors such as close person-to-person proximity, repetitive exposure, and poor ventilation (98,290–293). Persons with TB disease who use drugs illicitly might be reluctant or unable to name other contacts who engage in illicit drug use or venues where drugs are used illicitly (291–293). The inability to generate a comprehensive list of contacts or venues can contribute to incomplete contact investigations, ongoing transmission of TB, and missed opportunities to prevent cases of TB disease. Therefore, if health-care staff members suspect that a patient with TB disease who uses drugs illicitly is not providing a complete contact list, the staff should expand the contact investigation by seeking alternative sources of information that can include the patient's social network and settings frequented by the patient (e.g., jail, homeless shelters, or venues where drugs are used illicitly).

Referrals and Linkage to Care

Persons who use drugs illicitly and who are identified to be infected with HIV, viral hepatitis, STDs, or TB should be referred and linked actively to medical care. Medical care includes

treatment for these infections as well as treatment for other health conditions that affect the lives and well-being of persons who use drugs illicitly, including treatment for substance use and mental disorders (294). Substance abuse treatment serves as a preventive intervention for HIV infection, viral hepatitis, STDs, and TB (116,126,295). Referral to and linkage with mental health services provide a supportive role for persons receiving treatment for infectious diseases and substance use disorders, including persons who are receiving treatment for hepatitis C infection, because HCV treatment regimens are associated with increased levels of depression (294,296,297).

Three approaches to referrals and linkage to care are used commonly. First, persons who use drugs illicitly are referred, following a needs assessment process, for medical treatment, care, and supportive services. Assistance with follow-up can facilitate initial contact with and linkage to appropriate service providers (18). A second approach is the "strengths-based case management approach," which calls on clients to identify internal strengths and abilities and to develop a personal plan that includes meetings with case managers to acquire needed resources (298,299). A third approach is active linking, which can include health-care visits accompanied by a linkage coordinator or case manager to ensure that clients obtain appropriate medical care. Such accompaniment is especially important for the first appointment (300,301). TB programs have been using this approach to increase adherence to treatment (302). Active linking based on the principles of a "strengths-based, intensive case management approach" has been more successful than a mere referral in getting persons with newly diagnosed HIV infection to make at least one medical care visit (298,303). Linkage-to-care approaches are effective in improving health-care outcomes; on the other hand, referral alone has not been effective in enhancing linkage and adherence to care (304,305).

Supportive strategies or incentives can be helpful in increasing adherence and linkage to care, e.g., co-location of services, deployment of outreach workers, peer navigators, monetary incentives, and motivational enhancements (306). In a multisite study, onsite linkage to buprenorphine-naloxone treatment delivered in an infectious disease clinic was demonstrated to be more effective than offsite referrals (307). Persons interacting with the criminal justice system or leaving correctional facilities (jails or prisons) can benefit particularly from active linkage to HIV medical care, TB linkage interventions, HCV medical care, STD services, substance abuse treatment, and overdose prevention programs (308–311). HIV-related strategies carried out in different venues and facilities, such as the "seek, test, treat, and retain" strategy, target persons who use drugs illicitly and help to identify those who are HIV-positive and link them to care

(312). Such strategies also can support those in the criminal justice system who need to be linked to care during and after incarceration (308,313–315).

Medical Treatment for Infectious Diseases

Persons who use drugs illicitly need to receive appropriate treatment for infectious diseases and relevant health education messages from trained personnel. An infected person who receives a diagnosis of HIV infection, viral hepatitis, STDs, or TB should be referred to care providers and receive primary medical care and evaluation for progression of infection to disease, as well as treatment. In addition, infected persons need to be provided with counseling and guidance on how to stay healthy and prevent disease progression. They also should be instructed about how to reduce the risk for transmitting their infections to others, receive encouragement to seek further medical evaluation, and, if necessary, be given information about the importance of adhering to medical treatment regimens. Most persons who use drugs illicitly are capable of adhering actively to complex medical regimens (148,316–319). Persons who use drugs illicitly and are HIV-positive are capable of adhering to HIV treatment (318,319). Antiretroviral therapy for HIV infection reduces HIV transmission (320). Therefore, past or current illicit use of drugs should not be considered a contraindication to successful treatment for infectious diseases. Treatment of infectious diseases reduces and potentially prevents transmission of infectious diseases in the communities where persons who use drugs illicitly reside (317). Sex partners and drug-using partners and contacts of infected persons should be identified and provided with prevention information, in addition to referral for medical evaluation and for treatment, if necessary.

Adherence to treatment of infectious diseases among persons who use drugs illicitly can be enhanced by addressing different comorbid conditions, including mental disorders and such other factors as poverty-related issues, including homelessness and limited access to transportation (321–323). HIV treatment is greatly improved by treatment of substance abuse (9). Among persons who use drugs illicitly and who have active TB, use of incentives and enablers to encourage clinic visits has been associated with improved treatment adherence (98,134,324,325), better doctor-patient relationships, and delivery of TB treatment in substance abuse treatment programs or methadone-maintenance programs (326). Directly observed therapy (DOT) for TB, in which the infected person receives treatment for TB infection or TB disease in the presence of a provider, and shorter treatment regimens have improved treatment adherence and completion among patients, including those who use drugs illicitly (3).

There is a potential for harmful medication interactions or toxic effects in the treatment of persons with multiple infections who inject drugs illicitly. Adverse effects of medications can include the effects of HIV antiretroviral medications on liver, kidney, and neurologic functions. Providers should consider how different antiretroviral medications or antibiotics might interact with methadone or with drugs used illicitly when selecting a medical treatment regimen for persons who inject drugs illicitly and have multiple infections (9,327,328). For example, rifampin, a first-line medication for treating TB, interacts both with methadone (for treating addiction to heroin) and with efavirenz and nevirapine (for treating HIV infection) (329,330).

Before 2002, the National Institutes of Health (NIH) considered illicit use of drugs a contraindication for HCV treatment, meaning that persons who used drugs illicitly were routinely denied medical treatment for HCV infection. In 2002, NIH issued a consensus statement that HCV treatment for persons who use drugs illicitly should be considered on a case-by-case basis (331). Since then, according to some studies, illicit use of drugs during HCV therapy has been associated with lower rates of adherence and with increased risk for reinfection (332,333) although this association has not been demonstrated consistently (334). Other studies have indicated that HCV treatment adherence among persons who use drugs illicitly was increased by use of integrated service models that included mental health and substance abuse treatment (335,336), peer-based support groups (335), and a specific version of DOT for HCV treatment (337). Persons who use drugs illicitly should be counseled to avoid alcohol and other drugs that are harmful to the liver and to seek treatment for substance use and, if necessary, for mental disorders (338).

Delivery of Integrated Prevention Services

Persons who use drugs illicitly can benefit from comprehensive (or at least combination) services that meet their individual clinical needs or community needs. They can be expected to benefit from synergy among services that are delivered jointly at the service delivery level as integrated services.

Comprehensive Interventions

The Joint United Nations Programme on HIV/AIDS (UNAIDS), the United Nations Office on Drugs and Crime (UNODC), and the World Health Organization (WHO) have endorsed nine interventions for comprehensive HIV prevention for persons who inject drugs illicitly (5). This comprehensive package includes syringe exchange programs; substance abuse treatment, including medication-assisted therapy; voluntary HIV counseling and testing; antiretroviral therapy for those who are HIV-infected; STD prevention and

treatment; condom distribution; information, education, and communication for persons who inject drugs illicitly and for their partners; hepatitis diagnosis and treatment or vaccination; and TB prevention, diagnosis, and treatment (5).

In endorsing comprehensive prevention using nine interventions for HIV prevention (also referred to as "combination prevention"), UNAIDS, UNODC, and WHO have noted that although each intervention is useful for HIV prevention and care for persons who inject drugs illicitly, the nine interventions form a package and have the greatest beneficial impact when delivered together to a person who needs them (5). Thus, comprehensive prevention can bring scientifically based behavioral, biomedical, and structural interventions to persons who use drugs illicitly (281,339) because it offers a multipronged approach for addressing complex social and public health needs (113,281,340). Decisions about the comprehensive interventions to be offered in a particular program or community need to be influenced by three factors: the local epidemiology of infectious diseases and substance use and mental disorders, the spectrum of already existing services, and the patterns of illicit drug use (5).

Integrated Services

At the service delivery level, service integration offers an opportunity to optimize the effect of comprehensive interventions. CDC defines service integration as a distinct method of service delivery that provides persons with seamless services from multiple programs or areas within programs without repeated registration procedures, waiting periods, or other administrative barriers (18). Service integration differs from system coordination, in which services from multiple agencies are provided but persons might have to visit different locations and register separately for each provider's programs to obtain these services (18). Service integration is intended to enhance the receipt of comprehensive or multiple interventions that persons who use drugs illicitly need and to target methods of service delivery, with an emphasis on co-locating services or having a single point of entry. Recently, European agencies and partners have called for targeted delivery of services to persons who inject drugs and have suggested that services should be combined, organized, and delivered according to user needs and local conditions (341).

Thus, comprehensive prevention refers to the range, content, type, and combination of interventions that persons need. Delivery and outcomes of comprehensive services for individual and public health benefits can be enhanced by following the principles of service integration at the service delivery level.

Programmatic Initiatives on Service Integration

Syringe exchange programs provide integrated preventive services for persons who use drugs illicitly (275,342). These

services include screening for HBV and HCV infections, vaccination for HAV and HBV (343), and HIV and STD testing (252). Other integrated services include integration of HIV, TB, and substance abuse treatment services (83); integration of HCV and HIV prevention services (343,344); and integration of viral hepatitis, HIV, and STD services (345). In New York State several substance abuse treatment centers have implemented a comprehensive prevention program of outreach, HIV education, counseling, testing, referral, and partner notification (343). The Massachusetts Department of Public Health has integrated its HIV, hepatitis, and addiction services (346). San Diego offers an integrated program of hepatitis, STD, and HIV prevention services (347).

Programmatic evidence supports the need for providing comprehensive or integrated services for persons who use drugs illicitly (113,339,348–352). Other integrated guidelines emphasize the importance of integrated services for optimizing prevention of and treatment of HIV infection, viral hepatitis, STDs, and TB (18,148,353,354).

Evaluation and Research Initiatives on Integration

The scientific evidence is increasing for development, implementation, and evaluation of projects that focus on program collaboration and service integration (349,350,354–356). For example, description of the process of implementing integrated services provides rich information on the feasibility and benefits of this effort (132,214,335,336,342–345,347,357–365). Studies that examined outcomes of integrated services show a decrease in high-risk behaviors; an increase in testing for HIV infection, viral hepatitis, STDs, or TB; an increase in prevention and treatment services; and better adherence to prevention and treatment regimens (340,356,366–369). Economic analyses demonstrate the cost or cost-effectiveness of integrated services (346,347,370–372).

The scientific evidence is largely built on observational studies and demonstration projects. These studies and projects provide sufficient evidence for implementing and evaluating the effectiveness of integrated prevention services (132,214,335,336,340,342–345,347,356–372).

Future Research and Allocation Approaches

New research studies and demonstration projects, including quasi-experimental studies (373,374) and cost-effectiveness studies, would add to the evidence base for integrated services. Such new initiatives would provide a basis for estimating the specific effect of integrated services relative to other concurrent public health services (e.g., comprehensive but not integrated

services, limited integrated services vs. expanded integrated services) and would control for possible confounders (e.g., changes in drug use, injection use, sexual risk behaviors, the drug market, reimbursement mechanisms, funding opportunities).

It is also relevant to identify whether there are certain subpopulations of persons who use drugs illicitly (e.g., younger persons, racial and ethnic minority persons) who need or who would benefit from integrated services more than other subpopulations. To strengthen the evidence-base for integrated services, conducting systematic reviews or a meta-analysis of the effects of integrated services and grading the evidence will be relevant (110,375–379). Meta-analyses of observational studies of public health programs can provide useful information, because although randomized controlled trials have their advantages, they might still have weaknesses in terms of their implementation and analysis or their application to public health programs (380,381).

Mathematical modeling, as well as spatiotemporal epidemiology methods, can inform public health decision making (382,383). The Bradford Hill criteria and other methods for assessing causality remain relevant for evaluation of integrated services (384–387). Clinical and health outcomes can be enhanced by population-specific funding streams and allocation of resources for programs for persons who use drugs illicitly or for integrated services for this population. Tracking the monetary resources allocated for this population, as well as the resources devoted to integrated services for this population can enhance delivery of integrated programs and can be useful in evaluating the cost-effectiveness of integrated services.

Examples of Integrated Services in Particular Settings

Many settings, including primary care settings, are important venues for providing integrated services. Examples of integrated services that are based on recommendations and guidelines of science-based public health strategies for prevention and treatment of infectious diseases for persons who use drugs illicitly, as summarized in this guidance, have been provided (Table). By definition, services that are infection-specific or disorder-specific are nonintegrated services and are not represented in tabular form. Recommended science-based public health strategies that health-care providers and public health providers can implement to reduce the risk for HIV infection, viral hepatitis, STDs, and TB among persons who use drugs illicitly have been summarized (Box 5), and a list of recommendations and guidelines in which these strategies are outlined is provided (Appendix B).

Recommendations and Reports

TABLE. Examples of integrated prevention services that can be delivered in different settings to persons who use drugs illicitly and examples of monitoring and evaluation indicators

STD clinical setting	TB clinical setting	Correctional institution	HIV clinical setting	Setting for treatment of substance use disorders	Setting for treatment of mental disorders
Examples of integrated prevention services					
Unless already known to be HIV-positive, all patients seeking treatment for STDs screened routinely for HIV infection during each visit for a new concern, regardless of whether the patient is known or suspected to have specific risk behaviors for HIV infection	All patients who have confirmed or suspected TB screened for HIV infection Referrals to care for HIV-positive persons documented and tracked Access or referral to services for sterile drug injection or clean preparation equipment and education on prevention of overdose	Routine HIV testing, TB screening, and vaccination for viral hepatitis A and B Screening of young women in jails and juvenile detention centers for gonorrhea and chlamydia HCV testing conducted	TB, syphilis, chlamydia, and gonorrhea screening conducted for newly diagnosed HIV-positive persons HBV immunization and HCV testing for all patients Ongoing, routine assessment of risk behaviors and at least annual screening for syphilis and other STDs	Routine HIV testing, TB screening, and vaccination for viral hepatitis A and B provided or via coordinated referral HCV testing provided or via coordinated referral HIV-infected patients referred to HIV clinical services during and after treatment for substance abuse and progress of HIV/AIDS status tracked	Routine HIV testing, TB screening, and vaccination for viral hepatitis A and B (HAV/HBV) provided or via coordinated referral HCV testing provided or via coordinated referral HIV-infected patients referred to HIV clinical services, during and after treatment for mental disorders and progress of HIV/AIDS status tracked
STD clinics routinely offer HBV vaccination as recommended to patients	Comprehensive HIV, STD, and viral hepatitis prevention services, as well as assessment services for reproductive health, drug use, alcohol misuse, and mental health	Access to sterile drug injection or clean preparation equipment and condoms	Partner services for HIV-positive persons	Chlamydia and gonorrhea urine-based screening at intake for all patients	Chlamydia and gonorrhea urine-based screening at intake for all patients
Referrals to care for HIV-positive persons documented and tracked	Case management for housing and for prevention and treatment of drug use, alcohol misuse, and mental health disorders	Education on prevention of overdose	Access to sterile drug injection or clean preparation equipment and condoms	Syphilis screening for patients at intake per local epidemiologic data	Syphilis screening for patients at intake per local epidemiologic data
Partner services offered to HIV-positive persons	Persons addicted to opiates offered medication-assisted therapy while incarcerated or via referral at discharge	Education on prevention of overdose	Education on prevention of overdose	Access to sterile drug injection or clean preparation equipment and condoms	Access to sterile drug injection or clean preparation equipment and condoms
Access to sterile drug preparation equipment and condoms	Persons who inject drugs referred for substance abuse treatment including medication assisted therapy	Comprehensive health risk assessment services for TB, HIV, STDs, and viral hepatitis as well as counseling for reproductive health, drug use, alcohol misuse, and mental health disorders	Comprehensive health risk assessment services for TB, STDs, and viral hepatitis as well as partner services and behavioral health interventions for reproductive health, drug use, alcohol misuse, and mental health disorders	Education on prevention of overdose	Education on prevention of overdose
Education on prevention of overdose	Case management for housing/drug/alcohol/mental health services and discharge planning to inmates for appropriate follow-up care in the community	Routine screening for syphilis, chlamydia, and gonorrhea		Persons at high risk recruited and referred to STD/HIV prevention behavioral health interventions	Persons at high risk recruited and referred to STD/HIV prevention behavioral health interventions
Persons at high risk recruited and referred to HIV prevention behavioral health interventions				Routine screening for syphilis, chlamydia, and gonorrhea	Routine screening for syphilis, chlamydia, and gonorrhea
Persons who inject drugs referred for substance abuse treatment including medication-assisted therapy					
Examples of monitoring and evaluation indicators					
% of persons treated for an STD who are tested for HIV infection	% of persons treated for TB who are tested for HIV infection	% of inmates screened for infection with HIV, TB, and viral hepatitis	% of HIV-positive persons who are screened for TB, syphilis, chlamydia, or gonorrhea	% of persons screened for HIV infection, TB, gonorrhea, chlamydia, and viral hepatitis	% of persons screened for HIV infection, TB, gonorrhea, chlamydia, and viral hepatitis
% of eligible persons receiving HBV vaccination	% of persons with newly diagnosed HIV/TB co-infection who are referred and linked to quality HIV care	No. of inmates diagnosed with syphilis, chlamydia, or gonorrhea	% of HIV-positive persons offered partner services	% and no. of patients diagnosed with syphilis, chlamydia, or gonorrhea	% and no. of patients diagnosed with syphilis, chlamydia, or gonorrhea
% of persons at high risk for HIV infection who are enrolled in HIV behavioral health interventions	% of homeless persons being treated for TB who receive case management for social services	% of inmates receiving HAV/ HBV vaccination	% of high-risk persons who have TB, STD, or viral hepatitis infection	% of tested persons who test positive for HIV, TB, or viral hepatitis	% of tested persons who test positive for HIV, TB, or viral hepatitis
		% of tested inmates who test positive for HIV, TB, or viral hepatitis		% of persons receiving HAV/ HBV vaccination	% of persons receiving HAV/ HBV vaccination
		% of inmates with diagnosed HIV infection, syphilis, chlamydia, gonorrhea, TB, or viral hepatitis who receive comprehensive discharge planning and continued care		No. of persons determined to have TB, STDs, or viral hepatitis	No. of persons determined to have TB, STDs, or viral hepatitis

Abbreviations: HAV = hepatitis A virus; HBV = hepatitis B virus; HIV = human immunodeficiency virus; STD = sexually transmitted disease; TB = tuberculosis.

Special Considerations for Prevention and Control of Infectious Diseases

Several factors are integral to the success of prevention of HIV infection, viral hepatitis, STDs, and TB among persons who use drugs illicitly. These factors include understanding how contextual factors, mental health needs, and fear of criminalization or stigmatization, can affect prevention and treatment efforts, and how effective patient-provider relations and communication can help ensure that the needs of persons who use drugs illicitly are met.

Contextual Factors

The general environment, with its different influencing factors (e.g., laws, policies, social factors) and different levels of influence (e.g., macro and micro), affects risk behaviors and transmission of HIV infection, viral hepatitis, STD, and TB (10,388–390). Contextual factors influence differentially the exposure of majority and minority racial and ethnic groups to risky environments, risk-reduction interventions, and access to prevention and treatment services (335,391–394). As an example, the nature of a neighborhood influences risk behaviors (391,392). Black persons who use drugs illicitly have been more likely to be arrested and to receive longer sentences (10,27). Spatial or geographic access to pharmacies that sell syringes over the counter has been lower in areas that have lower proportions of non-Hispanic whites (84). Laws that inadvertently make pregnant drug-using women reluctant to seek prenatal care because of fear of incarceration or fear of losing the newborn child to foster care and prevention programs that do not offer training or services in drug overdose prevention can have a negative impact on the health and well-being of persons who use drugs illicitly (84,88,275,395).

Persons who use drugs illicitly often live in unstable housing or experience periods of homelessness. Their lives are complicated by other factors, such as poverty, unemployment, lack of social support, and discrimination because of prior incarceration. Their health status is often poor because of inconsistent health care, poor nutrition, lack of health insurance, and interruptions in care due to incarceration and loss to follow-up after incarceration (13,396). Long waiting periods during appointments for medical care and the need for repeat visits to receive HAV and HBV vaccinations, HIV and HCV treatment, and test results for infectious diseases are often barriers to receipt of prevention and treatment services (397–402). Providing prevention and treatment services in convenient locations and at convenient times reduces the need for repeat visits and can increase the likelihood of obtaining necessary services (403,404). Providing

BOX 5. Science-based public health strategies for persons who use drugs illicitly to reduce human immunodeficiency virus (HIV) infection, viral hepatitis, sexually transmitted diseases (STDs), and tuberculosis (TB)

- Recommend services for prevention and treatment of substance use and mental disorders.
- Provide information or training in overdose prevention.
- Refer to outreach workers.
- Assess risk for illicit use of drugs.
- Assess risk for HIV infection, viral hepatitis, STDs, and TB.
- Screen for HIV, viral hepatitis, STDs, and TB.
- Provide prevention counseling for HIV infection, viral hepatitis, STDs, and TB.
- Vaccinate against hepatitis A and B and human papillomavirus, as recommended.
- Recommend or offer services for prevention of mother-to-child transmission of infectious diseases.
- Provide information on risk-reduction of high-risk behaviors.
- Provide health education and risk-reduction interventions and programs.
 - Provide substance abuse treatment, including medication-assisted therapy.
 - Provide access to new, sterile needles and to clean drug preparation equipment.
 - Provide access to condoms.
- Provide partner services and contact follow-up.
- Provide public health and medical services to those who test positive for HIV infection, viral hepatitis, STDs, and TB.
- Provide referral and linkage to treatment and care.
- Offer treatment adherence counseling.
- Provide information about interactions of medications and drugs.
- Implement integrated services.
- Address social needs, as feasible.

Sources: See Appendix B for a list of recommendations and guidelines that outline these public health strategies.

treatment for HIV infection, viral hepatitis, STDs, and TB is in itself a preventive intervention that reduces the risk for transmitting infection to others who live in the same high-risk environments or engage in similar risk behaviors. Coordination with public agencies (e.g., Medicaid services and state AIDS drug assistance programs) that provide or reimburse for health care can mitigate barriers associated with cost of care (405).

Mental Health Needs

Persons with substance use disorders are at elevated risk for depression, anxiety, and severe mental illness, compared with persons who do not have substance use disorders (15). At least in part, persons might use drugs illicitly and drink alcohol in excess to self-treat pre-existing or concurrent mental disorders (406,407). Persons with HIV infection who use drugs illicitly often live in socially and economically disadvantaged communities characterized by a high prevalence of psychosocial problems (408). Similarly, depressive symptoms are highly prevalent among HCV-infected persons who use drugs illicitly (409,410). Persons who use drugs illicitly and have depressive symptoms are less likely to be tested for HIV infection than are persons who use drugs illicitly and do not have such symptoms (399). Mental health disorders often hinder persons who use drugs illicitly from receiving health-care services, and such disorders can be a barrier to eligibility for treatment. For example, uncontrolled depression is a contraindication for starting HCV antiviral treatment; thus, screening for and treating depression are prerequisites for providing HCV treatment to HCV-infected persons who use drugs illicitly (338). Providers of mental health services have an important role in substance abuse treatment and clinical HCV treatment.

Fear of Criminalization or Stigmatization

The fear of being arrested because of illicit drug use can prevent persons who use drugs illicitly from seeking prevention services for HIV infection, viral hepatitis, STDs, or TB (248,411). They might fear that interacting with health authorities, prevention providers, or substance abuse treatment programs will lead to arrest or prosecution (253,412). Thus, while the intent of the laws is to reduce illicit drug use, the laws also might unintentionally reduce use of prevention and treatment services by persons who use drugs illicitly.

Perceptions held by peers of persons who use drugs illicitly might stigmatize the use of prevention and treatment services (413–415). For example, persons who inject drugs illicitly might be deterred from participating in syringe services programs for fear of stigmatization (416). Persons who use drugs illicitly cite fear of social discrimination as a reason for not getting tested for HIV infection (417). They often are marginalized socially and estranged from their families; consequently, they might fear being dually stigmatized as having HIV infection or another disease. Because of these fears, persons who use drugs illicitly might have concerns about confidentiality when visiting medical providers or using prevention or treatment services. Community-based organizations, health-care providers, and law enforcement staff should work together to ensure that persons who use prevention services are treated according to ethical principles and human rights considerations, that confidential and identifying information are protected, and that no unintended harm is done (109,418–420).

Patient-Provider Relations and Communication

How persons who use drugs illicitly and health-care providers perceive each other can be a barrier to a person's receipt of services. Persons who use drugs illicitly have reported avoiding screening or counseling and testing because they perceive health-care providers to be uncaring, indifferent, or unfamiliar with treating patients with substance use disorders (399,403,411). Tension in the client-provider relationship can result from the patient's perception that the provider cares more about the disease than about the person with the disease, often making persons who use drugs illicitly feel unacknowledged (421). They might also feel that providers have not given them sufficient information on the effectiveness, complexity, and side effects of medical treatment regimens (422).

Health-care providers might have negative perceptions of persons who use drugs illicitly (332,400,411). For example, HIV and HCV treatment providers might perceive persons who use drugs illicitly as not likely to adhere to treatment regimens or to keep appointments (393,396,423). Such perceptions have led to decreased initiation of medical care by persons who use drugs illicitly (402). In spite of such perceptions, however, health-care providers can be poor predictors of patients' treatment adherence (424); a number of studies have shown that persons who use drugs illicitly have adhered to medical treatment regimens, particularly when special considerations and incentives were provided (243,318,425–427). Researchers have formulated 13 principles for managing health-care relationships with users of heroin and cocaine (332,428). Although these principles were developed specifically for HCV treatment, they can be used for treating other medical conditions, including HIV infection (203,332,428; Box 6).

In addition to ensuring conditions for successful delivery of services for persons who use drugs illicitly, administrative directors and decision makers at local venues providing services to this population need to be cognizant of relevant programmatic considerations. These considerations have been summarized (Box 7).

Practical Aspects of Delivery of Integrated Prevention Services

Overview

Many public health systems have separate organizational structures and programs for the delivery of prevention and treatment services for HIV infection, viral hepatitis, STDs, and TB. These structures and programs often operate separately from substance abuse treatment centers or mental health services, with separate funding streams, management structures, and operating procedures. Integrated prevention

BOX 6. Principles for managing health-care relationships between providers and persons who use drugs illicitly

- Develop a professional relationship that shows mutual respect and avoids blame or judgment.
- Educate persons who use drugs illicitly about health care and how to advocate for their own health.
- Include persons who use drugs illicitly in decisions about their treatment.
- Establish, where practical and affordable, a multidisciplinary case-management team.
- Have a primary care provider be responsible for coordinating care.
- Develop an understanding about the responsibilities of persons who use drugs illicitly and their service providers.
- Respond to behaviors that run against agreed-upon expectations or limits.
- Reduce barriers to accessing health care.
- Establish realistic healthful behavior goals to which persons who use drugs illicitly can commit.
- Emphasize the importance of risk reduction measures.
- Recognize that success in building relationships and healthful behaviors might require several attempts.
- Learn about local health service resources for persons who use drugs illicitly.
- Avoid common pitfalls in treating persons who use drugs illicitly (e.g., having unrealistic expectations, becoming frustrated or angry, moralizing, assigning blame, and withholding therapy).

Sources: Des Jarlais DC, Semaan S. HIV prevention for injecting drug users: the first 25 years and counting. *Psychosom Med* 2008;70:606-11; Edlin BR, Kresina TF, Raymond DB, et al. Overcoming barriers to prevention, care, and treatment of hepatitis C in illicit drug users. *Clin Infect Dis* 2005;40(Suppl 5):S276-85; Edlin BR. Hepatitis C prevention and treatment for substance users in the United States: acknowledging the elephant in the living room. *Int J Drug Policy* 2004;15:81-91.

implies service coordination to ensure delivery and receipt of prevention services (e.g., screening, testing, prevention counseling) for two or more infections or health conditions during a single visit at a venue (336,361). The need for holistic services is particularly great for persons who use drugs illicitly because of increased risk among these persons for having or acquiring multiple infections and health conditions. Delivery of integrated prevention services can help with this need (385) because it can improve the efficiency and the quality of services provided, maximize opportunities for comprehensive services, and reduce service duplication and procurement and distribution costs (148,346).

BOX 7. Programmatic considerations for providers of public health programs to reduce infectious diseases in persons who use drugs illicitly*

- Have knowledge of local syndemics.[†]
- Build partnerships (e.g., with patients, other public services).
- Provide recommended science-based comprehensive services.
- Establish stronger linkages to prevention and care services.
- Deliver integrated services, as relevant and feasible.

*This box provides considerations as recommended in this report.

[†]Syndemics refer to the synergistic interaction of two or more coexistent diseases and to the resultant excess-burden of disease. Source: Singer M, Clair S. Syndemics and public health: reconceptualizing disease in bio-social context. *Med Anthropol Q* 2003;17:423-41.

Referrals, based on the needs of persons who use drugs illicitly, can be made for treatment, care, and supportive services and can include necessary assistance to facilitate initial and follow-up contact with appropriate service providers. Referrals to other service providers through a coordinated referral system represent a useful approach that can improve service provision. Providing treatment for HIV infection, viral hepatitis, STDs, and TB should be facilitated as interventions for preventing transmission of these diseases. Where feasible, treatment for substance use and mental disorders needs to be integrated with prevention and treatment services for HIV infection, viral hepatitis, STDs, and TB, thereby reducing barriers to care associated with illicit use of drugs.

Factors influencing integration of prevention services include separate, often categorical programs (362); program differences in approaches to service delivery; a lack of staff training in implementing integrated services (132,351); program resistance to integration because of fear that it will lower the quality of core services (148,360,362); and providers' resistance to providing prevention services for additional infectious diseases or health conditions, because of concerns about demands on staff and staff burnout (344,351,362,368). Success in reducing these barriers can be rewarded by efficiencies gained through integration of prevention services and improvement in clinical and public health outcomes for persons who use drugs illicitly (367).

Although maximizing opportunities for providing comprehensive services might be ideal, service integration might not be achievable in every setting because it is dependent on local needs and because of funding, organizational, or policy constraints (214). Providing prevention services for HIV infection, viral hepatitis, STDs, and TB for persons who use drugs illicitly, including treatment for substance use and mental disorders, requires coordinated and

collaborative planning approaches, an integrated service delivery plan, and a plan for monitoring and evaluating integrated service delivery (9,352,359,429). An overview of the key practical components necessary for implementing integrated services is provided (Figure 1).

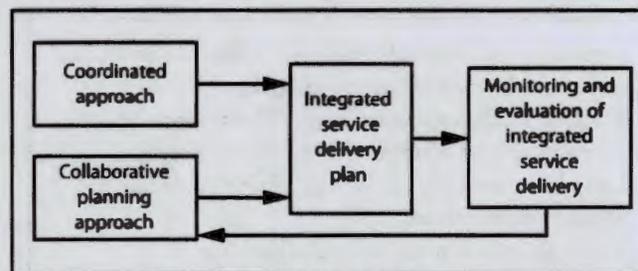
Coordinated and Collaborative Planning Approaches

Health officials who aim to improve delivery of integrated prevention services for persons who use drugs illicitly need to use the best available evidence to understand the local needs regarding services for HIV infection, viral hepatitis, STDs, and TB for this population. They also need to consider the extent to which integrated services are offered and the collaborations that are in place to prevent and reduce infectious diseases, as well as substance use and mental disorders. Relevant settings for integrated services include those that interact with or serve persons who use drugs illicitly, such as outreach programs; syringe services programs; public health clinics; jails, prisons, and juvenile detention centers; and substance use and mental disorders treatment centers.

In general, collaborative planning for service integration requires a high-level coordinating body composed of key staff with expertise in designing, implementing, and managing service delivery for HIV infection, viral hepatitis, STDs, and TB. The composition and authority of the coordinating body are locally determined, and need to be endorsed officially at the highest level possible to enable it to leverage resources and identify or develop policies that support integrated prevention services. Because service integration requires commitment and communication among the agencies whose services are to be integrated, the coordinating body needs to include leaders from these agencies. The coordinating body needs to also include representation from community-based organizations that provide prevention services and representation from the community of persons who use drugs illicitly.

Although strategies for limited service integration might be implemented with existing resources, extensive integration might require additional investments. Cost-sharing among programs might be one way to facilitate collaboration and integration among programs that agree to integrate their services; another way to facilitate such collaboration and integration might include providing free test kits or vaccines through grants and other initiatives (21). The coordinating body also can work to reduce the stigmatization of persons who use drugs illicitly, a factor that often leads to reluctance to fund programs designed to help this population. Ensuring that participating programs are reimbursed adequately and ethically for their cooperation in any plan for integrated services is

FIGURE 1. Key practical components recommended to implement integrated services*



* This figure displays components of integrated services as recommended in this report.

essential (1,343,430). Guidance from state and regional public health officials might be required for implementing integrated services at the local and agency levels; the particulars are best determined locally.

Integrated Service Delivery Plan

The coordinating body needs to develop a mutually beneficial plan across programs. The plan needs to clarify the specific opportunities for collaboration and integration, to use this information to reduce operational barriers, and to outline the specific steps for delivery of integrated services. When developing the plan, the coordinating body needs to evaluate the strengths and weaknesses of the various programs that might be involved in planning and delivering integrated prevention services.

The plan needs to describe how services are currently provided and whether an integrated approach would be an improvement over a single infection- or disease-specific approach. The plan also needs to describe needed changes in policies, procedures, and methods of service delivery; additional training required for staff; and strategies to monitor and evaluate integrated service delivery (70,148).

The coordinating body needs to ensure that the proposed plan does not adversely affect the delivery of services or the mission of the program, meets the public health needs of persons who use drugs illicitly, is acceptable to providers and clients, and is consistent with state and local laws and policies. The plan must ensure that core program activities are sustained and are based on a realistic assessment of each program's capacity for collaboration or integration. The service plan needs to include clear guidance for implementing public health strategies in a coordinated approach. On the basis of available resources, the plan needs to indicate whether specific prevention services are to be provided on-site by cross-trained staff or by providers at other sites to whom those in need of these services are referred through a clearly defined referral and linkage-to-care system. The plan also needs to define the roles and responsibilities of all service providers, ensure that they

are trained appropriately, and clarify lines of communication among venues or programs participating in the proposed delivery of integrated prevention services. The plan needs to specify how confidentiality will be maintained and how client information (e.g., risk assessment, test results, vaccination histories) will be shared among service providers.

The plan also needs to specify the needs for staff training. Whether prevention services are provided in a single or in a coordinated fashion between multiple locations or services, providers might need training in the screening, diagnosis, treatment, and prevention of other related infectious diseases, along with training about issues related to co-infection. Studies have demonstrated that training is essential to integrating services in prevention and treatment settings for substance use and mental disorders (132,351,368). One example of successful cross-training programs for service providers is a hepatitis training program that SAMHSA developed and provided to more than 150 substance abuse treatment programs (21), including training modules on the delivery of hepatitis services to persons who use drugs illicitly in New York City (343). Training in the prevention of multiple conditions can be provided either by expanding an established training program for the treatment of a single infection or disease or by providing separate but coordinated training in the prevention or treatment of each infection or disease (362). Moreover, training in the provision of integrated service delivery should continue after services have been integrated (431).

In addition to cross-training, service providers might need training that is specific to working with persons who use drugs illicitly. Training sessions should address how illicit use of drugs affects persons' lives and how to be sensitive to the stigma and discrimination related to illicit use of drugs and infectious diseases. Improved sensitivity and understanding among service providers about prevention needs might help improve patient-provider relations and reduce barriers to service recipients when they discuss illicit use of drugs with service providers.

Monitoring and Evaluation of Integrated Service Delivery

Monitoring and evaluation have been defined as systematic and rigorous applications of scientific qualitative and quantitative methods to assess the design, implementation, and outcomes of programs (432,433). Monitoring and evaluation projects frequently require such resources as evaluator expertise, staff, time, and a sizeable budget (432). Relevant frameworks and publications can assist in developing and conducting monitoring and evaluation of integrated services (432,434-437). Three tiers of evaluation questions (Are the right things being done? Are they being done right? Are they being done on a large enough scale?) also can be used to determine what is being done, ensure

that enough persons benefit from the program, and achieve the intended outcomes and impact (436). Thus, monitoring and evaluation projects of integrated services can focus on reductions in new infections resulting from service integration, as well as on other health outcomes, such as changes in mortality rates. Pertinent monitoring and evaluation questions of integrated service delivery programs can assess the extent to which these programs identify comorbid infections and diseases, provide relevant prevention and treatment services, and prevent and treat comorbid infections and diseases. An overview of integrated prevention services that can be delivered in multiple settings and in an integrated fashion has been provided (Table).

Other aspects of monitoring and evaluation include those that assess integration strategies (e.g., coordinating groups, co-location of services, pooled funding, cross-training of staff). An organizational index can measure operating costs and can provide an objective structured method to evaluate the organizational process associated with program collaboration and system integration (355).

Monitoring and evaluation activities can benefit from cost-effectiveness analysis that compares the relative costs and outcomes of two or more programs (438). Cost-effectiveness of a program typically is expressed as an incremental cost-effectiveness ratio, i.e., the ratio of change in costs to the change in the outcomes (e.g., years of life gained, number of infections averted, and quality-adjusted life years saved) (439,440). Cost-effectiveness analysis can be useful in comparing similar outcomes of different programs (e.g., integrated vs. nonintegrated programs, limited integrated programs vs. expanded integrated programs). Programs are considered cost-saving when the program implementation cost is less than the health care costs avoided by the program. For example, if an integrated program incurs \$10,000 for screening and treatment costs and avoids \$20,000 in future treatment cost, the program is cost-saving. The program can still be considered to be cost-effective even if it does not avert enough sequelae cost to be cost-saving. A program that has a net cost (program cost minus averted sequelae cost) that is lower than the threshold cost being used per case of infection averted might be considered cost-effective, compared to another program, even if it is more expensive, if it prevented more cases (441,442). When calculating the costs and benefits of integrated service programs, researchers and program planners need to define the perspective of interest (e.g., a specific program, a community-based organization, the entire health care system, or society as a whole). The perspective determines the costs and benefits to be included in the calculations. For example, a societal perspective cost-effectiveness analysis includes all costs and benefits associated with a program, whereas a health care-system perspective cost-effectiveness analysis includes direct medical costs but excludes costs borne solely by patients (e.g., transportation and lost productivity). Economic analysis

can be considered with other factors (e.g., population prevalence and disease prevention goals) in implementing and evaluating integrated services.

From a practical perspective, a monitoring and evaluation plan that discusses and depicts the relationship between implementation and outcomes can guide monitoring and evaluation activities. The plan specifies the goals and objectives of the program and it can be used to develop a conceptual framework that links the input, activities, output, outcomes, and impact of integrated services. An example of how to lay out these components is provided (Figure 2). The plan also can establish realistic expectations for the monitoring and evaluation activities. In addition, monitoring and evaluation plans need to describe in sufficient detail how to evaluate the process, outcomes, and effectiveness, including cost-effectiveness of service integration. Local stakeholders need to be involved in developing monitoring and evaluation plans and in setting goals for improving the delivery and effectiveness of integrated prevention services (368). Monitoring and evaluation activities can be supported by data systems that track services and client data. Data collected for each activity before services are integrated can be used as baseline measures of prevention services, and changes in those measures can be used to assess the effectiveness of service integration. In addition, there is a need to define and to monitor routinely indicators for delivery of new services that are provided as a result of implementing integrated services (Table), including indicators of clients' perspectives and satisfaction. Surveys of persons who use drugs illicitly can assess during the planning phase their opinions about the feasibility of proposed integrated services, and, as part of process evaluations, the extent to which integrated prevention services are implemented as planned. Surveys of frontline service providers can assess during the planning phase their opinions about the feasibility of various proposed integrated services, and as part of process evaluations, the extent to which integration prevention activities are implemented as planned.

Surveillance data for HIV infection, viral hepatitis, STDs, or TB can be examined jointly so that health officials can analyze trends in disease prevalence and co-infection. Joint examination of surveillance data might include reviewing or publishing data on similar variables from the separate surveillance systems (443,444), collecting and analyzing data on a standardized set of variables, and integrating discrete surveillance systems into a single entity.

Sharing surveillance information across jurisdictions can be complicated by political, legislative, or regulatory issues. The sharing of combined data on multiple infectious diseases must be consistent with data confidentiality standards for each disease. For example, when HCV data are incorporated into an existing HIV data system (445), the data should be treated

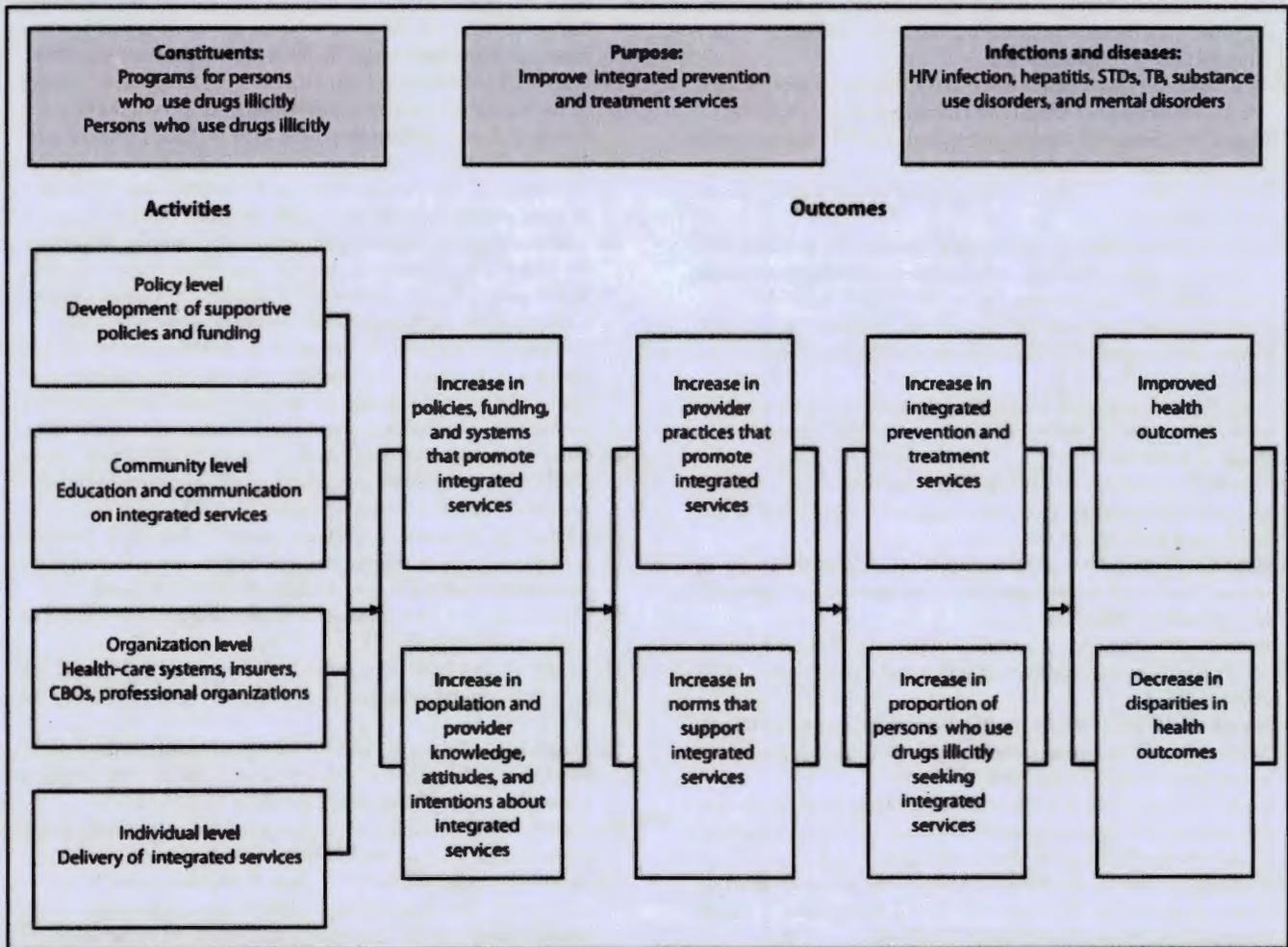
with the same strict security and confidentiality protections required for all U.S. HIV surveillance data (446,447).

Conclusion

This guidance is intended to support the efforts of agencies, programs, and providers to implement science-based public health strategies for integrated prevention services at venues that serve persons who use drugs illicitly. It summarizes multiple current (as of 2011) guidelines or recommendations for the prevention and control of HIV infection, viral hepatitis, STDs, and TB for persons who use drugs illicitly and provides a summary of published scientific and programmatic literature. An integrated approach to service delivery for persons who use drugs illicitly need to incorporate recommended science-based public health strategies. The 12 science-based public health strategies are as follows: 1) prevention and treatment of substance use and mental disorders; 2) outreach programs; 3) risk assessment for illicit use of drugs; 4) risk assessment for HIV infection, viral hepatitis, STDs, and TB; 5) screening, diagnosis, and counseling for HIV infection, viral hepatitis, STDs, and TB; 6) vaccination; 7) prevention of mother-to-child transmission of HIV infection, viral hepatitis, and STDs; 8) interventions for reduction of risk behaviors; 9) partner services and contact follow-up; 10) referrals and linkage to care; 11) medical treatment for HIV infection, viral hepatitis, STDs, and TB; and 12) delivery of integrated prevention services.

The integration of prevention services must make epidemiologic and programmatic sense, and it should be contextually appropriate and consistent with state and local laws and policies. All persons who use drugs illicitly are not at equal risk for HIV infection, viral hepatitis, STDs, or TB, and service integration is not feasible in all settings. However, opportunities exist to improve prevention services and eliminate duplication of health services. Program collaboration and service integration can provide persons who use drugs illicitly with increased access to services, improve the timeliness of service delivery, and increase the effectiveness of efforts to prevent infectious diseases that share common risk factors, behaviors, and social determinants. Collaborative planning at the local level with a coordinating body is needed to develop plans across programs to reduce operational barriers and to clarify delivery of integrated services. Feasibility studies and monitoring and evaluation studies can ensure the success of integrated services delivered to prevent and reduce HIV infection, viral hepatitis, STDs, and TB, as well as to prevent and treat substance use and mental disorders among persons who use drugs illicitly. Consolidated recommendations and guidelines of science-based public health strategies as summarized in this guidance can have synergistic effects in enhancing efforts of health-care providers and public health providers to optimize

FIGURE 2. Simplified logic model recommended to monitor and evaluate integrated services for persons who use drugs illicitly*



Abbreviations: HIV = human immunodeficiency virus; STDs = sexually transmitted diseases; TB = tuberculosis; CBOs = community-based organizations.
* This figure summarizes the process recommended in this report.

prevention and treatment, use resources efficiently, and improve health outcomes in persons who use drugs illicitly.

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Appendix A

Search and Evidence Acquisition for the Guidance

The National Guideline Clearinghouse database was searched for current recommendations and guidelines using the keyword combinations:

- (substance abusers OR drug users) AND (HIV prevention)
- (substance abusers OR drug users) AND (Tuberculosis prevention OR TB prevention)
- (substance abusers OR drug users) AND (sexually transmitted diseases prevention OR STDs prevention)
- (substance abusers OR drug users) AND (Hepatitis C prevention OR viral hepatitis prevention)
- (substance abusers OR drug users) AND (mental disorders prevention)

The MEDLINE_OVID search for the literature on integration was broken down into three sections each with MeSH and key words: disease or treatment (HIV, STD, TB, substance abuse, and mental disorder), drug use, integration (index term delivery of health care, integrated)

Disease or treatment

1. HIV Infections/
2. HIV infection\$.ti,ab
3. HIV infected.ti,ab
4. Sexually Transmitted Diseases/
5. Sexually Transmitted Diseases, Bacterial/
6. Sexually Transmitted Diseases, Viral/
7. Std\$.ti,ab
8. Sexually transmitted disease\$.ti,ab
9. Hepatitis, Viral, Human/
10. Hepatitis C/
11. Hepatitis B/
12. HVC.ti,ab
13. Hepatitis.ti,ab
14. Tuberculosis/
15. TB.ti,ab
16. Substance abuse Treatment Centers/
17. (Substance or drug\$) adj2 (treat\$).ti,ab
18. OR/1-17

Drug use

19. Substance Abuse, Intravenous/
20. Heroin Dependence/
21. Cocaine Related Disorders/
22. Opioid-Related Disorders/
23. Substance Related Disorders/
24. Drug User/
25. ((cocaine or heroin or crack or meth or opioid or inject\$ methamphetamine or drug or substance) adj2 (abus\$ OR addict\$ OR use\$ or dependence)).ti,ab
26. (idu or idus or ivdu or ivdus).ti,ab.
27. OR/19-26

Integration

28. Delivery of Health Care, Integrated/
29. Integrat\$.ti,ab
30. OR/28-29
31. 18, 27, and 30
32. Limit to 2000-2011

NOTE: No other limits applied.

Abbreviations: / = index term; ti = title; ab = abstract.

Appendix B

Recommendations and Guidelines

- CDC. Program collaboration and service integration: enhancing the prevention and control of HIV/AIDS, viral hepatitis, sexually transmitted diseases, and tuberculosis in the United States. Atlanta, GA: US Department of Health and Human Services, CDC; 2009. Available at http://www.cdc.gov/nchhstp/programintegration/docs/207181-C_NCHHSTP_PCSI%20WhitePaper-508c.pdf.
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Recommendations and Reports

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Tab 42

Federal Register of August 7, 2013
(78 FR 48177)

Dated: August 2, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-19051 Filed 8-6-13; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-0883]

Purdue Pharma L.P.; Withdrawal of Approval of a New Drug Application for Oxycontin

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of a new drug application (NDA) for OXYCONTIN (oxycodone hydrochloride) Extended-Release Tablets, held by Purdue Pharma L.P. (Purdue), One Stamford Forum, Stamford, CT 06901-3431. Purdue has voluntarily requested that approval of this application (NDA 20-553) be withdrawn and has waived its opportunity for a hearing.

DATES: Effective August 7, 2013.

FOR FURTHER INFORMATION CONTACT: Patrick Raulerson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6368, Silver Spring, MD 20993-0002, 301-796-3522.

SUPPLEMENTARY INFORMATION: FDA approved NDA 20-553 for OXYCONTIN (oxycodone hydrochloride) Extended-Release Tablets, 10 milligrams (mg), 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg, (original OxyContin), on December 12, 1995. A reformulated version of these products, OXYCONTIN (oxycodone hydrochloride) Extended-Release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg (reformulated OxyContin), is the subject of NDA 22-272, also held by Purdue and initially approved on April 5, 2010. Reformulated OxyContin was developed with physicochemical properties that are intended to make the tablet more difficult to manipulate for purposes of abuse or misuse. Both original and reformulated OxyContin are opioid agonist products. Original OxyContin was indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

In correspondence dated August 10, 2010, Purdue notified FDA that it had

ceased shipment of original OxyContin, and FDA subsequently moved original OxyContin to the "Discontinued Drug Product List" section of the Orange Book. In a letter to FDA dated March 19, 2013, Purdue requested that FDA withdraw approval of NDA 20-553 for original OxyContin, noting that the original formulation of OxyContin was subject to abuse and misuse, and that it was "not possible to develop labeling or REMS provisions that would create a positive risk/benefit ratio for the original formulation of OxyContin." In that letter, Purdue waived its right to a hearing.

On April 18, 2013, FDA published notice of its determination that original OxyContin, NDA 20-553, was withdrawn from sale for reasons of safety or effectiveness (78 FR 23273). The notice concluded that "[o]riginal OxyContin . . . poses an increased potential for abuse by certain routes of administration, when compared to reformulated OxyContin. Based on the totality of the data and information available to the Agency at this time, FDA concludes that the benefits of original OxyContin no longer outweigh its risks."

Under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(e)), and under authority delegated by the Commissioner to the Director, Center for Drug Evaluation and Research, approval of NDA 20-553, and all amendments and supplements thereto, is withdrawn (see **DATES**). Distribution of this product in interstate commerce without an approved application is illegal and subject to regulatory action (see sections 505(a) and 301(d) of the FD&C Act (21 U.S.C. 355(a) and 331(d)).

Dated: July 30, 2013.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 2013-18694 Filed 8-6-13; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Submission for OMB Review; 30-day Comment Request: National Institute of Mental Health Data Access Request and Use Certification

SUMMARY: Under the provisions of Section 3507(a)(1)(D) of the Paperwork Reduction Act of 1995, the National Institute of Mental Health (NIMH), the National Institutes of Health, has submitted to the Office of Management

and Budget (OMB) a request for review and approval of the information collection listed below. This proposed information collection was previously published in the **Federal Register** on May 28, 2013, Volume 78, Number 102, Pages 31947-31948 and allowed 60-days for public comment. No comments were received. The purpose of this notice is to allow an additional 30 days for public comment. The National Institute of Mental Health (NIMH), National Institutes of Health, may not conduct or sponsor, and the respondent is not required to respond to, an information collection that has been extended, revised, or implemented on or after October 1, 1995, unless it displays a currently valid OMB control number.

Direct Comments to OMB: Written comments and/or suggestions regarding the item(s) contained in this notice, especially regarding the estimated public burden and associated response time, should be directed to the: Office of Management and Budget, Office of Regulatory Affairs, *OIRA_submission@omb.eop.gov* or by fax to 202-395-6974, Attention: NIH Desk Officer.

DATES: Comment Due Date: Comments regarding this information collection are best assured of having their full effect if received within 30 days of the date of this publication.

FOR FURTHER INFORMATION CONTACT: To obtain a copy of the data collection plans and instruments, or request more information on the proposed project, contact: Keisha Shropshire, NIMH Project Clearance Liaison, Science Policy and Evaluation Branch, OSPPC, NIMH, NIH, Neuroscience Center, 6001 Executive Boulevard, MSC 9667, Rockville Pike, Bethesda, MD 20892, or call 301-443-4335 or email your request, including your address to: *kshropsh@mail.nih.gov*. Formal requests for additional plans and instruments must be requested in writing.

Proposed Collection: The National Institute of Mental Health Data Access Request and Use Certification (previously National Database for Autism Research Data Access Request), 0925-0667, Revision, Expiration Date: 01/31/2016; National Institute of Mental Health (NIMH), National Institutes of Health (NIH).

Need and Use of Information Collection: NIMH recently received OMB approval for use of the National Database for Autism Research (NDAR) Data Use Certification (DUC) Form. NIMH is interested in renaming this form the "NIMH Data Access Request and Use Certification (DUC) Form" and using it to meet the unique data access

Tab 43

FDA Alert – Information for Healthcare
Professionals: Pemoline Tablets and
Chewable Tablets (marketed as Cylert)
(October 2005)

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The content on this page is provided for reference purposes only. This content has not been altered or updated since it was archived.

[Home](#) [Drugs](#) [Drug Safety and Availability](#) [Postmarket Drug Safety Information for Patients and Providers](#)

Drugs

Information for Healthcare Professionals: Pemoline Tablets and Chewable Tablets (marketed as Cylert)

FDA ALERT [10/2005]: Liver Injury Risk and Market Withdrawal

The Agency has concluded that the overall risk of liver toxicity from Cylert and generic pemoline products outweighs the benefits of this drug. In May 2005, Abbott chose to stop sales and marketing of Cylert in the U.S. All generic companies have also agreed to stop sales and marketing of this product (Pemoline tablets and chewable tablets). Cylert is a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). This product is considered second line therapy for ADHD because of its association with life threatening hepatic failure (see **BOXED WARNING in product label and patient package insert, available at [Cylert Labeling Information \(PDF - 60KB\)](#)**)¹

FDA intends to update this page when additional information or analyses become available.

Adverse reactions or quality problems experienced with the use of this Product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax, using the contact information at the bottom of this page.

Recommendations

Healthcare professionals who prescribe Cylert, or any of its generics, should transition their patients to an alternative therapy. Cylert will remain available through pharmacies and wholesalers until supplies are exhausted; no additional product will be available.

Data Summary

FDA is aware of 13 reports of liver failure resulting in liver transplant or death, usually within four weeks of onset of signs and symptoms of liver failure. Although the absolute number of reported cases of liver failure with pemoline is not large, the reporting rate for liver failure with pemoline is 10 to 25 times greater than the background rate of liver failure in the general population.

Despite diminished use of Cylert and generic pemoline products since the addition of the boxed warning in 1999 (about 1/5 the number of prescriptions now compared to before the boxed warning) and restrictive labeling (e.g., boxed warning, second line therapy, Medication Guide), a risk of liver failure remains (FDA is aware of 1 new case of pemoline-associated liver failure since the introduction of the boxed warning in 1999). Given the availability of multiple other drug treatments for ADHD, including 1 that is not scheduled and several products that can be given once a day, FDA has concluded that the risk of liver failure with this drug outweighs the potential benefits.

[Cylert Labeling Information \(PDF - 60KB\)](#)²

Related Information

- [Information about Medications Used to Treat Attention-Deficit/Hyperactivity Disorder \(ADHD\)](#)³

Contact FDA

1-800-332-1088
1-800-FDA-0178 Fax
Report a Serious Problem

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Regular Mail: Use postage-paid [FDA Form 3500](#)⁵

Mail to: MedWatch 5600 Fishers Lane
Rockville, MD 20857

Page Last Updated: 08/13/2013

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Tab 44

FDA Public Health Advisory – Pergolide
(marketed as Permax) (March 29, 2007)

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Drugs

Public Health Advisory - Pergolide (marketed as Permax)

This product is not currently available for purchase in the U.S.

3/29/2007

The FDA is notifying you that the companies that manufacture and distribute pergolide have agreed to withdraw this drug from the market due to the potential for heart valve damage. Two new studies showed that patients with Parkinson's disease who were treated with pergolide had an increased chance of serious damage to their heart valves when compared to patients who did not receive the drug. Pergolide is a member of a class of drugs known as dopamine agonists and is used with levodopa and carbidopa to manage the signs and symptoms (tremors and slowness of movement) of Parkinson's disease.

Patients with Parkinson's disease who are taking pergolide should:

- Contact their healthcare professional to discuss alternate treatment options.
- **NOT** stop taking Pergolide without consulting their healthcare professional, since stopping pergolide too quickly can be dangerous and several other effective treatments are available.

Healthcare professionals who prescribe pergolide should consider the following:

- Assess the patient's need for dopamine agonist (DA) therapy. If continued treatment with a DA is necessary, another DA should be substituted for pergolide. There are other dopamine agonists approved for the treatment of Parkinson's disease that are not associated with heart valve damage. Published transition regimens describe the conversion from one DA to another.
- If treatment with a DA is to be discontinued, **pergolide should not be stopped abruptly**, because rapid discontinuation of all dopamine agonist therapies can be dangerous. Instead, gradually decrease the dose of pergolide.
- Patients who will be taken off pergolide should be told that other effective options for treatment exist, including three other DAs that are not associated with damage to heart valves.

In 2006, a boxed warning regarding the risk of serious heart valve damage was added to the labeling for pergolide. The two recent studies, published in *The New England Journal of Medicine* in January 2007, confirm earlier studies that also described this problem. Pergolide is marketed by Valeant under the trade name Permax and sold and manufactured as the generic drug pergolide by Par and Teva.

In light of this additional safety information and the availability of alternative treatments for Parkinson's disease that do not have comparable safety problems, the companies that manufacture and sell pergolide have stopped shipping pergolide for distribution and will, in cooperation with FDA, work to remove from the market both the name brand Permax (pergolide) and the generic versions of pergolide. The effect of this voluntary withdrawal on supplies of pergolide currently in pharmacies will not be immediate. This delay will allow time for healthcare professionals and patients to discuss appropriate treatment options and to change treatments.

One of the drugs that was included in the recent studies showing increased chance of heart valve problems is Dostinex (cabergoline), another dopamine agonist. This drug is approved in the U.S. for the treatment of hyperprolactinemic disorders (conditions in which there are elevated levels of prolactin in the blood). Dostinex is **not** approved in the U.S. for the treatment of Parkinson's disease. For hyperprolactinemic disorders, a considerably lower dose of Dostinex is used. At these lower doses of Dostinex, there appears to be little chance of heart problems; therefore, Dostinex will remain on the US market for the treatment of hyperprolactinemic disorders.

The FDA is working with the manufacturers of pergolide to determine if it is possible to make the drug available to those few patients who are currently taking pergolide where previous efforts to switch to a different treatment have been unsuccessful, or where efforts subsequent to this advisory to switch therapies are also unsuccessful. In the interim, healthcare professionals and patients should consider all treatment options with the understanding that in the future, the drug may no longer be available.

Related Information

- [Pergolide \(marketed as Permax\) Information](#)¹
Issued 3/29/2007
- [Pergolide \(marketed as Permax\) - Overview](#)² [ARCHIVED]
Podcast - March 29, 2007
- [Pergolide \(marketed as Permax\) - Full Version](#)³ [ARCHIVED]
Podcast - March 29, 2007

Contact FDA

1-800-332-1088
1-800-FDA-0178 Fax
Report a Serious Problem

[MedWatch Online](#)⁴

Regular Mail: Use postage-paid [FDA Form 3500](#)⁵

Mail to: MedWatch 5600 Fishers Lane
Rockville, MD 20857

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U.S. Department of **Health & Human Services**

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Tab 45

Final Minutes of October 19, 2000 Meeting
of the FDA Nonprescription Drugs Advisory
Committee “Safety Issues of
Phenylpropanolamine (PPA) in Over-the-
Counter (OTC) Products”

Final Minutes

October 19, 2000

Nonprescription Drugs Advisory Committee

Food and Drug Administration

Center for Drug Evaluation and Research

Holiday Inn, 2 Montgomery Avenue, Gaithersburg, MD

Safety Issues of Phenylpropanolamine (PPA) in Over-the-Counter Drug (OTC) Products

The meeting was held at the Holiday Inn, Gaithersburg, MD. Prior to the meeting, the members, consultants and guests reviewed background material from the FDA, from the Hemorrhagic Stroke Project conducted by Yale investigators and also material which the Consumer Healthcare Products Association had submitted for the committee's review. In order for the public to be informed, the background material was also available on the Dockets page the day before the meeting. There were approximately 150 persons in attendance. The meeting started at 8 a.m. and ended at 4:00 p.m.

Attendance:

NDAC Members Present: Eric Brass, M.D., Ph.D., Chair, Richard Neill, M.D., Edwin Gilliam, Ph.D., Julie Johnson, Pharm.D., Hari Sachs, M.D., Louis Cantilena, M.D., Ph.D., Francis Lam, Pharm.D., Donald Uden, Pharm.D., Henry Williams, M.D., George Blewitt, M.D.(non-voting)

NDAC Members Absent: Edward Krenzelok,

Consultants: Statisticians and Epidemiologists: Ralph D'Agostino, Ph.D., Janet Daling, Ph.D.; Janet Elashoff, M.D., **Neurologists:** Sid Gilman, M.D., **Consumer Rep:** Susan Cohen

Non-voting Guest: Epidemiologist: Steven Kittner, M.D., MPH; **Neurologist:** Steven Warach, M.D., Ph.D.

FDA Participants: Janet Woodcock, M.D., Robert DeLap, M.D., Ph.D., Charles Ganley, M.D., Linda Katz, M.D., MPH, Robert Sherman, Lois La Grenade, M.D., MPH.

Open Public Hearing: Three presentations

Brian Strom, M.D., MPH, University of Pennsylvania representing Whitehall Corporation;
David E. Schteingart, M.D., University of Michigan representing Chattem;
Sidney Wolfe, M.D., Director, Public Citizen's Health Research Group

Historical Overview

Robert L. Sherman, DOTCDP, described the Regulatory History of OTC PPA.

Yale Presentation

Walter Kernan, M.D. presented the Final Report of the Hemorrhagic Stroke Project (HSP). The committee asked clarification questions following the presentation.

Consumer Healthcare Products Association

The Consumer Healthcare Products Association had several speakers who made comments about the HSP. R. William Soller, Ph.D., Senior Vice President and Director of Science and Technology CHPA; Noel S. Weiss, M.D., Dr. P.H., University of Washington; Lewis Kuller, M.D., Dr. Ph.H.; Robert B. Wallace, M.D., Philip B. Gorelich, M.D., Charles H. Hennekens, M.D., Dr. P.H., University of Miami School of Medicine. NDAC asked clarification questions following all of these statements.

FDA

Lois La Grenade, M.D., M.P.H., OPDRA, presented her Divisions epidemiological analysis of the agencies post marketing data on risks related to PPA, and presented a critique of the HSP. Charles Ganley, M.D., Director, DOTCDP gave an overview on how the FDA views safety issues and how the deliberations today would contribute to bringing closure to the PPA rulemaking.

Committee Discussion and Vote:

Following these presentations the committee discussed issues before beginning the vote on the following questions. The Chair revised question A and the subparts:

Questions Related to the Results and Interpretation of the Hemorrhagic Stroke Project :

A. Do the results from the HSP study for subjects in the 18 – 49 years of age

suggest that PPA is **safe** from risk of hemorrhagic stroke,
suggest that there is an **association** between PPA and hemorrhagic stroke,
or are **inconclusive**.

1. For females 18 – 49 using PPA as appetite suppression
0=Safe 13=Association 1=Inconclusive
2. For females 18 –49 using PPA as decongestants
0=Safe 6=Association 8=Inconclusive
3. For females 18 –49 using PPA on first exposure
0=Safe 13=Association 1=Inconclusive
4. For Men 18-49 using PPA as appetite suppression

- | | | | |
|--|--------|---------------|-----------------|
| | 0=Safe | 0=Association | 14=Inconclusive |
|--|--------|---------------|-----------------|
5. For Men 18-49 using PPA as decongestant

0=Safe	0=Association	14=Inconclusive
--------	---------------	-----------------
 6. For Men 18-49 using PPA on first exposure

0=Safe	0=Association	14=Inconclusive
--------	---------------	-----------------
 7. For the entire population (men and women) using PPA as appetite suppression

0=Safe	13=Association	1=Inconclusive
--------	----------------	----------------
 8. For the entire population (men and women) using PPA as decongestant

0=Safe	5=Association	9=Inconclusive
--------	---------------	----------------
 9. For the entire population (men and women) using PPA on first exposure

0=Safe	13=Association	1=Inconclusive
--------	----------------	----------------

B. Does the HSP provide information on which populations may be at greater or lesser risk?

The issue was discussed, and members pointed out the limitation of subgroup data.

Questions Related to the Availability of PPA in the OTC Market.

C. There is a body of data collected over the years that has suggested a possible association between PPA use and hemorrhagic stroke. Taking all currently available information into account, do the data support the conclusion that:

1. There is not an association between PPA use and hemorrhagic stroke?
2. There is an association between PPA use and hemorrhagic stroke?
3. The association still remains uncertain because of insufficient information?

0=no association	13= Yes Association	1=uncertain
------------------	---------------------	-------------

D. Considering your answer to question C, can PPA be considered to be generally recognized as safe for use as:

1. a decongestant ?

0=Yes	12 = No	2=Abstain
-------	---------	-----------

2. an appetite suppressant?

0=Yes

13=No

1=Abstain

- a) When answering this question, please address whether dose is an important consideration.

During the discussion, members could not conclude there was any dose relationship however they did think there was some evidence to suggest this relationship.

In making the risk/benefit analysis the following comments were made:

What does the consumer loose if is taken off the market?

One member stated that when a drug is only marginally useful, any degree of risk is much less tolerable.

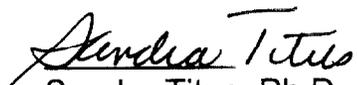
In discussing appetite suppression: In the long term 95% of people gain the weight back. Since there is no study on long-term use and the short term benefits for weight reduction are marginal no risks are acceptable. Regarding PPA for coughs many members felt here are other products that are equally good and that do not have this risk profile.

It was pointed out that the PPA study was in reality similar to an actual use study because it described how consumers use products. It was troubling that a high proportion of subjects were hypertensive and were taking PPA. This indicates that labeling alone could not be relied upon to communicate warnings.

Another member pointed out that the dose that seems to be causing the problem is not a massive overdose and so it becomes doubtful if one could effectively label or expect that consumers would follow the label.

A verbatim transcript of this meeting will be available on the FDA's Dockets Management Branch Website approximately 30 days after the meeting. The address is [HTTP://www.fda.gov/ohrms/dockets/ac/acmenu.htm](http://www.fda.gov/ohrms/dockets/ac/acmenu.htm).

I certify that I attended the October 19, 2000 meeting of the Nonprescription Drugs Advisory Committee and that these minutes accurately reflect what transpired.

 11/1/00
Sandra Titus, Ph.D. Date
Executive Secretary, NDAC

 11/13/00
Eric Brass, M.D., Ph.D. Date
Chair, NDAC

Tab 46

FDA Public Health Advisory – Safety of
Phenylpropanolamine (November 6, 2000)

Archived Content

The content on this page is provided for reference purposes only. It was current when produced, but is no longer maintained and may be outdated.

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Drugs

Safety of Phenylpropanolamine

Food and Drug Administration
Public Health Advisory
Subject: Safety of Phenylpropanolamine

November 6, 2000

The Food and Drug Administration (FDA) is issuing a public health advisory concerning phenylpropanolamine hydrochloride. This drug is widely used as a nasal decongestant (in over-the-counter and prescription drug products) and for weight control (in over-the-counter drug products). FDA is taking steps to remove phenylpropanolamine from all drug products and has requested that all drug companies discontinue marketing products containing phenylpropanolamine.

Phenylpropanolamine has been marketed for many years. A recent study reported that taking phenylpropanolamine increases the risk of hemorrhagic stroke (bleeding into the brain or into tissue surrounding the brain) in women. Men may also be at risk. Although the risk of hemorrhagic stroke is very low, FDA recommends that consumers not use any products that contain phenylpropanolamine.

FDA's Nonprescription Drugs Advisory Committee (NDAC) recently discussed this study and other information on phenylpropanolamine. NDAC determined that there is an association between phenylpropanolamine and hemorrhagic stroke and recommended that phenylpropanolamine not be considered safe for over-the-counter use.

Although this risk of hemorrhagic stroke is very low, FDA has significant concerns because of the seriousness of a stroke and the inability to predict who is at risk. FDA does not consider the conditions for which phenylpropanolamine is used (over-the-counter or by prescription) as justifying the risk of this serious event. Other products are available for use.

In the meantime, consumers can identify over-the-counter cough-cold, nasal decongestant, and weight control products containing this ingredient by looking for "phenylpropanolamine" in the list of active ingredients on the label. Consumers can check with their health care provider or pharmacist to see whether their prescription cough-cold or nasal decongestant product contains phenylpropanolamine. We advise consumers to discuss alternative over-the-counter and prescription products with their health care providers or pharmacists.

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U.S. Department of **Health & Human Services**

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Tab 47

Federal Register of August 14, 2001
(66 FR 42665)

responsible for assuring that the labeling and advertising of prescription drugs is truthful and not misleading. Section 502(n) of the act (21 U.S.C 352(n)) prohibits the advertising of prescription drugs that is false or misleading or that fails to provide required information about product risks. Although advertising of prescription drugs was once primarily addressed to health professionals, consumers increasingly have become a primary target audience, and "direct-to-consumer" (DTC) advertising has dramatically increased in the past few years. However, DTC advertising raises many questions and issues. While it may alert consumers to new information and facilitate treatment of their medical problems, it also may confuse consumers and adversely impact the relationship between patients and their health care providers. In August 1997, when the agency issued its draft guidance on consumer directed broadcast advertisements, FDA announced that it would evaluate the effects of the guidance and of DTC promotion in general within 2 years of finalizing the guidance.

The guidance was finalized on August 9, 1999 (64 FR 43197). In the **Federal**

Register notice announcing availability of the final guidance, FDA reiterated its intent to evaluate the effects of the guidance, including effects on the public health, within 2 years. As part of that evaluation, the agency conducted a baseline public information collection focused on recent patients, concerning the effects of DTC advertising on patient-doctor interactions and attitudes toward DTC advertising in general (OMB Control No. 0910-0399). The purpose of the proposed information collection is to followup on the agency's 1999 patient survey and expand information collection to include physicians. FDA needs information from physicians and patients about their reactions to, and behaviors that stem from, DTC prescription drug advertising in order to develop policy on appropriate requirements for regulating drug product promotional materials.

The collection effort will consist of two separate parts: A patient survey and a physician survey. The patient survey will be conducted through national randomized telephone interviews with a national probability sample with 775 adults 18 years of age and over who have recently visited a physician. The

sample will be limited to those respondents who have seen a doctor or other health care professional in the last 3 months. Patient respondents will be asked their views about any prescription drug they may have received and prescription drugs in general, and their attitudes and behavior in relation to DTC advertising. Demographic information will also be collected.

The physician survey will be conducted through telephone interviews with a national probability sample of office based physicians who engage in patient care at least half of the time. The sampling frame of physicians will consist of names drawn from the American Medical Association's physician masterfile. In an effort to maximize the response rate for physicians, prenotification letters will be mailed to all potential physician respondents. The survey itself will cover DTC-related patient interactions, perceived patient outcomes, attitudes toward appropriate DTC categories, and general opinions about DTC advertising. Demographic information will also be collected.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
11,625 (consumer screener)	1	11,625	.017	197.6
775 (consumer survey)	1	775	.333	258.1
3,333 (physician screener)	1	3,333	.017	56.7
500 (physician survey)	1	500	.250	125.0
Total				637.4

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

In the **Federal Register** of March 19, 2001 (66 FR 15494), the agency requested comments on the proposed collections of information. Comments were received from 31 organizations and individuals. The comments were grouped according to similarity.

1. Seven comments were unrelated to the proposed information collection.

2. Sixteen comments addressed general aspects of the information collection. Of these, 12 comments were supportive of the information collection as proposed. Four comments recommended a focus on behaviors rather than attitudes. This included two comments, which suggested a case study design rather than a survey. We note that the proposed physician survey does ask the physician to focus on a specific event when answering questions about their interaction with a patient who had asked about a

prescription drug, as well as any specific drugs that were discussed during the interaction. In addition, both the patient and physician surveys ask questions about the effect of DTC advertising on behaviors occurring during an office visit.

3. Eight comments addressed specific aspects of the questionnaire, including wording, sample, and additional areas of inquiry. The questionnaires were extensively revised to reflect these comments.

A pilot test of the questionnaires was conducted by the contractor to confirm estimates of timing, identify problems related to questionnaire wording and order of presentation, and ensure that the questionnaire placed a minimal burden on respondents. The pretest included nine patient test respondents and nine physician test respondents.

The pretest revealed that no substantive changes were necessary.

Dated: August 7, 2001.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 01-20363 Filed 8-13-01; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01N-0196]

Phenylpropanolamine; Proposal to Withdraw Approval of New Drug Applications and Abbreviated New Drug Applications; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is proposing to withdraw approval of 16 new drug applications (NDAs) and 8 abbreviated new drug applications (ANDAs). These are the approved applications for prescription and over-the-counter (OTC) drug products containing phenylpropanolamine. FDA is offering the holders of the applications an opportunity for a hearing on the proposal. All other drug products containing phenylpropanolamine that are considered new drugs (e.g., extended-release products and any prescription product) are also subject to this notice. FDA is taking this action because of the association of phenylpropanolamine with increased risk of hemorrhagic stroke.

DATES: Submit written requests for a hearing by September 13, 2001. Submit data and information in support of the hearing request by October 15, 2001. An applicant planning to withdraw or reformulate a product covered by the applications listed in this notice should inform the agency as early as possible, preferably on or before October 15, 2001.

ADDRESSES: A request for a hearing, supporting data, and other comments are to be identified with Docket No. 01N-0196 and submitted to the Dockets

Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Communications pertaining to withdrawal or reformulation of products covered by applications listed in this notice should be directed to the Division of Pulmonary and Allergy Drug Products (HFD-570), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, rm. 10B-45, Rockville, MD 20857, or the Office of Generic Drugs (HFD-600), 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:

For information on medical/scientific issues: Gerald M. Rachanow or Robert L. Sherman, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

For general information concerning this notice: Mitchell Weitzman, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

Phenylpropanolamine is an ingredient used in prescription and OTC drug

products as a nasal decongestant to relieve stuffy nose or nasal congestion and in OTC weight control drug products to control appetite. Phenylpropanolamine was included in the agency's OTC drug review. Although phenylpropanolamine was regarded as effective for weight control and as a nasal decongestant, final classification of the ingredient was deferred pending the resolution of issues pertaining to its safety.

II. Products Subject to This Notice

This notice applies to all OTC and prescription immediate-release and extended-release drug products containing phenylpropanolamine that are marketed under approved applications. The agency is aware that a number of prescription products and some OTC extended-release products containing phenylpropanolamine, all of which are considered new drugs, have been marketed without an approved application. This notice also applies to all of these products. This notice does not apply to immediate-release OTC drug products marketed under the OTC drug monograph system; FDA intends to address these products in a separate document to be published in a future issue of the **Federal Register**.

The following applications are affected by this notice:

Application Number	Drug	Applicant
NDA 11-694	Dimetane-DC Syrup	A. H. Robins Co., P.O. Box 8299, Philadelphia, PA 19101.
NDA 12-152	Ornade Extended-Release Capsule	SmithKline-Beecham, 1250 South Collegeville Rd., P.O. Box 5089, Collegeville, PA 19426.
NDA 12-436	Dimetapp Extended-Release Tablet	Whitehall-Robins, 5 Giralda Farms, Madison, NJ 07940.
NDA 13-087	Dimetapp Elixir	Do.
NDA 18-050	Corsym Extended-Release Suspension.	Medeva Americas, Inc., 755 Jefferson Rd., P.O. Box 1710, Rochester, NY 14603.
NDA 18-099	Contact Extended-Release Capsule	SmithKline Beecham Consumer Health, L. P., 1500 Littleton Rd., Parsippany, NJ 07054.
NDA 18-298	Tavist-D Extended-Release Tablet	Novartis Consumer Health, Inc., 560 Morris Ave., Summit, NJ 07901.
NDA 18-556	Demazin Extended-Release Tablet	Schering-Plough HealthCare Products, Three Oak Way, P.O. Box 603, Berkeley Heights, NJ 07922.
NDA 18-809	Phenylpropanolamine Hydrochloride (HCL) Chlorpheniramine Maleate Extended-Release Capsule.	Schwarz Pharma, 6140 West Executive Dr., Mequon, WI 53092.
NDA 19-410	Hycomine Syrup	Endo Pharmaceuticals, Inc., 500 Endo Blvd., Garden City, NY 11530.
NDA 19-411	Hycomine Pediatric Syrup	Do.
NDA 19-613	Contact Extended-Release Tablet	Novartis Consumer Health, Inc.
NDA 20-640	Tavist-D Extended-Release Tablet	Do.
ANDA 71-099	Bromatapp Extended-Release Tablet	Teva Pharmaceuticals, USA, 1090 Horsham Rd., P.O. Box 1090, North Wales, PA 19454.
ANDA 88-359	Drize Extended-Release Capsule	B. F. Ascher & Co., Inc., 15501 West 109th St., Lenexa, KS 66219.
ANDA 88-681	Chlorpheniramine Maleate and Phenylpropanolamine HCL Extended-Release Capsule.	Chelsea Laboratories, 896 Orlando Ave., West Hempstead, NY 11552.
ANDA 88-687	Bipheta Elixir	Morton Grove Pharmaceuticals, Inc., 6451 Main St., Morton Grove, IL 60053.
ANDA 88-688	Bromanate Elixir	Alpharma, U.S. Pharmaceuticals Division, 333 Cassell Dr., suite 3500, Baltimore, MD 21224.
ANDA 88-723	Bromanate DC Syrup	Do.
ANDA 88-904	Myphetane DC Syrup	Morton Grove Pharmaceuticals, Inc.

Application Number	Drug	Applicant
ANDA 88-940	Chlorpheniramine Maleate and Phenylpropanolamine HCL Extended-Release Capsule.	Geneva Pharmaceuticals, Inc., 2555 West Midway Blvd., P.O. Box 446, Broomfield, CO 80038.

III. Recent Data on the Safety of Phenylpropanolamine

A. Introduction and Rationale for Developing a Study

Spontaneous case reports and published case series, accumulated from 1969 to 1991, suggested a possible association between phenylpropanolamine use and an increased risk of hemorrhagic stroke. At that time, however, it was not possible to prove or disprove an association. In an effort to resolve this issue, representatives of the manufacturers of products containing phenylpropanolamine and agency staff met in 1991 to plan a study that could further examine whether there was an association between phenylpropanolamine use and the risk of hemorrhagic stroke. An epidemiologic case-control study was determined to be the most feasible study design to evaluate the possible association between exposure to phenylpropanolamine and a rare outcome such as hemorrhagic stroke. The industry sponsors of the study selected investigators at Yale University School of Medicine to conduct the study. The following discussion is based on the study report (Ref. 1) submitted to FDA.

B. The Yale Hemorrhagic Stroke Project

1. Study Design

The Yale Hemorrhagic Stroke Project (Ref. 1) was designed as a case-control study. Because several case reports had described strokes in young women who took phenylpropanolamine as an appetite suppressant, often after the first dose, the study examined three questions: (1) Whether all users of phenylpropanolamine (the study cohort included men and women aged 18 to 49 years), compared with nonusers, had an increased risk of hemorrhagic stroke; (2) the possible association between phenylpropanolamine use and hemorrhagic stroke by type of exposure (appetite suppressant or cough-cold product); and (3) among women age 18 to 49 years, the possible association between first use of phenylpropanolamine and hemorrhagic stroke and the possible association between use of phenylpropanolamine-containing appetite suppressants and hemorrhagic stroke.

The study was performed between December 1994 and July 1999 and involved men and women 18 to 49 years old who were hospitalized with a primary subarachnoid hemorrhage (SAH) or a primary intracerebral hemorrhage (ICH). Eligible case subjects had no prior history of stroke and were able to be interviewed within 30 days of their event. The subjects were recruited from hospitals in four geographic regions of the United States.

Both SAH and ICH were determined by clinical symptoms and specific diagnostic information from computed tomography (CT). Magnetic resonance imaging was accepted for the diagnosis of SAH or ICH only if other studies were not diagnostic. Subjects were ineligible for enrollment if they died within 30 days, were not able to communicate within 30 days of their stroke, had a previously diagnosed brain lesion predisposing to hemorrhage risk (e.g., arteriovenous malformation, vascular aneurysm, or tumor), or had a prior history of stroke. Subjects who first experienced stroke symptoms after being in the hospital for 72 hours (e.g., for an unrelated matter) were also excluded.

For each case subject, random digit dialing (matched to the first three digits of the case subject) was used to identify two control subjects who were matched on: (1) Gender, (2) race (African-American versus non-African-American), (3) age (within 3 years for case subjects less than 30 years old and within 5 years for subjects 30 years or over), and (4) telephone exchange. Cases and control subjects were interviewed to ascertain medical history, medication use, and habits affecting health, such as use of tobacco and alcohol. Interviews of control subjects were completed within 30 days of the subject's stroke event to minimize seasonal differences in the likelihood of exposure to cough-cold drug products. Eligibility criteria for control subjects were the same as for case subjects except for the stroke event. During the consent procedure, all subjects (cases and controls) were told that the study was designed to examine causes of hemorrhagic stroke in young persons without specific mention of phenylpropanolamine or other potential risk factors. Case and control subjects were interviewed by a trained interviewer using a structured

questionnaire developed for this study. Subjects were classified as exposed to phenylpropanolamine if they reported use within 3 days of the stroke event for case subjects or a corresponding date for control subjects. Reported exposures were verified by the study investigators, who documented the actual product(s) used and their ingredients.

The exposure window refers to the interval before the focal time when the subject's exposure to phenylpropanolamine was assessed. For all analyses except first-dose use, the exposure window was defined as the index day before focal time and the preceding 3 calendar days. For first-dose use, a subject was considered exposed if phenylpropanolamine use occurred on the index day before the focal time or on the preceding calendar day, with no other phenylpropanolamine use during the preceding 2 weeks. To maintain a consistent reference group for all analyses, nonexposure was defined as no use of phenylpropanolamine within the 2 weeks preceding the focal time. Exposure windows were defined similarly in the matched case controls, based on the focal time for the corresponding case.

2. Statistical Analysis

Case and control subjects were compared on a variety of clinical and demographic features, including those used in matching. Statistical comparisons were made using chi-square tests and the Fisher's exact test (where appropriate) for categorical variables, and the Student *t*-test for continuous variables. For the analyses of the primary endpoints, conditional logistic models for matched sets (with a variable number of controls per case) were used to estimate odds ratios, lower limits of the one-sided 95 percent confidence intervals, and *p*-values for the risk factors under investigation. One-tailed statistical results were reported because the focus of the study was whether phenylpropanolamine use increases the risk of stroke. Each logistic model was estimated with two mutually exclusive binary exposure terms: (1) The subject's primary exposure status as defined by the specific aim (e.g., phenylpropanolamine use in the 3-day window; yes/no), and (2) phenylpropanolamine users who were not exposed within the 3-day window

(but with some exposure within 2 weeks of the focal time).

In multivariate conditional logistic models (using asymptotic methods), adjustments were made for race (African-American compared with non-African-American), history of hypertension (yes/no), and current cigarette smoking (current compared with never or ex-smoker) as these are major risk factors for stroke. Other underlying diseases and/or conditions were also examined to determine if any of these, when added to this basic adjusted model, altered the matched odds ratio by at least 10 percent.

3. Study Results

There were 702 case subjects, including 425 subjects (60 percent) with an SAH and 277 (40 percent) with an ICH, and 1,376 control subjects. Hemorrhage was associated with an aneurysm in 307 subjects (44 percent), an arteriovenous malformation in 50 subjects (7 percent), and a tumor in one subject (0.1 percent). Two control subjects were located for each of 674 case subjects (96 percent) and one control subject for each of 28 case subjects (4 percent). All control subjects were matched to their case subjects on gender and telephone exchange. Age matching was successful for 1,367 controls (99 percent) and race matching was achieved for 1,321 controls (96 percent). Twenty-seven case subjects and 33 control subjects reported phenylpropanolamine use within the 3-day exposure window.

Compared with control subjects, case subjects were significantly more likely to be African-American (21 percent compared with 17 percent). Case subjects were also more likely to report lower educational achievement (20 percent did not graduate from high school compared with 9 percent of control subjects), current cigarette smoking (51 percent compared with 30 percent), a history of hypertension (39 percent compared with 20 percent), family history of hemorrhagic stroke (9 percent compared with 5 percent), heavy alcohol use (14 percent compared with 7 percent), and recent cocaine use (2 percent compared with less than 1 percent). For all other clinical variables examined, case and control subjects were not dissimilar. Case subjects were significantly ($p < 0.05$) less likely to report use of nonsteroidal anti-inflammatory drugs and significantly more likely to report use of caffeine and nicotine in the 3 days before their event. Of the factors examined, only education was found to change the adjusted odds ratio for the association between phenylpropanolamine and hemorrhagic

stroke by more than 10 percent, and this demographic factor was included in all subsequent models.

Analyses of the study results were consistent with an association between hemorrhagic stroke and use of phenylpropanolamine (in a nasal decongestant or weight control drug product) in the 3 days prior to the event. Such use of phenylpropanolamine, compared with no use in the prior 2 weeks, was associated with a relative risk for hemorrhagic stroke of 1.67 (unadjusted odds ratio) ($p = 0.040$). The corresponding adjusted odds ratio was 1.49 (lower limit of the one-sided 95 percent confidence interval (LCL)=0.93, $p = 0.084$).

The relative risks of hemorrhagic stroke observed with use of the two types of phenylpropanolamine-containing products (in the 3-day exposure window, compared with no use in the prior 2 weeks) were as follows. For cough-cold products, the unadjusted odds ratio was 1.38 ($p = 0.163$) and the adjusted odds ratio was 1.23 (LCL=0.75, $p = 0.245$). For weight control products, the unadjusted odds ratio was 11.98 ($p = 0.007$) and the adjusted odds ratio was 15.92 (LCL=2.04, $p = 0.013$).

To analyze the relation between recency of phenylpropanolamine exposure and risk for hemorrhagic stroke, odds ratios were also calculated according to the timing of the most recent phenylpropanolamine use. The prespecified definition for current use was use of any phenylpropanolamine-containing product on the day of the event (before focal time) or the preceding calendar day. Prior use was defined as use 2 or 3 calendar days before the focal time. The odds ratio was slightly higher for current use (adjusted odds ratio (AOR)=1.61, LCL=0.93, $p = 0.078$) than for prior use (AOR=1.16, LCL=0.47, $p = 0.393$). Within current use, odds ratios were then calculated according to first use or nonfirst use. First use was defined as current use with no other use within the prior 2 weeks. Nonfirst use included other uses within the 2-week interval. The odds ratio was higher for first use (AOR=3.14, LCL=1.16, $p = 0.029$) than for nonfirst use (AOR=1.20, LCL=0.61, $p = 0.329$). All first uses of phenylpropanolamine ($n = 13$) reported in these data were in cough-cold drug products.

In women using phenylpropanolamine in weight control drug products (3-day exposure window, versus no use in the prior 2 weeks), the unadjusted odds ratio for hemorrhagic stroke was 12.19 ($p = 0.006$) and the adjusted odds ratio was 16.58 (LCL=2.22, $p = 0.011$). Among the

Hemorrhagic Stroke Project subjects, all hemorrhagic stroke events that occurred within the 3-day exposure window were in women. In the analyses of the possible association between hemorrhagic stroke and first day use of phenylpropanolamine, 11 of the 13 first day use events were in women (7 cases compared with 4 controls). The unadjusted odds ratio was 3.50 ($p = 0.039$) and the adjusted odds ratio was 3.13 (LCL=1.05, $p = 0.042$).

Based on the findings that risk for hemorrhagic stroke seemed to be concentrated among current users, the association between current phenylpropanolamine dose and risk for hemorrhagic stroke was examined. Among 21 exposed control subjects, the median current dose of phenylpropanolamine (i.e., total amount taken on the index day or preceding day) was 75 milligrams (mg). Analysis according to dose shows that the odds ratio was higher for current doses above the median (greater than 75 mg) (AOR=2.31, LCL=1.10, $p = 0.031$) than for lower doses (AOR=1.01, LCL=0.43, $p = 0.490$). Among first-dose users, four of eight cases and two of five controls were exposed to greater than 75 mg of phenylpropanolamine. To examine the potential effect of ambiguity in the correct focal time, the odds ratios were recalculated after excluding all 154 case subjects who were classified as having a definite ($n = 76$) or uncertain ($n = 78$) sentinel symptom preceding the stroke event. The magnitude of the adjusted odds ratios did not change substantially.

4. Study Conclusions

According to the investigators, several features of the study supported the validity of the study findings regarding an association between phenylpropanolamine use and risk for hemorrhagic stroke in subjects between 18 and 49 years of age. First, in addition to the finding of elevated odds ratios that reached statistical significance, the magnitude of the odds ratios for phenylpropanolamine use as an appetite suppressant (15.92) and as a first-dose use (3.14) remained large even after adjustment for important clinical features. Second, the data showed an association between both types of phenylpropanolamine drug products (nasal decongestants and weight control products) and hemorrhagic stroke. Because so few men were exposed to phenylpropanolamine in this study ($n = 19$), it was not possible to determine whether their risk for hemorrhagic stroke (in association with use of phenylpropanolamine) is different from that of women.

5. FDA's Evaluation of the Study

Observational studies, particularly case-control studies, are potentially subject to a number of biases, and this case-control study is no exception. The hallmark of a good case-control study is that biases are anticipated and measures are instituted in the design and analysis stages to minimize biases to the greatest extent possible.

Strict diagnostic criteria, as described in section III.B.1 of this document, were developed to ensure accurate identification of hemorrhagic stroke cases in the target population. A number of steps were taken to minimize misclassification bias. One of the investigators confirmed the stroke by reviewing the medical records of suspected cases, without knowledge of the exposure status. Inclusion and exclusion criteria were clearly defined for both cases and controls. Exposure was clearly defined, an exposure window was identified, and exposure was ascertained by trained interviewers. Interviewers were randomly assigned to cases or controls, and questions were asked about multiple medications, thus blinding subjects to the exact exposure under study. Because phenylpropanolamine use might be seasonal, controls were identified and interviewed within 30 days of the date of their matched case subject's stroke, to ensure that cases and controls had an equal opportunity of exposure. Controls were also matched to cases for day of the week and time of day of the stroke. This matching strategy ensured the probability that exposure to any medication or other covariates (e.g., alcohol drinking or cigarette smoking) was similar between cases and controls.

The investigators attempted to identify two controls per case by using random digit dialing (with a match for the first three digits of the telephone number). This was considered a good strategy for two reasons. First, controls were chosen completely at random. Second, controls were population-based, so that the results are generalizable to the source population from which the cases and controls were drawn. Matching on race and educational level was slightly unequal between cases and controls. The investigators further controlled for these inequalities by adjustment during analysis. The agency concludes that matching was largely successful.

The investigators reduced the possibility of misclassification of phenylpropanolamine use by using a highly structured questionnaire. Each reported medication was verified by asking subjects to present the actual

container or by picking out reported brand-name medications from a book containing photographs. Verification of medication use in the 3-day window prior to the focal time was 96 percent and 94 percent for cases and controls, respectively. The investigators conducted two additional steps to further ensure that the possibility of exposure misclassification error was reduced to an absolute minimum: (1) Only "definite" and "possible" exposure responses were considered in the analyses, and (2) the use of other OTC drugs between cases and controls was compared to ensure that the cases did not have greater recall of the use of any drugs as a reason for their stroke. Based on this analysis, the agency finds no evidence of recall or misclassification bias.

A key element in designing a case-control study of a rare event is calculating the sample size and/or power to ensure the study is large enough to detect a difference if one really exists. FDA had concerns that the study might be underpowered to detect an association because the original sample size calculation was based on an odds ratio of five for an association between hemorrhagic stroke and first-day use of phenylpropanolamine. This ratio was not determined by any public health or clinical considerations, but on considerations related to time and cost constraints. The investigators' difficulties in recruiting controls contributed to the study taking longer than expected. Despite these limitations, this was the largest prospective case-control study ever conducted on hemorrhagic stroke. In spite of initial reservations about the adequacy of sample size and power, the agency finds that this study identified an association between phenylpropanolamine use and hemorrhagic stroke, as explained below.

The agency notes that the three most important risk factors (race, history of hypertension, and cigarette smoking) were included in the multivariate analysis (basic adjusted model). The confounding effect of the other covariates was examined if adding any of them to the basic model altered the odds ratio estimate by 10 percent. High school education was the only covariate determined to change the odds ratio by at least 10 percent.

Because the study had a matched design, the agency considers the conditional logistic regression model appropriate to calculate both unadjusted and adjusted odds ratios. In addition, the number of exposures was small, particularly for analysis of appetite suppressant and first use. Thus, the authors calculated the confidence

interval of the unadjusted odds ratio based on an exact method.

Hypertension is the single most important risk factor for a stroke. Misclassification of hypertension status could result in residual confounding. FDA examined the possible effects of this residual confounding on the results of the study. The agency found that the odds ratio for appetite suppressant use was 15.92, a substantial increase in risk. Its very magnitude makes it difficult to explain by confounding alone. Because product labeling advises hypertensive persons to avoid phenylpropanolamine use, the association of phenylpropanolamine use with hypertension should be negative. Such a negative association would result in biasing the result towards no association if the confounding factor is not controlled for. In addition to the steps taken by the investigators, the agency examined this further by additional analyses restricted to subjects without a past history of hypertension, and the results were not significantly different, thereby providing additional evidence that confounding by hypertension was not present in the study.

FDA requested that the Yale investigators explore the possible impact of cigarette smoking and alcohol consumption in more detail. The investigators found that the odds ratios for phenylpropanolamine and stroke were essentially unchanged by inclusion of any quantitative measures of smoking and alcohol consumption.

The investigators examined the association between current phenylpropanolamine dose and risk for hemorrhagic stroke. Among 21 exposed control subjects, the median current dose of phenylpropanolamine (i.e., the total amount taken on the index day or preceding day) was 75 mg. The adjusted odds ratio was higher for current doses above 75 mg than for lower doses. Among first dose users, four of eight cases and two of five controls were exposed to greater than 75 mg of phenylpropanolamine. As 75 mg is a single dose of many OTC extended-release phenylpropanolamine cough-cold drug products with recommended adult dosing every 12 hours (150 mg a day), the agency further evaluated the association between risk of hemorrhagic stroke and a range of current phenylpropanolamine doses. Exploratory analyses suggest that there may be an increased risk of hemorrhagic stroke with labeled doses at or above 75 mg a day. Although not statistically significant, a trend toward a dose-ordering of odds ratios was seen.

C. Additional Reports

FDA reviewed its adverse events reporting system (AERS) for spontaneous reports of hemorrhagic stroke from 1991 to 2000 and identified 22 cases, 16 in the 18 to 49 age group with 13 cases in women (Ref. 2). In all cases, the suspect drug was an extended-release product containing 75 mg of phenylpropranolamine per unit dose. Of 11 cases for which the indication of use was provided, 10 reported use for respiratory symptoms.

D. Advisory Committee Recommendations

On October 19, 2000, at a public meeting, FDA's Nonprescription Drugs Advisory Committee (NDAC) discussed the Yale Hemorrhagic Stroke Project and additional case reports of hemorrhagic stroke since 1991. The investigators of the Yale study presented the study results and their conclusions. Industry representatives raised concerns about the design of the study that they believed made interpretation of the results difficult (Ref. 3). When NDAC was asked if, taking all currently available information into account, the data support the conclusion that there is an association between phenylpropranolamine and an increased risk of hemorrhagic stroke, 13 of 14 committee members voted (with 1 voting "uncertain") that there is such an association (Ref. 4). When asked whether phenylpropranolamine can be generally recognized as safe for use as a nasal decongestant, 12 of the 14 committee members voted (with 2 abstaining) that phenylpropranolamine could not be considered to be generally recognized as safe for OTC nasal decongestant use. When asked whether phenylpropranolamine can be generally recognized as safe for use as an appetite suppressant, 13 of the 14 committee members voted (with 1 abstaining) that phenylpropranolamine could not be considered to be generally recognized as safe for OTC weight control use. Minutes of the NDAC meeting are available in the Dockets Management Branch (address above) under the docket number listed in brackets in the heading of this document.

IV. The Agency's Tentative Conclusions on the Safety of Phenylpropranolamine

The agency concludes that the Yale study (Ref. 1) was well designed and demonstrated that the association between phenylpropranolamine use (as an appetite suppressant and first time use as a nasal decongestant) and an increased risk of hemorrhagic stroke was significant and was most striking in

women. The case-control design was best suited for this study because the outcome under investigation was rare. All reasonable steps were taken to minimize bias and confounding. Quality control measures were built into the design. Analyses were appropriate for the type of study and were performed according to the protocol. The strengths of the study lie in the clarity of its objectives, the meticulous adherence to sound epidemiology practices in its design and execution, and the consistency of the findings, regardless of the analytic methods. Its only limitation was in the power and sample size, discussed earlier. Despite this limitation, the study was nevertheless able to find a consistent association between phenylpropranolamine use and hemorrhagic stroke, particularly in women.

Although the Yale study focused on men and women 18 to 49 years of age, the agency has no reason to believe that the increased risk of hemorrhagic stroke is limited to this population. While the Yale study was being conducted, FDA continued to receive spontaneous reports of hemorrhagic stroke with cough-cold products that contain high doses of phenylpropranolamine. Some reports indicate that only one dose was administered.

FDA believes that the data from the Yale study demonstrating an association between phenylpropranolamine and hemorrhagic stroke, taken together with spontaneous reports and reports in the published medical literature, provide evidence that nasal decongestant and weight control drug products containing phenylpropranolamine are no longer shown to be safe. Because hemorrhagic strokes often lead to catastrophic, irreversible outcomes and the factors that may predispose some individuals to develop this adverse event are not fully known, individuals at risk cannot be adequately warned. The agency tentatively concludes that the benefits of the intended uses of this ingredient do not outweigh the potential risk. All of the applications listed in section II of this document are for nasal decongestant use of phenylpropranolamine. None are for appetite control.

Accordingly, the Director of the Center for Drug Evaluation and Research (CDER) concludes with respect to the NDA and ANDA products containing phenylpropranolamine listed in section II of this document that phenylpropranolamine is no longer shown to be safe for use under the conditions that formed the basis upon which the applications were initially approved. The Director is proposing to

withdraw approval of those NDAs and ANDAs in accordance with section 505(e)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(e)(2)). This notice of opportunity for a hearing applies to all persons who manufacture or distribute a drug product that contains phenylpropranolamine and that are considered new drugs (e.g., extended-release products and any prescription product).

In lieu of requesting a hearing, manufacturers of products containing phenylpropranolamine as a nasal decongestant are urged to reformulate their products to remove phenylpropranolamine. Reformulated products may result in products that require an approved NDA or ANDA prior to marketing. Inquiries regarding proposed reformulations should be sent to the Division of Pulmonary and Allergy Drug Products (address above) or the Office of Generic Drugs (address above), as appropriate.

V. Notice of Opportunity for a Hearing

The Director has evaluated the information discussed above and, on the grounds stated, is proposing to withdraw approval of the previously listed NDAs and ANDAs. Therefore, notice is given to the holders of the NDAs and ANDAs listed in section II of this document that the Director proposes to issue an order, under section 505(e)(2) of the act, withdrawing approval of the NDAs and ANDAs and all amendments and supplements thereto. The Director finds that new evidence of clinical experience, not contained in the applications or not available to the Director until after the applications were approved, evaluated together with the evidence available to the Director when the applications were approved, shows that phenylpropranolamine is not shown to be safe for use under the conditions that formed the basis upon which the applications were approved.

In accordance with section 505 of the act and part 314 (21 CFR part 314), applicants and all other persons subject to this notice are hereby given an opportunity for a hearing to show why approval of the NDAs or ANDAs should not be withdrawn.

An applicant who decides to seek a hearing shall file: (1) On or before September 13, 2001, a written notice of appearance and request for hearing, and (2) on or before October 15, 2001, the data, information, and analyses relied on to demonstrate that there is a genuine issue of material fact to justify a hearing, as specified in § 314.200. Any other interested person

may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for a hearing, a notice of appearance and request for a hearing, information and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in § 314.200 and in 21 CFR part 12.

The failure of an applicant to file a timely written notice of appearance and request for hearing, as required by § 314.200, constitutes an election by that person not to use the opportunity for a hearing concerning the action proposed and a waiver of any contentions concerning the legal status of that person's drug products. Any new drug product marketed without an approved new drug application is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for a hearing that there is no genuine and substantial issue of fact that precludes the withdrawal of approval of the applications, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions under this notice of opportunity for a hearing are to be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (section 505 (21 U.S.C. 355)) and under authority delegated to the Director, CDER (21 CFR 5.82).

VI. References

The following references are on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Horwitz et al., "Phenylpropranolamine & Risk of Hemorrhagic Stroke: Final Report of The Hemorrhagic Stroke Project," May 2000 in Comment No. C230, Docket No. 76N-052N and Comment No. C114, Docket No. 81N-0022.

2. Phenylpropranolamine Case Reports From 1991-2000 on File in Docket Nos. 76N-052N and 81N-0022.

3. Consumer Healthcare Products Association (CHPA), "Comments on the Hemorrhagic Stroke Project Report," May 24, 2000, in Comment No. C231, Docket No. 76N-052N and Comment No. C113, Docket No. 81N-0022.

4. Food and Drug Administration, Summary Minutes of Nonprescription Drugs Advisory Committee Meeting, October 19, 2000.

Dated: June 1, 2001.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 01-20300 Filed 8-13-01; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N-0068]

FDA Tissue Reference Group—The Process; Public Workshop

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public workshop.

The Food and Drug Administration (FDA) is announcing a public workshop entitled "FDA Tissue Reference Group—The Process." This public workshop is intended to provide information about the tissue reference group history, process, and other related matters. The FDA public workshop follows the American Association of Tissue Banks annual meeting held from August 25 to August 28, 2001.

Date and Time: The public workshop will be held on August 29, 2001, from 9:30 a.m. to 11:30 a.m.

Location: The public workshop will be held at the Marriott Wardman Park Hotel, 2660 Woodley Rd. NW., Washington, DC 20008.

Contact: Martha Wells, Center for Biologics Evaluation and Research (HFM-305), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-6106, or Ruth Solomon (address above), 301-827-6107, FAX 301-827-2844.

Registration: No preregistration is required. Registration at the site will be done on a space available basis on the day of the public workshop, beginning at 8:30 a.m. There is no registration fee. If you need special accommodations due to a disability, please contact Martha Wells at least 7 days in advance.

Transcripts: Transcripts of the public workshop may be requested in writing from the Freedom of Information Office (HFI-35), Food and Drug Administration, 5600 Fishers Lane, rm. 12A-16, Rockville, MD 20857,

approximately 15 working days after the public workshop at a cost of 10 per page. The public workshop transcript will also be available on the Internet at <http://www.fda.gov/cber/minutes/workshop-min.htm>.

SUPPLEMENTARY INFORMATION: The Tissue Reference Group (TRG) is part of the Tissue Action Plan, which was developed to implement the "Proposed Approach to the Regulation of Cellular and Tissue-based Products" dated February 28, 1997 (62 FR 9721, March 4, 1997). The purpose of the TRG is to provide a single reference point for product specific questions from sponsors or their designated representatives about jurisdiction, policy, and regulation of human cells, tissues, and cellular and tissue-based products (HCT/Ps). The agenda for the public workshop includes the following: (1) History of the TRG; (2) TRG process for making recommendations to the FDA Center Directors; (3) request for designation process; (4) confidentiality and the Freedom of Information Act process; and (5) factors for regulation of HCT/Ps solely under section 361 of the Public Health Service Act. The public workshop information is posted on the Internet at <http://www.fda.gov/cber/meetings/trgproc082901.htm>.

Dated: August 8, 2001.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 01-20362 Filed 8-13-01; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, DHHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by agencies of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by contacting Wendy R. Sanhai, Ph.D., at the Office of Technology Transfer,

Tab 48

Federal Register of February 20, 2002
(67 FR 7702)

Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved under a new drug application (NDA). Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary to gain approval of an NDA. The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book." Under FDA regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162). Regulations also provide that the agency

must make a determination as to whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved (§ 314.161(a)(1) (21 CFR 314.161(a)(1))). FDA may not approve an ANDA that does not refer to a listed drug.

On August 31, 2001, AAI International submitted a citizen petition (Docket No. 01P-0383/CP1) under 21 CFR 10.30 to FDA requesting that the agency determine whether azathioprine 25-mg tablet was withdrawn from sale for reasons of safety or effectiveness. Azathioprine 25-mg tablet is the subject of NDA 016-324. FDA approved NDA 016-324, currently held by Prometheus Laboratories, Inc. (Prometheus), on March 21, 1980. FDA has determined that azathioprine 25-mg tablet was withdrawn from sale.

FDA has reviewed its records and, under § 314.161, has determined that azathioprine 25-mg tablet was not withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will continue to list azathioprine 25-mg tablet in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to azathioprine 25-mg tablet may be approved by the agency.

Dated: February 11, 2002.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 02-4030 Filed 2-19-02; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 02N-0035]

Mylan Pharmaceuticals et al.; Withdrawal of Approval of 34 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of 34 abbreviated new drug applications (ANDAs). The holders of the applications notified the agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

DATES: Effective March 22, 2002.

FOR FURTHER INFORMATION CONTACT: Florine P. Purdie, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: The holders of the applications listed in the table in this document have informed FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications. The applicants have also, by their request, waived their opportunity for a hearing.

ANDA No.	Drug	Applicant
61-530	Penicillin V Potassium Tablets USP, 250 milligrams (mg) and 500 mg.	Mylan Pharmaceuticals, Inc., 781 Chestnut Ridge Rd., P.O. Box 4310 Morgantown, WV 26504-4310.
61-829	Ampicillin for Oral Suspension USP, 125 mg/5 milliliters (mL) and 250mg/5 mL.	Do.
62-067	Amoxicillin Capsules USP, 250 mg and 500 mg	Do.
62-104	Neomycin Sulfate with Hydrocortisone Ointment USP, 0.35% and 1%.	Clay-Park Laboratories, Inc., 1700 Bathgate Ave., Bronx, NY 10457.
62-280	Nystatin and Triamcinolone Acetonide Ointment USP	Do.
62-372	Mezlin (sterile mezlocillin sodium)	Bayer Corp. Pharmaceutical Division, 400 Morgan Lane, West Haven, CT 06516.
62-697	Mezlin (sterile mezlocillin sodium)	Do.
71-099	Bromatapp ER (brompheniramine maleate/phenylpropanolamine hydrochloride (HCl)) Extended-Release Tablets, 12 mg/75 mg.	Copley Pharmaceuticals, Inc., 25 John Rd. Canton, MA 02021.
71-551	Flurazepam HCl Capsules USP, 30 mg	Purepac Pharmaceutical Co., 200 Elmora Ave., Elizabethtown, NJ 07207.
71-927	Flurazepam HCl Capsules USP, 15 mg	Do.
72-027	Fentanyl Citrate and Droperidol Injection	AstraZeneca LP, 1800 Concord Pike, P.O. Box 8355, Wilmington, DE 19803-8355.
72-070	Nalbuphine HCl Injection USP, 10 mg/mL	Do.
72-073	Nalbuphine HCl Injection USP, 20 mg/mL	Do.
72-921	Prazosin HCl Capsules USP, 2 mg	Purepac Pharmaceutical Co.
72-991	Prazosin HCl Capsules USP, 1 mg	Do.
72-992	Prazosin HCl Capsules USP, 5 mg	Do.
73-690	Calcitonin-Salmon Injection, 200 international units/mL	AstraZeneca LP.

ANDA No.	Drug	Applicant
74-579	Betamethasone Dipropionate Cream USP, 0.05% (base)	Clay-Park Laboratories, Inc.
75-263	Midazolam HCl Injection, 5 mg (base)/mL	AstraZeneca LP.
75-348	Ketorolac Tromethamine Injection USP, 15 mg/mL and 30 mg/mL.	Apothecon, Inc., P.O. Box 4500, Princeton, NJ 08543-4500.
75-355	Labetalol HCl Injection USP, 5 mg/mL	Do.
75-620	Midazolam HCl Injection, 1 mg (base)/mL and 5 mg (base)/mL.	Do.
75-641	Midazolam HCl Injection, 5 mg (base)/mL	Do.
75-642	Bisoprololone Fumarate and Hydrochlorothiazide Tablets	Do.
75-707	Famotidine Injection, 10 mg/mL	Do.
75-708	Famotidine Injection, 10 mg/mL (preservative free)	Do.
83-115	Niacin Tablets USP, 500 mg	Impax Laboratories, Inc., 30831 Huntwood Ave., Hayward, CA 94544.
84-968	Nitrofurazone Ointment USP, 0.2%	Clay-Park Laboratories, Inc.
85-130	Nitrofurazone Topical Solution USP, 0.2%	Do.
86-424	Triple Sulfa Vaginal Cream	Altana Inc., 60 Baylis Rd., Melville, NY 11747.
86-810	Fluocinolone Acetonide Cream USP, 0.01%	Clay-Park Laboratories, Inc.
86-811	Fluocinolone Acetonide Cream USP, 0.025%	Do.
89-784	Meperidine HCl Injection USP, 50 mg/mL	AstraZeneca LP.
89-788	Meperidine HCl Injection USP, 1,000 mg/mL	Do.

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) and under authority delegated to the Director, Center for Drug Evaluation and Research (21 CFR 5.82), approval of the applications listed in the table in this document, and all amendments and supplements thereto, is hereby withdrawn, effective March 22, 2002.

Dated: February 12, 2002.

Steven K. Galson,

Deputy Director, Center for Drug Evaluation and Research.

[FR Doc. 02-4091 Filed 2-19-02; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01D-0064]

Draft Special Control Guidance Document on Encapsulated Amalgam, Amalgam Alloy, and Dental Mercury Labeling; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of the draft guidance entitled "Special Control Guidance Document on Encapsulated Amalgam, Amalgam Alloy, and Dental Mercury Labeling." This draft guidance is neither final nor is it in effect at this time. Elsewhere in this issue of the **Federal Register**, the agency is proposing to classify encapsulated amalgam into class II, to amend the classification

regulation for amalgam alloy to provide for special controls, and to reclassify dental mercury into class II. The draft guidance document is intended to serve as a special control for these devices.

DATES: Submit written or electronic comments on the draft guidance by May 21, 2002. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies on a 3.5" diskette of the draft guidance entitled "Special Control Guidance Document on Encapsulated Amalgam, Amalgam Alloy, and Dental Mercury Labeling" to the Division of Small Manufacturers Assistance (HFZ-220), Center for Devices and Radiological Health (CDRH), Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850. Send two self-addressed adhesive labels to assist that office in processing your request, or fax your request to 301-443-8818. Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. Comments should be identified with the docket number found in brackets in the heading of this document. See the **SUPPLEMENTARY INFORMATION** section for information on electronic access to the draft guidance.

FOR FURTHER INFORMATION CONTACT: Susan Runner, Center for Devices and Radiological Health (HFZ-410), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301-827-5283.

SUPPLEMENTARY INFORMATION:

I. Background

Elsewhere in this issue of the **Federal Register**, the agency is proposing to classify encapsulated amalgam into class II, to amend the classification regulation for amalgam alloy to provide for special controls, and to reclassify dental mercury into class II. The draft guidance document is intended to serve as a special control for these devices. The guidance document contains recommendations concerning the content and format of labeling for these devices.

II. Significance of Guidance

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). This draft guidance document represents the agency's current thinking on encapsulated amalgam, amalgam alloy, and dental mercury labeling. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the applicable statutes and regulations. This draft guidance document is issued as a level 1 guidance consistent with the GGP regulations.

III. Electronic Access

In order to receive the draft guidance entitled "Special Control Guidance Document on Encapsulated Amalgam, Amalgam Alloy, and Dental Mercury Labeling" via your fax machine, call the CDRH Facts-On-Demand system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. At the first voice prompt press 1 to enter the system. At the second voice prompt press 1 to order a document. Enter the document

Tab 49

Federal Register of February 22, 2014
(79 FR 75988)

B. Public Response and NCUA's Current Plan

NCUA received eight comments in response to its first notice, four comments in response to its second notice, six in response to the third notice, eleven in response to the fourth notice, and five in response to the fifth notice. The comments have been posted on the interagency EGRPRA Web site, <http://www.EGRPRA.gov>, and can be viewed by clicking on "Comments." NCUA is actively reviewing the comments received about specific ways to reduce regulatory burden, as well as conducting its own analyses. Because the main purpose of this notice is to request comment on the next category of regulations, NCUA will not discuss specific recommendations received in response to earlier notices here. As NCUA develops initiatives to reduce burden on specific subjects in the future—whether through regulatory, legislative, or other channels—it will discuss the public's recommendations that relate to its proposed actions.

III. Request for Comment on Agency Programs, Capital and Corporate Credit Union Categories

NCUA is asking the public to identify the ways in which the rules in the category of Agency Programs, Capital and Corporate Credit Unions may be outdated, unnecessary, or unduly burdensome. If the implementation of a comment would require modifying a statute that underlies the regulation, the comment should, if possible, identify the needed statutory change. NCUA encourages comments that not only deal with individual rules or requirements but also pertain to certain product lines. A product line approach is consistent with EGRPRA's focus on how rules interact, and may be especially helpful in exposing redundant or potentially inconsistent regulatory requirements. NCUA recognizes that commenters using a product line approach may want to make recommendations about rules that are not in the current request for comment. They should do so since the EGRPRA categories are designed to stimulate creative approaches rather than limiting them.

Specific issues to consider. While all comments are welcome, NCUA specifically invites comment on the following issues:

- *Need for statutory change.* Do any of the statutory requirements underlying these regulations impose redundant, conflicting or otherwise unduly burdensome requirements? Are there less burdensome alternatives?

- *Need and purpose of the regulations.* Are the regulations consistent with the purposes of the statutes that they implement? Have circumstances changed so that the regulation is no longer necessary? Do changes in the financial products and services offered to consumers suggest a need to revise certain regulations or statutes? Do any of the regulations impose compliance burdens not required by the statutes they implement?

- *General approach/flexibility.* Generally, is there a different approach to regulating that NCUA could use that would achieve statutory goals while imposing less burden? Do any of the regulations in this category or the statutes underlying them impose unnecessarily inflexible requirements?

- *Effect of the regulations on competition.* Do any of the regulations in this category or the statutes underlying them create competitive disadvantages for credit unions compared to another part of the financial services industry?

- *Reporting, recordkeeping and disclosure requirements.* Do any of the regulations in this category or the statutes underlying them impose particularly burdensome reporting, recordkeeping or disclosure requirements? Are any of these requirements similar enough in purpose and use so that they could be consolidated? What, if any, of these requirements could be fulfilled electronically to reduce their burden? Are any of the reporting or recordkeeping requirements unnecessary to demonstrate compliance with the law?

- *Consistency and redundancy.* Do any of the regulations in this category impose inconsistent or redundant regulatory requirements that are not warranted by the purposes of the regulation?

- *Clarity.* Are the regulations in this category drafted in clear and easily understood language?

- *Burden on small insured institutions.* NCUA has a particular interest in minimizing burden on small insured credit unions (those with less than \$10 million in assets). More than half of federally-insured credit unions are small—having \$10 million in assets or less—as defined by NCUA in Interpretative Ruling and Policy Statement 03–2, Developing and Reviewing Government Regulations. NCUA solicits comment on how any regulations in this category could be changed to minimize any significant economic impact on a substantial number of small credit unions.

NCUA appreciates the efforts of all interested parties to help us eliminate outdated, unnecessary or unduly burdensome regulatory requirements.

IV. Regulations About Which Burden Reduction Recommendations Are Requested Currently

AGENCY PROGRAMS, CAPITAL, AND CORPORATE CREDIT UNIONS

Subject	Code of Federal Regulations (CFR) Citation
Community Development Revolving Loan Program.	12 CFR Part 705.
Central Liquidity Facility Designation of low-income status; receipt of secondary capital accounts by low-income designated credit unions.	12 CFR Part 725. 12 CFR 701.34.
Prompt Corrective Action.	12 CFR Part 702.
Adequacy of Reserves Corporate Credit Unions	12 CFR 741.3(a). 12 CFR Part 704.

By the National Credit Union Administration Board on December 15, 2005.

Mary F. Rupp,

Secretary of the Board.

[FR Doc. 05–24368 Filed 12–21–05; 8:45 am]

BILLING CODE 7535–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 341, and 357

[Docket Nos. 1976N–0052N (formerly 1976N–052N) and 1981N–0022 (formerly 81N–0022)]

RIN 0910–AF34, 0910–AF45

Phenylpropanolamine-Containing Drug Products for Over-the-Counter Human Use; Tentative Final Monographs

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking (notice) for over-the-counter (OTC) nasal decongestant and weight control drug products containing phenylpropanolamine preparations. This proposed rule reclassifies phenylpropanolamine preparations from their previously proposed monograph status (Category I) for these uses to nonmonograph (Category II)

status based on safety concerns. FDA is issuing this proposed rule after considering new data and information on the safety of phenylpropanolamine as part of its ongoing review of OTC drug products.

DATES: Submit written and electronic comments and new data by March 22, 2006. Written and electronic comments on the agency's economic impact determination by March 22, 2006. Please see section X of this document for the effective date of any final rule that may be published based on this proposal.

ADDRESSES: You may submit comments, identified by Docket Nos. 1976N-0052N and 1981N-0022 and/RIN number 0910-AF34 and 0910-AF45, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.
- Agency Web site: <http://www.fda.gov/dockets/ecomments>. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]: Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No(s), and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to <http://www.fda.gov/ohrms/dockets/default.htm>, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Gerald M. Rachanow or Robert L. Sherman, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5426, Silver Spring, MD 20993, 301-796-2090.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published an advance notice of proposed rulemaking (ANPR) under 21 CFR 330.10(a)(6) to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Cough-Cold Panel). This Panel was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. This Panel recommended monograph (Category I) status for phenylpropanolamine preparations (phenylpropanolamine bitartrate, phenylpropanolamine hydrochloride, and phenylpropanolamine maleate) as an oral nasal decongestant.

In the **Federal Register** of February 26, 1982 (47 FR 8466), FDA published an ANPR to establish a monograph for OTC weight control drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel). This Panel was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. This Panel recommended monograph status for phenylpropanolamine hydrochloride for weight control use. However, after the Panel submitted its report, FDA became aware of and discussed studies indicating that certain dosages of phenylpropanolamine cause blood pressure elevation (47 FR 8466). Therefore, in the preamble to the Panel's report, FDA specifically requested data and information on the extent to which phenylpropanolamine induces or

aggravates hypertension (47 FR 8466 at 8468).

In the **Federal Register** of January 15, 1985 (50 FR 2220), FDA published a proposed regulation for OTC nasal decongestant drug products in the form of a tentative final monograph. Because the issues concerning the safety of phenylpropanolamine for nasal decongestant and weight control use were closely related, FDA stated in that document that it was deferring phenylpropanolamine and would consider the issues concurrently in a future **Federal Register** publication (50 FR 2220 at 2221).

Phenylpropanolamine was not included in the October 30, 1990 (55 FR 45788), proposed rule or the August 8, 1991 (56 FR 37792), final rule for OTC weight control drug products, in which 111 weight control active ingredients were determined to be nonmonograph. Benzocaine and phenylpropanolamine hydrochloride, the two ingredients the Miscellaneous Internal Panel classified as Category I, were deferred to a future publication. The current document addresses phenylpropanolamine. FDA will discuss benzocaine for weight control use in a future issue of the **Federal Register**.

In a letter to the Nonprescription Drug Manufacturers Association dated March 9, 1993 (Ref. 1), FDA stated that, based on a relatively small number of spontaneous reports of intracranial bleeding associated with weight control drug products containing phenylpropanolamine, FDA's principal safety concern was the possibility that phenylpropanolamine might increase the risk of stroke. FDA further stated that although the available data could not support a conclusion that phenylpropanolamine increased the rate of strokes, these data could not rule out the possibility of an increased stroke risk associated with OTC phenylpropanolamine use.

Phenylpropanolamine preparations also were not included in the final rule for OTC nasal decongestant drug products that published in the **Federal Register** of August 23, 1994 (59 FR 43386). FDA stated that because of still unresolved safety issues concerning phenylpropanolamine preparations, it was deferring action on this drug (59 FR 43386).

In the **Federal Register** of February 14, 1996 (61 FR 5912), FDA published a proposed regulation requiring new warning labeling for all OTC phenylpropanolamine preparations. In that document, FDA stated that dose-response studies submitted by drug manufacturers to investigate phenylpropanolamine's effects on blood

pressure were inadequate to alleviate FDA's concern that phenylpropanolamine used in OTC drug products might increase the risk of hemorrhagic stroke.

Spontaneous case reports and published case series accumulated from 1969 to 1991 suggested a possible association between phenylpropanolamine use and an increased risk of hemorrhagic stroke. Thus, the status of phenylpropanolamine had been deferred pending further study. In an effort to resolve these issues, representatives of the manufacturers of products containing phenylpropanolamine and FDA staff met in 1991 to plan a study that could further examine whether there was an association between phenylpropanolamine use and risk of hemorrhagic stroke. An epidemiologic case-control study was determined to be the most feasible study design to evaluate the possible association between exposure to phenylpropanolamine and a rare outcome such as hemorrhagic stroke. The industry sponsors of the study selected investigators at Yale University School of Medicine to conduct the study. The Yale investigators submitted protocols to FDA for review. The results of the study are discussed in section II of this document.

In this proposed rule, FDA proposes to categorize all phenylpropanolamine preparations as nonmonograph (Category II) for OTC use in both nasal decongestant and weight control drug products. This action is based on reports published in the medical literature, FDA's initial review of adverse drug event reports associated with OTC phenylpropanolamine drug products between 1969 and 1991, continuing adverse drug event reports since 1991, and the results of the Yale Hemorrhagic Stroke Project (Ref. 2). Because safety concerns are the basis for this proposed nonmonograph status, FDA does not address the effectiveness of phenylpropanolamine preparations in this document.

II. Data on the Safety of Phenylpropanolamine from the Yale Hemorrhagic Stroke Project

A. Introduction and Rationale

The following discussion was developed from the study report (Ref. 2) submitted to FDA.

The Yale Hemorrhagic Stroke Project (Ref. 2) was a case-control study. Because several case reports had involved strokes in young women who took phenylpropanolamine as an

appetite suppressant, often after a first dose, the study examined three questions: (1) Whether all users of phenylpropanolamine, compared to nonusers, had an increased risk of hemorrhagic stroke, (2) the possible association between phenylpropanolamine and hemorrhagic stroke by type of exposure (appetite suppressant or cough-cold product), and (3) among women age 18 to 49 years, the possible association between first use of phenylpropanolamine and hemorrhagic stroke and the possible association between use of phenylpropanolamine-containing appetite suppressants and hemorrhagic stroke.

The study was performed between December 1994 and July 1999 and involved men and women 18 to 49 years old who were hospitalized with a primary subarachnoid hemorrhage (SAH) or a primary intracerebral hemorrhage (ICH) (unrelated to ischemic infarction, trauma, cerebral thrombosis, or thrombolytic therapy). The subjects were recruited from 44 hospitals in 4 geographic regions of the United States.

Both SAH and ICH were determined by clinical symptoms and specific diagnostic information from computed tomography. Magnetic resonance imaging was accepted for the diagnosis of SAH or ICH only if other procedures were not diagnostic. Because misclassification of exposure status by surrogate responders could increase or reduce the observed odds ratio and the true level of risk (Ref. 2), subjects were ineligible for enrollment if they died (n=389) or were not able to communicate (n=194) within 30 days after their event. Subjects were also ineligible if they had a previously diagnosed brain lesion predisposing to hemorrhage risk (e.g., arteriovenous malformation, vascular aneurysm, or tumor) (n=48), a prior stroke (n=120), or first experienced stroke symptoms after being in the hospital for 72 hours (e.g., for an unrelated matter) (n=33).

For each case subject, random digit dialing (matched to the first three digits of the case subject's telephone number) was used to identify two control subjects who were matched on: (1) Gender, (2) race (African-American versus non-African-American), (3) age (within 3 years for case subjects less than 30 years and within 5 years for subjects 30 years or over), (4) educational level, and (5) telephone exchange (as a surrogate for socioeconomic status). Case subjects and control subjects were interviewed to ascertain medical history, medication use, and habits affecting health, such as use of tobacco and alcohol. Interviews

of control subjects were completed within 30 days of the case subject's stroke event to minimize seasonal differences in the likelihood of exposure to cough-cold drug products. Eligibility criteria for control subjects were the same as for case subjects except for the stroke event. During the consent procedure, all subjects (cases and controls) were told that the study was designed to examine causes of hemorrhagic stroke in young persons without specific mention of phenylpropanolamine or other potential risk factors. Case and control subjects were interviewed by a trained interviewer using a structured questionnaire developed for this study. Reported phenylpropanolamine exposures were verified by the study investigators, who documented the actual product(s) used and their ingredients.

A focal time (the calendar day and the time of onset of symptoms plausibly related to hemorrhagic stroke that caused a subject to seek medical help) was identified for each case subject. The focal time used for each control subject was matched to the day of the week and the time of day that corresponded to the case subject's focal time. Control subjects were interviewed within 7 days of their focal time to minimize recall bias.

The exposure window referred to the interval before the focal time (onset of symptoms) when the status of a subject's exposure to phenylpropanolamine was defined. For analyses other than those involving first use of phenylpropanolamine, the exposure window was defined as 4 days preceding the focal time. For first use of phenylpropanolamine, the exposure window was within 24 hours before the focal time, provided that the subject had not used any other phenylpropanolamine products during the preceding 2 weeks. To maintain a consistent reference group, nonexposure for all analyses was defined as no use of phenylpropanolamine within 2 weeks before the focal time. Exposure windows for control subjects were matched to those for the corresponding case subjects.

B. Statistical Analysis

Case and control subjects were compared on a variety of clinical and demographic features, including those used in matching, to determine the comparability of the two groups. Statistical comparisons were made using chi-square tests and the Fisher's exact test (where appropriate) for categorical variables, and the Student t-test for continuous variables. For the

analyses of the primary endpoints, conditional logistic models for matched sets (with a variable number of controls per case) were used to estimate odds ratios, lower limits of the one-sided 95 percent confidence intervals, and p-values for the risk factors under investigation. One-tailed statistical results were reported because the focus of the study was whether phenylpropranolamine use increased the risk of stroke and this was the pre-specified analysis. Each logistic model was estimated with two mutually exclusive binary exposure terms: (1) The subject's primary exposure status as defined by the specific aim (e.g., phenylpropranolamine use in the 3-day window; yes/no), and (2) phenylpropranolamine users who were not exposed within the 3-day window (but with some exposure within 2 weeks of the focal time).

In multivariate conditional logistic models (using asymptotic methods), adjustments were made for race (African-American compared with non-African-American), history of hypertension (yes/no), and current cigarette smoking (current compared with never or ex-smoker) because these are the major risk factors for stroke. Other underlying diseases and/or conditions (i.e. diabetes, polycystic kidney disease, congestive heart failure, sickle cell anemia, and clotting disorders) were also examined to determine if any of them, when added to this basic adjusted model, altered the matched odds ratio by at least 10 percent.

C. Study Results

There were 702 case subjects, including 425 subjects (60 percent) with an SAH and 277 (40 percent) with an ICH, and 1,376 control subjects. Hemorrhage was associated with an aneurysm in 307 subjects (44 percent), an arteriovenous malformation in 50 subjects (7 percent), and a tumor in one subject (0.1 percent). Two control subjects were located for each of 674 case subjects (96 percent) and one control subject for each of 28 case subjects (4 percent). All control subjects were matched to their case subjects on gender and telephone exchange. Age matching was successful for 1,367 controls (99 percent) and race matching was achieved for 1,321 controls (96 percent). Twenty-seven case subjects and 33 control subjects reported phenylpropranolamine use within the 3-day exposure window.

Compared to control subjects, case subjects were significantly more likely to be African-American (21 percent compared with 17 percent). Case

subjects were also more likely to report lower educational achievement (20 percent did not graduate from high school compared with 9 percent of control subjects), current cigarette smoking (51 percent compared with 30 percent), a history of hypertension (39 percent compared with 20 percent), family history of hemorrhagic stroke (9 percent compared with 5 percent), heavy alcohol use (14 percent compared with 7 percent), and recent cocaine use (2 percent compared with less than 1 percent). For all other clinical variables examined, case and control subjects were not dissimilar. Case subjects were significantly (0.05) less likely to report use of nonsteroidal anti-inflammatory drugs and significantly more likely to report use of caffeine and nicotine in the 3 days before their event. Of the factors examined, only education changed the adjusted odds ratio for the association between phenylpropranolamine and hemorrhagic stroke by more than 10 percent, and this demographic factor was included in all subsequent models.

Analyses of the study results demonstrated an association between hemorrhagic stroke and use of phenylpropranolamine (in both nasal decongestant and weight control drug products) in the 3 days prior to the event. Such use of phenylpropranolamine, compared to no use in the prior 2 weeks, was associated with a relative risk for hemorrhagic stroke of 1.67 (unadjusted odds ratio) ($p=0.040$). The corresponding adjusted odds ratio was 1.49 (lower limit of the one-sided 95 percent confidence interval (LCL)=0.93, $p=0.084$).

The relative risks of hemorrhagic stroke observed with use of the two types of phenylpropranolamine-containing products (in the 3-day exposure window, compared to no use in the prior 2 weeks) were as follows. For cough-cold products, the unadjusted odds ratio was 1.38 ($p=0.163$) and the adjusted odds ratio (AOR) was 1.23 (LCL=0.75, $p=0.245$). For weight control products, the unadjusted odds ratio was 11.98 ($p=0.007$) and the AOR was 15.92 (LCL=2.04, $p=0.013$).

To analyze the relation between recency of phenylpropranolamine exposure and risk for hemorrhagic stroke, odds ratios were also calculated according to the timing of the most recent phenylpropranolamine use. The pre-specified definition for current use was use of any phenylpropranolamine-containing product on the day of the event (before focal time) or the preceding calendar day. Prior use was defined as use 2 or 3 calendar days before the focal time. The odds ratio was slightly higher for current use

(AOR=1.61, LCL=0.93, $p=0.078$) than for prior use (AOR=1.16, LCL=0.47, $p=0.393$). Within current use, odds ratios were then calculated according to first use or non-first use. First use was defined as current use with no other use within the prior 2 weeks. Non-first use included other uses within the 2-week interval. The odds ratio was higher for first use (AOR=3.14, LCL=1.16, $p=0.029$) than for non-first use (AOR=1.20, LCL=0.61, $p=0.329$). All first uses of phenylpropranolamine ($n=13$) reported in these data were in cough-cold products.

In women using phenylpropranolamine in weight control drug products (3-day exposure window, versus no use in the prior 2 weeks), the unadjusted odds ratio for hemorrhagic stroke was 12.19 ($p=0.006$) and the AOR was 16.58 (LCL=2.22, $p=0.011$). All hemorrhagic stroke events that occurred within the 3-day exposure window were in women. In the analyses of the association between hemorrhagic stroke and first-day use of phenylpropranolamine, 11 of the 13 first-day use events were in women (7 cases compared with 4 controls). The unadjusted odds ratio was 3.50 ($p=0.039$) and the AOR was 3.13 (LCL=1.05, $p=0.042$).

Based on the findings that risk for hemorrhagic stroke seemed to be concentrated among current users, the association between current phenylpropranolamine dose and risk for hemorrhagic stroke was examined. Among 21 exposed control subjects, the median current dose of phenylpropranolamine (i.e., total amount taken on the index day or preceding day) was 75 milligrams (mg). Analysis according to dose shows that the odds ratio was higher for current doses above the median (greater than 75 mg) (AOR=2.31, LCL=1.10, $p=0.031$) than for lower doses (AOR=1.01, LCL=0.43, $p=0.490$). Among first-dose users, four of eight cases and two of five controls were exposed to greater than 75 mg of phenylpropranolamine. To examine the potential effect of ambiguity in the correct focal time, the odds ratios were recalculated after excluding all 154 case subjects who were classified as having a definite ($n=76$) or uncertain ($n=78$) sentinel symptom preceding the stroke event. The magnitude of the AORs did not change substantially.

D. Study Conclusions

According to the investigators, several features of the study supported the validity of the study findings regarding a demonstrated association between phenylpropranolamine use and risk of hemorrhagic stroke in subjects between

18 and 49 years of age. First, in addition to the finding of elevated odds ratios that reached statistical significance, the magnitude of the odds ratios for phenylpropanolamine use as an appetite suppressant (15.92) and as a first-dose use (3.14) remained large even after adjustment for important clinical features. Second, the data demonstrate an association between both types of phenylpropanolamine drug products (nasal decongestant and weight control) and hemorrhagic stroke. Because so few men were exposed to phenylpropanolamine in this study (n=19), it was not possible to determine whether their risk for hemorrhagic stroke (when using phenylpropanolamine) is different from that of women.

E. FDA's Evaluation of the Study

Observational studies, particularly case-control studies, are potentially subject to a number of biases, and this case-control study is no exception. The hallmark of a good case-control study is that biases are anticipated and measures are instituted in the design and analysis stages to minimize biases to the greatest extent possible.

Strict diagnostic criteria, as described previously, were developed to ensure accurate identification of hemorrhagic stroke cases in the target population. A number of steps were taken to minimize misclassification bias. One of the investigators confirmed the stroke by reviewing the medical records of suspected cases, without knowledge of the exposure status. Inclusion and exclusion criteria were clearly defined for both cases and controls. Exposure was clearly defined, an exposure window was identified, and exposure was ascertained by trained interviewers. Interviewers were randomly assigned to cases or controls, and questions were asked about multiple medications, thus blinding subjects to the exact exposure under study. The interviews were highly structured and scripted to protect against interviewer bias. Because phenylpropanolamine use might be seasonal, controls were identified and interviewed within 30 days of the date of their matched case subject's stroke, to ensure that cases and controls had similar opportunities for exposure. Controls were also matched to cases for day of the week and time of day of the stroke. This matching strategy helped increase the probability that exposure to any seasonal medication or other covariates (e.g., alcohol drinking or cigarette smoking) was similar between cases and controls.

The investigators attempted to identify two controls per case by using

random digit dialing (with a match for the first three digits of the telephone number). Because controls were population-based, the results were generalizable to the source population from which the cases and controls were drawn. Matching on race and educational level was slightly unequal between cases and controls. The investigators further controlled for these inequalities by adjustment during analysis. The agency concludes that matching was largely successful.

The investigators reduced the possibility of misclassification of phenylpropanolamine use by using a highly structured questionnaire. Each reported medication was verified by asking subjects to present the actual container or by picking out reported brand-name medications from a book containing photographs. Verification of medication use in the 3-day window prior to the focal time was 96 and 94 percent for cases and controls, respectively. The investigators conducted two additional steps to further ensure that the possibility of exposure misclassification error was reduced to an absolute minimum: (1) Only "definite" and "possible" exposure responses were considered in the analyses, and (2) the use of other OTC drugs between cases and controls were compared to ensure that the cases did not have greater recall of the use of any drugs as a reason for their stroke. Based on this analysis, FDA did not find any evidence of recall or misclassification bias.

Several key elements of study design and conduct determine the success of a case-control study. Studies must have adequate sample size and/or power to detect a difference between treatment groups if a difference really exists, and detection of rare events can require substantial numbers of study subjects. FDA had concerns that the protocol might result in an underpowered study because the sample size calculation was based on an odds ratio of five for an association between first-day use of phenylpropanolamine and hemorrhagic stroke. This ratio was derived primarily from study conduct considerations, such as time and cost, rather than on predictive epidemiologic data that may have suggested that a greater number of subjects would be needed to show a difference between groups. Because case-control studies also demand adherence to strict matching criteria between case and control subjects, the duration of this study was longer than expected due to difficulties in recruiting well-matched controls.

The resultant study was the largest prospective case-control study ever

conducted on hemorrhagic stroke. FDA finds that, despite these limitations, this study was well-conducted and the statistical analyses demonstrate an association between phenylpropanolamine and hemorrhagic stroke, as explained as follows.

FDA notes that the three most important risk factors (race, history of hypertension, and cigarette smoking) were included in the multivariate analysis (basic adjusted model). The confounding effect of the other covariates was examined if adding any of them to the basic model altered the odds ratio estimate by 10 percent. High school education was the only covariate determined to change the odds ratio by at least 10 percent.

Because the study had a matched design, FDA considers the conditional logistic regression model appropriate to calculate both unadjusted and AORs. In addition, the number of exposures was small, particularly for analysis of appetite suppressant and first use, thus, the authors calculated the confidence interval of the unadjusted odds ratio based on an exact method.

Hypertension is the single most important risk factor for a stroke. Misclassification of hypertension status could result in residual confounding. FDA examined the possible effects of this residual confounding on the results of the study. FDA found that the odds ratio for appetite suppressant use was 15.92, a substantial increase in risk. Its very magnitude makes it difficult to explain by confounding alone. Because product labeling advises hypertensive persons to avoid phenylpropanolamine use, the association of phenylpropanolamine use with hypertension should be negative. Such a negative association would result in biasing the result towards no association if the confounding factor is not controlled for. In addition to the steps taken by the investigators, FDA examined this further by additional analyses restricted to subjects without a past history of hypertension, and the results were not significantly different, thereby providing additional evidence that confounding by hypertension was not present in the study.

FDA requested the Yale investigators to explore the possible impact of cigarette smoking and alcohol consumption in more detail. The investigators found that the odds ratios for phenylpropanolamine and stroke were essentially unchanged by inclusion of several qualitative and quantitative measures of smoking and alcohol consumption.

The investigators examined the association between current

phenylpropanolamine dose and risk for hemorrhagic stroke. Among 21 exposed control subjects, the median current dose of phenylpropanolamine (i.e., the total amount taken on the index day or preceding day) was 75 mg. The AOR was higher for current doses above 75 mg than for lower doses. Among first dose users, four of eight cases and two of five controls were exposed to greater than 75 mg of phenylpropanolamine. As 75 mg is a single dose of many OTC extended-release phenylpropanolamine cough-cold drug products with recommended adult dosing every 12 hours (150 mg a day), the agency further evaluated the association between risk of hemorrhagic stroke and a range of current phenylpropanolamine doses. Exploratory analyses suggest that there may be an increased risk of hemorrhagic stroke with labeled doses at or above 75 mg a day. Although not statistically significant, a trend toward a dose-ordering of odds ratios was seen. The odds ratio was higher (AOR=2.31, LCL=1.10, p=0.031) for current doses above 75 mg than for doses below 75 mg (AOR=1.01, LCL=0.43, p=0.490).

FDA concludes that the Yale study (Ref. 2) was well-designed and demonstrated an association between use of phenylpropanolamine and an increased risk of hemorrhagic stroke. The increased risk was most striking in women and was associated with both use in appetite suppressants and first-dose use in cough-cold products. The case-control design was best suited for this study because the outcome under investigation was rare. The investigators took reasonable steps to minimize bias and confounding and built quality control measures into the study design. Analysis was appropriate for the type of study and was performed according to the protocol. The study had clear objectives and sound epidemiology practices were used in its design and execution.

F. Additional Reports

FDA reviewed its adverse events reporting system for spontaneous reports of hemorrhagic stroke from 1991 to 2000 and identified 22 cases, 16 in the 18 to 49 age group with 13 cases in women (Ref. 3). In all cases, the suspect drug was an extended-release product containing 75 mg of phenylpropanolamine per unit dose. Of 11 cases for which the indication for use was provided, 10 reported use for respiratory symptoms. FDA believes that the fact that there were no reports associated with immediate release drug products marketed under the OTC drug monograph system may be related to the

lack of a requirement to submit any such reports to the agency.

Therefore, the absence of such reports does not indicate these products are not associated with adverse events.

G. Advisory Committee Recommendations

On October 19, 2000, at a public meeting, FDA presented to its Nonprescription Drugs Advisory Committee (NDAC) the regulatory history of OTC phenylpropanolamine (including FDA's concerns about case reports of hemorrhagic stroke associated with phenylpropanolamine prior to 1991), the data from the Yale Hemorrhagic Stroke Project, and additional case reports of stroke since 1991.

The Yale investigators presented the study results and their conclusions. Industry representatives raised concerns about the design of the study that they believed made interpretation of the results difficult (Ref. 4). NDAC evaluated whether the Yale study showed an association between phenylpropanolamine use and an increased risk of stroke in different populations aged 18 to 49 (female, male, both) and for different uses (nasal decongestant, appetite suppressant, all) (Ref. 5). More importantly, NDAC was asked if the data support the conclusion that there is an association between phenylpropanolamine and an increased risk of hemorrhagic stroke, taking into account all currently available information, including: (1) Phenylpropanolamine's effects on blood pressure, (2) spontaneous reports of hemorrhagic stroke associated with phenylpropanolamine from 1969 to 1991, (3) case reports in the medical literature, (4) continuing adverse drug reports to FDA from 1991 to the present, and (5) the results of the Yale Hemorrhagic Stroke Project. Thirteen of 14 NDAC members voted (with 1 voting "uncertain") that there is such an association (Ref. 5). When asked whether phenylpropanolamine can be generally recognized as safe for use as a nasal decongestant, 12 of the 14 NDAC members voted (with 2 abstaining) that phenylpropanolamine could not be considered to be generally recognized as safe for OTC nasal decongestant use. In addition, when asked whether phenylpropanolamine can be generally recognized as safe for use as an appetite suppressant, 13 of the 14 NDAC members voted (with 1 abstaining) that phenylpropanolamine could not be considered to be generally recognized as safe for OTC weight control use.

III. FDA's Tentative Conclusions on the Safety of Phenylpropanolamine

FDA believes that the known scientific evidence supports the conclusion that nasal decongestant and weight control drug products containing phenylpropanolamine cannot be generally recognized as safe and should no longer be available for OTC use. This evidence includes the results of the Yale study suggesting an association between phenylpropanolamine and hemorrhagic stroke, previous and continuing adverse event reports, reports in the published medical literature, and the biological plausibility related to phenylpropanolamine's ability to cause increases in blood pressure. As stated in section II.E of this document, FDA concludes that the Yale study (Ref. 2) was well-designed and demonstrated an association between use of phenylpropanolamine and an increased risk of hemorrhagic stroke. The increased risk was most striking in women and was associated with both use in appetite suppressants and first-dose use in cough-cold products. The case-control design was best suited for this study because the outcome under investigation was rare. The investigators took reasonable steps to minimize bias and confounding and built quality control measures into the study design. Analysis was appropriate for the type of study and was performed according to the protocol. The study had clear objectives and sound epidemiology practices were used in its design and execution. Regardless of the analytic methods used, the findings were consistent.

Although the Yale study focused on men and women 18 to 49 years of age, FDA has no data to show that the increased risk of hemorrhagic stroke is limited to a specific age range. While the Yale study was being conducted, FDA received spontaneous reports of hemorrhagic stroke in people 28 to 54 years of age with cough-cold products that contain OTC doses of phenylpropanolamine.

Because the factors that may cause some individuals to be particularly sensitive to the effects of phenylpropanolamine are unknown, individuals at risk cannot be adequately warned through labeling. Although there is no other active ingredient that is generally recognized as safe and effective for OTC weight control use, OTC nasal decongestant drug products can be reformulated with other ingredients, such as pseudoephedrine and phenylephrine. Because hemorrhagic strokes often lead to catastrophic, irreversible outcomes,

FDA concludes that the benefits of the intended uses of phenylpropanolamine do not outweigh the potential risk, and that phenylpropanolamine is not considered to be generally recognized as safe.

IV. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule might have a significant economic impact on a substantial number of small entities, an agency must consider alternatives that would minimize any significant economic impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by state, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation) in any one year.

FDA tentatively concludes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. As shown as follows, FDA does not believe the proposed rule will be economically significant as defined by the Executive order. Based on its preliminary Regulatory Flexibility Analysis, FDA tentatively concludes that this proposed rule would not impose a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for the proposed rule, because the proposed rule is not expected to result in an expenditure that would exceed \$100 million adjusted for inflation in any one year. The current inflation-adjusted statutory threshold is about \$110 million.

The purpose of the proposed rule is to establish that phenylpropanolamine preparations are not generally recognized as safe for OTC use both as a nasal decongestant and for weight control. This proposed rule would assure the removal of OTC drug products containing

phenylpropanolamine, if any are still marketed, and prohibit future marketing of such products.

FDA believes that the benefits of this rule justify the costs. Our estimate of the benefits of complete elimination of phenylpropanolamine preparations suggests that they could be as high as \$250 million to \$625 million annually, if estimated using a willingness to pay approach. The vast majority of these benefits are not directly attributable to this rule, however, because industry previously took voluntary action to discontinue production and marketing of phenylpropanolamine preparations.

Similarly, most costs of product withdrawal or reformulation have already been incurred because of the voluntary actions. However, a few affected products may still be available and products that have been withdrawn could still, in principle, be reintroduced in the absence of the rule. Any remaining products containing phenylpropanolamine will need to cease OTC marketing upon the effective date of any final rule, but can be reformulated with another ingredient, where applicable. Products that are reformulated will also need to be relabeled.

A. Background for Analysis of Impact

In November 2000, FDA issued a public health advisory on the safety of phenylpropanolamine and announced that it would take steps to remove phenylpropanolamine from all drug products and had requested all drug companies to voluntarily discontinue marketing products containing phenylpropanolamine (Ref. 6). As a result of this announcement and the publication of the Yale Hemorrhagic Stroke Project, national chain drugstore and major and smaller manufacturers voluntarily removed phenylpropanolamine-containing OTC drug products from the market. Manufacturers of phenylpropanolamine-containing OTC drug products were aware of the potential health problem and some manufacturers of OTC nasal decongestant drug products containing phenylpropanolamine had already reformulated or were in the process of reformulating their products to remove phenylpropanolamine in advance of FDA's announcement. Nevertheless, a number of factors markedly accelerated this trend:

- The recommendation of FDA's NDAC
- The publication of the results of the Yale Hemorrhagic Stroke Project
- FDA's subsequent announcement of its intent to reclassify phenylpropanolamine as a Category II

ingredient, and FDA's request for a voluntary recall.

These events led to the voluntary removal from the market of most remaining phenylpropanolamine-containing OTC drug products. Both market forces (i.e., avoidance of tort liability) and FDA's request for a voluntary recall contributed to the decision by retail establishments and manufacturers to discontinue sales. Because public awareness, market forces, and FDA's announcement and request to voluntarily withdraw occurred within a short span of time, it is not possible for FDA to disentangle the impact these various factors had on manufacturers' decisions to voluntarily recall phenylpropanolamine drug products.

OMB guidelines on economic impact analyses direct agencies to estimate costs and benefits from an appropriate baseline. "This baseline should be the best assessment of the way the world would look absent the proposed regulation" (Ref. 7). We do not believe that the conditions prior to FDA's announcement of its intent to classify this ingredient as nonmonograph are the appropriate baseline because the publication of the Yale Hemorrhagic Stroke Project in a leading medical journal alone would have generated a market response. We acknowledge that the timing and wording of FDA's public announcement and request for voluntary recalls contributed to the magnitude of the incurred costs. However, because the costs attributable to the withdrawal of phenylpropanolamine-containing OTC drug products have already occurred, and may have occurred absent this proposed rule, albeit at a slower pace, FDA believes present conditions are the appropriate baseline from which to estimate the impact of this proposed rule.

Even if all of these costs were attributed to this proposed rule, however, they would not rise to the \$100 million per year threshold sufficient to categorize this rule as economically significant under section 3.f. of E.O. 12866. Nonetheless, we account for as much of the cost as possible using 2000 as the baseline year for the number of affected products

B. Costs of Regulation

a. *Costs of removing products from the market.* FDA finds that a number of affected firms incurred substantial costs from these voluntary product withdrawals. In addition, we are not aware of any phenylpropanolamine-containing OTC drug products currently marketed, so we believe the removal-

related costs have already been incurred.

The voluntary product withdrawals primarily affected two major OTC drug markets—weight control and cough-cold medications. The weight control drug products sector reported \$48 million in annual sales for phenylpropanolamine-containing drug products in 2000. The much larger cough-cold products sector had total sales of about \$1.2 billion (Ref. 8), but FDA does not have an estimate of the proportion of this figure that included only phenylpropanolamine-containing products. As a result, FDA cannot estimate the total sales of all OTC drug product lines that contained phenylpropanolamine.

In 2000, FDA's drug listing system included approximately 400 drug products containing phenylpropanolamine, with approximately 100 manufacturers and 250 distributors and repackers. Many of the 400 products were marketed by distributors and hence do not represent unique formulations. FDA estimates that there may have been around 150 distinct products for both cough-cold and weight loss. Not all of these products, however, were reformulated. Some manufacturers had already added product lines containing a substitute active ingredient and had no plans to reformulate the older product. The sales volume of some products was too small to cover the cost of reformulation. Also, only one substitute active ingredient was available for weight control drug products. Hence, FDA estimates that only about 100 products were reformulated.

The cost to reformulate a product varies greatly depending on the nature of the change in formulation, the product, the process, and the size of the firm. To reformulate, manufacturers also have to redo validation (product, process, new supplier), conduct stability tests, and change master production records. FDA estimates that the full cost of reformulation ranged from \$100,000 to \$500,000 per product. Assuming that 100 products were reformulated implies a total estimated one-time reformulation cost of from \$10 million to \$50 million.

Manufacturers that reformulated would also have incurred costs to relabel their products. They would have had to revise the active (and for some the inactive) ingredient list and may have had to make other labeling changes if they removed the phenylpropanolamine from a combination product and did not replace it with another ingredient. FDA believes that relabeling costs of the type required by this proposed rule generally averaged about \$3,000 to \$4,000 per

stockkeeping unit (SKU) (individual products, packages, and sizes). Assuming 350 OTC SKUs in the marketplace were relabeled, the total one-time costs of relabeling would have ranged from \$1.05 to \$1.4 million.

Using 2000 as the baseline year for affected products, the total estimated one-time costs for reformulation and labeling range from \$11 million to \$51 million. Annualized over 20 years yields annual costs of \$0.7 - \$3.4 million (at 3 percent) and \$1.0 - \$4.8 million (at 7 percent).

b. *Distributional issues and impact on industry.* Other costs incurred by the industry include costs associated with the recall and destruction of inventory and the loss of product sales. FDA does not have reliable information to estimate either the incremental impacts of recalling and destroying product or to distinguish the market response to the results of the Yale study from FDA's announcement and request for voluntary withdrawal. Moreover, industry costs would be offset substantially by countervailing events including avoided lawsuits associated with continued marketing of products containing phenylpropanolamine and possibly reduced insurance costs. The value of lost profit due to lost product sales would generally be offset as firms gain sales by distributing substitute products. These gains and losses represent transfers within the industry and are not a social cost.

Reports of withdrawal related expenses from trade press and some 10-K filings with the Securities and Exchange Commission include other costs not attributable to costs of this regulation, such as set-asides for potential litigation. Because of this, we cannot use these reports as a basis for estimating regulatory costs. These reports, however, provide anecdotal information about the magnitude of the impact of the voluntary actions on specific firms. One of the hardest hit large multinational firms explained that the Company immediately ceased global production and shipments of any products containing phenylpropanolamine and voluntarily withdrew any such products from customer warehouses and retail store shelves. As a result, the Company recorded a special charge of \$80,000,000 to provide primarily for product returns and the write-off of inventory" (Ref. 9). Another heavily impacted large firm claimed that withdrawal would cost between \$51 and \$68 million (Ref. 10). Similarly, a large private-label manufacturer reportedly took a \$24 million charge against earnings (Ref. 11). These last two figures likely

included costs of product reformulation as well as lost inventory value and sales revenues. These accounts represent projections and are estimates for financial reporting requirements but do not accurately reflect actual costs used for regulatory impact analyses.

FDA believes that the lost sales estimates may be overstated, as alternative cough-cold drug products were widely available. Most manufacturers quickly offered alternative products and received offsetting increases in sales revenues. OMB guidelines for economic analysis state that, "[t]he preferred measure of cost is the 'opportunity cost of the resources used or the benefits forgone as a result of the regulatory action'" (Ref. 7).

The costs of reformulation, recalls, and lost inventories are clearly "opportunity costs," but the company sales revenues lost from recalled phenylpropanolamine-containing cough-cold drug products were likely matched by increased sales of other phenylpropanolamine-free products, frequently manufactured by the same or competing drug companies. These distributional effects are important to individual firms, but are not considered "opportunity costs."

c. *Summary of costs.* The regulatory costs of the proposed rule would include: (1) The one-time costs to reformulate and relabel affected products, (2) lost inventory, and (3) the cost of recalls. We estimate one-time costs of \$11 million to \$51 million for reformulation and labeling. Annualized over 20 years yields annual costs of \$0.7 - \$3.4 million (at 3 percent) and \$1.0 - \$4.8 million (at 7 percent). We lack sufficient information to estimate the value of lost inventories or the costs of recall. The uncertainty associated with the costs presented in financial reports and the inability to adjust for transfers makes it impossible to use these data to estimate the potential incremental regulatory impact of this proposed rule.

C. Benefits of Regulation

The benefit of removing phenylpropanolamine-containing products from the market was the reduction in the number of hemorrhagic strokes that would otherwise occur each year. Because phenylpropanolamine-containing OTC drug products have already been removed from the market, most of the expected health benefits are attributable to these past voluntary product withdrawals, rather than to FDA's future regulatory action. FDA has estimated that phenylpropanolamine causes 200 to 500 hemorrhagic strokes per year in people 18 to 49 years old (Ref. 5).

Assigning a monetary value to the prevention of strokes is problematic and there is no consensus on how it should be calculated. Taylor (Ref. 12) used a lifetime cost model to estimate the cost, by type of stroke. The model accounts for direct medical costs and indirect costs, such as earnings and premature mortality and morbidity. Updating this estimate to 2003 dollars (Ref. 13) and weighting it for the occurrence rate of subarachnoid and intracerebral hemorrhage (60 percent and 40 percent, respectively) (Ref. 14) results in an estimated figure of about \$304,719 for the lifetime cost of stroke per person. With these values, the monetized benefit of preventing from 200 to 500 strokes per year by removing all phenylpropanolamine-containing OTC drug products from the market ranges from \$60.9 million to \$152.4 million per year. When groups less than 18 and over 49 years old (the ages of the subjects in the Yale Hemorrhagic Stroke Project) are included, the total yearly benefits will be higher.

Another method of calculating benefits is to value the statistical-lives saved due to the removal of drug products containing phenylpropanolamine. Assuming a mortality rate from phenylpropanolamine-caused strokes of about 25 percent, an estimated 50 to 125 lives saved per year in people 18 to 49 years old would be attributed to the removal of products containing phenylpropanolamine. The value of a statistical-life has been estimated to range from \$1.6 million to \$8.5 million 1986-dollars (Ref. 15). Using a rough midpoint value of \$5 million per statistical-life, the estimated benefit of averting these stroke-induced fatalities ranges from \$250 million to \$625 million per year. Again, FDA is not asserting that this proposed rule will generate such benefits, because the benefit-producing activities have already occurred. Nevertheless, to the extent that some phenylpropanolamine-containing OTC drug products might remain available or might return to the market, some fraction of these benefits would be attributable to the issuance of this proposed rule.

D. Small Business Impacts

A drug manufacturer is defined as small by the Small Business Administration if it employs fewer than 750 people. Approximately 70 percent of all OTC drug manufacturers meet the definition of a small entity, and FDA believes that the same rate applies to manufacturers of phenylpropanolamine-containing OTC drug products. Hence, 70 of the 100 manufacturers were

classified as small. The cost to distributors and repackers was not significant because the manufacturers of the products bore the brunt of the recall costs, product destruction, and usually were responsible for designing new labels. As explained in this section, to the extent that there are still phenylpropanolamine-containing OTC drug products being marketed, the impact on a manufacturer can vary greatly depending on the number and type of phenylpropanolamine-containing products it produces, the availability of substitute ingredients, and the number of SKUs that will require reformulation and/or relabeling. For example, a small branded product manufacturer may have to reformulate three products and relabel nine SKUs for a total one-time reformulation and relabeling cost ranging from \$327,000 (3 products x \$100,000 reformulation + 9 SKUs x \$3,000 label) to \$1.536 million (3 products x \$500,000 reformulation + 9 SKUs x \$4,000 label). Because there is only one substitute available for OTC weight control drug products, the manufacturer would have to cease production of its existing product and the impact to the firm would be lost sales. The lost sales could be partially offset by sales of a substitute product, if marketed. The cost of the voluntary product recall would also vary by firm and again depend on the number and quantity of products that needed to be recalled and destroyed.

Because these products must be manufactured in compliance with the pharmaceutical current good manufacturing practices (21 CFR parts 210 and 211), all firms would have the necessary skills and personnel to perform these tasks either in-house or by contractual arrangement. No additional professional skills are needed. In addition, there are no other Federal rules that duplicate, overlap, or conflict with the proposed rule.

FDA considered but rejected alternatives such as leaving products containing this ingredient on the OTC market, or not publicly announcing our intent to reclassify phenylpropanolamine as a Category II ingredient. These alternatives were unacceptable because the health risk posed by products containing phenylpropanolamine was greater than the benefits the products provided, especially given the number of substitute OTC drug products available that did not pose such risks. To have further delayed the removal of OTC phenylpropanolamine drug products from the market would have left consumers exposed to an unacceptable level of risk.

Because the cost of removal and reformulation of phenylpropanolamine containing OTC drug products has already been incurred when the products were voluntarily recalled, and FDA has chosen to use the present as a baseline for its analysis, FDA tentatively concludes that this proposed rule will not have a significant impact on a substantial number of small entities.

V. Paperwork Reduction Act of 1995

FDA tentatively concludes that there are no paperwork requirements in this document under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*).

VI. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

VIII. Request for Comments

Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket numbers found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

IX. Time for Submission of New Data

The OTC drug review procedures (21 CFR 330.10(a)(7)(iii)) provide for a 12-month period after publication of a TFM for any interested person to file new data and information to support a condition excluded from the monograph

in the TFM. As discussed in section I of this document, FDA has published proposed and final rules for OTC nasal decongestant and weight control drug products and deferred a decision on the status of phenylpropanolamine so new data on this ingredient could be included in the record before a TFM or notice of proposed rulemaking was published. Manufacturers have been aware of this deferral for a number of years and have waited for the results of the study described in section II of this document to resolve the monograph status of phenylpropanolamine. It has taken many years for the phenylpropanolamine study to be completed, and the results indicate a major safety concern about this ingredient. FDA does not believe that any additional significant new safety data and information will be presented in the next 12 months. Because of the need to address and finalize FDA action on the existing safety concerns, and because there has already been public consideration of the issues before an FDA advisory committee, the comment period and the time for submission of new data is 90 days. FDA considers it an important public health concern to complete its classification of phenylpropanolamine preparations in OTC drug products as quickly as possible.

X. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

XI. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site address, but we are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

1. Comment No. LET86, Docket No. 1981N-0022 (formerly Docket No. 81N-0022).
2. Horwitz et al., "Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of The Hemorrhagic Stroke Project," May 10, 2000 in Comment No. C230, Docket No. 1976N-0052N (formerly Docket No. 76N-052N) and Comment No. RPT14, Docket No. 1981N-0022 (formerly Docket No. 81N-0022).
3. Phenylpropanolamine case reports from 1991 to 2000 on file in Docket Nos. 1976N-0052N (formerly 76N-052N) and 1981N-0022 (formerly 81N-0022).

4. Consumer Healthcare Products Association (CHPA), "Comments on the Hemorrhagic Stroke Project Report," May 24, 2000, in Comment No. C231, Docket No. 1976N-0052N (formerly Docket No. 76N-052N) and Comment No. C113, Docket No. 1981N-0022 (formerly Docket No. 81N-0022).

5. Food and Drug Administration, Transcript of Nonprescription Drugs Advisory Committee meeting, October 19, 2000, in Docket Nos. 1976N-0052N, (formerly 76N-052N) and 1981N-0022 (formerly 81N-0022).

6. Food and Drug Administration, Public Health Advisory, "Safety of Phenylpropanolamine," November 6, 2000, Comment No. M1 in Docket No. 1976N-0052N (formerly 76N-052N) and Comment No. M7 in Docket No. 1981N-0022 (formerly 81N-0022).

7. Office of Management and Budget, "Guidelines to Standardized Measures of Costs and Benefits and the Format of Accounting Statements," M0008, March 22, 2000, downloaded from <http://www.whitehouse.gov/omb/memoranda/index.html>, accessed June, 13, 2001.

8. Jarvis, Lisa, "PPA Ban Is a Serious Threat to OTC Diet Aids," Chemical Market Reporter, November 20, 2000.

9. U.S. Security and Exchange Commission, Form 10-K, Voluntary Market Withdrawals, fiscal year ended December 31, 2000, American Home Products Corp., in Docket Nos. 1976N-0052N (formerly Docket No. 1976N-052N) and 1981N-0022.

10. F-D-C Reports—"The Tan Sheet," "Dexatrim Natural Fattens Chattem's First Quarter; Extensions Planned," vol. 9, no. 14, April 2, 2001.

11. F-D-C Reports—"The Tan Sheet," "AHP Dimetapp, Robitussin PPA Withdrawals Lead To \$80 Mil. Charge In 2000," vol. 9, no. 5, January 29, 2001.

12. Taylor, Thomas N., "The Medical Economics of Stroke," *Drugs*, supp. 3:51-58, 1997.

13. U.S. Census Bureau, No. 768, Consumer Price Index by Major Group., downloaded from <http://www.census.gov/statab/freq/00s0768.txt>, accessed June 12, 2001. U.S. Bureau of Labor Statistics, accessed July 23, 2004. Updated 1999 data to 2003 (18.56 percent increase in medical care CPI).

14. Kernan, Walter N. et al., "Phenylpropanolamine and the Risk of Hemorrhagic Stroke," *The New England Journal of Medicine*, 343: 1826-1832, 2000.

15. Fisher, A., L., G. Chestnut, and D. M. Violette, "The Value of Reducing Risks of Death: a Note on New Evidence," *Journal of Policy Analysis and Management*, 8: 88-100, 1989.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 341

Labeling, Over-the-counter drugs.

21 CFR Part 357

Labeling, Over-the-counter drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 310, 341 (as proposed in the **Federal Register** of September 9, 1976 (41 FR 38312)), and 357 (as proposed in the **Federal Register** of February 26, 1982 (47 FR 8466)) be amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b-263n.

2. Section 310.545 is amended by redesignating the text of paragraph (a)(20) as paragraph (a)(20)(i) and by adding paragraph (a)(20)(i) heading, by adding paragraphs (a)(6)(ii)(D), (a)(20)(ii), and (d)(35), and by revising paragraph (d)(2) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(6) * * *

(ii) * * *

(D) Approved as of January 23, 2006. Any phenylpropanolamine ingredient.

* * * * *

(a) * * *

(20) * * *

(i) Approved as of February 8, 1991.

* * *

(ii) Approved as of January 23, 2006. Any phenylpropanolamine ingredient.

* * * * *

(d) * * *

(2) February 10, 1992, for products subject to paragraph (a)(20)(i) of this section.

* * * * *

(35) January 23, 2006, for products subject to paragraphs (a)(6)(ii)(D) and (a)(20)(ii) of this section.

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTI-ASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

§ 341.20 [Amended]

4. Section 341.20 of the proposed rule published at 41 FR 38312 is amended by removing paragraph (e) and redesignating paragraphs (f), (g), and (h) as paragraphs (e), (f), and (g), respectively.

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

5. The authority citation for 21 CFR part 357 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

§ 357.510 [Amended]

6. Section 357.510 of the proposed rule published at 47 FR 8466 is amended by removing and reserving paragraph (b).

§ 357.520 [Removed]

7. Section 357.520 of the proposed rule published at 47 FR 8466 is removed.

§ 357.550 [Amended]

8. Section 357.550 of the proposed rule published at 47 FR 8466 is amended by removing and reserving paragraphs (c)(2) and (d)(2).

§ 357.555 [Removed]

9. Section 357.555 of the proposed rule published at 47 FR 8466 is removed.

Dated: December 5, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. E5-7646 Filed 12-21-05; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 54

[REG-138647-04]

RIN 1545-BE30

Employer Comparable Contributions to Health Savings Accounts Under Section 4980G; Hearing

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Notice of public hearing on proposed rulemaking.

SUMMARY: This document contains a notice of public hearing on proposed regulations providing guidance on employer comparable contributions to Health Savings Accounts (HSAs) under section 4980G.

DATES: The public hearing is being held on February 23, 2006, at 10 a.m. The IRS must receive outlines of the topics to be discussed at the hearing by February 2, 2006.

ADDRESSES: The public hearing is being held in the IRS Auditorium, Internal Revenue Service Building, 1111 Constitution Avenue, NW., Washington, DC. Send submissions to: CC:PA:LPD:PR (REG-138647-04), Room 5203, Internal Revenue Service, POB 7604, Ben Franklin Station, Washington, DC 20044. Submissions may be hand delivered between the hours of 8 a.m. and 4 p.m. to CC:PA:LPD:PR (REG-138647-04), Courier's Desk, Internal Revenue Service, 1111 Constitution Avenue, NW., Washington, DC. Alternatively, taxpayers may submit electronic outlines of oral comments directly to the IRS Internet site <http://www.irs.gov/regs>.

FOR FURTHER INFORMATION CONTACT:

Concerning submission of comments, the hearing, and/or to be placed on the building access to attend the hearing, Kelly Banks at (202) 622-7180 (not a toll-free number).

SUPPLEMENTARY INFORMATION: The subject of the public hearing is the notice of proposed rulemaking (REG-138647-04) that was published in the **Federal Register** on August 26, 2005 (70 FR 50233).

The rules of 26 CFR 601.601(a)(3) apply to the hearing.

A period of 10 minutes is allotted to each person for presenting oral comments. The IRS will prepare an agenda containing the schedule of speakers. Copies of the agenda will be made available, free of charge, at the hearing.

Because of access restrictions, the IRS will not admit visitors beyond the immediate entrance area more than 30 minutes before the hearing starts. For information about having your name placed on the building access list to attend the hearing, see the **FOR FURTHER INFORMATION CONTACT** section of this document.

Guy R. Traynor,

Acting Chief, Publications and Regulations Branch, Associate Chief Counsel, (Procedure and Administration).

[FR Doc. E5-7650 Filed 12-21-05; 8:45 am]

BILLING CODE 4830-01-P

DEPARTMENT OF DEFENSE

Office of the Secretary

32 CFR Part 153

[0790-AH73]

Criminal Jurisdiction Over Civilians Employed by or Accompanying the Armed Forces Outside the United States, Service Members, and Former Service Members

AGENCY: Department of Defense.

ACTION: Proposed rule.

SUMMARY: The Military Extraterritorial Jurisdiction Act of 2000 (MEJA) establishes Federal criminal jurisdiction over whoever engages in conduct outside the United States that would constitute an offense punishable by imprisonment for more than one year (*i.e.*, a felony offense) while employed by or accompanying the Armed Forces outside the United States, certain members of the Armed Forces subject to the Uniform Code of Military Justice and former members of the Armed Forces.

DATES: Comments must be received on or before February 21, 2006.

ADDRESSES: Forward comments to the Deputy General Counsel (Personnel and Health Policy), 1600 Defense Pentagon, Washington, DC 20301-1600.

FOR FURTHER INFORMATION CONTACT: Mr. Robert Reed, 703-695-1055.

SUPPLEMENTARY INFORMATION:

Executive Order 12866, "Regulatory Planning and Review"

This proposed regulatory action is a significant regulatory action, as defined by Executive Order 12866 and has been reviewed by OMB and approved for publication.

Regulatory Flexibility Act of 1980 (5 U.S.C. 605(b))

This regulatory action will not have a significant adverse impact on a substantial number of small entities.

Unfunded Mandates Act of 1995 (Sec. 202, Pub. L. 104-4)

This regulatory action does not contain a Federal mandate that will result in the expenditure by State, local, and tribal governments, in aggregate, or by the private sector of \$100 million or more in any 1 year. This rule making will not significantly or uniquely affect small governments.

Paperwork Reduction Act of 1995 (44 U.S.C. Chapter 35)

This regulatory action will not impose any additional reporting or

Tab 50

Federal Register of February 20, 2014
(79 FR 9744)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2001-N-0274 (formerly 01N-0196)]

Phenylpropanolamine; Withdrawal of Approval of 13 New Drug Applications and 7 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of 13 new drug applications (NDAs) and 7 abbreviated new drug applications (ANDAs) for products containing phenylpropanolamine. The basis for the withdrawals is that the

products are no longer considered safe due to the association of phenylpropanolamine use with increased risk of hemorrhagic stroke. The holders of these NDAs and ANDAs have waived their opportunity for a hearing.

DATES: Effective February 20, 2014.

FOR FURTHER INFORMATION CONTACT: Emily Helms Williams, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6280, Silver Spring, MD 20993-0002, 301-796-3381.

SUPPLEMENTARY INFORMATION: On November 3, 2000, the Director of FDA's Center for Drug Evaluation and Research (the Director) sent a letter to holders of NDAs and ANDAs for drug products containing phenylpropanolamine requesting that they voluntarily

discontinue marketing any such products due to developments indicating an association between phenylpropanolamine use and increased risk of hemorrhagic stroke. Subsequently, in a notice published in the **Federal Register** on August 14, 2001 (66 FR 42665), the Director offered an opportunity for a hearing on a proposal to issue an order, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(e)) and 21 CFR 314.150(a)(2), withdrawing approval of 13 NDAs and 8 ANDAs for products containing phenylpropanolamine. (Although the August 14, 2001, notice stated that FDA proposed to withdraw approval of 16 NDAs and 8 ANDAs, the notice listed only 13 NDAs and 8 ANDAs.) The following products, all of which have been discontinued, were listed in the notice:

TABLE 1—NDAs AND ANDAs FOR WHICH FDA HAS PROPOSED TO WITHDRAW APPROVAL OF THE APPLICATIONS

Application No.	Drug	Applicant
NDA 11-694	Dimetane-DC Syrup	A.H. Robins Co., P.O. Box 8299, Philadelphia, PA 19101.
NDA 12-152	Ornade Extended-Release Tablet	SmithKline-Beecham, 1250 South Collegeville Rd., P.O. Box 5089, Collegeville, PA 19426.
NDA 12-436	Dimetapp Extended-Release Tablet	Whitehall-Robins, 5 Giralda Farms, Madison, NJ 07940.
NDA 13-087	Dimetapp Elixir	Do.
NDA 18-050	Corsym Extended-Release Suspension	Medeva Americas, Inc., 755 Jefferson Rd., P.O. Box 1710, Rochester, NY 14603.
NDA 18-099	Contac Extended-Release Capsule	SmithKline Beecham Consumer Health, L.P., 1500 Littleton Rd., Parsippany, NJ 07054.
NDA 18-298	Tavist-D Extended-Release Tablet	Novartis Consumer Health, Inc., 560 Morris Ave., Summit, NJ 07901.
NDA 18-556	Demazin Extended-Release Tablet	Schering-Plough HealthCare Products, Three Oak Way, P.O. Box 603, Berkeley Heights, NJ 07922.
NDA 18-809	Phenylpropanolamine Hydrochloride (HCl) Chlorpheniramine Maleate Extended-Release Capsule.	Schwarz Pharma, 6140 West Executive Dr., Mequon, WI 53092.
NDA 19-410	Hycomine Syrup	Endo Pharmaceuticals, Inc., 500 Endo Blvd., Garden City, NY 11530.
NDA 19-411	Hycomine Pediatric Syrup	Do.
NDA 19-613	Contac Extended-Release Tablet	Novartis Consumer Health, Inc.
NDA 20-640	Tavist-D Extended-Release Tablet	Do.
ANDA 71-099	Bromatapp Extended-Release Tablet	Teva Pharmaceuticals, USA, 1090 Horsham Rd., P.O. Box 1090, North Wales, PA 19454.
ANDA 88-359	Drize Extended-Release Capsule	B. F. Ascher & Co., Inc., 15501 West 109th St., Lenexa, KS 66219.
ANDA 88-681	Chlorpheniramine Maleate and Phenylpropanolamine HCl Extended-Release Capsule.	Chelsea Laboratories, 896 Orlando Ave., West Hempstead, NY 11552.
ANDA 88-687	Biphetap Elixir	Morton Grove Pharmaceuticals, Inc., 6451 Main St., Morton Grove, IL 60053.
ANDA 88-688	Bromanate Elixir	Alpharma, U.S. Pharmaceuticals Division, 333 Cassell Dr., suite 3500, Baltimore, MD 21224.
ANDA 88-723	Bromanate DC Syrup	Do.
ANDA 88-904	Myphetane DC Syrup	Morton Grove Pharmaceuticals, Inc.
ANDA 88-940	Chlorpheniramine Maleate and Phenylpropanolamine HCl Extended-Release Capsule.	Geneva Pharmaceuticals, Inc., 2555 West Midway Blvd., P.O. Box 446, Broomfield, CO 80038.

FDA issued the notice after an epidemiologic case-control study conducted by investigators at Yale University School of Medicine (Yale Hemorrhagic Stroke Project) demonstrated an association between phenylpropanolamine (an ingredient used in prescription and over-the-counter (OTC) drug products as a nasal

decongestant to relieve stuffy nose or nasal congestion and in OTC weight control drug products to control appetite) and increased risk of hemorrhagic stroke. The notice included FDA's belief that the data from the Yale Hemorrhagic Stroke Project, taken together with spontaneous reports of hemorrhagic stroke and reports in the

published medical literature, provided evidence that nasal decongestant and weight control drug products containing phenylpropanolamine are no longer safe. The Director proposed to withdraw approval of the NDA and ANDA products containing phenylpropanolamine based on her conclusion that they were no longer

shown to be safe for use under the conditions that formed the basis upon which the applications were approved.

In the August 14, 2001, notice, FDA provided the NDA and ANDA holders an opportunity to request a hearing to show why approval of the NDAs or ANDAs should not be withdrawn. One company, KV Pharmaceutical, requested a hearing by letter dated September 13, 2001, but that request was subsequently withdrawn by letter dated October 15, 2001. No other party requested a hearing on this matter following publication of the notice in the **Federal Register**. As stated above, all products listed in the notice were subsequently discontinued.

Subsequent to the August 14, 2001, notice, one of the ANDAs listed in that notice was withdrawn. In a notice published in the **Federal Register** of February 20, 2002 (67 FR 7702), FDA withdrew approval of ANDA 71–099 for BROMATAPP Extended-Release Tablets after the application holder informed FDA that the product was no longer being marketed and requested withdrawal.

In a letter to FDA dated February 25, 2013, Pfizer requested on behalf of its subsidiaries, Wyeth Pharmaceuticals, Inc. and A.H. Robins, that FDA withdraw approval of NDA 11–694 for DIMETANE–DC under § 314.150(d), noting that the product has been discontinued and is no longer marketed. In that letter, Pfizer and its named subsidiaries waived any opportunity for a hearing provided under the August 14, 2001, notice. In a response letter of March 28, 2013, the Agency acknowledged A.H. Robins' agreement to permit FDA to withdraw approval of DIMETANE–DC under § 314.150(d) and to waive its opportunity for a hearing.

For the reasons discussed in the August 14, 2001 notice, the Director, under section 505(e)(2) of the FD&C Act and under authority delegated to her by the Commissioner, finds that new evidence of clinical experience, not contained in the applications listed in table 1 and not available at the time the applications were approved, shows that phenylpropanolamine is not shown to be safe for use under the conditions of use that formed the basis upon which the applications were approved (21 U.S.C. 355(e)(2)). Therefore, approval of the NDAs listed in table 1 is hereby withdrawn. Furthermore, the Director finds that the ANDAs listed in table 1 refer to the drugs that are the subject of the NDAs listed above. Therefore, as required under section 505(j)(6) of the FD&C Act, approval of the ANDAs listed in table 1 is also withdrawn.

Under 21 CFR 314.161 and 314.162(a)(1), FDA will remove the

products containing phenylpropanolamine named in table 1 from the list of drug products with effective approvals published in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations." FDA will not approve or accept ANDAs that refer to these drug products.

Dated: February 14, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014–03596 Filed 2–19–14; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2014–N–0200]

Standards for the Interoperable Exchange of Information for Tracing of Human, Finished, Prescription Drugs, in Paper or Electronic Format; Establishment of a Public Docket

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of docket; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is establishing a public docket to receive information and comments on standards for the interoperable exchange of information associated with transactions involving human prescription drugs in a finished dosage form (prescription drugs) to comply with new requirements in the Drug Supply Chain Security Act (DSCSA). We are seeking information from drug manufacturers, repackagers, wholesale distributors, dispensers (primarily pharmacies) and other drug supply chain stakeholders and interested parties, including standards organizations, State and Federal Agencies, and solution providers. In particular, stakeholders and other interested parties are requested to comment about the interoperable exchange of transaction information, transaction history, and transaction statements, in paper or electronic format, for each transfer of product in which a change of ownership occurs. This action is related to FDA's implementation of the DSCSA.

DATES: Submit either electronic or written comments by April 21, 2014.

ADDRESSES: Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm.

1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Connie T. Jung, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20933, 301–796–3130.

SUPPLEMENTARY INFORMATION:

I. Background

On November 27, 2013, the DSCSA (Title II, Pub. L. 113–54) was signed into law. The DSCSA outlines critical steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed within the United States. Section 202 of the DSCSA, which adds section 582 to the Federal Food, Drug, and Cosmetic Act (FD&C Act), directs the Secretary of Health and Human Services (the Secretary) to establish standards for the interoperable exchange of transaction information, transaction history, and transaction statements, in paper or electronic format, in consultation with other appropriate Federal officials, manufacturers, repackagers, wholesale drug distributors, dispensers, and other pharmaceutical distribution supply chain stakeholders.

FDA has been engaged in efforts to improve the security of the drug supply chain for many years to protect U.S. patients from unsafe, ineffective, and poor quality drugs. Since the formation of the first FDA Counterfeit Drug Task Force in 2003, FDA has strongly advocated for a multilayered approach to securing the supply chain and protecting consumers from the threats posed by counterfeit and diverted drugs. The ability to track and trace finished prescription drugs plays a significant role in providing transparency and accountability in the drug supply chain. Under section 505D of the FD&C Act (21 U.S.C. 355e), FDA has been evaluating existing and emerging standards, system attributes and needs, and adoption of track and trace and authentication systems and technology. The system that will be established under DSCSA will enhance FDA's ability to help protect U.S. consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful by improving detection and removal of potentially dangerous drugs from the drug supply chain.

FDA is announcing the establishment of a public docket to provide an opportunity for interested persons to

Tab 51

Federal Register of August 17, 2011
(76 FR 51037)

An estimated total of 450 new patients (150 patients with HACO MRSA infection and 300 patients without HACO MRSA infection) will be contacted for the MRSA interview annually. This estimate is based on the numbers of MRSA cases reported by the EIP sites annually (<http://www.cdc.gov/abcs/reports-findings/survreports/mrsa08.html>) who are 18 years of age or older, had onset of the MRSA infection

in the community or within 3 days of hospital admission, and history of hospitalization in the prior 3 months. There are no costs to respondents other than their time. The total response burden for the study is estimated as follows:

The OMB-approved ABCs MRSA form (#0920–0802) will be used to identify patients to be contacted for a telephone interview. These 450 patients will be

screened for eligibility and those considered to be eligible will complete the telephone interview. We anticipate that 350 of the 450 patients screened will complete the telephone interview across all 7 EIP sites per year. We anticipate the screening questions to take about 5 minutes and the telephone interview 20 minutes per respondent.

TABLE—ESTIMATED BURDEN

Type of respondents	Form name	Number of respondents	Number of responses per respondent	Average burden per respondent (in hours)	Total burden (in hours)
Hospital Patients	Screening Form	450	1	5/60	38
	Telephone interview	350	1	20/60	117
Total	155

Dated: August 10, 2011.

Daniel Holcomb,

Reports Clearance Officer, Centers for Disease Control and Prevention.

[FR Doc. 2011–20919 Filed 8–16–11; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2010–P–0507]

Determination That Halflytely and Bisacodyl Tablets Bowel Prep Kit (Containing Two Bisacodyl Delayed Release Tablets, 5 Milligrams) Was Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that Halflytely and Bisacodyl Tablets Bowel Prep Kit (polyethylene glycol (PEG) 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and two bisacodyl delayed release tablets, 5 milligrams (mg) (10-mg bisacodyl)) was withdrawn from sale for reasons of safety or effectiveness. The Agency will not accept or approve abbreviated new drug applications (ANDAs) for bowel prep kits containing PEG–3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and two bisacodyl delayed release tablets, 5 mg.

FOR FURTHER INFORMATION CONTACT:

Nikki Mueller, Center for Drug Evaluation and Research, Food and

Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6312, Silver Spring, MD 20993–0002, 301–796–3601.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the “listed drug,” which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is generally known as the “Orange Book.” Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the Agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

On September 23, 2010, FDA received a citizen petition (Docket No. FDA–2010–P–0507), submitted under § 10.30 (21 CFR 10.30), from Perrigo Company (Perrigo). The petition requests that the Agency determine whether Halflytely and Bisacodyl Tablets Bowel Prep Kit (PEG–3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and two bisacodyl delayed release tablets, 5 mg) (Halflytely and Bisacodyl Tablets Bowel Prep Kit (10-mg bisacodyl)), manufactured by Braintree Laboratories, Inc. (Braintree), was withdrawn from sale for reasons of safety or effectiveness.

Halflytely and Bisacodyl Tablets Bowel Prep Kit (10-mg bisacodyl) (NDA 21–551) was approved on September 24, 2007. Halflytely and Bisacodyl Tablets Bowel Prep Kit (10-mg bisacodyl) was indicated for the cleansing of the colon as preparation for colonoscopy in adults. Braintree informed FDA that it ceased to manufacture and market Halflytely and Bisacodyl Tablets Bowel Prep Kit (10-mg bisacodyl) as of July 17, 2010. The drug product was then moved to the “Discontinued Drug Product List” section of the Orange Book.

FDA has reviewed its records concerning the withdrawal of Halflytely and Bisacodyl Tablets Bowel Prep Kit (10-mg bisacodyl). FDA has also independently evaluated relevant literature, data from clinical trials, and

reports of possible postmarketing adverse events. FDA has determined, under § 314.161, that Halflytely and Bisacodyl Tablets Bowel Prep Kit (10-mg bisacodyl) was withdrawn from sale for reasons of safety or effectiveness.

Braintree discontinued this product containing a total dose of 10 milligrams of bisacodyl from sale after receiving approval from FDA on July 16, 2010, for NDA 21-551/S-013, Halflytely and Bisacodyl Tablets Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and one bisacodyl delayed release tablet, 5 mg (5-mg bisacodyl)). The data available from a clinical study comparing the 10-mg version of Halflytely and Bisacodyl Tablets Bowel Prep Kit to a 5-mg version of the drug product showed that the Halflytely and Bisacodyl Tablets Bowl Prep Kit (5-mg bisacodyl) has comparable effectiveness to the 10-mg product and has a safety advantage over the 10-mg product because there is less abdominal fullness and cramping in the patients treated with the 5-mg product. Furthermore, the 10-mg product may be associated with ischemic colitis.

FDA has also reviewed the latest approved labeling for the 10-mg product and has determined that it would need to be updated with additional safety information if Braintree were to reintroduce the 10-mg product to the market. FDA has determined that additional clinical studies of safety and efficacy would be necessary before Halflytely and Bisacodyl Tablets Bowel Prep Kit (10-mg bisacodyl) could be considered for reintroduction to the market. Accordingly, the Agency will remove Halflytely and Bisacodyl Tablets Bowel Prep Kit (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and two bisacodyl delayed release tablets, 5 mg) from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to this drug product.

Dated: August 10, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011-20853 Filed 8-16-11; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2007-D-0068; formerly Docket No. 2007D-0290]

Draft Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells; Withdrawal of Draft Guidance

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; withdrawal.

SUMMARY: The Food and Drug Administration (FDA) is announcing the withdrawal of a draft guidance entitled “Draft Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs)” dated July 2007.

DATES: August 17, 2011.

FOR FURTHER INFORMATION CONTACT:

Tami Belouin, Center for Biologics Evaluation and Research, Food and Drug Administration (HFM-17), 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448, 301-827-6210.

SUPPLEMENTARY INFORMATION: In a notice published in the *Federal Register* of July 26, 2007 (72 FR 41080), FDA announced the availability of a draft guidance entitled “Draft Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs).”

FDA has carefully considered the comments received on the draft guidance and, since that document issued in 2007, has gained additional experience with point of care devices and the autologous cells selected by them. Based on these comments and experience, FDA believes that the draft guidance would not, if finalized in current form, reflect FDA’s current thinking. For these reasons, FDA is withdrawing the draft guidance entitled “Draft Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs).”

Dated: August 10, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011-20862 Filed 8-16-11; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2010-D-0246]

Guidance for Industry on Residual Drug in Transdermal and Related Drug Delivery Systems; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled “Residual Drug in Transdermal and Related Drug Delivery Systems.” This guidance provides recommendations to developers and manufacturers of transdermal drug delivery systems (TDDS), transmucosal drug delivery systems (TMDS), and topical patch products regarding use of an appropriate scientific approach during product design and development—as well as during manufacturing and product life-cycle management—to ensure that the amount of residual drug substance at the end of the labeled use period is minimized. The guidance is applicable to investigational new drug applications, new drug applications, abbreviated new drug applications, and supplemental new drug applications for TDDS, TMDS, and topical patch products.

DATES: Submit either electronic or written comments on Agency guidances at any time.

ADDRESSES: Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

Submit electronic comments on the guidance to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Terrance Ocheltree, Center for Drug Evaluation and Research, Food and Drug Administration, Bldg. 21, rm. 1609, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-1988.

SUPPLEMENTARY INFORMATION:

Tab 52

FDA Drug Safety Communication – FDA
Recommends Against Continued Use of
Propoxyphene (November 19, 2010)

[Home](#) [Drugs](#) [Drug Safety and Availability](#)

Drugs

FDA Drug Safety Communication: FDA recommends against the continued use of propoxyphene

[Safety Announcement](#)

[Additional Information for Patients](#)

[Additional Information for Healthcare Professionals](#)

[Data Summary](#)

[References](#)

Safety Announcement

[11-19-2010] The U.S. Food and Drug Administration (FDA) is recommending against continued prescribing and use of the pain reliever propoxyphene because new data show that the drug can cause serious toxicity to the heart, even when used at therapeutic doses. FDA has requested that companies voluntarily withdraw propoxyphene from the United States market.

Propoxyphene is an opioid pain reliever used to treat mild to moderate pain. It is sold under various names as a single-ingredient product (e.g., Darvon) and as part of a combination product with acetaminophen (e.g., Darvocet).

FDA's recommendation is based on all available data including data from a new study that evaluated the effects that increasing doses of propoxyphene have on the heart (see Data Summary below). The results of the new study showed that when propoxyphene was taken at therapeutic doses, there were significant changes to the electrical activity of the heart: prolonged PR interval, widened QRS complex and prolonged QT interval. These changes, which can be seen on an electrocardiogram (ECG), can increase the risk for serious abnormal heart rhythms. FDA has concluded that the safety risks of propoxyphene outweigh its benefits for pain relief at recommended doses.

In July 2009, FDA announced an ongoing [safety review](#)¹ of propoxyphene, which included evaluating its potential effects on the heart.

Additional Information for Patients

If you currently take propoxyphene-containing products, you should:

- Talk to your healthcare professional about discontinuing propoxyphene and switching to alternative pain medicines.
- Talk to your healthcare professional if you have any concerns about propoxyphene.
- Contact your healthcare professional right away if you experience an abnormal heart rate or rhythm or other symptoms including dizziness, lightheadedness, fainting or heart palpitations.
- Report any side effects with propoxyphene to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Dispose of unused propoxyphene in your household trash by following the recommendations outlined in the [Federal Drug Disposal Guidelines](#):²

- Take your propoxyphene out of its original container and mix it with an undesirable substance, such as used coffee grounds or kitty litter. The medication will be less appealing to children and pets, and unrecognizable to people who may intentionally go through your trash.
- Put the medication in a sealable bag, empty can, or other container to prevent it from breaking out of a garbage bag.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals:

- Stop prescribing and dispensing propoxyphene-containing products to patients.
- Contact patients currently taking propoxyphene-containing products and ask them to discontinue the drug.
- Inform patients of the risks associated with propoxyphene.
- Discuss alternative pain management strategies other than propoxyphene with your patients.
- Be aware of the possible risk of cardiac conduction abnormalities (prolonged QT, PR, and QRS intervals) in patients taking propoxyphene and assess patients for these events if they present with any signs or symptoms of arrhythmia.
- Report any side effects with propoxyphene to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Data Summary

Following receipt of a Citizen Petition requesting the withdrawal of propoxyphene-containing products from the United States market, FDA convened an Advisory Committee meeting on January 30, 2009. After presentations by FDA, the

petitioner, and the company reviewing the efficacy and safety data from the propoxyphene drug applications, the literature and postmarketing safety databases, the committee voted by a narrow margin (14-to-12) against the continued marketing of propoxyphene products. Those who voted for propoxyphene to remain on the market advised requiring improved labeling, particularly with warnings about use in elderly patients and about use with concomitant opioids or alcohol. Finally, there was general agreement that additional information about the cardiac effects of propoxyphene would be relevant in further weighing the risk and benefit. As a result, under new authorities given to FDA by the Food and Drug Administration Amendments Act (FDAAA), the agency required the drug manufacturer to conduct a thorough QT study to formally evaluate the effects of propoxyphene on cardiac electrophysiology. In order to determine a safe supratherapeutic dose to incorporate into the Thorough QT study, FDA required the drug manufacturer to first conduct a multiple-ascending dose (MAD) study.

The MAD study was a randomized, double-blind, placebo-controlled sequential multiple-ascending dose study of propoxyphene for 11 days. The study was conducted in healthy volunteers. The first cohort of study subjects was dosed with a total daily dose of 600 mg of propoxyphene (the maximum labeled dose) and the second cohort was dosed with a total daily dose of 900 mg. Additional doses were planned, however the study was placed on clinical hold due to safety concerns. Study subjects were monitored with telemetry and intermittent ECG recordings, comparable to the monitoring that would occur during a Thorough QT study. The drug manufacturer has submitted to FDA the results from the 600 mg and 900 mg cohorts.

Significant QTc interval prolongations were observed with the propoxyphene 600 mg and 900 mg dose levels. With the 600 mg daily dose, at steady state on Treatment Day 11, the largest mean change of QTcF* ($\Delta\Delta\text{QTcF}$) was 29.8 milliseconds (ms), which occurred 7 hours after the last dose; with the 900 mg dose the largest mean change was 38.2 ms, which occurred 2 hours after the last dose. It is recognized in the International Conference on Harmonisation (ICH) E14 Guideline¹ that drugs that prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic. In addition, a dose-dependent prolongation of PR and QRS intervals was observed in the study.

Because the elderly and patients with renal insufficiency have a reduction in the clearance of propoxyphene and its cardioactive metabolite, norpropoxyphene, through the kidneys, these populations can be especially susceptible to proarrhythmic effects of the drug.

FDA has concluded that the safety risks of propoxyphene outweigh its limited benefits²⁻⁶ for pain relief at recommended doses.

*QTcF is the QT interval corrected for heart rate using the Fridericia formula (cubic root – $\text{QTcF} = \text{QT}/\text{RR}^{1/3}$).

References

- Guidance for Industry – E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2005.
- Beaver WT. Mild analgesics. A review of their clinical pharmacology. II. *Am J Med Sci.* 1966;251:576-99 concl.
- Lasagna L. The clinical evaluation of morphine and its substitutes as analgesics. *Pharmacol Rev.* 1964;16:47-83.
- Collins SL, Edwards JE, Moore RA, McQuay HJ. Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database Syst Rev.* 2000;(2):CD001440.
- Collins SL, Edwards JE, Moore RA, McQuay HJ. Single-dose dextropropoxyphene in post-operative pain: a quantitative systematic review. *Eur J Clin Pharmacol.* 1998;54:107-12.
- Veterans Health Administration Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel. Review of the Efficacy and Safety of Propoxyphene. March 2006.

Related Information

- [Propoxyphene-Containing Products](#)³
- [Xanodyne agrees to withdraw propoxyphene from the U.S. market](#)⁴ [ARCHIVED]
- [Questions and Answers - FDA recommends against the continued use of propoxyphene](#)⁵
- [FDA Takes Actions on Darvon, Other Pain Medications Containing Propoxyphene \(July 7, 2009\)](#)⁶ [ARCHIVED]
- [Safe Disposal of Unused Medication](#)⁷
- [FDA Drug Safety Podcast for Healthcare Professionals: FDA recommends against the continued use of propoxyphene](#)⁸ [ARCHIVED]

Contact FDA

1-800-332-1088
1-800-FDA-0178 Fax
Report a Serious Problem

[MedWatch Online](#)⁹

Regular Mail: Use postage-paid [FDA Form 3500](#)¹⁰

Mail to: MedWatch 5600 Fishers Lane
Rockville, MD 20857

Page Last Updated: 11/30/2010

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7. </NewsEvents/PublicHealthFocus/ucm226353.htm>
8. </Drugs/DrugSafety/DrugSafetyPodcasts/ucm235226.htm>
9. <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>
10. <http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf>

Tab 53

Federal Register of March 10, 2014
(79 FR 13308)

other than safety or effectiveness. ANDAs that refer to ZEFAZONE (cefmetazole sodium) Injection, EQ 1 g base/vial and EQ 2 g base/vial, and ZEFAZONE (cefmetazole sodium) IV Solution, EQ 20 mg base/mL and EQ 40 mg base/mL, may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for these drug products should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: March 4, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-05059 Filed 3-7-14; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-N-0198]

Xanodyne Pharmaceuticals, Inc., et al.; Withdrawal of Approval of 8 New Drug Applications and 46 Abbreviated New Drug Applications for Propoxyphene Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of 8 new drug applications (NDAs) and 46 abbreviated new drug applications (ANDAs) for prescription pain medications containing propoxyphene. The holders of these applications have agreed in writing to permit FDA to withdraw approval of the applications and have waived their opportunity for a hearing.

DATES: Effective March 10, 2014.

FOR FURTHER INFORMATION CONTACT:

David Joy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6254, Silver Spring, MD 20993-0002, 301-796-3601.

SUPPLEMENTARY INFORMATION:

Propoxyphene is an opioid pain relief medication marketed under brand names such as Darvon and Darvocet. In 1957, FDA approved NDAs 010996 and 010997 for propoxyphene hydrochloride (HCl), alone and in combination with other active ingredients, both of which are currently held by Xanodyne Pharmaceuticals, Inc. (Xanodyne).

In 2010, after receiving new clinical data showing that when propoxyphene is taken at therapeutic doses, the drug puts patients at risk of potentially serious or even fatal heart rhythm abnormalities, and other information

including new epidemiological data, FDA concluded that the risks of propoxyphene outweigh its benefits as a pain reliever. In separate telephone conversations on November 18, 2010, FDA asked Xanodyne and the holders of marketed generic propoxyphene drug products to permit FDA to withdraw approval of their applications and to waive their opportunity for a hearing. In a separate notice published elsewhere in this issue of the **Federal Register**, FDA notifies other holders of ANDAs for pain medications containing propoxyphene of their opportunity to request a hearing if they wish to challenge the Agency's proposal to withdraw approval of their applications.

Xanodyne and manufacturers of generic propoxyphene products identified in table 1 have written to FDA asking the Agency to withdraw approval of their applications for propoxyphene-containing products and have waived their opportunity for a hearing. Some products approved under the applications identified in table 1 were discontinued in the past, before FDA's November 2010 determination that the risks of propoxyphene outweigh its benefits. Not included in table 1 are NDAs and ANDAs for which **Federal Register** notices were previously published announcing withdrawal of approval.

TABLE 1—PROPOXYPHENE DRUG PRODUCTS FOR WHICH APPLICATION HOLDERS REQUESTED WITHDRAWAL OF APPROVAL

Application No.	Drug	Applicant or holder
NDA 010996	Darvon Compound (aspirin, caffeine, and propoxyphene HCl) Capsules, 389 milligrams (mg)/32.4 mg/32 mg. Darvon Compound-65 (aspirin, caffeine, and propoxyphene HCl) Capsules, 389 mg/32.4 mg/65 mg. Darvon with ASA (aspirin and propoxyphene HCl) Capsules, 325 mg/65 mg.	Xanodyne Pharmaceuticals, Inc., One Riverfront Pl., Newport, KY 41071.
NDA 010997	Darvon (propoxyphene HCl) Capsules, 32 mg and 65 mg	Do.
NDA 016829	Darvon-N with ASA (aspirin and propoxyphene napsylate) Capsules, 325 mg/100 mg.	AAIPharma Inc., 2320 Scientific Park Dr., Wilmington, NC 28405.
NDA 016844	Darvocet (acetaminophen and propoxyphene HCl) Tablets, 325 mg/32.5 mg.	Do.
NDA 016861	Darvon-N (propoxyphene napsylate) Suspension, 50 mg/5 milliliters.	Do.
NDA 016862	Darvon-N (propoxyphene napsylate) Tablets, 100 mg	Do.
NDA 016863	Darvon-N with ASA (aspirin and propoxyphene napsylate) Tablets, 325 mg/100 mg.	Do.
NDA 017122	Darvocet-N 50 (acetaminophen and propoxyphene napsylate) Tablets, 325 mg/50 mg. Darvocet-N 100 (acetaminophen and propoxyphene napsylate) Tablets, 650 mg/100 mg.	Xanodyne Pharmaceuticals, Inc.
ANDA 040139	Acetaminophen and Propoxyphene HCl Tablets, 650 mg/65 mg.	Watson Laboratories, Inc., 400 Interpace Pkwy., Parsippany, NJ 07054.
ANDA 040507	Acetaminophen and Propoxyphene HCl Tablets, 650 mg/65 mg.	Vintage Pharmaceuticals, 150 Vintage Dr., Huntsville, AL 35811.
ANDA 040569	Propoxyphene HCl Capsules, 65 mg	Mylan Pharmaceuticals, 781 Chestnut Ridge Rd., Morgantown, WV 26505.
ANDA 040908	Propoxyphene HCl Capsules, 65 mg	Vintage Pharmaceuticals.
ANDA 070115	Acetaminophen and Propoxyphene Napsylate Tablets, 325 mg/50 mg.	Mutual Pharmaceutical Co., Inc., 1100 Orthodox St., Philadelphia, PA 19124.
ANDA 070116	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Do.

TABLE 1—PROPOXYPHENE DRUG PRODUCTS FOR WHICH APPLICATION HOLDERS REQUESTED WITHDRAWAL OF APPROVAL—Continued

Application No.	Drug	Applicant or holder
ANDA 070145	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Mylan Pharmaceuticals.
ANDA 070146	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	IVAX Pharmaceuticals, Subsidiary of Teva Pharmaceuticals USA, 400 Chestnut Ridge Rd., Woodcliff Lake, NJ 07677.
ANDA 070443	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Sandoz Inc., 2555 W. Midway Blvd., Broomfield, CO 80038.
ANDA 070615	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Mutual Pharmaceutical Co., Inc.
ANDA 070771	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Do.
ANDA 070775	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Do.
ANDA 070910	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Actavis Elizabeth LLC, 200 Elmora Ave., Elizabeth, NJ 07202.
ANDA 072195	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Mylan Pharmaceuticals.
ANDA 074119	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Teva Pharmaceuticals, 1090 Horsham Rd., North Wales, PA 19454.
ANDA 074843	Acetaminophen and Propoxyphene Napsylate Tablets, 325 mg/50 mg and 650 mg/100 mg.	Vintage Pharmaceuticals.
ANDA 075738	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Mallinckrodt Inc., 675 McDonnell Blvd., Hazelwood, MO 63042.
ANDA 076429	Darvocet A500 (acetaminophen and propoxyphene napsylate) Tablets, 500 mg/100 mg.	Xanodyne Pharmaceuticals, Inc.
ANDA 076609	Acetaminophen and Propoxyphene Napsylate Tablets, 650 mg/100 mg.	Watson Laboratories, Inc., 4955 Orange Dr., Fort Lauderdale, FL 33314.
ANDA 076743	Acetaminophen and Propoxyphene Napsylate Tablets, 325 mg/100 mg.	Cornerstone Therapeutics Inc., 1255 Crescent Green Dr., Cary, NC 27518.
ANDA 076750	Acetaminophen and Propoxyphene Napsylate Tablets, 500 mg/100 mg.	Do.
ANDA 077196	Acetaminophen and Propoxyphene Napsylate Tablets, 500 mg/100 mg.	Watson Laboratories, Inc.
ANDA 077677	Acetaminophen and Propoxyphene Napsylate Tablets, 325 mg/50 mg and 650 mg/100 mg.	Wockhardt USA LLC, 20 Waterview Blvd., Parsippany, NJ 07054.
ANDA 077821	Acetaminophen and Propoxyphene Napsylate Tablets 650 mg/100 mg.	Mirror Pharmaceuticals LLC, 140 New Dutch Ln., Fairfield, NJ 07004.
ANDA 080044	Aspirin, Caffeine, and Propoxyphene HCl Capsules, 389 mg/32.4 mg/65 mg.	Sandoz, Inc., 4700 Sandoz Dr., Wilson, NC 27893.
ANDA 080269	Propoxyphene HCl Capsules, 65 mg	Par Pharmaceuticals, Inc., 1 Ram Ridge Rd., Spring Valley, NJ 10977.
ANDA 080530	Dolene (propoxyphene HCl) Capsules, 65 mg	Heritage Pharmaceuticals Inc., 105 Fieldcrest Ave., Edison, NJ 08837.
ANDA 080783	Propoxyphene HCl Capsules, 65 mg	Valeant Pharmaceuticals North America LLC, 700 Route 202/206 North, Bridgewater, NJ 08807.
ANDA 083101	Aspirin, Caffeine, and Propoxyphene HCl Capsules, 389 mg/32.4 mg/65 mg.	Sandoz, Inc., 2555 W. Midway Blvd., Broomfield, CO 80038.
ANDA 083113	Propoxyphene HCl Capsules, 65 mg	Private Formulations Inc.
ANDA 083125	Propoxyphene HCl Capsules, 65 mg	Sandoz, Inc.
ANDA 083185	Propoxyphene HCl Capsules, 65 mg	Nexgen Pharma, Inc., 17802 Gillette Ave., Irvine, CA 92614.
ANDA 083186	Propoxyphene HCl Capsules, 65 mg	Mutual Pharmaceutical Co. Inc.
ANDA 083464	Propoxyphene HCl Capsules, 32 mg	Private Formulations Inc.
ANDA 083501	Propoxyphene HCl Capsules, 65 mg	West-Ward Pharmaceutical Corp., 435 Industrial Way West, Eatontown, NJ 07724.
ANDA 083528	Propoxyphene HCl Capsules, 32 mg	Mylan Pharmaceuticals, 781 Chestnut Ridge Rd., Morgantown, WV 26505.
ANDA 083688	Propoxyphene HCl Capsules, 65 mg	Sandoz Inc., 506 Carnegie Center, Princeton, NJ 08540.
ANDA 083689	Acetaminophen and Propoxyphene HCl Tablets, 325 mg/32 mg.	Mylan Pharmaceuticals.
ANDA 083870	Propoxyphene HCl Capsules, 65 mg	Sandoz, Inc.
ANDA 083978	Acetaminophen and Propoxyphene HCl Tablets, 650 mg/65 mg.	Mylan Pharmaceuticals.
ANDA 084014	Propoxyphene HCl Capsules, 32 mg	Sandoz, Inc., 4700 Sandoz Dr., Wilson, NC 27893.
ANDA 084999	Wygesic (acetaminophen and propoxyphene HCl) Tablets, 650 mg/65 mg.	Caraco Pharmaceutical Laboratories, Ltd., 1150 Elijah McCoy Dr., Detroit, MI 48202.
ANDA 086495	Propoxyphene HCl Capsules, 65 mg	Sandoz, Inc.
ANDA 088615	Propoxyphene HCl Capsules, 65 mg	Teva Pharmaceuticals.
ANDA 089025	Aspirin, Caffeine, and Propoxyphene HCl Capsules, 389 mg/32.4 mg/65 mg.	Do.

TABLE 1—PROPOXYPHENE DRUG PRODUCTS FOR WHICH APPLICATION HOLDERS REQUESTED WITHDRAWAL OF APPROVAL—Continued

Application No.	Drug	Applicant or holder
ANDA 089959	Acetaminophen and Propoxyphene HCl Tablets, 650 mg/65 mg.	Sandoz Inc., 2555 W. Midway Blvd., Broomfield, CO 80038.

Therefore, under sections 505(e) and 505(j)(6) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(e) and 355(j)(6)) and under authority delegated to the Director of the Center for Drug Evaluation and Research by the Commissioner of Food and Drugs, approval of the applications listed in table 1 and all amendments and supplements thereto, is withdrawn (see **DATES**). Introduction or delivery for introduction of these products into interstate commerce without an approved application is illegal and subject to regulatory action (see sections 505(a) and 301(d) of the FD&C Act (21 U.S.C. 355(a) and 331(d))).

Dated: March 4, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-05063 Filed 3-7-14; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-N-0199]

MK Laboratories, Inc., et al.; Proposal To Withdraw Approval of Three Abbreviated New Drug Applications for Propoxyphene Products; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER) is proposing to withdraw approval of three abbreviated new drug applications (ANDAs) for propoxyphene drug products from multiple sources and is announcing an opportunity for holders of those ANDAs to request a hearing on this proposal.

DATES: Submit written requests for a hearing by April 9, 2014; submit data and information in support of the hearing request by May 9, 2014.

ADDRESSES: Requests for a hearing, supporting data, and other comments are to be identified with Docket No. FDA-2014-N-0199 and submitted to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: David Joy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6254, Silver Spring, MD 20993-0002, 301-796-3601.

SUPPLEMENTARY INFORMATION: Propoxyphene is an opioid pain relief medication first approved by FDA in 1957. It has been marketed as a single active ingredient drug product and in combination with other active ingredients such as acetaminophen. It has been marketed under brand names

such as Darvon and Darvocet and in generic forms.

After receiving clinical data and other information showing that propoxyphene puts patients at risk of potentially serious and even fatal heart rhythm abnormalities, FDA determined that the risks of propoxyphene outweigh its benefits. On November 18, 2010, FDA asked Xanodyne Pharmaceuticals, Inc. (Xanodyne), the maker of Darvon and Darvocet, and manufacturers of then marketed generic propoxyphene drug products to voluntarily withdraw their products from the U.S. market. In a separate notice published elsewhere in this issue of the **Federal Register**, FDA is withdrawing approval of 8 NDAs and 46 ANDAs from multiple sources, whose application holders have agreed in writing to permit FDA to withdraw approval of the applications and have waived their opportunity for a hearing.

Although the holders of the approved applications listed in Table 1 are believed to have discontinued marketing these products prior to November 2010, FDA has not received correspondence from these application holders requesting that the Agency withdraw approval of the identified applications. Hence, in accordance with section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(e)), we hereby notify the application holders listed in Table 1 of their opportunity to request a hearing on CDER’s proposal to withdraw approval of the listed applications.

TABLE 1—PROPOXYPHENE DRUG PRODUCT APPLICATIONS FOR WHICH FDA PROPOSES TO WITHDRAW APPROVAL

Application No.	Drug	Applicant or holder
ANDA 083544	Kesso-Gesic (propoxyphene hydrochloride (HCl)) Capsules, 65 milligrams (mg).	MK Laboratories Inc., 424 Grasmere Ave., Fairfield, CT 06430.
ANDA 084551	Propoxyphene HCl Capsules, 65 mg	Whitworth Towne Paulsen Inc.
ANDA 084553	Compound 65 (aspirin, caffeine, and propoxyphene HCl) Capsules, 389 mg/32.4 mg/65 mg.	Alra Labs, 3850 Clearview Ct., Gurnee, IL 60031.

I. Safety Concern

NDAs 010996 and 010997 for propoxyphene HCl alone and in combination with aspirin and caffeine, both held by Xanodyne, were initially approved in 1957 solely on the basis of safety. The 1962 amendments to the

FD&C Act required that drugs be shown to be effective as well as safe. To implement the 1962 amendments, FDA initiated the Drug Efficacy Study Implementation (DESI) review to evaluate the effectiveness of drugs that had been previously approved on safety grounds alone. In its DESI review of

propoxyphene HCl; propoxyphene HCl with aspirin; and propoxyphene HCl with aspirin, phenacetin, and caffeine, FDA concluded that these drugs were effective for the relief of mild to moderate pain (34 FR 6264, April 8, 1969).

Tab 54

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(79 FR 13310)

TABLE 1—PROPOXYPHENE DRUG PRODUCTS FOR WHICH APPLICATION HOLDERS REQUESTED WITHDRAWAL OF APPROVAL—Continued

Application No.	Drug	Applicant or holder
ANDA 089959	Acetaminophen and Propoxyphene HCl Tablets, 650 mg/65 mg.	Sandoz Inc., 2555 W. Midway Blvd., Broomfield, CO 80038.

Therefore, under sections 505(e) and 505(j)(6) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(e) and 355(j)(6)) and under authority delegated to the Director of the Center for Drug Evaluation and Research by the Commissioner of Food and Drugs, approval of the applications listed in table 1 and all amendments and supplements thereto, is withdrawn (see **DATES**). Introduction or delivery for introduction of these products into interstate commerce without an approved application is illegal and subject to regulatory action (see sections 505(a) and 301(d) of the FD&C Act (21 U.S.C. 355(a) and 331(d))).

Dated: March 4, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-05063 Filed 3-7-14; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-N-0199]

MK Laboratories, Inc., et al.; Proposal To Withdraw Approval of Three Abbreviated New Drug Applications for Propoxyphene Products; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER) is proposing to withdraw approval of three abbreviated new drug applications (ANDAs) for propoxyphene drug products from multiple sources and is announcing an opportunity for holders of those ANDAs to request a hearing on this proposal.

DATES: Submit written requests for a hearing by April 9, 2014; submit data and information in support of the hearing request by May 9, 2014.

ADDRESSES: Requests for a hearing, supporting data, and other comments are to be identified with Docket No. FDA-2014-N-0199 and submitted to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: David Joy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6254, Silver Spring, MD 20993-0002, 301-796-3601.

SUPPLEMENTARY INFORMATION: Propoxyphene is an opioid pain relief medication first approved by FDA in 1957. It has been marketed as a single active ingredient drug product and in combination with other active ingredients such as acetaminophen. It has been marketed under brand names

such as Darvon and Darvocet and in generic forms.

After receiving clinical data and other information showing that propoxyphene puts patients at risk of potentially serious and even fatal heart rhythm abnormalities, FDA determined that the risks of propoxyphene outweigh its benefits. On November 18, 2010, FDA asked Xanodyne Pharmaceuticals, Inc. (Xanodyne), the maker of Darvon and Darvocet, and manufacturers of then marketed generic propoxyphene drug products to voluntarily withdraw their products from the U.S. market. In a separate notice published elsewhere in this issue of the **Federal Register**, FDA is withdrawing approval of 8 NDAs and 46 ANDAs from multiple sources, whose application holders have agreed in writing to permit FDA to withdraw approval of the applications and have waived their opportunity for a hearing.

Although the holders of the approved applications listed in Table 1 are believed to have discontinued marketing these products prior to November 2010, FDA has not received correspondence from these application holders requesting that the Agency withdraw approval of the identified applications. Hence, in accordance with section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(e)), we hereby notify the application holders listed in Table 1 of their opportunity to request a hearing on CDER’s proposal to withdraw approval of the listed applications.

TABLE 1—PROPOXYPHENE DRUG PRODUCT APPLICATIONS FOR WHICH FDA PROPOSES TO WITHDRAW APPROVAL

Application No.	Drug	Applicant or holder
ANDA 083544	Kesso-Gesic (propoxyphene hydrochloride (HCl)) Capsules, 65 milligrams (mg).	MK Laboratories Inc., 424 Grasmere Ave., Fairfield, CT 06430.
ANDA 084551	Propoxyphene HCl Capsules, 65 mg	Whitworth Towne Paulsen Inc.
ANDA 084553	Compound 65 (aspirin, caffeine, and propoxyphene HCl) Capsules, 389 mg/32.4 mg/65 mg.	Alra Labs, 3850 Clearview Ct., Gurnee, IL 60031.

I. Safety Concern

NDAs 010996 and 010997 for propoxyphene HCl alone and in combination with aspirin and caffeine, both held by Xanodyne, were initially approved in 1957 solely on the basis of safety. The 1962 amendments to the

FD&C Act required that drugs be shown to be effective as well as safe. To implement the 1962 amendments, FDA initiated the Drug Efficacy Study Implementation (DESI) review to evaluate the effectiveness of drugs that had been previously approved on safety grounds alone. In its DESI review of

propoxyphene HCl; propoxyphene HCl with aspirin; and propoxyphene HCl with aspirin, phenacetin, and caffeine, FDA concluded that these drugs were effective for the relief of mild to moderate pain (34 FR 6264, April 8, 1969).

In January 2009, FDA held a joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to address the safety and efficacy of propoxyphene and propoxyphene combination products for the treatment of mild to moderate pain. The committee members voted 14 to 12 against the continued marketing of propoxyphene products but noted that additional information about the drug's cardiac effects would be relevant in weighing its risks and benefits. Using authority under the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), FDA required Xanodyne to conduct a safety study of the effects of propoxyphene on the heart at higher than recommended doses.

Before proceeding with the cardiac safety study, the company first conducted a study on healthy volunteers to determine an appropriate dose. In this study, the healthy volunteers in one group were given a total daily dose of 600 mg of propoxyphene (the maximum approved dose), and volunteers in the second group were given a total daily dose of 900 mg (a dose higher than recommended in product labeling). The results showed that there were significant changes to the electrical activity of the heart (prolonged PR interval, widened QRS complex, and prolonged QT interval), at both the 600 and 900 mg doses. These changes, which can be seen on an electrocardiogram, can increase the risk for serious abnormal heart rhythms. In light of these new scientific findings, CDER determined the postmarketing safety signals for this drug have taken on new importance, and the overall balance of risk and benefit can no longer be considered favorable. Memoranda explaining CDER's determination are available on FDA's Web site and will be placed in Docket No. FDA-2014-N-0199 (Refs. 1 and 2).

On November 19, 2010, FDA issued a Drug Safety Communication recommending against the continued prescription and use of propoxyphene drug products. This recommendation was based on all available data, including the new data showing that when propoxyphene is taken at therapeutic doses, it can cause significant changes to the electrical activity of the heart. FDA has concluded that this safety risk outweighs propoxyphene's benefits for pain relief at recommended doses. Based on this information, FDA asked the manufacturers of currently marketed propoxyphene products to voluntarily remove their products from the market.

Therefore, based on all available data, notice is given to the holders of the approved applications listed in Table 1 and to all other interested persons that the Director of CDER proposes to issue an order, under section 505(e) of the FD&C Act, withdrawing approval of the applications, amendments, and supplements upon the grounds that scientific data show the listed drugs are unsafe under the conditions of use for which they were approved.

II. Hearing Procedures

In accordance with section 505(e) of the FD&C Act, the applicants are hereby provided an opportunity to request a hearing to show why approval of the applications listed in Table 1 should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of the drug products covered by these applications.

An applicant who decides to seek a hearing must file the following: (1) A written notice of participation and request for hearing (see **DATES**) and (2) the data, information, and analyses relied on to demonstrate that there is a genuine and substantial issue of fact that requires a hearing to resolve (see **DATES**). Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for a hearing, notice of participation and request for a hearing, the information and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in § 314.200 (21 CFR 314.200) and in 21 CFR part 12.

The failure of an applicant to file a timely written notice of participation and request for a hearing, as required by § 314.200, constitutes an election by that applicant not to avail itself of the opportunity for a hearing concerning CDER's proposal to withdraw approval of the applications and constitutes a waiver of any contentions concerning the legal status of the drug products. FDA will then withdraw approval of the applications, and the drug products may not thereafter be lawfully introduced or delivered for introduction into interstate commerce. Any new drug product introduced or delivered for introduction into interstate commerce without an approved application is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If a request for a hearing is not complete or is not supported, the Commissioner of Food and Drugs will enter summary

judgment against the person who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions under this notice of opportunity for a hearing must be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

This notice is issued under section 505(e) of the FD&C Act and under the authority delegated to the Director of CDER by the Commissioner of Food and Drugs.

III. References

FDA has placed the following references on display in the Division of Dockets Management (see **ADDRESSES**). They may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>.

1. Memorandum to Dr. Woodcock: Recommendation on a Regulatory Decision for Propoxyphene-Containing Products (November 18, 2010, Hertz and Avigan); <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234349.pdf>.

2. Memorandum to Dr. Woodcock on Propoxyphene-Containing Products (November 18, 2010, Rappaport); <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234340.pdf>.

Dated: March 4, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-05062 Filed 3-7-14; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Agency Information Collection Activities: Proposed Collection: Public Comment Request

AGENCY: Health Resources and Services Administration, HHS.

ACTION: Notice.

SUMMARY: In compliance with the requirement for opportunity for public comment on proposed data collection projects (Section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995), the Health Resources and Services

Tab 55

Letter from Deborah Shapse, MD, Medical
Director, Organon, Inc., Re: Voluntary
Market Withdrawal of Raplon[®]
(rapacuronium bromide) for Injection, All
Batches (March 27, 2001)

VOLUNTARY MARKET WITHDRAWAL

Adverse Drug Reaction

March 27, 2001

Re: RAPLON® (rapacuronium bromide) for Injection

ALL BATCHES

NDC 0052-0490-15 (100 mg)

NDC 0052-0495-16 (200 mg)

NDC 0052-0490-86 (100 mg sample)

In light of the recent safety issues raised, regarding RAPLON® and its possible association with the occurrence of bronchospasm, we are voluntarily withdrawing the product. We feel a strong responsibility to the clinicians that not only use our products, but also entrust the lives of their patients on the reliability of these products. Our primary concern and goal in this endeavor is to ensure the safety of each patient.

The Food and Drug Administration (FDA) was notified immediately of this decision and the planned market withdrawal of all unused product.

The RAPLON® package insert lists bronchospasm as an adverse event which occurred in 3.2% of patients in premarketing clinical trials. We have now received reports of several serious adverse bronchospasm events including a few unexplained fatalities. In each of these cases the cause is unknown, as there were multiple drugs administered and other conditions present. From our surveillance of postmarketing spontaneous reporting, it appears that the incidence is within labeling, however, the severity of these events, up to and including mortality that has been reported postmarketing, was not seen in clinical trials. These reports are made voluntarily from a population of unknown size and the exact frequency can not be determined.

Please examine your stock immediately to determine if you have any RAPLON® in your inventory. If so, discontinue using the material and have your hospital pharmacy or wholesaler promptly return via parcel post to our West Orange facility: ATTENTION: RETURN MARKET WITHDRAWAL.

You will be reimbursed by credit memo for the returned goods and postage.

Please return the enclosed card immediately providing the requested information.

Organon is making every effort to fully investigate all reported adverse events and to perform a complete analysis of all clinical and laboratory data available for each report.

We appreciate your assistance in this matter. If there are any questions regarding this market withdrawal please contact:

Customer Services: 8-5 pm
Attention: Sean Gallagher, Assistant Director of Marketing Administration or
Darla Desiderio, Supervisor of Customer Service
Phone: 1-800-241-8812

Sincerely,

Deborah Shapse, MD
Medical Director

Enclosure

Tab 56

Federal Register of March 19, 2012
(77 FR 16039)

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Circulatory System Devices Panel of the Medical Devices Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the Agency on FDA's regulatory issues.

Date and Time: The meeting will be held on April 25 and 26, 2012, from 8 a.m. to 6 p.m.

Location: Holiday Inn, Ballroom, 2 Montgomery Village Ave., Gaithersburg, MD 20879. The hotel's phone number is 301-948-8900.

Contact Person: Jamie Waterhouse, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301-796-3063, email: Jamie.Waterhouse@fda.hhs.gov, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), and follow the prompts to the desired center or product area. Please call the Information Line for up-to-date information on this meeting. A notice in the **Federal Register** about last minute modifications that impact a previously announced advisory committee meeting cannot always be published quickly enough to provide timely notice. Therefore, you should always check the Agency's Web site and call the appropriate advisory committee hot line/phone line to learn about possible modifications before coming to the meeting.

Agenda

On April 25, 2012, the committee will discuss, make recommendations and vote on information related to a supplement to the premarket approval application (PMA) for the HeartWare Ventricular Assist System (HVAS) sponsored by HeartWare, Inc. The HVAS is an implantable electrically powered centrifugal-flow rotary blood pump with external driver and power source(s). It is the first ventricular assist device that does not require the creation of an abdominal pump pocket. The HVAS is indicated for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory, advanced heart failure.

On April 26, 2012, the committee will discuss, make recommendations and vote on information related to the PMA for the Subcutaneous Implantable Cardioverter Defibrillator (S-ICD)

System sponsored by Cameron Health, Inc. The S-ICD is the first implantable defibrillator that does not require the implantation of an electrode either on or in the heart. The S-ICD is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias. The device is capable of delivering high energy defibrillation shocks as well as bradycardia demand mode cardiac pacing. The study provides data from the treatment of induced acute and chronic episodes of ventricular tachycardia/ventricular fibrillation and spontaneous episodes. In addition to the investigational device exemption study, clinical data were also obtained from using studies outside the United States and registries.

FDA intends to make background material available to the public no later than 2 business days before the meeting. If FDA is unable to post the background material on its Web site prior to the meeting, the background material will be made publicly available at the location of the advisory committee meeting, and the background material will be posted on FDA's Web site after the meeting. Background material is available at <http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>. Scroll down to the appropriate advisory committee link.

Procedure

Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person on or before April 17, 2012. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. on April 25 and 26, 2012. Those individuals interested in making formal oral presentations should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before April 10, 2012. Time allotted for each presentation may be limited. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for the scheduled open public hearing session. The contact person will notify interested persons regarding their request to speak by April 12, 2012.

Persons attending FDA's advisory committee meetings are advised that the Agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact AnnMarie Williams, at AnnMarie.Williams@fda.hhs.gov, 301-796-5966, at least 7 days in advance of the meeting.

FDA is committed to the orderly conduct of its advisory committee meetings. Please visit our Web site at <http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/ucm111462.htm> for procedures on public conduct during advisory committee meetings.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: March 13, 2012.

Jill Hartzler Warner,

Acting Associate Commissioner for Special Medical Programs.

[FR Doc. 2012-6484 Filed 3-16-12; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration**

[Docket No. FDA-2012-N-0190]

Abbott Laboratories et al.; Withdrawal of Approval of 35 New Drug Applications and 64 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of 35 new drug applications (NDAs) and 64 abbreviated new drug applications (ANDAs) from multiple applicants. The holders of the applications notified the Agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

DATES: *Effective Date:* April 18, 2012.

FOR FURTHER INFORMATION CONTACT: Florine P. Purdie, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6366, Silver Spring, MD 20993-0002, 301-796-3601.

SUPPLEMENTARY INFORMATION: The holders of the applications listed in table 1 in this document have informed

FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications under the process in

§ 314.150(c) (21 CFR 314.150(c)). The applicants have also, by their requests, waived their opportunity for a hearing. Withdrawal of approval of an

application or abbreviated application under § 314.150(c) is without prejudice to refiling.

TABLE 1

Application No.	Drug	Applicant
NDA 005545	Dicumarol Tablets	Abbott Laboratories, PA77/Bldg. AP30-1E, 200 Abbott Park Rd., Abbott Park, IL 60064-6157.
NDA 005845	Benadryl (diphenhydramine hydrochloride (HCl)), Benadryl with Ephedrine Sulfate, and Caladryl (diphenhydramine HCl and calamine).	McNeil Consumer Healthcare, Division of McNeil-PPC, Inc., 7050 Camp Hill Rd., Fort Washington, PA 19034-2299.
NDA 006146	Benadryl (diphenhydramine HCl) Injection	Do.
NDA 006773	Artane (trihexyphenidyl HCl) Tablets and Capsules and Artane (trihexyphenidyl) Elixir.	Lederle Laboratories, d/b/a Wyeth Pharmaceuticals, P.O. Box 8299, Philadelphia, PA 19101-8299.
NDA 009486	Benadryl (diphenhydramine HCl) Injection Preservative Free.	McNeil Consumer Healthcare.
NDA 010021	Placidyl (ethchlorvynol) Capsules	Abbott Laboratories, 200 Abbott Park Rd., Abbott Park, IL 60064.
NDA 011552	Stelazine (trifluoperazine HCl)	GlaxoSmithKline, P.O. Box 13398, Five Moore Dr., Research Triangle Park, NC 27709-3398.
NDA 012524	Enduron (methyclothiazide) Tablets, 2.5 milligrams (mg) and 5 mg.	Abbott Laboratories, PA77/Bldg. AP30-1E, 200 Abbott Park Rd., Abbott Park, IL 60064-6157.
NDA 012775	Enduronyl and Enduronyl Forte (methyclothiazide and deserpidine) Tablets.	Do.
NDA 014684	Aventyl (nortriptyline HCl) Capsules	Eli Lilly and Co., Lilly Corp. Center, Indianapolis, IN 46285.
NDA 017577	Ditropan (oxybutynin chloride) Tablets	Janssen Pharmaceuticals Inc., c/o Johnson & Johnson Pharmaceutical Research and Development, LLC, 920 Route 202, P.O. Box 300, Raritan, NJ 08869.
NDA 018473	Ventolin (albuterol) Inhalation Aerosol ¹	GlaxoSmithKline.
NDA 018557	Fansidar (sulfadoxine and pyrimethamine) Tablets, 500 mg and 25 mg.	Hoffman-La Roche, Inc., 340 Kingsland St., Nutley, NJ 07110-1199.
NDA 018709	Capozide (captopril and hydrochlorothiazide) Tablets	Bristol-Myers Squibb Co., P.O. Box 4000, Princeton, NJ 08543-4000.
NDA 018814	Heparin Sodium in 5% Dextrose Injection	Baxter Healthcare Corp., 1620 Waukegan Rd., MPGR-AL, McGaw Park, IL 60085.
NDA 019297	Novantrone (mitoxantrone HCl) Injection	EMD Serono, One Technology Place, Rockland, MA 02370.
NDA 019508	Axid (nizatidine) Capsules	SmithKline Beecham Corp., d/b/a GlaxoSmithKline, P.O. Box 13398, Five Moore Dr., Research Triangle Park, NC 27709-3398.
NDA 019915	Monopril (fosinopril sodium) Tablets, 10 mg, 20 mg, and 40 mg.	Bristol-Myers Squibb Co.
NDA 019946	Nuromax (doxacurium chloride) Injection 1 mg/milliliter (mL).	Abbott Laboratories, P76/Bldg. AP30-1E, Abbott Park, IL 60064-6157.
NDA 019960	Manoplax (flosequinan) Tablets	Do.
NDA 020057	Ceredase (alglucerase) Injection	Genzyme Corp., 500 Kendall St., Cambridge, MA 02142.
NDA 020088	Norplant System (levonorgestrel) Implants	Wyeth Pharmaceuticals, Inc., P.O. Box 8299, Philadelphia, PA 19101-8299.
NDA 020101	Prozac (fluoxetine HCl) Oral Solution, 20 mg/5 mL	Eli Lilly and Co.
NDA 020236	Serevent (salmeterol xinafoate) Inhalation Aerosol ¹	GlaxoSmithKline.
NDA 020286	Monopril-HCT (fosinopril sodium and hydrochlorothiazide) Tablets, 20 mg/12.5 mg and 10 mg/12.5 mg.	Bristol-Myers Squibb Co.
NDA 020403	Zofran (ondansetron HCl) Injection	Glaxo Wellcome Manufacturing Pte Limited, d/b/a GlaxoSmithKline, 1250 Collegeville Rd., UP4110, Collegeville, PA 19426.
NDA 020627	Norplant II System (levonorgestrel) Implants	Wyeth Pharmaceuticals, Inc.
NDA 020828	Fortovase (saquinavir) Capsules, 200 mg	Hoffman-La Roche, Inc.
NDA 020860	Levlite (ethinyl estradiol and levonorgestrel) Tablets	Bayer HealthCare Pharmaceuticals Inc., P.O. Box 1000, Montville, NJ 07045.
NDA 020984	Raplon (rapacuronium bromide) for Injection	Organon USA Inc., 2000 Galloping Hill Rd., Kenilworth, NJ 07033.
NDA 021120	Novantrone (mitoxantrone HCl) Injection	EMD Serono.
NDA 021793	Reglan ODT (metoclopramide) Tablets	Meda Pharmaceuticals Inc., 200 North Cobb Parkway, Suite 428, Marietta, GA 30062.
ANDA 040207	Prochlorperazine Maleate Tablets USP, 5 mg and 10 mg.	Duramed Pharmaceuticals, Inc., 400 Chestnut Rd., Woodcliff Lake, NJ 07677.
ANDA 040231	Chlorpromazine HCl Oral Concentrate USP, 30 mg/mL	Pharmaceutical Associates, Inc., 201 Delaware St., Greenville, SC 29605.
NDA 050526	Statinic (erythromycin) Topical Solution, 1.5%	Bristol-Myers Squibb Co.

TABLE 1—Continued

Application No.	Drug	Applicant
NDA 050687	Banan (cefepodoxime proxetil) Tablets, 100 mg and 200 mg.	Daiichi Sankyo, Inc., 399 Thornall St., 11th Floor, Edison, NJ 08837.
NDA 050688	Banan (cefepodoxime proxetil) Granules for Oral Suspension, 50 mg/5 mL and 100 mg/5 mL.	Do.
ANDA 064098	Amikacin Sulfate Injection USP, 250 mg (base)/mL	Hospira, Inc., 275 North Field Dr., Bldg. H2-2, Lake Forest, IL 60045.
ANDA 064106	Mitomycin for Injection USP, 20 mg Vial	Do.
ANDA 070505	Metoclopramide Injection USP, 5 mg/mL	Do.
ANDA 070506	Metoclopramide Injection USP, 5 mg/mL	Do.
ANDA 070566	Nitropress (sodium nitroprusside for Injection USP), 50 mg.	Do.
ANDA 071015	Haloperidol Oral Solution USP, 2 mg/mL	Teva Pharmaceuticals USA, 1090 Horsham Rd., P.O. Box 1090, North Wales, PA 19454.
ANDA 071554	Thiothixene HCl Oral Solution USP, 5 mg/mL	Do.
ANDA 073058	Fluphenazine HCl Oral Solution USP, 5 mg/mL	Do.
ANDA 073479	Pentamidine Isethionate for Injection, 300 mg Vial	Hospira, Inc.
ANDA 074636	Iopamidol Injection USP, 41%, 51%, 61%, 76%	Do.
ANDA 074898	Iopamidol Injection USP, 41%, 51%, 61%, 76%	Do.
ANDA 075065	Acyclovir Sodium for Injection	Do.
ANDA 075176	Haloperidol Decanoate Injection, 50 mg/mL and 100 mg/mL.	Do.
ANDA 075409	Midazolam HCl Injection, 1 mg (base)/mL and 5 mg (base)/mL.	Do.
ANDA 075884	Milrinone Lactate Injection, 1 mg/mL	Do.
ANDA 076306	Topiramate Tablets, 25 mg, 50 mg, 100 mg, and 200 mg.	Roxane Laboratories, Inc., 1809 Wilson Rd., Columbus, OH 43228.
ANDA 077138	Ciprofloxacin Injection USP in 5% Dextrose Injection	Teva Pharmaceuticals USA.
ANDA 077223	Terbinafine HCl Tablets, 250 mg (base)	Roxane Laboratories, Inc.
ANDA 077784	Risperidone Tablets, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg.	Ratiopharm Inc., c/o Columbia Pharma Consulting Services Inc., 490 Northwest Datewood Dr., Suite 400, Issaquah, WA 98027.
ANDA 078241	Sumatriptan Succinate Tablets, 25 mg, 50 mg, and 100 mg (base).	Roxane Laboratories, Inc.
ANDA 078318	Sumatriptan Injection, 4 mg (base)/0.5 mL and 6 mg (base)/0.5 mL.	TEVA Parenteral Medicines, Inc., 19 Hughes, Irvine, CA 92618.
ANDA 078416	Prednisolone Sodium Phosphate Oral Solution, 5 mg (base)/5 mL.	Vintage Pharmaceuticals, 120 Vintage Dr., Huntsville, AL 35811.
ANDA 078517	Venlafaxine HCl Tablets, 25 mg (base), 37.5 mg (base), 50 mg (base), 75 mg (base), and 100 mg (base).	PLIVA Hrvatska d.o.o., c/o Barr Laboratories, Inc., 400 Chestnut Ridge Rd., Woodcliff Lake, NJ 07677
ANDA 080997	Succinylcholine Chloride Injection USP, 20 mg/mL	Organon USA Inc.
ANDA 081125	Dexamethasone Sodium Phosphate Injection USP, 4 mg/mL.	TEVA Parenteral Medicines, Inc., 19 Hughes, Irvine, CA 92618.
ANDA 081126	Dexamethasone Sodium Phosphate Injection USP	Do.
ANDA 081298	Chlorzoxazone Tablets, 250 mg	Ranbaxy Inc., U.S. Agent for Ohm, 600 College Rd. East, Princeton, NJ 08540.
ANDA 081299	Chlorzoxazone Tablets, 500 mg	Do.
ANDA 081310	Fluphenazine HCl Elixir USP, 2.5 mg/5 mL	Teva Pharmaceuticals USA.
ANDA 087005	Trichlormethiazide Tablets, 4 mg	Par Pharmaceutical, Inc., One Ram Ridge Rd., Spring Valley, NY 10977.
ANDA 087007	Trichlormethiazide Tablets, 2 mg	Do.
ANDA 087032	Chlorpromazine HCl Oral Concentrate USP, 30 mg/mL	Morton Grove Pharmaceuticals, Inc., U.S. Agent for Wockhardt EU Operations (Swiss) AG, 6451 West Main St., Morton Grove, IL 60053.
ANDA 087053	Chlorpromazine HCl Oral Concentrate USP, 100 mg/mL.	Do.
ANDA 087406	Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg.	Barr Laboratories, Inc., 400 Chestnut Ridge Rd., Woodcliff Lake, NJ 07677.
ANDA 087585	Potassium Chloride for Injection Concentrate USP, 2 mEq/mL.	Luitpold Pharmaceuticals, Inc., One Luitpold Dr., P.O. Box 9001, Shirley, NY 11967.
ANDA 088143	Trifluoperazine Oral Solution USP, 10 mg/mL	Morton Grove Pharmaceuticals, Inc., U.S. Agent for Wockhardt EU Operations (Swiss) AG.
ANDA 088194	Thioridazine HCl Tablets USP, 50 mg	Ivax Pharmaceuticals, Inc., Subsidiary of Teva Pharmaceuticals USA, 400 Chestnut Ridge Rd., Woodcliff Lake, NJ 07677.
ANDA 088227	Thioridazine HCl Oral Solution USP (Concentrate), 100 mg/mL.	Morton Grove Pharmaceuticals, Inc., U.S. Agent for Wockhardt EU Operations (Swiss) AG.
ANDA 088258	Thioridazine HCl Oral Solution USP (Concentrate), 30 mg/mL.	Do.
ANDA 088270	Thioridazine HCl Tablets USP, 10 mg	Ivax Pharmaceuticals, Inc., Subsidiary of Teva Pharmaceuticals USA.
ANDA 088271	Thioridazine HCl Tablets USP, 15 mg	Do.

TABLE 1—Continued

Application No.	Drug	Applicant
ANDA 088272	Thioridazine HCl Tablets USP, 25 mg	Do.
ANDA 088273	Thioridazine HCl Tablets USP, 100 mg	Do.
ANDA 088456	Thioridazine HCl Tablets USP, 100 mg	Teva Pharmaceuticals USA.
ANDA 088493	Thioridazine HCl Tablets USP, 10 mg	Do.
ANDA 088850	Hydroflumethiazide Tablets USP, 50 mg	Par Pharmaceutical, Inc.
ANDA 088907	Reserpine and Hydroflumethiazide Tablets, 0.125 mg/ 50 mg.	Do.
ANDA 088933	Sulfinpyrazone Tablets, 100 mg	Do.
ANDA 088934	Sulfinpyrazone Capsules USP, 200 mg	Do.
ANDA 089135	Methyclothiazide Tablets, 2.5 mg	Do.
ANDA 089136	Methyclothiazide Tablets, 5 mg	Do.
ANDA 089173	A-MethaPred (methylprednisolone sodium succinate for injection USP), 500 mg (base)/Vial.	Hospira, Inc.
ANDA 089174	A-MethaPred (methylprednisolone sodium succinate for injection USP), 1 gram (base)/Vial.	Do.
ANDA 089207	Methylprednisolone Tablets USP, 16 mg	Par Pharmaceutical, Inc.
ANDA 089208	Methylprednisolone Tablets USP, 24 mg	Do.
ANDA 089209	Methylprednisolone Tablets USP, 32 mg	Do.
ANDA 089457	Perphenazine Tablets USP, 16 mg	Ivax Pharmaceuticals, Inc., Subsidiary of Teva Pharma- ceuticals USA.
ANDA 089602	Thioridazine HCl Oral Solution USP, 30 mg/mL	Teva Pharmaceuticals USA.
ANDA 089603	Thioridazine HCl Oral Solution USP, 100 mg/mL	Do.
ANDA 089624	Reversol (edrophonium chloride injection USP), 10 mg/ mL).	Organon USA Inc.
ANDA 089657	Methocarbamol and Aspirin Tablets, 400 mg/325 mg	Par Pharmaceutical, Inc.
ANDA 089708	Perphenazine Tablets USP, 4 mg	Ivax Pharmaceuticals, Inc., Subsidiary of Teva Pharma- ceuticals USA.

¹ This product included an oral pressurized metered-dose inhaler that contained chlorofluorocarbons (CFCs) as a propellant. CFCs may no longer be used as a propellant for any albuterol or salmeterol metered-dose inhalers (see 70 FR 17168, April 4, 2005; 71 FR 70870, December 7, 2006).

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(e)) and under authority delegated to the Director, Center for Drug Evaluation and Research, by the Commissioner, approval of the applications listed in table 1 in this document, and all amendments and supplements thereto, is hereby withdrawn, effective April 18, 2012. Introduction or delivery for introduction into interstate commerce of products without approved new drug applications violates section 301(a) and (d) of the FD&C Act (21 U.S.C. 331(a) and (d)). Drug products that are listed in table 1 in this document that are in inventory on the date that this notice becomes effective (see the **DATES** section) may continue to be dispensed until the inventories have been depleted or the drug products have reached their expiration dates or otherwise become violative, whichever occurs first.

Dated: February 16, 2012.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 2012-6591 Filed 3-16-12; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Agency Information Collection Activities: Proposed Collection: Comment Request

In compliance with the requirement for opportunity for public comment on proposed data collection projects (section 3506(c)(2)(A) of Title 44, United States Code, as amended by the Paperwork Reduction Act of 1995, Pub. L. 104-13), the Health Resources and Services Administration (HRSA) publishes periodic summaries of proposed projects being developed for submission to the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995. To request more information on the proposed project or to obtain a copy of the data collection plans and draft instruments, email paperwork@hrsa.gov or call the HRSA Reports Clearance Officer at (301) 443-1984.

Comments are invited on: (a) The proposed collection of information for the proper performance of the functions of the agency; (b) the accuracy of the agency's estimate of the burden of the proposed collection of information; (c) ways to enhance the quality, utility, and

clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques or other forms of information technology.

Proposed Project: Enrollment and Re-Certification of Entities in the 340B Drug Pricing Program (OMB No. 0915-0327)—Revision

Section 602 of Public Law 102-585, the Veterans Health Care Act of 1992, enacted section 340B of the Public Health Service Act (PHS Act) "Limitation on Prices of Drugs Purchased by Covered Entities." Section 340B provides that a manufacturer who sells covered outpatient drugs to eligible entities must sign a pharmaceutical pricing agreement with the Secretary of Health and Human Services in which the manufacturer agrees to charge a price for covered outpatient drugs that will not exceed an amount determined under a statutory formula.

Covered entities which choose to participate in the section 340B Drug Pricing Program must comply with the requirements of section 340B(a)(5) of the PHS Act. Section 340B(a)(5)(A) prohibits a covered entity from accepting a discount for a drug that would also generate a Medicaid rebate.

Tab 57

FDA Public Health Advisory – Safety of
Vioxx (September 30, 2004)

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Drugs

FDA Public Health Advisory: Safety of Vioxx

9/30/2004

Merck & Co., Inc. today announced a voluntary withdrawal of Vioxx from the U.S. market due to safety concerns. Vioxx is a prescription COX-2 selective, non-steroidal anti-inflammatory drug (NSAID) that was approved by FDA in May 1999 for the relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of menstrual symptoms. It is also approved for the relief of the signs and symptoms of rheumatoid arthritis in adults and children.

The Agency was informed by Merck & Co., Inc. on September 27, 2004, that the Data Safety Monitoring Board for an ongoing long-term study of Vioxx (APPROVe) had recommended that the study be stopped early for safety reasons. The study was being conducted in patients at risk for developing recurrent colon polyps. The study showed an increased risk of cardiovascular events (including heart attack and stroke) in patients on Vioxx compared to placebo, particularly those who had been taking the drug for longer than 18 months. Based on this new safety information, Merck and FDA officials met the next day, September 28, 2004, and during that meeting FDA was informed that Merck was voluntarily withdrawing Vioxx from the market place.

The risk that an individual patient taking Vioxx will suffer a heart attack or stroke related to the drug is very small. Patients who are currently taking Vioxx should contact their physician for guidance regarding discontinuation and alternative therapies.

FDA is working closely with Merck to coordinate the withdrawal of this product from the U.S. market place. Healthcare professionals are advised to contact Merck at 1-888-368-4699 or at www.merck.com¹ or at the FDA's Drug Information Office at 301-827-4573 or 1-888-463-6332 or go to the [Vioxx Information](#)² page on FDA's website at for questions about this product.

Page Last Updated: 08/15/2013

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 U.S. Department of **Health & Human Services**

Links on this page:

1. <http://www.merck.com/>

2. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders
/ucm103420.htm

Tab 58

Announcement by Merck (worldwide
withdrawal of VIOXX)



Merck Announces Voluntary Worldwide Withdrawal of VIOXX-R-

September 30, 2004 08:15 AM Eastern Daylight Time

WHITEHOUSE STATION, N.J.--(BUSINESS WIRE)--Sept. 30, 2004--Merck & Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX(R) (rofecoxib), its arthritis and acute pain medication. The company's decision, which is effective immediately, is based on new, three-year data from a prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial.

The trial, which is being stopped, was designed to evaluate the efficacy of VIOXX 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX, and in this respect, are similar to the results of two placebo-controlled studies described in the current U.S. labeling for VIOXX.

"Although we believe it would have been possible to continue to market VIOXX with labeling that would incorporate these new data, given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take."

"We are taking this action because we believe it best serves the interests of patients," said Raymond V. Gilmartin, chairman, president and chief executive officer of Merck. "Although we believe it would have been possible to continue to market VIOXX with labeling that would incorporate these new data, given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take."

APPROVe was a multi-center, randomized, placebo-controlled, double-blind study to determine the effect of 156 weeks (three years) of treatment with VIOXX on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal adenoma. The trial enrolled 2,600 patients and compared VIOXX 25 mg to placebo. The trial began enrollment in 2000.

VIOXX was launched in the United States in 1999 and has been marketed in more than 80 countries. In some countries, the product is marketed under the trademark CEOXX. Worldwide sales of VIOXX in 2003 were \$2.5 billion.

Results of the VIGOR (VIOXX Gastrointestinal Outcomes Research) study, released in March 2000, demonstrated that the risk of gastrointestinal toxicity with VIOXX was less than with naproxen, but indicated an increased risk of cardiovascular events versus naproxen. However, in other studies including Merck's Phase III studies that were the basis of regulatory

approval of the product, there was not an increased risk of cardiovascular events with VIOXX compared with placebo or VIOXX compared with other non-naproxen non-steroidal anti-inflammatory drugs (NSAIDs). Merck began long-term randomized clinical trials to provide an even more comprehensive picture of the cardiovascular safety profile of VIOXX.

"Merck has always believed that prospective, randomized, controlled clinical trials are the best way to evaluate the safety of medicines. APPROVe is precisely this type of study - and it has provided us with new data on the cardiovascular profile of VIOXX," said Peter S. Kim, Ph.D., president of Merck Research Laboratories. "While the cause of these results is uncertain at this time, they suggest an increased risk of confirmed cardiovascular events beginning after 18 months of continuous therapy. While we recognize that VIOXX benefited many patients, we believe this action is appropriate."

Merck has informed the U.S. Food and Drug Administration and regulatory authorities in other countries of its decision. The company also is in the process of notifying health care practitioners in the United States and other countries where VIOXX is marketed. Patients who are currently taking VIOXX should contact their health care providers to discuss discontinuing use of VIOXX and possible alternative treatments. In addition, patients and health care professionals may obtain information from www.merck.com and www.vioxx.com, or may call (888) 36-VIOXX (1-888-368-4699).

The results of clinical studies with one molecule in a given class are not necessarily applicable to others in the class. Therefore, the clinical significance of the APPROVe trial, if any, for the long-term use of other drugs in this class, consisting of COX-2 specific inhibitors and NSAIDs, is unknown. The company will work with regulatory authorities in the 47 countries where ARCOXIA is approved to assess whether changes to the prescribing information for this class of drugs, including ARCOXIA, are warranted. Merck is continuing to seek approval for ARCOXIA in other countries, including the United States.

Merck will continue its extensive clinical program to collect additional longer-term data for ARCOXIA, its medication for arthritis and acute pain.

With regard to financial guidance, prior to today's announcement, Merck remained comfortable with its 2004 earnings per share guidance of \$3.11 to \$3.17. The company currently expects earnings per share to be negatively affected by \$0.50 to \$0.60 as a result of today's announcement. This estimate includes foregone sales, writeoffs of inventory held by Merck, customer returns of product previously sold and costs to undertake the pullback of the product. Included in this cost estimate is the expectation of foregone fourth quarter sales of VIOXX of \$700 million to \$750 million. In addition, Merck expects that worldwide approximately one month of inventory is held by customers and will be returned.

At this point it is uncertain which of these costs will be recorded in the third quarter and which will be recorded in the fourth quarter. Therefore, at this point, Merck is retracting the third quarter guidance it had previously provided.

Merck will report third-quarter earnings on Oct. 21. At that point, the company will provide additional information regarding the costs for product withdrawal.

About Merck

Merck & Co., Inc. is a global research-driven pharmaceutical company. Merck discovers, develops, manufactures and markets a broad range of innovative products to improve human and animal health, directly and through its joint ventures.

Forward Looking Statement

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the cautionary statements in Item 1 of Merck's Form 10-K for the year ended Dec. 31, 2003, and in its periodic reports on Form 10-Q and Form 8-K (if any), which the company incorporates by reference.

VIOXX(R) (rofecoxib) is a registered trademark of Merck & Co., Inc.

Contacts

Merck & Co., Inc.

Media:

Anita Larsen, 908-423-6022

Investor:

Michael Rabinowitz, 908-423-5185

Tab 59

Federal Register of December 21, 2010
(75 FR 80061)

TABLE 1—Continued

Committee name	Tentative date(s) of meeting(s)
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION	
Food Advisory Committee	March 30–31.
CENTER FOR TOBACCO PRODUCTS	
Tobacco Products Scientific Advisory Committee	January 10–11, March 17–18, May, July, September, and November date(s), if needed, to be determined.
CENTER FOR VETERINARY MEDICINE	
Veterinary Medicine Advisory Committee	April 11, September 12.
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH	
Science Advisory Board	November 9–10.

Dated: December 16, 2010.

Jill Hartzler Warner,
*Acting Associate Commissioner for Special
Medical Programs.*

[FR Doc. 2010–31961 Filed 12–20–10; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2010–N–0626]

Abbott Laboratories, Inc.; Withdrawal of Approval of a New Drug Application for MERIDIA

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of a new drug application (NDA) for MERIDIA (sibutramine hydrochloride (HCl)) oral capsules held by Abbott Laboratories, Inc. (Abbott), 100 Abbott Park Rd., Abbott Park, IL 60064. Abbott has voluntarily requested that approval of this application be withdrawn, thereby waiving its opportunity for a hearing.

DATES: Effective December 21, 2010.

FOR FURTHER INFORMATION CONTACT: Nicole Mueller, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6312, Silver Spring, MD 20993–0002, 301–796–3601.

SUPPLEMENTARY INFORMATION: On October 7, 2010, FDA requested that Abbott voluntarily withdraw MERIDIA (sibutramine HCl) oral capsules from the market, based on FDA's recent analysis of clinical trial data from the Sibutramine Cardiovascular Outcomes

Trial (SCOUT) that indicated that MERIDIA poses an increased risk of heart attack and stroke. In a letter dated October 12, 2010, Abbott requested that FDA withdraw approval of NDA 20–632 for MERIDIA (sibutramine HCl) oral capsules under § 314.150(d) (21 CFR 314.150(d)). In that letter, Abbott also waived its opportunity for a hearing, provided under § 314.150(a). In FDA's acknowledgment letter of November 1, 2010, the agency stated that based on the review of the SCOUT data and the assessment of the September 15, 2010, meeting of FDA's Endocrinologic and Metabolic Drugs Advisory Committee at which the SCOUT data were reviewed, we find the benefits of MERIDIA (sibutramine HCl) oral capsules, indicated for the management of obesity, including weight loss and maintenance of weight loss, no longer outweigh the risks in any identifiable patient population. FDA also acknowledged that Abbott waived its opportunity for a hearing.

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(e)), § 314.150(d), and under authority delegated by the Commissioner of Food and Drugs to the Director, Center for Drug Evaluation and Research, approval of NDA 20–632, and all amendments and supplements thereto, is withdrawn (see **DATES**). Distribution of this product in interstate commerce without an approved application is illegal and subject to regulatory action (see sections 505(a) and 301(d) of the FD&C Act (21 U.S.C. 355(a) and 331(d)).

Dated: December 6, 2010.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 2010–31986 Filed 12–20–10; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Allergy and Infectious Diseases; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of Allergy and Infectious Diseases Special Emphasis Panel, Unsolicited Multi-Project (P01) Grant Applications.

Date: January 12, 2011.

Time: 1 p.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6700B Rockledge Drive, Bethesda, MD 20817. (Telephone Conference Call.)

Contact Person: Roberta Binder, PhD, Scientific Review Officer, Scientific Review Program, Division of Extramural Activities, NIAID/NIH/DHHS, 6700B Rockledge Drive, Room 3130, Bethesda, MD 20892–7616. 301–496–7966. rbinder@niaid.nih.gov.

(Catalogue of Federal Domestic Assistance Program Nos. 93.855, Allergy, Immunology, and Transplantation Research; 93.856, Microbiology and Infectious Diseases Research, National Institutes of Health, HHS)

Tab 60

FDA Public Health Advisory – Tegaserod
maleate (marketed as Zelnorm) (March 30,
2007)

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Drugs

Public Health Advisory: Tegaserod maleate (marketed as Zelnorm)

3/30/2007

FDA is issuing this public health advisory to inform patients and health care professionals that the sponsor of Zelnorm (tegaserod maleate), Novartis Pharmaceuticals Corporation, has agreed to stop selling Zelnorm. Zelnorm is being taken off the market because a new safety analysis has found a higher chance of heart attack, stroke, and worsening heart chest pain that can become a heart attack in patients treated with Zelnorm compared to those treated with a sugar pill they thought was Zelnorm.

FDA announces the following, effective immediately:

- At FDA's request, Novartis Pharmaceuticals Corporation has agreed to stop selling Zelnorm.
- Patients being treated with Zelnorm should contact their physician to discuss alternative treatments for their condition.
- Patients who are taking Zelnorm should seek emergency medical care right away if they experience severe chest pain, shortness of breath, dizziness, sudden onset of weakness or difficulty walking or talking or other symptoms of a heart attack or stroke.
- Physicians who prescribe Zelnorm should work with their patients and transition them to other therapies as appropriate to their symptoms and need.

Zelnorm is a prescription medication approved for short term treatment of women with irritable bowel syndrome with constipation and for patients younger than 65 years with chronic constipation. In late February and early March 2007, Novartis Pharmaceuticals gave FDA the results of new analyses of 29 clinical studies of Zelnorm for treatment of a variety of gastrointestinal tract conditions; the data from all the studies were combined to assess the chance of side effects on the heart and blood vessels. In each study, patients were assigned at random to either Zelnorm or a sugar pill they thought was Zelnorm. These 29 studies included 11,614 patients treated with Zelnorm and 7,031 treated with a sugar pill. The average age of patients in these studies was 43 years and most patients—88%—were women.

The number of patients who suffered a heart attack, stroke or severe heart chest pain that can turn into a heart attack was small. However, patients treated with Zelnorm had a higher chance of having any of these serious and life-threatening side effects than did those who were treated with a sugar pill. Thirteen patients treated with Zelnorm (0.1%) had serious and life-threatening cardiovascular side effects; among these, four patients had a heart attack (one died), six had a type of severe heart chest pain which can quickly turn into a heart attack, and three had a stroke. Among the patients taking the sugar pill, only one (or 0.01%) had symptoms suggesting the beginning of a stroke that went away without complication.

There may be patients for whom no other treatment options are available and in whom the benefits of Zelnorm treatment outweigh the chance of serious side effects. FDA will work with Novartis to allow access to Zelnorm for those patients through a special program.

FDA has also indicated to Novartis a willingness to consider limited re-introduction of Zelnorm at a later date if a population of patients can be identified in whom the benefits of the drug outweigh the risks. However, before FDA makes a decision about limited re-introduction, any proposed plan would be discussed at a public advisory committee meeting.

Related Information

- [Tegaserod maleate \(marketed as Zelnorm\) - Overview](#)¹ [ARCHIVED]
Podcast - March 30, 2007

- [Tegaserod maleate \(marketed as Zelnorm\) - Full Version²](#) [ARCHIVED]
Podcast - March 30, 2007

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2. </Drugs/DrugSafety/DrugSafetyPodcasts/ucm078972.htm>

Tab 61

FDA News Release, “FDA Permits
Restricted Use of Zelnorm for Qualifying
Patients” (July 27, 2007)

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News & Events

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE

July 27, 2007

Media Inquiries:

Rita Chappelle, 301-827-6242

Consumer Inquiries:

888-INFO-FDA

FDA Permits Restricted Use of Zelnorm for Qualifying Patients

The U.S. Food and Drug Administration announced that it is permitting the restricted use of Zelnorm (tegaserod maleate) under a treatment investigational new drug (IND) protocol to treat irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in women younger than 55 who meet specific guidelines.

In some instances, patients with a serious or life-threatening disease or condition who are not enrolled in a clinical trial may be treated with a drug not approved by the FDA. Generally, such use is allowed within guidelines called a treatment IND, when no comparable or satisfactory alternative drug or therapy is available.

In addition to the age and gender restrictions, the IND protocol for Zelnorm limits use of the drug to those with IBS-C or CIC whose physicians decide the drug is medically necessary. Patients must sign consent materials to ensure they are fully informed of the potential risks and benefits of Zelnorm.

On March 30, 2007, the FDA asked Novartis, the manufacturer of Zelnorm, to suspend its U.S. marketing and sales because a safety analysis found a higher chance of heart attack, stroke, and unstable angina (heart/chest pain) in patients treated with Zelnorm compared with treatment with an inactive substance (placebo).

At that time, the FDA indicated that there might be patients for whom the benefits of Zelnorm treatment outweigh the risks and for whom no other treatment options were available. FDA committed to work with Novartis to allow access to Zelnorm for those patients through a special program. That work yielded this IND protocol.

"These patients must meet strict criteria and have no known or pre-existing heart problems and be in critical need of this drug," said Steven Galson, M.D., M.P.H., director of FDA's Center for Drug Evaluation and Research (CDER). "Zelnorm will remain off the market for general use."

Irritable bowel syndrome is a disorder characterized most commonly by cramping, abdominal pain, bloating, constipation, and diarrhea. IBS causes a great deal of discomfort and distress, but it does not permanently harm the intestines and does not lead to disease. For some people, however, IBS can be disabling. They may be unable to work, attend social events, or even travel short distances.

Patients are considered to have chronic constipation if they have fewer than three complete spontaneous bowel movements per week and at least one of the following symptoms for at least 25 percent of those bowel movements: straining, hard stools, incomplete evacuation.

Physicians with IBS-C or CIC patients who meet the IND criteria should contact Novartis at 888-669-6682 or 866-248-1348. Those who do not qualify for the Zelnorm treatment protocol may contact FDA's Division for Drug Information about other options at 888-463-6332.

For more information:

Novartis Zelnorm Web page
www.zelnorm.com

National Institute of Diabetes and Digestive and Kidney Diseases—Irritable Bowel Syndrome
<http://digestive.niddk.nih.gov/ddiseases/pubs/ibs/>

International Foundation for Functional Gastrointestinal Disorders
www.iffgd.org

FDA Center for Drug Evaluation and Research
www.fda.gov/cder

#

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11. <ssLINK/ucm144575.htm>

Tab 62

FDA Zelnorm (tegaserod maleate)
Information, (April 2, 2008)

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Drugs

Zelnorm (tegaserod maleate) Information

Novartis, the manufacturer of Zelnorm, has notified the FDA that they will no longer provide Zelnorm (tegaserod maleate) under a treatment investigational new drug application (T-IND) protocol to treat irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in women younger than 55.

Novartis has agreed to continue to supply Zelnorm for use in emergency situations. Requests for Zelnorm for this purpose may be made to the FDA which in turn authorizes shipment of the drug by the manufacturer.

An emergency situation is defined as one that is immediately life-threatening or serious enough to qualify for hospitalization. FDA may deny authorization, even in life-threatening situations, if available evidence fails to provide a reasonable basis for concluding that Zelnorm may be effective for the intended use, or if exposure to Zelnorm would pose an unreasonable or a significant additional risk to patients. The following conditions are cause for denial of authorization:

- prior history of heart attack or stroke
- unstable angina
- hypertension
- hyperlipidemia
- diabetes
- age greater than 55 years
- smoking
- obesity
- depression
- anxiety
- suicidal ideation

Physicians with patients who may qualify for treatment with Zelnorm for emergency use may contact FDA's Division for Drug Information about the emergency IND process at druginfo@fda.hhs.gov.

Background

On March 30, 2007, the FDA asked Novartis to suspend its U.S. marketing and sales because a safety analysis found a higher chance of heart attack, stroke, and unstable angina (heart/chest pain) in patients treated with Zelnorm compared with treatment with an inactive substance (placebo).

On July 27, 2007, the FDA announced that it was permitting the restricted use of Zelnorm (tegaserod maleate) under a treatment investigational new drug (IND).

Related Information

- [Questions and Answers About the Voluntary Discontinuation of Zelnorm's \(tegaserod maleate\) Treatment Investigational New Drug \(IND\)¹ \[ARCHIVED\]](#) (4/2/2008)
- [Historical Information on Zelnorm \(tegaserod maleate\)² \[ARCHIVED\]](#)

Page Last Updated: 05/11/2012

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U.S. Department of **Health & Human Services**

Links on this page:

1. </Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103237.htm>
2. </Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103257.htm>

Tab 63

"Dear Pharmacist" Letter from Warner-Lambert Company (March 22, 2000)



William R. Sigmund II, M.D.
M.H.S., F.A.C.C.
Vice President

March 22, 2000

**IMPORTANT DRUG WARNING
PRODUCT WITHDRAWAL**

Dear Pharmacist:

Following discussions with the U.S. Food and Drug Administration, Warner-Lambert Company has voluntarily discontinued the sale and distribution of Rezulin® (troglitazone) Tablets, its therapy for the treatment of type 2 diabetes. We have attached to this letter the Company's and the FDA's March 21, 2000 press releases announcing this action.

Concurrent with this letter, we are notifying physicians of the withdrawal.

Effective immediately, please do not dispense any further prescriptions for Rezulin®. Patients presenting prescriptions for Rezulin® should be instructed to consult with their physicians regarding alternative therapies as soon as possible.

Warner-Lambert has discontinued its distribution of Rezulin® and will be taking steps to arrange for wholesale and pharmacy returns of all existing stocks to the Company. Warner-Lambert will reimburse patients for their out-of-pocket expenses for unused supplies of Rezulin®. Patients having questions regarding this procedure may call 1-877-798-7398 for instructions.

You will be contacted shortly regarding procedures for return of and credit for unused stocks. Should you have any question in the interim, please call our Medical Affairs Department at 1-800-223-0432 or contact a local Parke-Davis or Sankyo Parke Davis representative.

Sincerely,

A handwritten signature in black ink that reads 'William R. Sigmund II'.

William R. Sigmund II, M.D., M.H.S., F.A.C.C.
Vice President, Medical and Scientific Affairs

Tab 64

Warner-Lambert Company Press Release
(March 21, 2000)

FOR IMMEDIATE RELEASE:

Media Contact:
Jason Ford (973) 540-4268

Investor Relations Contacts:
George Shields (973) 540-6916
John Howarth (973) 540-4874

WARNER-LAMBERT VOLUNTARILY DISCONTINUES THE SALE OF REZULIN

MORRIS PLAINS, N.J. March 21, 2000--Warner-Lambert Company (NYSE:WLA) announced today that it is voluntarily discontinuing the sale of Rezulin® (troglitazone) Tablets, its therapy for the treatment of type 2 diabetes, although the Company continues to believe that the benefits of the drug outweigh its associated risks.

Patients taking Rezulin® should consult with their physicians as soon as possible to discuss alternative therapies. Warner-Lambert will work closely with the Food and Drug Administration and other constituencies to assure a safe and efficient transition for patients as they switch to alternative therapies.

The Company has always believed that it is essential for patients and physicians to receive accurate and objective information regarding the benefits and risks of Rezulin®. It was for this reason that Warner-Lambert requested a public meeting of the FDA's expert Advisory Committee. However, repeated media reports sensationalizing the risks associated with Rezulin® therapy have created an environment in which patients and physicians are simply unable to make well-informed decisions regarding the safety and efficacy of Rezulin. Under these circumstances, and after discussions this evening with the FDA, we have decided it is in the best interests of patients to discontinue marketing Rezulin® at this time.

#

Note to Editors: Warner-Lambert's news releases can be found on our website at www.warner-lambert.com or through Business Wire at www.businesswire.com

Tab 65

HHS News Press Release (March 21, 2000)
Rezulin to Be Withdrawn From the Market

HHS NEWS

U.S. Department of Health and Human Services

P00-8
FOR IMMEDIATE RELEASE
March 21, 2000

FOOD AND DRUG ADMINISTRATION
Print Media: 301-827-6242
Broadcast Media: 301-827-3434
Consumer Inquiries: 888-INFO-FDA

REZULIN TO BE WITHDRAWN FROM THE MARKET

FDA today asked the manufacturer of Rezulin (troglitazone) -- a drug used to treat type 2 diabetes mellitus-- to remove the product from the market. The drug's manufacturer, Parke-Davis/Warner-Lambert, has agreed to FDA's request.

FDA took this action after its review of recent safety data on Rezulin and two similar drugs, rosiglitazone (Avandia) and pioglitazone (Actos), showed that Rezulin is more toxic to the liver than the other two drugs. Data to date show that Avandia and Actos, both approved in the past year, offer the same benefits as Rezulin without the same risk.

"When considered as a whole, the pre-marketing clinical data and post-marketing safety data from Rezulin as compared to similar, alternative diabetes drugs indicate that continued use of Rezulin now poses an unacceptable risk to patients," said Dr. Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research. "We are now confident that patients have safer alternatives in this important class of diabetes drugs," she added.

Severe liver toxicity has been known to occur with Rezulin since 1997. In consultation with FDA, Parke-Davis has strengthened the drug's labeling several times and has recommended close monitoring of liver function in patients taking Rezulin.

In March 1999, FDA's Endocrine and Metabolic Drugs Advisory Committee reviewed the status of Rezulin and its risk of liver toxicity and recommended continued availability of this drug in a select group of patients -- patients not well-controlled on other diabetes drugs.

Since then, FDA has continued to actively monitor adverse events associated with Rezulin, as well as Avandia and Actos. After up to nine months of marketing experience with these two newer drugs, it has now become clear that these newer drugs have less risk of severe liver toxicity than Rezulin.

Patients using Rezulin are urged to contact their physicians for information about alternative treatments. Patients should not discontinue taking Rezulin or other treatments for diabetes without discussing alternative therapies with their physicians.

For more information about Rezulin, go to FDA's [MedWatch site](#).

[FDA News Page](#) | [FDA Home Page](#)

Office of Public Affairs

Hypertext uploaded by [jch](#) 2000-MAR-22.

Tab 66

FDA Public Health Advisory Letter from
Murray M. Lumpkin, M.D. Trovan
(Trovafloxacin/Alatrofloxacin Mesylate)
Interim Recommendations (June 9, 1999)

[Home](#) [Drugs](#) [Drug Safety and Availability](#) [Postmarket Drug Safety Information for Patients and Providers](#)

Drugs

Food and Drug Administration 09 June 1999 Trovan (Trovafoxacin / Alatrofoxacin Mesylate)

INTERIM RECOMMENDATIONS

Trovan (trovafoxacin / alatrofoxacin) was approved by FDA in 1997 for the treatment of a wide variety of infections.

Based on new safety data related to serious liver injury, described below, the Food and Drug Administration is today advising physicians that the drug Trovan should be reserved for use ONLY in the treatment of patients who meet ALL of the following treatment criteria:

- Have at least one of the following infections that is judged by the treating physician to be serious and life- or limb-threatening:
 - nosocomial pneumonia,
 - community acquired pneumonia,
 - complicated intra-abdominal infections (including post-surgical infections)
 - gynecologic and pelvic infections, or
 - complicated skin and skin structure infections, including diabetic foot infections;
- Receive their initial therapy in an in-patient health care facility (i.e., hospital or long-term nursing care facility); and
- The treating physician believes that, even given the new safety information, the benefit of the product for the patient outweighs the potential risk.

In most cases, it is expected that therapy in these patients would begin with the intravenous formulation of Trovan. Due to the bioavailability of oral Trovan, patients who have stabilized clinically on IV therapy may be switched to oral Trovan to complete their course of therapy, if deemed appropriate by the treating physician. In some patients with these kinds of serious and life- or limb-threatening infections, oral Trovan may be considered appropriate initial therapy. Use of oral Trovan to treat less serious infections is not warranted.

Therapy with Trovan beyond 14 days duration generally should not be used, because the risk of liver injury may increase substantially with exposure beyond 14 days. Trovan should be discontinued prior to 14 days of therapy if the patient experiences any clinical signs or symptoms of liver dysfunction, including fatigue, anorexia, yellowing of the skin and eyes, severe stomach pain with nausea and vomiting, or dark urine.

NEW SAFETY DATA

No reports of hepatic failure, liver transplant, or death due to possible hepatic etiology were reported in the 7000 patients in the pre-marketing clinical trials database exposed to Trovan. It is estimated that approximately 2,500,000 patients have received Trovan since approval for marketing. Following marketing of Trovan in the United States in February 1998, FDA began receiving reports of patients who experience serious hepatic reactions in association with the use of the product. In July of 1998, FDA had worked with Trovan's manufacturer to add information about hepatic toxicity to the Precautions section of Trovan's package insert.

Since that time, FDA has received reports of over 100 cases of clinically symptomatic liver toxicity in patients receiving Trovan. Some of these patients developed serious liver injury leading to liver transplant and/or death. At present, FDA is aware of 14 cases of acute liver failure that are strongly associated with Trovan exposure. Four of these patients required liver transplant (one of whom subsequently died). Five additional patients died of liver-related illness. Three patients recovered without transplantation, and the final outcome is still pending on two patients. These numbers of patients with acute liver failure, although few, represent a rate that appears to be significantly higher than would be expected to occur idiopathically in the general population - despite the under-reporting of cases that generally occurs to our post-market surveillance system.

Trovan-associated liver failure appears to be unpredictable. It has been reported with both short-term (a little as 2 days exposure) and longer-term drug exposure; therefore the efficacy of liver function monitoring in acceptably managing this risk is uncertain.

Trovan use exceeding 2 weeks duration appears to be associated with a substantially increased risk of acute liver failure.

Liver failure has also been reported following Trovan re-exposure.

These uncommon but very serious adverse reactions are typical of drug toxicities which, because of their rarity, may not always be detectable in clinical trials databases. However, such toxicities may become apparent after marketing when the product is used in a significantly broader population. As such, these adverse reactions are the types of important, new safety information the post-marketing spontaneous reporting system is designed to detect, as it did in this case.

CONCLUSIONS

FDA does not wish to deprive patients and physicians of access to effective antimicrobials, if the risk associated with these drugs can be managed successfully by other means. Based on the new safety data presently available to the agency and based on the availability of alternative products to treat other less serious indications for which this product was originally approved, FDA is issuing the interim recommendations outlined above.

FDA and Pfizer have agreed to a program that will limit the distribution of Trovan to in-patient health care facilities (hospitals and long-term nursing care facilities). Pfizer will be communicating in the near future with appropriate pharmacies to provide directions concerning possible return of their present inventories of Trovan.

FDA believes that this risk management program will better ensure that Trovan is used in clinical situations in which its benefits can be expected to outweigh its presently known risks. In this manner, FDA believes that Trovan can continue to be made available to those patients who may need it for treatment of serious and life- or limb-threatening infections, while minimizing other patients' risk of exposure to the product.

FDA advises patients presently taking Trovan NOT to discontinue their therapy until they have discussed their treatment options with their physician.

FDA and the manufacturer will continue to collect and evaluate data on Trovan's safety and will continue to assess the drug's benefit/risk profile. As further information or recommendations about Trovan become available, FDA will continue to inform the health care and patient communities.

FDA requests that any suspected adverse events thought associated with Trovan be reported to the agency through MedWatch, FDA's adverse event reporting system. Reports may be submitted to FDA by telephone (800-332-1088), by fax (800-332-0178) or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, Maryland 20857. Reports can also be filed via the Internet at www.fda.gov/medwatch¹. Reports may also be filed directly to the manufacturer.

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, Maryland

Page Last Updated: 01/27/2009

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1. <http://www.fda.gov/medwatch>

Tab 67

Federal Register of September 22, 1999
(64 FR 51325)

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration**

[Docket No. 99N-4004]

Wallace Laboratories et al.; Withdrawal of Approval of 18 New Drug Applications and 44 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of 18 new drug applications (NDA's) and 44 abbreviated new drug applications (ANDA's). The holders of the applications notified the agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

EFFECTIVE DATE: September 22, 1999.**FOR FURTHER INFORMATION CONTACT:**

Olivia A. Pritzlaff, Center for Drug Evaluation and Research (HFD-7), Food

and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: The holders of the applications listed in the table in this document have informed FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications. The applicants have also, by their request, waived their opportunity for a hearing.

Application No.	Drug	Applicant
NDA 4-253	Davitamin Tablets	Wallace Laboratories, 301B College Rd., East, Princeton, NJ 08540.
NDA 5-932	5% Aminosol	Abbott Laboratories, One Abbott Park Rd., Abbott Park, IL 60064-3500.
NDA 6-668	Redisol (cyanocobalamin) Tablets and Injection.	Merck & Co., Inc., 5 Sentry Pkwy., East (BLA-10), Blue Bell, PA 19422.
NDA 7-842	Flaxedil (gallamine triethiodide injection), 20 milligrams (mg)/milliliter (mL).	Kendall Healthcare Products Co., 15 Hampshire St., Mansfield, MA 02048.
NDA 9-295	Vibazine (buclizine hydrochloride) Tablets.	Pfizer Pharmaceuticals, 235 East 42d St., New York, NY 10017-5755.
NDA 10-460	Preludin (phenmetrazine hydrochloride) Tablets.	Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Rd., P.O. Box 368, Ridgefield, CT 06877.
NDA 10-639	Hydeltrasol (prednisolone sodium phosphate ophthalmic solution) Sterile Ophthalmic Solution.	Merck & Co., Inc., P.O. Box 4, BLA-20, West Point, PA 19486.
NDA 11-612	Daricon (oxyphenylcyclamine hydrochloride) Tablets.	Pfizer Pharmaceuticals.
NDA 11-752	Preludin (phenmetrazine hydrochloride) Endurets.	Boehringer Ingelheim Pharmaceuticals, Inc.
NDA 17-497	Synthetic Calcimar (calcitonin-salmon) for Injection.	Rhone-Poulenc Rorer Pharmaceuticals, Inc., 500 Arcola Rd., P.O. Box 1200, Collegeville, PA 19426-0107.
NDA 18-208	Pfi-Lith (lithium carbonate) Capsules.	Pfizer Pharmaceuticals.
NDA 18-237	Calciparine (heparin calcium) Injection.	Sanofi Pharmaceuticals, Inc., 90 Park Ave., New York, NY 10019.
NDA 18-342	Wellcovorin (leucovorin calcium) Tablets.	Glaxo Wellcome, Inc., 5 Moore Dr., P.O. Box 13398, Research Triangle Park, NC 27709.
NDA 18-499	Lactated Ringer's and Dextrose Injection USP.	Miles, Inc., Pharmaceutical Div., 4th and Parker Sts., P.O. Box 1986, Berkeley, CA 94701.
NDA 18-933	MVI-12 Powder	Astra USA, Inc., P.O. Box 4500, Westborough, MA 01581-4500.
NDA 19-498	Parathar (teriparatide acetate) for Injection.	Rhone-Poulenc Rorer Pharmaceuticals, Inc.
NDA 20-841	Lotemax (loteprednol etabonate ophthalmic suspension), 0.5% Ophthalmic Suspension.	Pharmos Corp., c/o Bausch & Lomb Pharmaceuticals, Inc., 8500 Hidden River Pkwy., Tampa, FL 33637.
NDA 50-762	Trovan/Zithromax Compliance Pak (trovafloxacin mesylate/azithromycin for oral suspension).	Pfizer Pharmaceuticals.
ANDA 60-082	Tetracycline (tetracycline) Capsules.	Pfizer, Inc., 235 East 42d St., New York, NY 10017-5755.
ANDA 60-290	Tetracycline Hydro-chloride Capsules USP, 250 mg and 500mg.	Purepac Pharmaceutical Co., 200 Elmora Ave., Elizabeth, NY 07207.
ANDA 60-458	Terramycin (oxytetracycline with polymyxin B sulfate) Topical Powder with Polymyxin B Sulfate.	Pfizer, Inc.
ANDA 60-586	Terramycin (oxytetracycline) IV.	Do.
ANDA 60-595	Terramycin (oxytetracycline) Syrup.	Do.
ANDA 60-731	Bacitracin Neomycin-Polymyxin with Hydrocortisone Acetate Ophthalmic Ointment 1%.	Altana, Inc., 60 Baylis Rd., Melville, NY 11747.
ANDA 61-009	Terra-Poly (oxytetracycline, polymyxin B sulfate) Vaginal Tablets.	Pfizer, Inc.
ANDA 61-010	Terramycin (oxytetracycline) Tablets.	Do.
ANDA 61-277	Penicillin G Potassium Tablets for Oral Solution USP.	Teva Pharmaceuticals, USA, 1510 Delp Dr., Kulpville, PA 19443.
ANDA 61-841	Terramycin (oxytetracycline) with Polymyxin B Sulfate Otic Ointment.	Pfizer, Inc.
ANDA 62-288	Gentamicin Sulfate Injection, 40 mg/mL.	Bristol Laboratories, P.O. Box 4755, Syracuse, NY 13221-4755.
ANDA 62-289	Gentamicin Sulfate Injection USP.	King Pharmaceuticals, Inc., 501 Fifth St., Bristol, TN 37620.
ANDA 62-598	Neomycin Sulfate-Triamcinolone Acetonide Cream.	Savage Laboratories, Inc., Division of Altana Inc., 60 Baylis Rd., Melville, NY 11747.
ANDA 62-607	Neomycin Sulfate-Triamcinolone Acetonide Ointment.	Pharmaderm, Division of Altana, Inc., 60 Baylis Rd., Melville, NY 11747.

Application No.	Drug	Applicant
ANDA 70-656	Dopamine Hydrochloride Injection USP, 40 mg/mL.	Abbott Laboratories.
ANDA 70-657	Dopamine Hydrochloride Injection USP, 80 mg/mL.	Do.
ANDA 73-611	Diphenhydramine Hydrochloride Cough Syrup, 12.5 mg/5 mL.	Cumberland-Swan, Inc., 1 Swan Dr., Smyrna, TN 37167.
ANDA 80-195	Potassium Chloride Injection.	Miles, Inc.
ANDA 80-211	Prednisolone Tablets, 5 mg.	Private Formulations, Inc., 460 Plainfield Ave., Edison, NJ 08818.
ANDA 80-830	Vitamin A Capsules USP, 15 mg.	Del Ray Labs, Inc., 22-20th Ave., NW., Birmingham, AL 35215.
ANDA 83-021	Sulfacetamide Sodium Ophthalmic Solution USP, 10%, 15%, and 30%.	AKORN, Inc., 1222 West Grand, Decatur, IL 62526.
ANDA 83-256	Alcohol in Dextrose Injection USP, 5%/5%.	Baxter Healthcare Corp., Rte. 120 and Wilson Rd., Round Lake, IL 60073-0490.
ANDA 84-652	Chlorotrianisene Capsules USP, 12 mg.	Banner Pharmacaps, 200730 Dearborn St., P.O. Box 2157, Chatsworth, CA 91313-2157.
ANDA 84-708	Triamcinolone Tablets, 2 mg.	Roxane Laboratories, Inc., P.O. Box 16532, Columbus, OH 43216-6532.
ANDA 84-775	Triamcinolone Tablets, 4 mg.	Teva Pharmaceuticals, USA.
ANDA 85-697	Phendimetrazine Tartrate Tablets, 35 mg (pink).	Private Formulations, Inc.
ANDA 85-914	Phendimetrazine Tartrate Tablets, 35mg.	Manufacturing Chemist, Inc., c/o Integrity Pharmaceutical Corp., 5767 Thunderbird Rd., Indianapolis, IN 46236.
ANDA 86-192	Hydrochlorothiazide Tablets, 25 mg and 50 mg.	M. M. Mast & Co., 4152 Ruple Rd., Cleveland, OH 44121.
ANDA 86-217	Chlordiazepoxide Capsules, 10 mg.	Do.
ANDA 86-259	Trichlormethiazide, 4 mg.	Do.
ANDA 86-521	Dextroamphetamine Sulfate Tablets, 5 mg.	Do.
ANDA 86-523	Phenazine Capsules, 35 mg.	Do.
ANDA 86-524	Phenazine Capsules, 35 mg.	Do.
ANDA 86-525	Phenazine Capsules, 35 mg.	Do.
ANDA 86-787	Sustac (nitroglycerin) Extended-release Oral Tablets, 10 mg.	Forest Laboratories, Inc., 909 Third Ave., New York, NY 10022-4731.
ANDA 87-255	Quinidine Sulfate Tablets, 200 mg.	Solvay Pharmaceuticals, Inc., 901 Sawyer Rd., Marietta, GA 30062.
ANDA 87-229	Nitrobon (nitroglycerin extended-release capsules) Capsules.	Inwood Laboratories, Inc., 909 Third Ave., New York, NY 10022-4731.
ANDA 87-305	Phendimetrazine Tartrate Tablets, 35 mg.	M. M. Mast & Co.
ANDA 87-544	Nitrobon (nitroglycerin extended-release capsules) Capsules.	Inwood Laboratories, Inc.
ANDA 87-917	Theophylline Syrup, 80 mg/15 mL.	Ferndale Laboratories, Inc., 780 West Eight Mile Rd., Ferndale, MI 48220.
ANDA 89-577	Hydrocortisone Sodium Succinate for Injection USP, 100 mg/mL.	Abbott Laboratories.
ANDA 89-578	A-Hydrocort (Hydrocortisone Sodium Succinate for Injection USP), 250 mg/vial.	Do.
ANDA 89-579	A-Hydrocort (Hydrocortisone Sodium Succinate for Injection USP), 500 mg/vial.	Do.
ANDA 89-580	A-Hydrocort (Hydrocortisone Sodium Succinate for Injection USP), 1 gram/vial.	Do.

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) and under authority delegated to the Director, Center for Drug Evaluation and Research (21 CFR 5.82), approval of the applications listed in the table in this document, and all amendments and supplements thereto, is hereby withdrawn, effective September 22, 1999.

Dated: September 8, 1999.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 99-24595 Filed 9-21-99; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Cardiovascular and Renal Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Cardiovascular and Renal Drugs Advisory Committee.

General Function of the Committee: To provide advice and

recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on October 14, 1999, 9 a.m. to 5:30 p.m.

Location: National Institutes of Health, Clinical Center, Bldg. 10, Jack Masur Auditorium, 9000 Rockville Pike, Bethesda, MD. Parking in the Clinical Center is reserved for Clinical Center patients and their visitors. If you must drive, please use an outlying lot such as Lot 41B. Free shuttle bus service is provided from Lot 41B to the Clinical Center every 8 eight minutes during rush hour and every 15 minutes at other times.

Contact Person: Joan C. Standaert, Center for Drug Evaluation and Research (HFD-110), Food and Drug Administration, 5630 Fishers Lane,

Tab 68

Federal Register of June 16, 2006
(71 FR 34940)

and resultant under-utilization; *Form Number*: CMS-R-52 (OMB#: 0938-0386); *Frequency*: Recordkeeping and Reporting—Annually; *Affected Public*: Business or other for-profit and Federal government; *Number of Respondents*: 4,757; *Total Annual Responses*: 4,757; *Total Annual Hours*: 160,702.

To obtain copies of the supporting statement and any related forms for the proposed paperwork collections referenced above, access CMS Web site address at <http://www.cms.hhs.gov/PaperworkReductionActof1995>, or E-mail your request, including your address, phone number, OMB number, and CMS document identifier, to Paperwork@cms.hhs.gov, or call the Reports Clearance Office on (410) 786-1326.

Written comments and recommendations for the proposed information collections must be mailed or faxed within 30 days of this notice directly to the OMB desk officer: OMB Human Resources and Housing Branch, Attention: Carolyn Lovett, New Executive Office Building, Room 10235,

Washington, DC 20503. Fax Number: (202) 395-6974.

Dated: June 9, 2006.

Michelle Shortt,

*Director, Regulations Development Group,
Office of Strategic Operations and Regulatory Affairs.*

[FR Doc. E6-9479 Filed 6-15-06; 8:45 am]

BILLING CODE 4120-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2006N-0222]

Merck & Co., Inc., et al.; Withdrawal of Approval of 65 New Drug Applications and 52 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing

approval of 65 new drug applications (NDAs) and 52 abbreviated new drug applications (ANDAs) from multiple applicants. The holders of the applications notified the agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

DATES: Effective June 16, 2006.

FOR FURTHER INFORMATION CONTACT:

Florine P. Purdie, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: The holders of the applications listed in the table in this document have informed FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications. The applicants have also, by their requests, waived their opportunity for a hearing.

Application No.	Drug	Applicant
NDA 1-645	Vitamin B6 (pyridoxine hydrochloride (HCl))	Merck & Co., Inc., 770 Sumneytown Pike, P.O. Box 4, BLA-20, West Point, PA 19486-0004
NDA 5-521	Heparin Sodium Injection USP	Eli Lilly and Co., Lilly Corporate Center, Indianapolis, IN 46285
NDA 5-657	Tubocurarine Chloride Injection USP	Bristol-Myers Squibb Co., P.O. Box 4500, Princeton, NJ 08543-4500
NDA 5-794	Sultrin Triple Sulfa Cream and Triple Sulfa Tablets	Ortho-McNeil Pharmaceutical, Inc., 1000 U.S. Highway 202, P.O. Box 300, Raritan, NJ 08869-0602
NDA 6-012	Folvron (folic acid and iron)	Lederle Laboratories, 401 North Middleton Rd., Pearl River, NY 10965
NDA 7-149	Rubramin (cyanocobalamin) Tablets and Capsules	Bristol-Myers Squibb Co.
NDA 7-504	Acthar (corticotropin for injection)	Aventis Pharmaceuticals, Inc., 200 Crossing Blvd., BX 2-309E, Bridgewater, NJ 08807
NDA 7-794	Neothylline (diphylline)	Teva Pharmaceuticals USA, 1090 Horsham Rd., P.O. Box 1090, North Wales, PA 19454
NDA 9-176	Cortril (hydrocortisone) Topical Ointment	Pfizer Global Pharmaceuticals, 235 East 42nd St., New York, NY 10017
NDA 10-028	Equanil (meprobamate) Tablets	Wyeth Pharmaceuticals, P.O. Box 8299, Philadelphia, PA 19101-8299
NDA 10-093	Biphetamine (dextroamphetamine and amphetamine) Capsules	Celltech Pharmaceuticals, Inc., 755 Jefferson Rd., P.O. Box 31710, Rochester, NY 14603
NDA 10-513	Ketonil (amino acids and electrolytes)	Merck & Co., Inc.
NDA 10-787	Iron Dextran Injection	Aventis Pharmaceuticals, Inc.
NDA 10-799	Dimetane (brompheniramine maleate) Tablets and Extendabs	Wyeth Consumer Healthcare, 5 Giralda Farms, Madison, NJ 07940
NDA 11-340	Cerumenex (triethanolamine polypeptide oleate-condensate), 10%	The Purdue Frederick Co., 1 Stamford Forum, Stamford, CT 06901-3431

Application No.	Drug	Applicant
NDA 11-960	Aristocort (triamcinolone diacetate) Syrup	Astellas Pharma US, Inc., 3 Parkway North, Deerfield, IL 60015-2548
NDA 11-984	Decadron Phosphate (dexamethasone sodium phosphate) Sterile Ophthalmic Solution	Merck & Co., Inc.
NDA 12-122	Glucagon (glucagon HCl) for Injection	Eli Lilly & Co.
NDA 12-281	Robaxial (methocarbamol USP and aspirin USP) Tablets	A.H. Robins Co., c/o Wyeth Pharmaceuticals, P.O. Box 8299, Philadelphia, PA 19101-8299
NDA 12-649	Periactin (cyproheptadine HCl)	Merck & Co., Inc.
NDA 12-703	Elavil (amitriptyline HCl) Tablets	AstraZeneca Pharmaceuticals, 1800 Concord Pike, P.O. Box 8355, Wilmington, DE 19803-8355
NDA 12-704	Elavil (amitriptyline HCl) Injection	Do.
NDA 13-220	Periactin (cyproheptadine HCl) Syrup, 2 milligrams (mg)/5 milliliters (mL)	Merck & Co., Inc.
NDA 13-400	Aldomet (methyldopa) Tablets	Do.
NDA 13-401	Aldomet (methyldopate HCl) Injection, 50 mg/mL	Do.
NDA 13-413	Dexacort Phosphate (dexamethasone sodium phosphate) in Respihaler	Celltech Pharmaceuticals, Inc.
NDA 16-016	Aldoclor-150 and -250 (methyldopa and chlorothiazide) Tablets, 250 mg/150 mg and 250 mg/250 mg	Merck & Co., Inc.
NDA 16-030	Bayer 8 Hour Aspirin and Measurin Aspirin (aspirin extended-release tablets), 650 mg	Bayer Healthcare, LLC, 36 Columbia Rd., P.O. Box 1910, Morristown, NJ 07962-1910
NDA 16-099	Atromid-S (clofibrate) Capsules	Wyeth Pharmaceuticals
NDA 16-745	Jergens Antibacterial Deodorant (triclocarban, 1%) Soap	Kao Brands Co., 2535 Springs Grove Ave., Cincinnati, OH 45214-1773
NDA 16-888	Selsun Blue (selenium sulfide) Cream/Shampoo, 1%	Abbott Laboratories, 625 Cleveland Ave., Columbus, OH 43215-1724
NDA 17-569	Renoquid (sulfacytine) Tablets	Glenwood LLC, 111 Cedar Lane, Englewood, NJ 07631
NDA 17-573	Vanceril (beclomethasone dipropionate) Inhalation Aerosol	Schering Corp., 2000 Galloping Hill Rd., Kenilworth, NJ 07033
NDA 17-659	Alupent (metaproterenol sulfate) Inhalation Solution, 5%	Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Rd., P.O. Box 368, Ridgefield, CT 06877-0368
NDA 17-781	Diprosone (betamethasone dipropionate) Lotion	Schering Corp.
NDA 17-820	Dobutrex (dobutamine HCl) Sterile Injection	Eli Lilly & Co.
ANDA 18-023	Lactated Ringer's Injection USP	B. Braun Medical, Inc., 2525 McGaw Ave., P.O. Box 19791, Irvine, CA 92623-9791
ANDA 18-026	5% Dextrose and 0.9% Sodium Chloride (NaCl) Injection	Do.
ANDA 18-046	10% Dextrose Injection USP	Do.
ANDA 18-047	10% Dextrose and 0.9% NaCl Injection USP	Do.
ANDA 18-184	0.45% NaCl Injection USP	Do.
ANDA 18-186	1/6 Molar Sodium Lactate Injection USP in Plastic Container	Do.
ANDA 18-197	Ibuprofen Tablets	BASF Corp., 8800 Line Ave., Shreveport, LA 71106
ANDA 18-252	Isolyte S (multi-electrolyte injection) Injection	B. Braun Medical, Inc.
ANDA 18-256	5% Dextrose in Ringer's Injection	Do.
NDA 18-257	Tonocard (tocainide HCl) Tablets, 400 mg and 600 mg	AstraZeneca Pharmaceuticals

Application No.	Drug	Applicant
ANDA 18-274	Isolyte S (multi-electrolyte injection) with 5% Dextrose in Plastic Container	B. Braun Medical, Inc.
NDA 18-389	Aldomet (methyldopa) Oral Suspension, 250 mg/5 mL	Merck & Co., Inc.
NDA 18-682	TZ-3 (1% tioconazole) Dermal Cream	Pfizer, Inc., 235 East 42nd St., New York, NY 10017
NDA 18-686	Normodyne (labetalol HCl USP) Injection, 5 mg/mL	Schering Corp.
NDA 18-687	Normodyne (labetalol HCl USP) Tablets	Do.
ANDA 18-721	Ringer's Injection USP	B. Braun Medical, Inc.
NDA 18-754	Orudis (ketoprofen) Capsules, 25 mg, 50 mg, and 75 mg	Wyeth Pharmaceuticals
NDA 18-792	Neopham (amino acids) Injection	Hospira, Inc., 275 North Field Dr., Dept. 389, Bldg. 2, Lake Forest, IL 60045
NDA 18-901	Aminess (essential amino acids injection with histidine)	Do.
NDA 18-911	Heparin Sodium in 5% Dextrose Injection and Heparin Sodium in NaCl Injection	Do.
NDA 19-083	Theophylline and 5% Dextrose Injection	B. Braun Medical, Inc.
NDA 19-107	Protropin (somatrem) for Injection	Genentech, Inc., 1 DNA Way MS1242, South San Francisco, CA 94080-4990
ANDA 19-138	Alphatrex (betamethasone dipropionate cream USP) 0.05%	Savage Laboratories, 60 Baylis Rd., Melville, NY 11747
ANDA 19-143	Alphatrex (betamethasone dipropionate ointment USP) 0.05%	Do.
NDA 19-383	Proventil (albuterol sulfate extended-release tablets USP) Repetabs	Schering Corp.
NDA 19-401	Pseudo-12 Suspension (pseudoephedrine polistirex extended-release suspension)	Celltech Pharmaceuticals, Inc.
NDA 19-523	Cysteine HCl Injection USP, 7.25%	Hospira, Inc.
NDA 19-589	Vancenase AQ (beclomethasone dipropionate) Nasal Spray	Schering Corp.
NDA 19-621	Ventolin (albuterol sulfate) Syrup	GlaxoSmithKline Pharmaceuticals, 5 More Dr., P.O. Box 13358, Research Triangle Park, NC 27709
NDA 20-035	Ergamisol (levamisole HCl) Tablets	Johnson & Johnson Pharmaceutical Research and Development, LLC, c/o Janssen Pharmaceutical Products, LP, 1125 Trenton-Harbourton Rd., K1-02B, Titusville, NJ 08560-0200
NDA 20-176	VitaPed (multivitamins)	Hospira, Inc.
NDA 20-338	Differin (adapalene) Solution, 0.1%	Galderma Laboratories, LP, 14501 North Freeway, Fort Worth, TX 76177
NDA 20-759	Trovan (trovafloxacin mesylate) Tablets, 100 mg and 200 mg	Pfizer, Inc.
NDA 20-760	Trovan (alatrofloxacin mesylate) Injection	Do.
NDA 20-847	Esclim (estradiol extended-release film) Transdermal System	Women First Healthcare, Inc., 380 Lexington Ave., New York, NY 10168
NDA 20-962	Emla (2.5% lidocaine and 2.5% prilocaine) Anesthetic Disc	AstraZeneca Pharmaceuticals
ANDA 40-023	Adrucil (fluorouracil injection USP), 50 mg/mL	Sicor Pharmaceuticals, Inc., 19 Hughes, Irvine, CA 92618
ANDA 40-147	Leucovorin Calcium Injection USP, 10 mg (base)/mL	Hospira, Inc.
NDA 50-039	Garamycin (gentamicin sulfate) Ophthalmic Solution	Schering Corp.

Application No.	Drug	Applicant
NDA 50-091	Chloroptic (chloramphenicol ophthalmic solution USP), 0.5%	Allergan, Inc., 2525 Dupont Dr., P.O. Box 19534, Irvine, CA 92623-9534
NDA 50-322	Neodecadron (neomycin sulfate and dexamethasone sodium phosphate) Sterile Ophthalmic Solution	Merck & Co., Inc.
NDA 50-368	Ilotycin (erythromycin) Ophthalmic Ointment	Eli Lilly & Co.
NDA 50-571	CefMax (cefmenoxime HCl) Injection	TAP Pharmaceutical Products, Inc., 675 North Field Dr., Lake Forest, IL 60045
NDA 50-648	Clindamycin Phosphate Injection in 5% Dextrose	Baxter Healthcare Corp., Route 120 & Wilson Rd., Round Lake, IL 60073
ANDA 60-429	Sumycin Capsules (tetracycline HCl capsules USP)	Apothecon, c/o Bristol-Myers Squibb Co., P.O. Box 4500, Princeton, NJ 08543-4500
ANDA 62-480	Gentacidin Solution (gentamicin sulfate ophthalmic solution USP)	Novartis Pharmaceuticals Corp., 1 Health Plaza, Bldg. 118, East Hanover, NJ 07936-1080
ANDA 62-597	Mytrex (nystatin and triamcinolone acetonide cream USP) 100,000 units/gram (g) and 1 mg/g	Savage Laboratories
ANDA 62-601	Mytrex (nystatin and triamcinolone acetonide ointment USP) 100,000 units/g and 1 mg/g	Do.
ANDA 62-750	Pipracil (piperacillin for injection), 2 g, 3 g, and 4 g	Wyeth Pharmaceuticals, Inc.
ANDA 63-186	Cephalexin Capsules USP, 250 mg and 500 mg	Apothecon, c/o Bristol-Myers Squibb Co.
ANDA 64-084	Sterile Bleomycin Sulfate for Injection USP, 15 and 30 units/vial	Sicor Pharmaceuticals, Inc.
ANDA 70-083	Ibuprofen Tablets USP, 400 mg	BASF Corp.
ANDA 70-099	Ibuprofen Tablets USP, 600 mg	Do.
ANDA 70-273	Alphatrex (betamethasone dipropionate lotion USP), 0.05%	Savage Laboratories
ANDA 70-745	Ibuprofen Tablets USP, 800 mg	BASF Corp.
ANDA 72-621	Acetylcysteine Solution USP, 10%	Roxane Laboratories, Inc., P.O. Box 16532, Columbus, OH 43216
ANDA 72-622	Acetylcysteine Solution USP, 20%	Do.
ANDA 72-995	Metoclopramide HCl Oral Solution, 10 mg/mL	Do.
ANDA 73-562	Diffunisal Tablets USP, 250 mg	Do.
ANDA 73-563	Diffunisal Tablets USP, 500 mg	Do.
ANDA 74-166	Toposar (etoposide injection USP), 20 mg/mL	Sicor Pharmaceuticals, Inc.
ANDA 74-541	Cimetidine HCl Oral Solution, 30 mg/5 mL	Roxane Laboratories, Inc.
ANDA 74-663	Acyclovir Sodium for Injection USP, 500 mg base/vial and 1 g base/vial	Hospira, Inc.
ANDA 75-179	Nabumetone Tablets	Copley Pharmaceutical, Inc., 1090 Horsham Rd., P.O. Box 1090, North Wales, PA 19454
ANDA 75-875	Carbamazepine Oral Suspension USP, 100 mg/5 mL	Taro Pharmaceutical Industries, Ltd., c/o Taro Pharmaceuticals, U.S. Agent, 5 Skyline Dr., Hawthorne, NY 10532
ANDA 80-643	Diphenhydramine HCl Elixir USP, 25 mg/10 mL	Roxane Laboratories, Inc.
ANDA 81-225	Adrucil (etoposide injection USP), 50 mg/mL	Sicor Pharmaceuticals, Inc.
ANDA 83-261	Pentobarbital Sodium Injection USP	Wyeth Pharmaceuticals
ANDA 83-383	Diucardin (hydroflumethiazide tablets USP) Tablets, 50 mg	Do.

Application No.	Drug	Applicant
ANDA 84-015	Bleph-10 (sulfacetamide sodium ophthalmic ointment USP) Ophthalmic Ointment, 10%	Allergan, Inc.
ANDA 84-514	Dilor (dyphylline tablets USP), 200 mg	Savage Laboratories
ANDA 84-751	Dilor-400 (dyphylline tablets USP), 400 mg	Do.
ANDA 85-035	Diphenoxylate HCl and Atropine Sulfate Tablets USP, 2.5 mg and 0.025 mg	R & S Pharma, LLC, 8407 Austin Tracy Rd., Fountain Run, KY 42133
ANDA 85-961	Methocarbamol Tablets USP, 500 mg	Clonmel Healthcare Ltd., c/o STADA Pharmaceuticals, Inc., U.S. Agent, 5 Cedar Brook Dr., Cranbury, NJ 08512
ANDA 85-963	Methocarbamol Tablets USP, 750 mg	Do.
ANDA 86-899	Isoetharine HCl Inhalation Solution USP, 1%	Roxane Laboratories, Inc.
ANDA 87-450	Chlorthalidone Tablets USP, 50 mg	Clonmel Healthcare Ltd.
ANDA 87-451	Chlorthalidone Tablets USP, 25 mg	Do.
ANDA 87-500	Aminophylline Tablets USP, 100 mg	Roxane Laboratories, Inc.
ANDA 87-501	Aminophylline Tablets USP, 200 mg	Do.
ANDA 88-253	T-Phyl (theophylline) Extended-Release Tablets, 200 mg	The Purdue Frederick Co.

Therefore, under section 505(e), of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), and under authority delegated to the Director, Center for Drug Evaluation and Research, by the Commissioner of Food and Drugs, approval of the applications listed in the table in this document, and all amendments and supplements thereto, is hereby withdrawn, effective June 16, 2006.

Dated: May 23, 2006.

Douglas C. Throckmorton,

Deputy Director, Center for Drug Evaluation and Research.

[FR Doc. E6-9440 Filed 6-15-06; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003E-0254]

Determination of Regulatory Review Period for Purposes of Patent Extension; INSPRA

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for INSPRA and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks,

Department of Commerce, for the extension of a patent that claims that human drug product.

ADDRESSES: Submit written comments and petitions to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100-670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the human drug product becomes effective and runs until the approval phase begins. The approval phase starts with the initial

submission of an application to market the human drug product and continues until FDA grants permission to market the product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted, as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product INSPRA (epiprenone). INSPRA is indicated for the treatment of hypertension. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for INSPRA (U.S. Patent No. 4,559,332) from Novartis Corp., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated June 16, 2003, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of INSPRA represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for

Tab 69

FDA Alert – Information for Healthcare Professionals: Valdecoxib (marketed as Bextra) (April 7, 2005)

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Drugs

Information for Healthcare Professionals: Valdecoxib (marketed as Bextra)

[For additional information, see [COX-2 and Non-Selective Non-Steroidal Anti-Inflammatory Drugs \(NSAIDs\)](#).]¹

FDA Alert [4/7/2005]:

FDA has requested that Pfizer voluntarily withdraw Bextra from the United States market. Pfizer has agreed to suspend sales and marketing of Bextra in the United States, pending further discussion with the Agency. At this time, the Agency has concluded that the overall risk versus benefit profile of Bextra is unfavorable. This conclusion is based on the potential increased risk for serious cardiovascular (CV) adverse events, which appears to be a class effect of non-steroidal anti-inflammatory drugs (NSAIDs) (excluding aspirin), an increased risk of serious skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other NSAIDs, and the fact that Bextra has not been shown to offer any unique advantages over the other available NSAIDs.

This information reflects FDA's current analysis of all available data concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

Recommendations

- FDA recommends that patients being treated with Bextra be switched to an alternative therapy.

Data Summary

- Bextra has been demonstrated to be associated with an increased risk of serious adverse CV events in two short-term trials in patients immediately post-operative from coronary artery bypass graft (CABG) surgery. Data are not available from long-term controlled clinical trials to evaluate the cardiovascular safety of Bextra following chronic use. FDA has concluded that it is reasonable to extrapolate the adverse CV risk information for Bextra from the short-term CABG trials to chronic use given the fact that other COX-2 selective NSAIDs have been shown in long-term controlled clinical trials to be associated with an increased risk of serious adverse CV events (e.g., death, MI, stroke), and the well described risk of serious, and often life-threatening gastrointestinal bleeding.
- Bextra is a sulfonamide and already carries a boxed warning in the package insert for serious and potentially life-threatening skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme). The reporting rate to FDA's spontaneous reporting system for these serious skin reactions is significantly greater for Bextra than other COX-2 selective agents. The risk of these serious skin reactions in individual patients is unpredictable, occurring in patients with and without a history of sulfa allergy, and after both short- and long term use.
- To date, there have been no studies that demonstrate an advantage of Bextra over other NSAIDs that might offset the concern about these serious skin risks, such as studies that show a GI safety benefit, better efficacy compared to other products, or efficacy in a setting of patients who are refractory to treatment with other products.
- Extensive data related to the cardiovascular safety of Bextra and other COX-2 selective and non-selective NSAIDs were presented at the Joint Meeting on February 16, 17, and 18, 2005, of the [Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee](#)².

Report serious adverse events to FDA's MedWatch using the contact information at the bottom of this page.

Questions? Call Drug Information, 1-888-INFO-FDA (automated) or 301-796-3400
druginfo@fda.hhs.gov

Related Information

- [COX-2 Selective \(includes Bextra, Celebrex, and Vioxx\) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs \(NSAIDs\)](#)³

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Page Last Updated: 08/13/2013

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U.S. Department of **Health & Human Services**

Links on this page:

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2. <http://www.fda.gov/ohrms/dockets/ac/cder05.html#ArthritisDrugs>
3. [/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103420.htm](#)
4. <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>
5. <http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf>

Tab 70

Federal Register of August 2, 2013
(78 FR 46984)

end of FY 2013, FDA estimates that 490 establishments will have been billed for establishment fees, before all decisions on requests for waivers or reductions are made. FDA estimates that a total of 20 establishment fee waivers or reductions will be made for FY 2013. In addition, FDA estimates that another 15 full establishment fees will be exempted this year based on the orphan drug exemption in section 736(k) of the FD&C Act. Subtracting 35 establishments (20 waivers, plus the estimated 15 establishments under the orphan exemption) from 490 leaves a net of 455 fee-paying establishments. FDA will use 455 for its FY 2014 estimate of establishments paying fees, after taking waivers and reductions into account. The fee per establishment is determined by dividing the adjusted total fee revenue to be derived from establishments (\$252,342,667) by the estimated 455 establishments, for an establishment fee rate for FY 2014 of \$554,600 (rounded to the nearest \$100).

B. Product Fees

At the beginning of FY 2013, the product fee was based on an estimate that 2,435 products would be subject to and would pay product fees. By the end of FY 2013, FDA estimates that 2,510 products will have been billed for product fees, before all decisions on requests for waivers, reductions, or exemptions are made. FDA assumes that there will be 45 waivers and reductions granted. In addition, FDA estimates that another 40 product fees will be exempted this year based on the orphan drug exemption in section 736(k) of the FD&C Act. FDA estimates that 2,425 products will qualify for product fees in FY 2013, after allowing for waivers and reductions, including the orphan drug products, and will use this number for its FY 2014 estimate. The FY 2014 product fee rate is determined by dividing the adjusted total fee revenue to be derived from product fees (\$252,342,667) by the estimated 2,425 products for a FY 2014 product fee of \$104,060 (rounded to the nearest \$10).

V. Fee Schedule for FY 2014

The fee rates for FY 2014 are set out in table 7 of this document:

TABLE 7—FEE SCHEDULE FOR FY 2014

Fee category	Fee rates for FY 2014
Applications: Requiring clinical data	\$2,169,100
Not requiring clinical data	
	1,084,550

TABLE 7—FEE SCHEDULE FOR FY 2014—Continued

Fee category	Fee rates for FY 2014
Supplements requiring clinical data	1,084,550
Establishments	554,600
Products	104,060

VI. Fee Payment Options and Procedures

A. Application Fees

The appropriate application fee established in the new fee schedule must be paid for any application or supplement subject to fees under PDUFA that is received after September 30, 2013. Payment must be made in U.S. currency by check, bank draft, or U.S. postal money order payable to the order of the Food and Drug Administration. Please include the user fee identification (ID) number on your check, bank draft, or postal money order. Your payment can be mailed to: Food and Drug Administration, P.O. Box 979107, St. Louis, MO 63197-9000.

If checks are to be sent by a courier that requests a street address, the courier can deliver the checks to: U.S. Bank, Attention: Government Lockbox 979107, 1005 Convention Plaza, St. Louis, MO 63101. (Note: This U.S. Bank address is for courier delivery only. Contact the U.S. Bank at 314-418-4013 if you have any questions concerning courier delivery.)

Please make sure that the FDA post office box number (P.O. Box 979107) is written on the check, bank draft, or postal money order.

Wire transfer payment may also be used. Please reference your unique user fee ID number when completing your transfer. The originating financial institution may charge a wire transfer fee. Please ask your financial institution about the fee and add it to your payment to ensure that your fee is fully paid. The account information is as follows: New York Federal Reserve Bank, U.S. Department of the Treasury, TREAS NYC, 33 Liberty St., New York, NY 10045, Acct. No.: 75060099, Routing No.: 021030004, SWIFT: FRNYUS33, Beneficiary: FDA, 1350 Piccard Drive, Rockville, MD.

Application fees can also be paid online with an electronic check (ACH). FDA has partnered with the U.S. Department of the Treasury to use Pay.gov, a Web-based payment application, for online electronic payment. The Pay.gov feature is available on the FDA Web site after the user fee ID number is generated.

The tax identification number of FDA is 53-0196965.

B. Establishment and Product Fees

FDA will issue invoices for establishment and product fees for FY 2014 under the new fee schedule in August 2013. Payment will be due on October 1, 2013. FDA will issue invoices in November 2014 for any products and establishments subject to fees for FY 2014 that qualify for fee assessments after the August 2013 billing.

Dated: July 29, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-18624 Filed 8-1-13; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-0869]

Pfizer, Inc.; Withdrawal of Approval of a New Drug Application for BEXTRA

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of a new drug application (NDA) for BEXTRA (valdecoxib) 10 milligram (mg) and 20 mg Tablets, held by Pfizer, Inc. (Pfizer), 235 East 42nd St., New York, NY 10017-5755. Pfizer has voluntarily requested that approval of this application be withdrawn and has waived its opportunity for a hearing.

DATES: Effective August 2, 2013.

FOR FURTHER INFORMATION CONTACT: Martha Nguyen, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6250, Silver Spring, MD 20993-0002, 301-796-3601.

SUPPLEMENTARY INFORMATION: FDA approved BEXTRA (valdecoxib) 10 mg and 20 mg Tablets on November 16, 2001. BEXTRA is indicated for relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis and for the treatment of primary dysmenorrhea. On April 7, 2005, FDA announced that it had concluded that the overall risk versus benefit profile of BEXTRA was unfavorable and that it had asked Pfizer to voluntarily withdraw BEXTRA from the market. Pfizer agreed and voluntarily suspended all sales and marketing of BEXTRA on July 21, 2005. In letters dated May 27, 2011, August 8,

2011, and October 31, 2011, Pfizer requested that FDA withdraw approval of NDA 21–341 for BEXTRA. In the letter dated October 31, 2011, Pfizer waived any opportunity for a hearing otherwise provided under 21 CFR 314.150 (§ 314.150). In FDA's letter of November 9, 2011, responding to Pfizer's letters dated May 27, 2011, August 8, 2011, and October 31, 2011, the Agency acknowledged Pfizer's request to withdraw approval of BEXTRA under § 314.150(d) and waive its opportunity for a hearing.

Therefore, under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(e)) and § 314.150(d), and under authority delegated by the Commissioner to the Director, Center for Drug Evaluation and Research, approval of NDA 21–341, and all amendments and supplements thereto, is withdrawn (see DATES). Distribution of this product in interstate commerce without an approved application is illegal and subject to regulatory action (see sections 505(a) and 301(d) of the FD&C Act (21 U.S.C. 355(a) and 331(d)).

Dated: July 30, 2013.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 2013–18657 Filed 8–1–13; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Indian Health Service

Office of Direct Service and Contracting Tribes; National Indian Health Outreach and Education; Cooperative Agreement Program

Announcement Type: Limited New and Competing Continuation
Funding Announcement Number: HHS–2013–IHS–NIHOE–0001
Catalog of Federal Domestic Assistance Number: 93.933

Key Dates

Application Deadline Date: September 6, 2013
Review Date: September 10, 2013
Earliest Anticipated Start Date: September 30, 2013
Proof of Non-Profit Status Due Date: September 6, 2013

I. Funding Opportunity Description

Statutory Authority

The Indian Health Service (IHS) is accepting competitive cooperative agreement applications for the National Indian Health Outreach and Education

(NIHOE) I limited competition cooperative agreement program. This award includes the following four components, as described in this announcement: “Line Item 128 Health Education and Outreach funds,” “Health Care Policy Analysis and Review,” “Budget Formulation” and “Tribal Leaders Diabetes Committee” (TLDC). This program is authorized under the Snyder Act, codified at 25 U.S.C. 13. This program is described in the Catalog of Federal Domestic Assistance (CFDA) under 93.933.

Background

The NIHOE program carries out health program objectives in the American Indian and Alaska Native (AI/AN) community in the interest of improving Indian health care for all 566 Federally-recognized Tribes, including Tribal governments operating their own health care delivery systems through self-determination contracts with the IHS and Tribes that continue to receive health care directly from the IHS. This program addresses health policy and health program issues and disseminates educational information to all AI/AN Tribes and villages. This program requires that public forums be held at Tribal educational consumer conferences to disseminate changes and updates in the latest health care information. This program also requires that regional and national meetings be coordinated for information dissemination as well as the inclusion of planning and technical assistance and health care recommendations on behalf of participating Tribes to ultimately inform IHS based on Tribal input through a broad based consumer network.

Purpose

The purpose of this IHS cooperative agreement is to further IHS's mission and goals related to providing quality health care to the AI/AN community through outreach and education efforts with the sole outcome of improving Indian health care. This award includes the following four health services components: Line Item 128 Health Education and Outreach funds, Health Care Policy Analysis and Review, Budget Formulation, and Tribal Leaders Diabetes Committee (TLDC).

Limited Competition Justification

Competition for the award included in this announcement is limited to national Indian health care organizations with at least ten years of experience providing education and outreach on a national scale. This limitation ensures that the awardee will

have: (1) A national information-sharing infrastructure which will facilitate the timely exchange of information between the Department of Health and Human Services (HHS) and Tribes and Tribal organizations on a broad scale; (2) a national perspective on the needs of AI/AN communities that will ensure that the information developed and disseminated through the projects is appropriate, useful and addresses the most pressing needs of AI/AN communities; and (3) established relationships with Tribes and Tribal organizations that will foster open and honest participation by AI/AN communities. Regional or local organizations will not have the mechanisms in place to conduct communication on a national level, nor will they have an accurate picture of the health care needs facing AI/ANs nationwide. Organizations with less experience will lack the established relationships with Tribes and Tribal organizations throughout the country that will facilitate participation and the open and honest exchange of information between Tribes and HHS. With the limited funds available for these projects, HHS must ensure that the education and outreach efforts described in this announcement reach the widest audience possible in a timely fashion, are appropriately tailored to the needs of AI/AN communities throughout the country, and come from a source that AI/ANs recognize and trust. For these reasons, this is a limited competition announcement.

II. Award Information

Type of Award

Cooperative Agreement.

Estimated Funds Available

The total amount of funding identified for the current fiscal year 2013 is approximately \$716,000. Three hundred thousand dollars (\$300,000) is estimated for outreach, education, and support to Tribes who have elected to leave their Tribal Shares with the IHS (this amount could vary based on Tribal Shares assumptions; Line Item 128 Health Education and Outreach funding will be awarded in partial increments based on availability and amount of funding); \$100,000 for the Health Care Policy Analysis and Review; \$16,000 for the Budget Formulation; and \$300,000 associated with providing legislative education, outreach and communications support to the IHS TLDC and to facilitate Tribal consultation on the Special Diabetes Program for Indians (SDPI). All competing and continuation awards

Tab 71

Federal Register of April 7, 1998
(63 FR 17011)

Board of Governors of the Federal Reserve System, April 2, 1998.

William W. Wiles,
Secretary of the Board.

[FR Doc. 98-9072 Filed 4-6-98; 8:45 am]

BILLING CODE 6210-01-F

FEDERAL RESERVE SYSTEM

Sunshine Act Meeting

AGENCY HOLDING THE MEETING: Board of Governors of the Federal Reserve System.

TIME AND DATE: 11:00 a.m., Monday, April 13, 1998.

PLACE: Marriner S. Eccles Federal Reserve Board Building, 20th and C Streets, NW., Washington, DC 20551.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

1. Personnel actions (appointments, promotions, assignments, reassignments, and salary actions) involving individual Federal Reserve System employees.

2. Any items carried forward from a previously announced meeting.

CONTACT PERSON FOR MORE INFORMATION: Joseph R. Coyne, Assistant to the Board; 202-452-3204.

SUPPLEMENTARY INFORMATION: You may call 202-452-3206 beginning at approximately 5 p.m. two business days before the meeting for a recorded announcement of bank and bank holding company applications scheduled for the meeting; or you may contact the Board's Web site at <http://www.bog.frb.fed.us> for an electronic announcement that not only lists applications, but also indicates procedural and other information about the meeting.

Dated: April 3, 1998.

William W. Wiles,
Secretary of the Board.

[FR Doc. 98-9268 Filed 4-3-98; 3:48 pm]

BILLING CODE 6210-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98N-0182]

Bulk Drug Substances To Be Used in Pharmacy Compounding; Request for Nominations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for nominations.

SUMMARY: The Food and Drug Administration (FDA) is preparing to

develop a list of bulk drug substances (bulk drugs) that may be used in pharmacy compounding that do not have a United States Pharmacopeia (USP) or National Formulary (NF) monograph and are not components of approved drugs. FDA is taking this action in accordance with provisions in the Food and Drug Administration Modernization Act of 1997 (FDAMA). To identify candidates for this bulk drugs list, FDA is encouraging interested groups and individuals to nominate specific bulk drug substances and is describing the information that should be provided to the agency in support of each nomination.

DATES: Nominations must be received by June 8, 1998, to receive consideration for inclusion on the bulk drugs list. Nominations received after this date will receive consideration for subsequent amendments to the list.

ADDRESSES: Send nominations to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Robert J. Tonelli, Center for Drug Evaluation and Research (HFD-332), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-0101.

SUPPLEMENTARY INFORMATION: President Clinton signed FDAMA (Pub. L. 105-115) into law on November 21, 1997. One of the issues addressed in this new legislation is the applicability of the Federal Food, Drug, and Cosmetic Act (the act) to the practice of pharmacy compounding. Compounding involves a process whereby a pharmacist or physician combines, mixes, or alters ingredients to create a customized medication for an individual patient. Section 127 of FDAMA, which adds section 503A to the act (21 U.S.C. 353a), describes the circumstances under which compounded drugs qualify for exemptions from certain adulteration, misbranding, and new drug provisions of the act. Section 127 becomes effective 1 year from the date of the FDAMA's enactment (section 503A(b) of the act).

Section 127 contains several restrictions regarding the bulk drug substances¹ that may be used as ingredients in compounding and still qualify for the applicable exemptions. It

¹The term "bulk drug substance" is defined in FDA's regulations at 21 CFR 207.3(a)(4) and incorporated in section 127 of FDAMA to mean "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances."

provides, among other things, that such substances must comply with the standards of an applicable USP or NF monograph, if one exists, and the USP chapter on pharmacy compounding; if a monograph does not exist, they must be components of drugs approved by FDA; and if neither of those criteria are satisfied, they must appear on a list that FDA develops and issues through regulations (section 503A(b)(1)(A)(i)(I) through (b)(1)(A)(i)(III) of the act).

In accordance with the bulk drug provisions in section 127, FDA is preparing to develop a list of bulk drug substances that may be used in compounding that do not have a USP or NF monograph and are not components of approved drugs. To identify candidates for this list, FDA is seeking public input in the form of specific bulk drug nominations. All interested groups and individuals are encouraged to nominate specific bulk drug substances for inclusion on the list. FDA intends for this nomination process to serve as its principal means of identifying list candidates. After evaluating the nominations and, as required by Congress, consulting with the United States Pharmacopeial Convention, Inc., and an advisory committee on compounding (section 503A(d) of the act), FDA will issue the list as a regulation under notice-and-comment rulemaking procedures.

Nominations should include the following information about the bulk drug substance being nominated and the product(s) that will be compounded using such substance. If the information requested is unknown or unavailable, that fact should be noted accordingly.

Bulk Drug Substance

- Ingredient name;
- Chemical name;
- Common name(s);
- Chemical grade or description of the strength, quality, and purity of the ingredient;
 - Information about how the ingredient is supplied (e.g., powder, liquid);
 - Information about recognition of the substance in foreign pharmacopeias and the status of its registration(s) in other countries, including whether information has been submitted to USP for consideration of monograph development; and
 - A bibliography of available safety and efficacy data², including any

²FDA recognizes that the available safety and efficacy data is unlikely to be of the same type, amount, or quality as would be required to support a new drug application, but this fact will not preclude a bulk drug substance from consideration for inclusion on the list.

relevant peer reviewed medical literature.

Compounded Product

- Information about the dosage form(s) into which the drug substance will be compounded (including formulations);
- Information about the strength(s) of the compounded product(s);
- Information about the anticipated route(s) of administration of the compounded product(s);
- Information about the past and proposed use(s) of the compounded product(s), including the rationale for its use or why the compounded product(s), as opposed to a commercially available product, is necessary;
- Available stability data for the compounded product(s); and
- Additional relevant information.

FDA cannot guarantee that all drugs nominated during the comment period will be considered for inclusion on the first published bulk drugs list. Nominations received during the comment period that are supported by the most complete and relevant information, as set forth previously, will likely be evaluated first. Nominations that are not evaluated during this first phase will receive consideration for list amendments, as the development and issuance of this list will be an ongoing process. Individuals and organizations also will be able to petition FDA to make additional list amendments after the list is published.

Interested groups and individuals should submit their bulk drug substance nominations to the Dockets Management Branch (address above). Two copies of the nominations are to be submitted, except that individuals may submit one copy. However, individuals are encouraged to consolidate their submissions through professional organizations. Nominations are to be identified with the docket number found in brackets in the heading of this document. Received nominations and supporting information will be treated as public information and will be available for inspection at the above address between 9 a.m. and 4 p.m., Monday through Friday.

Dated: April 1, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 98-9037 Filed 4-6-98; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Grassroots Regulatory Partnership Workshop

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

The Food and Drug Administration (FDA), (Office of Regulatory Affairs, Dallas District Office, Kansas District Office, Atlanta District Office, Nashville District Office, and New Orleans District Office) is announcing the following workshop: Grassroots Regulatory Partnership Workshop. The topic to be discussed is FDA regulatory requirements for the food-producing aquaculture industry. The purpose of the workshop is to promote open dialogue between FDA, the aquaculture industry, related trade associations, other government agencies, academia, and any other interested stakeholders on drug use, good manufacturing practices (GMP's) in processing systems, the seafood hazard analysis critical control point (HACCP) regulations, and any related topics.

Date and Time: The workshop will be held on Tuesday, May 12, 1998, 8:30 a.m. to 5 p.m. Registration will close on April 28, 1998.

Location: The workshop will be held at the Crowne Plaza—Downtown Jackson, 200 Amite St., Jackson, MS 39201, 601-969-5100, or 800-227-6963.

Contact: Richard D. Debo, Food and Drug Administration, New Orleans District Office (HFR-SE440), 4298 Elysian Fields Ave., New Orleans, LA 70122, 504-589-7166, FAX 504-589-4657.

Registration: Send registration information (including name, title, firm name, address, telephone, and fax number) to the contact person by April 28, 1998. There is no registration fee for this workshop. Space is limited; therefore, interested parties are encouraged to register early.

If you need special accommodations due to a disability, please contact Richard D. Debo at least 7 days in advance.

SUPPLEMENTARY INFORMATION: In 1995 President Clinton directed the heads of all Federal regulatory agencies to carry out a four step regulatory reinvention initiative. The basic idea of the President's initiative was to replace adversarial approaches with a partnership approach based on clear goals and cooperation. The President

specifically directed top management from regulatory agencies to hold "grassroots" workshops with regulated industry, and this workshop is designed to meet that requirement.

Priority will be given to those businesses located in the Dallas, Kansas, Atlanta, Nashville, and New Orleans Districts, which include the States of: Oklahoma, Texas, Arkansas, Iowa, Nebraska, Missouri, Kansas, Georgia, North Carolina, South Carolina, Tennessee, Alabama, Louisiana, and Mississippi. Companies located outside these States may register to attend the workshop and will be accepted if space is available.

Dated: March 20, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98-8970 Filed 4-6-98; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF THE INTERIOR

Fish and Wildlife Service

Marais des Cygnes Comprehensive Conservation Plan; Notice of Availability

SUMMARY: Pursuant to the Refuge Improvement Act of 1997, the U.S. Fish and Wildlife Service has published the Marais des Cygnes Comprehensive Conservation Plan. This plan describes how the FWS intends to manage the Marais des Cygnes NWR for the next 10-15 years.

ADDRESSES: A summary of the plan or the complete plan may be obtained by writing to U.S. Fish and Wildlife Service, Attn: Barbara Shupe, P.O. Box 25486 DFC, Denver, CO 80225 or U.S. Fish and Wildlife Service, Flint Hills NWR, P.O. Box 128, Hartford, KS 66854. Unless the full plan is specifically requested, the summary will be sent.

FOR FURTHER INFORMATION CONTACT: Adam Misztal, U.S. Fish and Wildlife Service, P.O. Box 25486 DFC, Denver, CO 80225, 303/236-8145 extension 607; fax 303/236-8680.

SUPPLEMENTARY INFORMATION: The plan calls for the restoration of native bottomland forest, prairie, and savannah. Wetlands would also be created and maintained on the Refuge. In addition, up to 1,500 acres would be farmed on the Refuge to reduce crop depredation on private lands and as a tool for native vegetation restoration. Various forms of wildlife-dependent recreation would also be provided for.

Tab 72

Federal Register of January 7, 1999
(64 FR 996)

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. 98N-0182]

List of Bulk Drug Substances That May Be Used in Pharmacy Compounding

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing a new regulation which will identify the bulk drug substances that may be used in pharmacy compounding under the exemptions provided by the Federal Food, Drug, and Cosmetic Act (the act) even though such substances are neither the subject of a current United States Pharmacopeia (USP) or National Formulary (NF) monograph nor a component of an FDA-approved drug. FDA's development and publication of this bulk drugs list is statutorily required by the Food and Drug Administration Modernization Act of 1997 (the Modernization Act).

DATES: Submit written comments on or before March 23, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Robert J. Tonelli, Center for Drug Evaluation and Research (HFD-332), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-7295.

SUPPLEMENTARY INFORMATION:

I. Background

President Clinton signed the Modernization Act (Pub. L. 105-115) into law on November 21, 1997. Section 127 of the Modernization Act, which added section 503A to the act (21 U.S.C. 353a), clarifies the status of pharmacy

compounding under Federal law. Under section 503A of the act, drug products that are compounded by a pharmacist or physician on a customized basis for an individual patient may be entitled to exemptions from three key provisions of the act: (1) The adulteration provision of section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning the good manufacturing practice requirements); (2) the misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug or abbreviated new drug applications).

To qualify for these statutory exemptions, a compounded drug product must satisfy several requirements. One of these requirements, found in section 503A(b)(1)(A) of the act, restricts the universe of bulk drug substances that a compounder may use. Section 503A(b)(1)(A) provides, in relevant part, that every bulk drug substance used in compounding: (1) Must comply with an applicable and current USP or NF monograph, if one exists, as well as the current USP chapter on pharmacy compounding; (2) if such a monograph does not exist, the bulk drug substance must be a component of an FDA-approved drug;¹ or (3) if a monograph does not exist and the bulk drug substance is not a component of an FDA-approved drug, it must appear on a list of bulk drug substances that may be used in compounding (i.e., the bulk drugs list being proposed in this rulemaking). The term "bulk drug substance" is defined in FDA regulations at 21 CFR 207.3(a)(4) to mean "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances" (see section 503A(b)(1)(A) of the act).

¹ To identify such FDA-approved drugs, compounders can consult the publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluation," commonly referred to as the "Orange Book."

II. Criteria for Bulk Drug Substances

According to section 503A(d)(2) of the act, the criteria for determining which substances should appear on the bulk drugs list "shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary of Health and Human Services may identify." The FDA, after consulting with the USP and the Pharmacy Compounding Advisory Committee, is proposing to use the following four criteria: (1) The chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists.

In evaluating candidates for the bulk drugs list under these criteria, the agency proposes to use a balancing test. No single one of these criteria will be considered to be dispositive. Rather, the agency will consider each criterion in the context of the others and balance them, on a substance-by-substance basis, in deciding whether a particular substance is appropriate for inclusion on the list.

Under the first criterion, the chemical characterization of the substance, FDA will consider each substance's purity, identity, and quality. Based on attributes such as the substance's chemical formula, melting point, appearance, and solubilities, FDA will determine whether the substance can be identified consistently based on its chemical characteristics. If a substance cannot be well characterized chemically, this criterion will weigh against its inclusion on the proposed bulk drugs list because there can be no assurance that its properties and toxicities when used in compounding would be the same as the properties and toxicities reported in the literature and considered by the agency.

Under the second criterion, FDA will consider the safety issues raised by the use of each substance in general pharmacy compounding. Based on FDA's review of the substances nominated to date, it is unlikely that candidates for the bulk drugs list will have been thoroughly investigated in well-controlled animal toxicology studies, or that there will be well-controlled clinical studies to substantiate their safe use in humans.

Thus, in evaluating list candidates, the agency is likely to have at its disposal either none or very little of the type or quality of information that is ordinarily required and evaluated as part of the drug approval process.

To evaluate the safety of the substances, then, the agency will rely on information about each substance's acute toxicity, repeat dose toxicity, and other reported toxicities, including mutagenicity, teratogenicity, and carcinogenicity. The agency will also rely on reports and abstracts in the literature about adverse reactions the substances have caused in humans. In applying the toxicity criterion, FDA may also consider the availability of alternative approved therapies when the toxicity of a particular substance appears to be significant. The existence of alternative approved therapies is likely to weigh against inclusion on the proposed list because the risks of using a substance with significant toxicities is more likely to outweigh the benefits when approved alternative therapies are available.

Under the third criterion, the historical use of the substance in pharmacy compounding, FDA will consider the length of time the substance has been used in pharmacy compounding, the medical conditions it has been used to treat, and how widespread its use has been. This criterion will weigh in favor of list inclusion for nominated substances that have enjoyed longstanding and widespread use in pharmacy compounding for a particular indication. Evidence of both widespread and longstanding use will be viewed by the agency as indicative of the substance's perceived usefulness and acceptance in the medical community. Fraudulent or "quack" remedies, on the other hand, will be less likely to be included on the list as a result of this criterion because the practice of compounding such drugs is not expected to be sufficiently prevalent and longstanding.

Under the fourth criterion, FDA will consider the available evidence of the substance's effectiveness or lack of effectiveness for a particular use, if any such evidence exists. When drugs go through the new drug approval process, they are required to demonstrate effectiveness under the substantial evidence standard described in section 505(d) of the act. FDA recognizes that few, if any, of the candidates for the bulk drugs list will have been studied in adequate and well-controlled investigations sufficient to satisfy this standard. Thus, in its balancing of the relevant criteria, the agency will take

into account whatever relevant evidence concerning effectiveness is available.

For example, for substances that have been widely used for a long period of time, the literature may include anecdotal reports of effectiveness for a particular use, or reports of one or more trials demonstrating effectiveness. Conversely, the literature may contain anecdotal or clinical evidence that a particular bulk drug substance was shown not to be effective for a particular use (negative effectiveness data).

When evaluating a bulk drug substance used to treat a less serious illness, FDA will generally be more concerned about the safety of the substance than about its effectiveness. Thus, the absence of effectiveness data, or the existence of mere anecdotal reports, will be less likely to preclude inclusion of the substance on the list. However, for a bulk drug substance used to treat a more serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy, particularly when there are alternative approved therapies. In those cases, the absence of effectiveness data, or the presence of negative effectiveness data, will weigh more heavily in FDA's balancing of the relevant criteria.

III. FDA Development of a Bulk Drugs List

A. Methodology

Although the Modernization Act directs FDA to develop a list of bulk drug substances for use in pharmacy compounding, it does not specify how candidates for the list should be identified. In a notice published in the **Federal Register** of April 7, 1998 (63 FR 17011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the list. In response to this request, FDA received nominations for 41 different drug substances. The nominations came from Abbott Laboratories, the American Academy of Dermatology, the Texas Pharmacy Association, the North Carolina Board of Pharmacy, Moss Pharmacy and Nutrition Center, the University of Texas MD Anderson Cancer Center, the International Academy of Compounding Pharmacists, Baxter Healthcare Corp., Scottsdale Skin & Cancer Center Ltd., Dermatology Associates, and Neil Brody, M.D.

Ten of the nominated substances (clotrimazole, fluocinonide, hydrocortisone, hydroquinone, mechlorethamine, pramoxine, quinacrine hydrochloride, salicylic acid, tretinoin, and triamcinolone) are the subject of a USP or NF monograph or

are components of FDA-approved drugs. As such, they already qualify for use in pharmacy compounding under section 503A(b)(1)(A)(i) of the act (assuming they satisfy all other applicable requirements of the act). Therefore, FDA dismissed these substances as list candidates and will not address them further in this proposed rulemaking. An additional substance (sulfadimethoxine) was eliminated as a list candidate after being withdrawn by its sponsor at the inaugural meeting of the Pharmacy Compounding Advisory Committee. It too will not be addressed further in this proposed rulemaking.

The remaining 30 nominations were appropriate list candidates and were evaluated based on a balancing of the four criteria identified in section II of this document: (1) The chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists.²

The information that FDA assessed under each of the evaluation criteria was obtained from journal reports and abstracts from reliable medical sources, including peer reviewed medical literature. This information is available for viewing at the Dockets Management Branch (address above) under Docket No. 98N-0182. Some of this information was submitted in support of the nominations. The remainder FDA gathered through independent searches of medical and pharmaceutical data bases. FDA did not review any raw data.

The nature, quantity, and quality of the information assessed by FDA varied considerably from substance to substance. In some cases there was very little data. For example, the agency found only two relevant journal articles concerning thymol iodide. For other substances, such as taurine and sodium butyrate, reports in the literature were more plentiful and sometimes comprised hundreds of articles. In those cases, the agency reviewed a limited sample of the available literature sources.

Because FDA's assessment of the nominated substances was far less rigorous and far less extensive than the agency's ordinary evaluation of drugs as part of the new drug approval process,

²In making its evaluations, the agency did not consider whether any of the nominated substances are manufactured by an establishment registered under section 510 of the act (see 21 U.S.C. 353a(b)(1)(A)(ii)). This registration requirement is one of a number of other conditions that must be satisfied to qualify for the applicable compounding exemptions.

the inclusion of a drug substance on the proposed bulk drugs list should not, in any way, be equated with an approval, endorsement, or recommendation of the substance by FDA. Nor should it be assumed that substances on the proposed list have been proven to be safe and effective under the standards normally required to receive agency approval. In fact, any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA-approved, or otherwise endorsed by FDA generally or for a particular indication, will cause such drug to be misbranded under section 502(a) of the act.

On October 14 and 15, 1998, FDA consulted with the Pharmacy Compounding Advisory Committee, created under section 503A(d)(1) of the act about the contents of this proposed rule (see 63 FR 47301, September 4, 1998). The discussion included the criteria FDA proposes to use to evaluate candidates for the bulk drugs list and the nominations that FDA has already received.³ In general, the advisory committee agreed with the approach taken by the agency in evaluating the nominated bulk drug substances and the agency's tentative conclusions regarding whether these substances should be included on the bulk drugs list. The agency has taken into consideration all of the advisory committee's recommendations in developing this proposed rule, and the agency intends to continue to consult with the Pharmacy Compounding Advisory Committee in evaluating future candidates for the bulk drugs list.

After evaluating the comments on this proposed rule, FDA is proposing to issue the bulk drugs list as a final rule which will be codified in the Code of Federal Regulations (CFR). The final version of the rule may include all, or only some, of the substances proposed for inclusion on the list in this proposal, depending on the comments received. Individuals and organizations will be able to petition FDA to amend the list (to add or delete bulk drug substances) at any time after the final rule is published. Amendments to the list will be proposed through rulemaking.

With regard to nominated substances discussed in this proposed rulemaking (substances proposed for inclusion on the proposed list and substances that have been nominated but are still under consideration by the agency), FDA intends to exercise its enforcement discretion regarding regulatory action

during the pendency of this proposed rulemaking. For further information on this subject, see the guidance for industry entitled "Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act" (see 63 FR 64723, November 23, 1998).

B. Nominated Drug Substances Being Proposed for Inclusion on the Bulk Drugs List

Under section 503A(d)(2) of the act, FDA is proposing that the following 20 drug substances, which are neither the subject of a current USP or NF monograph nor components of FDA-approved drugs, be included in the list of bulk drug substances that may be used in compounding under the exemptions provided in section 503A of the act (sections 501(a)(2)(B), 502(f)(1), and 505). When a salt or ester of an active moiety is listed, e.g., diloxanide furoate, only that particular salt or ester may be used. Neither the base compound nor other salts or esters of the same active moiety qualify for section 503A of the act's compounding exemptions, unless separately listed.

The following bulk drugs list is being proposed in § 216.23 of title 21 of the CFR. (Section 216.23 will be included in new part 216, which is currently intended to include all FDA regulations whose primary purpose is implementation of the pharmacy compounding provisions found in section 503A of the act):

Bismuth citrate. Bismuth citrate is well characterized chemically. It has been used extensively in compounded products for short-term treatment of several gastrointestinal disorders, including *Helicobacter pylori*-associated ulcers. At doses reported in the literature for these indications, bismuth citrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of bismuth citrate's effectiveness for these indications is also reported in the literature.

Caffeine citrate. Caffeine citrate is well characterized chemically. As a central nervous system stimulant, caffeine citrate has been used extensively and for many years in compounded products to treat apnea in premature infants. At doses reported in the literature for this indication, caffeine citrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of caffeine citrate's effectiveness for this indication is also reported in the literature.

Cantharidin. Cantharidin, which is well characterized chemically, is a substance obtained from the Chinese blister beetle, among other beetle species, that has been used topically in the treatment of warts and molluscum contagiosum, often in patients with compromised immune systems. Limited anecdotal evidence of cantharidin's effectiveness for these indications is reported in the literature. Although cantharidin is an extremely toxic substance, it is apparently used only in the professional office setting and not dispensed for home use. Because of cantharidin's toxicity, FDA is proposing to include it on the bulk drugs list for topical use in the professional office setting only.

Choline bitartrate. Choline bitartrate is well characterized chemically. It has been used to treat Alzheimer's-type dementia. It has also been used to treat infantile colic. At doses reported in the literature for these indications, choline bitartrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of choline bitartrate's effectiveness for these indications is also reported in the literature. Additionally, FDA has previously established that choline bitartrate is generally recognized as safe, as a dietary supplement, when used in accordance with good manufacturing practices (see 21 CFR 182.8250 (45 FR 58837, September 5, 1980)).

Diloxanide furoate. Diloxanide furoate is well characterized chemically. It has been used to treat parasitic diseases such as intestinal amoebiasis. At doses reported in the literature for these indications, diloxanide furoate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of diloxanide furoate's effectiveness for these indications is also reported in the literature.

Dimercapto-1-propanesulfonic acid. Dimercapto-1-propanesulfonic acid (DMPS), a chelating agent, is well characterized chemically. DMPS has been used to treat heavy metal poisoning. At doses reported in the literature for this indication, DMPS appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of DMPS's effectiveness for this indication is also reported in the literature.

³A transcript of the advisory committee meeting may be found at the Dockets Management Branch (address above) under Docket No. 98N-0182.

*Ferric subsulfate.*⁴ Ferric subsulfate is well characterized chemically. It has been used as a topical hemostatic agent to control bleeding associated with minor surgical procedures, biopsies, and minor gynecological surgery involving the cervix. At doses reported in the literature for this indication, ferric subsulfate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of ferric subsulfate's effectiveness for this indication is also reported in the literature. However, because the literature is limited to topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

Ferric sulfate hydrate. Ferric sulfate hydrate is well characterized chemically. It has been used topically as a hemostatic agent to control bleeding from dermatological and dental procedures. At doses reported in the literature for these indications, ferric sulfate hydrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of ferric sulfate hydrate's effectiveness for this indication is also reported in the literature. However, because the literature is limited to topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

Glutamine. Glutamine, the most abundant free amino acid found in the human body, is well characterized chemically. Glutamine is involved in a wide variety of metabolic processes, including regulation of the body's acid-base balance. For years, glutamine has been used in compounding as a supplement in parenteral nutrition regimens in adults. At doses reported in the literature for this use, glutamine appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of glutamine's effectiveness for this indication is also reported in the literature.

Guaiacol. Guaiacol is well characterized chemically. It has been used for decades in compounded products as an expectorant. At doses reported in the literature for this indication, guaiacol appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited

anecdotal evidence of guaiacol's effectiveness for this indication is also reported in the literature.

Iodoform. Iodoform is well characterized chemically. It has been used for the control of acute epistaxis (nosebleeds) and as a paste for dental root fillings. Iodoform has tested positive in in vitro mutagenicity assays and in an in vitro transformational assay in mammalian cells. However, in 2-year bioassays conducted by the National Toxicology Program, iodoform was found to be noncarcinogenic in rats and mice. At doses reported in the literature for these indications, iodoform appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of iodoform's effectiveness for these indications is also reported in the literature. However, because the literature is limited to the topical and intradental use of this substance, FDA is proposing to include it on the bulk drugs list for topical and intradental use only.

Metronidazole benzoate. Metronidazole benzoate, which is well characterized chemically, has been used to treat parasitic diseases such as amoebiasis and giardiasis. The base of this substance (metronidazole) is an FDA-approved drug which has a bitter taste. The benzoate salt apparently renders metronidazole tasteless, however, so metronidazole benzoate is sometimes prescribed instead of the metronidazole base to increase patient compliance, especially in children. Serious adverse reactions associated with the use of metronidazole benzoate have not been commonly reported, and limited anecdotal evidence of its effectiveness is reported in the literature. Although the agency is proposing to include metronidazole benzoate on the bulk drugs list, it is specifically seeking public comment on metronidazole benzoate's solubility and appropriate dosing, as questions about these issues have been raised in the literature.

Myrrh gum tincture. Myrrh is a gum resin obtained from the stem of *Commiphora molmol* and other species of camphora. Myrrh is a mixture of many substances and has not been well characterized chemically. Myrrh has been used in its natural form and as a tincture to treat inflammatory disorders of the mouth and pharynx. The preparation reviewed by FDA is the tincture, which, at doses reported in the literature for those indications, appears to be relatively nontoxic. Serious adverse reactions associated with the use of myrrh gum tincture have not been

commonly reported. Limited anecdotal evidence of myrrh gum tincture's effectiveness for those indications is also reported in the literature. Because the literature is limited to the topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

Phenindamine tartrate. Phenindamine tartrate is well characterized chemically. It is an antihistamine that has been used to treat hypersensitivity reactions including urticaria (hives) and rhinitis (nasal inflammation). At doses reported in the literature for this indication, phenindamine tartrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Additionally, in developing the over-the-counter monograph for antihistamine drug products, FDA previously established that phenindamine tartrate, under the conditions established in the monograph (including particular labeling and dosage limits), is generally recognized as safe and effective for over-the-counter antihistamine use (see 21 CFR 341.12; 57 FR 58356, December 9, 1992). Limited anecdotal evidence of phenindamine tartrate's effectiveness as an antihistamine is reported in the literature.

Phenyltoloxamine dihydrogen citrate. Phenyltoloxamine dihydrogen citrate, a structural isomer of diphenhydramine, is well characterized chemically. It has been used as an antihistamine. At doses reported in the literature for this indication, phenyltoloxamine dihydrogen citrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of phenyltoloxamine dihydrogen citrate's effectiveness as an antihistamine is reported in the literature.

Piracetam. Piracetam, a derivative of the amino acid gamma-amino butyric acid, is well characterized chemically. Piracetam is believed by some to enhance certain cognitive skills, and has been used to treat Down's syndrome, dyslexia, and Alzheimer's disease, among other cognitive disorders. At doses reported in the literature for these indications, piracetam appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of piracetam's effectiveness for these indications is reported in the literature.

Sodium butyrate. Sodium butyrate is a short chain fatty acid that is well characterized chemically. It has been

⁴ Both ferric subsulfate solution and ferric subsulfate powder were nominated for inclusion on the bulk drugs list. FDA combined them under one entry for ferric subsulfate.

used rectally in an enema formulation to treat several inflammatory bowel conditions, including ulcerative colitis and diversion colitis. At doses reported in the literature for these indications, sodium butyrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of sodium butyrate's effectiveness for these indications is also reported in the literature. However, because the literature is limited to the use of sodium butyrate rectally in an enema formulation, FDA is proposing to include it on the bulk drugs list for use in this dosage form and route of administration only.

Taurine. Taurine, an amino acid with several important physiological functions, including a role in bile acid conjugation, is well characterized chemically. It has been used for years in compounding as a component in parenteral nutrition solutions for infants and adult patients. At doses reported in the literature for this use, taurine appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of taurine's effectiveness for this indication is also reported in the literature.

Thymol iodide. Thymol iodide is well characterized chemically. It has been used as a topical agent for its absorbent, protective, and antimicrobial properties. At doses reported in the literature for these indications, thymol iodide appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of thymol iodide's effectiveness for these indications is also reported in the literature. FDA notes, however, that it was able to identify only two relevant articles concerning this substance. Because the literature is limited to the topical use of thymol iodide, FDA is proposing to include it on the bulk drugs list for topical use only.

Tinidazole. Tinidazole is a chemically well-characterized derivative of 5-nitromidazole. It has been used, often in conjunction with diloxanide furoate, which also appears on this proposed list, to treat parasitic diseases such as amoebiasis and giardiasis. At doses reported in the literature for these indications, tinidazole appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of tinidazole's effectiveness for these indications is also reported in the literature.

C. Nominated Drug Substances Still Under Consideration for the Bulk Drugs List

The following 10 drug substances were nominated for inclusion on the proposed bulk drugs list. However, for the reasons described in section III.C of this document, they are still under review by the agency:

4-Aminopyridine. The drug substance 4-Aminopyridine (4-AP), which is well characterized chemically, is a potassium channel blocker that may enhance the release of acetylcholine from nerve terminals. It has been used to treat several neurological disorders, including Lambert-Eaton myasthenic syndrome, multiple sclerosis, and Alzheimer's disease. It also has been used to reverse the effects of nondepolarizing muscle relaxants. At doses reported in the literature, the side effects of 4-AP for most patients do not appear to be serious. However, there have been some reports of seizures associated with the use of 4-AP. FDA would like more information about the historical use, safety, and effectiveness of 4-AP before deciding whether to propose it for inclusion on the bulk drugs list. The Pharmacy Compounding Advisory Committee similarly expressed a desire for more information about 4-AP before making a recommendation about its status to the agency. FDA is soliciting public input on these and any other issues that are relevant to the agency's consideration of this substance for the bulk drugs list.

Betahistine dihydrochloride. Betahistine dihydrochloride is a chemically well characterized histamine analog. Formerly marketed as Serc tablets, betahistine dihydrochloride was approved by FDA to treat the symptoms of vertigo in patients with Meniere's disease. In 1970, however, FDA withdrew approval of the new drug application for Serc tablets because they were found to lack substantial evidence of effectiveness for this approved indication (see 35 FR 17563, November 14, 1970). FDA will consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include betahistine dihydrochloride on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

Cyclandelate. Cyclandelate, which is well characterized chemically, is a vasodilator that was formerly approved by FDA for two indications: (1) Treatment for intermittent claudication caused by arteriosclerosis obliterans, and (2) as a treatment for cognitive dysfunction in patients suffering from senile dementia of the multi-infarct or

Alzheimer's type. Cyclandelate was formerly marketed in Cyclospasmol capsules and tablets, which were removed from the market for lack of effectiveness for these approved indications (see 61 FR 64099, December 3, 1996). FDA will consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include cyclandelate on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

3,4-Diaminopyridine. The drug substance 3,4-Diaminopyridine (DAP), which is well characterized chemically, is a potassium channel blocker that may enhance the release of acetylcholine from nerve terminals. DAP has been used in the treatment of several neuromuscular disorders, including Lambert-Eaton myasthenic syndrome, myasthenia gravis, amyotrophic lateral sclerosis, and multiple sclerosis. At doses reported in the literature, DAP appears to be well tolerated and its toxicity appears to be dose related. There have been reports of seizures with its use, however, and DAP is contraindicated in patients with epilepsy. FDA would like more information about the historical use, safety, and effectiveness of DAP before deciding whether to propose it for inclusion on the bulk drugs list. The Pharmacy Compounding Advisory Committee similarly expressed a desire for more information about DAP before making a recommendation about its status to the agency. FDA is soliciting public input on these and any other issues that are relevant to the agency's consideration of this substance for the bulk drugs list.

Dinitrochlorobenzene. Dinitrochlorobenzene (DNCB), which is well characterized chemically, has been used in the treatment of recurrent melanoma and as a skin sensitizer to estimate immune system competency. It also has been used topically in the treatment of warts. Limited anecdotal evidence of DNCB's effectiveness for these indications is reported in the literature. DNCB is a highly toxic substance that may be fatal if inhaled, swallowed, or absorbed through skin. High concentrations of DNCB are also extremely destructive to tissues of the mucous membranes and upper respiratory tract, eyes, and skin. At the inaugural meeting of the Pharmacy Compounding Advisory Committee, the nominator of this substance withdrew it as a list candidate, but several members of the committee recommended that it still be considered. The Pharmacy Compounding Advisory Committee then voiced concerns about the safety of the

substance and expressed a desire for more information about it before making a recommendation to the agency. FDA agrees and, therefore, is requesting public input about the historical use, safety, and effectiveness of DNCB, as well as any other information that would be relevant to the agency's consideration of DNCB for the bulk drugs list.

Diphenylcyclopropenone.

Diphenylcyclopropenone, which is well characterized chemically, has been used for the topical treatment of extensive alopecia areata. The nomination of this substance was not received by FDA in time to permit a full discussion of it at the October 1998 meeting of the Pharmacy Compounding Advisory Committee. A decision about this substance is therefore being deferred until after FDA has had an opportunity to consult the Pharmacy Compounding Advisory Committee about it at a future meeting.

Hydrazine sulfate. Hydrazine sulfate is well characterized chemically and has been used to treat cachexia in cancer patients. The substance, however, is extremely toxic. Multiple exposures to hydrazine sulfate have caused liver and kidney damage, gastrointestinal damage, convulsions, and coma, among other conditions. Hydrazine sulfate is also considered by the International Agency for Research on Cancer to be a potential carcinogen to humans. In at least two clinical studies, hydrazine sulfate was shown to have no effect, or even a negative effect, on patients who received it. FDA would like more information about the historical use, safety, and effectiveness of hydrazine sulfate before deciding whether to propose it for inclusion on the bulk drugs list. The Pharmacy Compounding Advisory Committee similarly expressed a desire for more information about hydrazine sulfate before making a recommendation about its status to the agency. FDA is soliciting public input on these and any other issues that are relevant to the agency's consideration of this substance for the bulk drugs list.

Pentylentetrazole.

Pentylentetrazole, which is well characterized chemically, was approved by FDA for use in the treatment of senile confusion, depression, psychosis, fatigue, and debilitation, as well as for the relief of dizzy spells, mild behavioral disorders, irritability, and functional memory disorders in elderly patients. Pentylentetrazole was formerly marketed in numerous drug products, all of which were removed from the market for lack of effectiveness for these approved indications (see 47 FR 19208, May 4, 1982). FDA will

consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include pentylentetrazole on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

Silver protein mild. Mild silver protein is well characterized chemically. It has been used to treat conjunctivitis and by ophthalmologists as a preoperative chemical preparation of the eye. At doses reported in the literature for these indications, mild silver protein appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. When mild silver protein is administered internally, however, it can cause serious untoward side effects, including argyria, a permanent ashen-gray discoloration of the skin, conjunctiva, and internal organs (see 61 FR 53685, October 15, 1996). At this time, FDA is deferring a decision on this substance because questions were raised at the inaugural meeting of the Pharmacy Compounding Advisory Committee about its efficacy. FDA is soliciting public input on this issue and any other issues that are relevant to the agency's consideration of mild silver protein for the bulk drugs list.

Squaric acid dibutyl ester. Squaric acid dibutyl ester, which is well characterized chemically, is a contact sensitizer that has been used as a topical treatment for alopecia areata and warts. The nomination of this substance was not received by FDA in time to permit a full discussion of it at the October 1998 meeting of the Pharmacy Compounding Advisory Committee. A decision about this substance is therefore being deferred until after FDA has had an opportunity to consult the Pharmacy Compounding Advisory Committee about it at a future meeting.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select

regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to examine regulatory alternatives for small entities if the proposed rule is expected to have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act requires agencies to prepare an assessment of anticipated costs and benefits before enacting any rule that may result in an expenditure in any 1 year by State, local and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency has reviewed this proposed rule and has determined that it is consistent with the regulatory philosophy and principles identified in the Executive Order and these two statutes. The proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order. As discussed below, the agency certifies that this proposed rule will not have a significant economic impact on a substantial number of small entities. Also, because the rule is not expected to result in any annual expenditures, FDA is not required to prepare a cost/benefit analysis under the Unfunded Mandates Reform Act.

FDA is proposing to amend its regulations to include a list of bulk drugs that may be used in pharmacy compounding under certain conditions even though such substances are neither the subject of a USP or NF monograph nor components of FDA-approved drugs. FDA has requested and received nominations for bulk drugs to be included on this list. Twenty of the nominated substances are being proposed for inclusion, which means they would be eligible for use in pharmacy compounding under the exemptions provided by section 503A of the act. As a result, there would be no loss of any sales, or other economic impact, for compounded drug products containing these 20 substances.

FDA has proposed to include some of these substances on the list with a restriction on their route of administration or a requirement that the resulting compounded drug product be for professional office use only. As FDA is unaware that any of these drug substances are currently used in compounding outside of the proposed restrictions, the agency does not expect these restrictions to result in decreased sales of any compounded drug product.

Further, this regulation is not anticipated to impose any other compliance costs on bulk drug manufacturers or compounding pharmacies.

Ten additional nominated substances, while not being proposed for inclusion on the bulk drugs list, are still under review by the agency. As explained more fully in the guidance for industry entitled "Enforcement Policy During Implementation of section 503A of the Federal Food, Drug, and Cosmetic Act" (see notice of availability, 63 FR 64723, November 23, 1998), FDA intends to exercise its enforcement discretion regarding these 10 substances. In short, FDA does not intend to take regulatory action against a drug product that has been compounded with one of these substances while the substance is being evaluated during the pendency of this rulemaking proceeding, as long as the compounding complies with the other effective requirements in section 503A of the act and does not appear to present a significant safety risk.

Although usage or sales data for the nominated drug substances is limited, the agency further concludes that even if any of the 10 deferred drug substances were, in the future, to be excluded as candidates for the bulk drugs list, the economic impact would not be significant, particularly not for any substantial number of pharmacies or other small entities. The quantity demanded of these 10 drugs appears to be relatively small, especially when compared to the total number of prescription drugs dispensed annually in the United States. In addition, if any of the 10 substances were ultimately excluded from the list, sales of alternatives to the excluded drugs would be expected to reduce the economic impact of such exclusion.

At the October 1998 meeting of the Pharmacy Compounding Advisory Committee, a representative of the International Academy of Compounding Pharmacists (IACP) presented usage and sales data for four of the deferred substances: 3,4-DAP, 4-AP, hydrazine sulfate, and mild silver protein. According to the IACP representative, the drug substances 3,4-DAP and 4-AP are currently being used in compounding to treat patient populations estimated at 1,000 and 10,000 patients, respectively; hydrazine sulfate is currently being used to treat between 5,000 and 10,000 patients annually; and the annual production of mild silver protein is approximately 9 kilograms. FDA does not have a firm estimate of the number of patients being treated with mild silver protein, but estimates it to be several thousand.

Similarly, FDA does not have usage or sales data for the six other deferred drug substances, but estimates that their usage is also relatively low. The agency invites comments and data on any projected loss of sales or other compliance costs directly attributable to this proposal.

If a rule is expected to have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize these impacts. Section 503A of the act specifically directs FDA to develop a list of bulk drug substances that may be used in pharmacy compounding. The agency received nominations from the public for 41 bulk drugs to be included on this list. All the nominations are either proposed for inclusion on the list or are still under review. The agency therefore certifies that this proposal will not have a significant economic impact on a substantial number of small entities. The agency invites public comment and data on these issues, specifically the number and size of the bulk drug manufacturers and compounding pharmacies that sell any of the deferred substances, or drug products containing them, and any sales data on these compounded drug products.

The Unfunded Mandates Reform Act requires (in section 202) that agencies prepare an assessment of anticipated costs and benefits before proposing any expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any 1 year. The publication of FDA's list of bulk drug substances for use in pharmacy compounding is not expected to result in any expenditure of funds by State, local and tribal governments or the private sector. Because the proposed rule is not expected to result in any mandated expenditures, FDA is not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VII. Request for Comments

Interested persons may, on or before March 23, 1999, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that

individuals may submit one copy. Comments are to be identified with docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 216 be added as follows:

1. Part 216 is added to read as follows:

PART 216—PHARMACY COMPOUNDING

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

Sec.

216.23 Bulk drug substances for use in pharmacy compounding.

216.24 [Reserved]

Authority: 21 U.S.C. 351, 352, 353a, 355, 371.

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

§ 216.23 Bulk drug substances for use in pharmacy compounding.

(a) The following bulk drug substances, which are neither the subject of a current United States Pharmacopeia or National Formulary monograph nor components of the Food and Drug Administration approved drugs, may be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.

- Bismuth citrate.
- Caffeine citrate.
- Cantharidin (for topical use in the professional office setting only).
- Choline bitartrate.
- Diloxanide furoate.
- Dimercapto-1-propanesulfonic acid.
- Ferric subsulfate (for topical use only).
- Ferric sulfate hydrate (for topical use only).
- Glutamine.
- Guaiacol.
- Iodoform (for topical and intradental use only).
- Metronidazole benzoate.
- Myrrh gum tincture (for topical use only).
- Phenindamine tartrate.
- Phenyltoloxamine dihydrogen citrate.
- Piracetam.
- Sodium butyrate (for rectal enema use only).

Taurine.
Thymol iodide (for topical use only).
Tinidazole.

(b) FDA balances the following criteria in evaluating substances considered for inclusion on the list set forth in paragraph (a) of this section: The chemical characterization of the substance; the safety of the substance; the historical use of the substance in pharmacy compounding; and the available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists.

(c) Based on evidence currently available there are inadequate data to establish substantial evidence or general recognition of the safety or effectiveness of any of the drug substances set forth in paragraph (a) of this section, for any indication.

§ 216.24 [Reserved]

Dated: December 29, 1998.

William K. Hubbard,
Associate Commissioner for Policy
Coordination.

[FR Doc. 99-277 Filed 1-6-99; 8:45 am]

BILLING CODE 4160-01-F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 52 and 81

[FL-75-1-9806b; FRL 6196]

Designation of Areas for Air Quality Planning Purposes Florida: Redesignation of the Duval County Sulfur Dioxide Unclassifiable Area to Attainment

AGENCY: Environmental Protection
Agency (EPA).

ACTION: Proposed rule.

SUMMARY: On January 28, 1997, the Florida Department of Environmental Protection (DEP) submitted a request for redesignation to attainment for sulfur dioxide (SO₂) in Duval County, Florida. The redesignation request included five years of quality assured monitoring data which showed no exceedances of the National Ambient Air Quality Standards (NAAQS) for SO₂. Duval County was originally designated as an unclassifiable area in 1978 due to lack of adequate monitoring data. Sufficient data have now been collected to make affirmative declaration of attainment status. The EPA is redesignating Duval County from unclassifiable to attainment for SO₂ and approving three permits that provide SO₂ emission reductions.

In the Final Rules Section of this **Federal Register**, EPA is approving the

Florida State Plan submittal as a direct final rule without prior proposal because the Agency views this as a noncontroversial submittal and anticipates that it will not receive any significant, material, and adverse comments. A detailed rationale for the approval is set forth in the direct final rule and incorporated herein. If no significant, material, and adverse comments are received in response, to this rule, no further activity is contemplated in relation to this proposed rule. If EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. EPA will not institute a second comment period on this action.

DATES: Comments must be received in writing by February 8, 1999.

ADDRESSES: All comments should be addressed to Scott Martin at the EPA Regional Office listed below. Copies of the documents relevant to this proposed rule are available for public inspection during normal business hours at the following locations. The interested persons wanting to examine these documents should make an appointment with the appropriate office at least 24 hours before the day of the visit.

Environmental Protection Agency,
Region 4, Air Planning Branch, 61
Forsyth Street, SW, Atlanta, Georgia
30303-3104.

Florida Department of Environmental
Protection, Twin Towers Office
Building, 2600 Blair Stone Road,
Tallahassee, Florida 32399-2400.

FOR FURTHER INFORMATION CONTACT:
Scott Martin at (404) 562-9036.

SUPPLEMENTARY INFORMATION: See the information provided in the Direct Final action which is located in the Rules Section of this **Federal Register**.

Dated: November 10, 1998.

A. Stanley Meiburg,
Acting Regional Administrator, Region 4.
[FR Doc. 99-230 Filed 1-6-99; 8:45 am]

BILLING CODE 6560-50-M

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 90

[WT Docket No. 96-86; DA 98-2588]

The Development of Operational, Technical and Spectrum Requirements for Meeting Federal, State and Local Public Safety Agency Communication Requirements Through the Year 2010, Establishment of Rules and Requirements for Priority Access Service

AGENCY: Federal Communications
Commission.

ACTION: Proposed rule; extension of time
for comments.

SUMMARY: This document extends the time to file comments concerning the Commission's *Third Notice of Proposed Rule Making* ("Third Notice") adopted on August 6, 1998. Comments on the *Third Notice* were due on or before January 4, 1999, and Reply Comments were due on or before February 1, 1999. Because of the many petitions for reconsideration and clarification filed in response to the *First Report and Order* ("First Report") in this proceeding and the close proximity of the deadlines for responding to these petitions and the *Third Notice*, the Commission extended the time to file comments.

DATES: Comments are due on or before
January 19, 1999, and reply comments
are due on or before February 18, 1999.

ADDRESSES: Federal Communications
Commission, Office of the Secretary,
Publications Branch, Room TW-B204,
The Portals II, 445 12th St., SW,
Washington, D.C. 20554.

FOR FURTHER INFORMATION CONTACT:
Peter Daronco or Michael Pollak, at the
Public Safety & Private Wireless
Division, (202) 418-0680.

SUPPLEMENTARY INFORMATION: This is a
summary of the Commission's *Order* in
WT Docket No. 96-86, adopted on
December 23, 1998, and released on
December 24, 1998, (DA 98-2588). The
full text of the *Order* is available for
inspection and copying during normal
business hours in the FCC Reference
Center, Room 239, 1919 M St., NW,
Washington, DC 20554. The complete
text of this decision may also be
purchased from the Commission's
duplicating contractor, International
Transcription Services, 1231 20th
Street, NW, Washington, DC 20036,
202-857-3800. Alternative formats
(computer diskette, large print, audio
cassette and Braille) are available to
persons with disabilities by contacting

Tab 73

Federal Register of April 22, 1999
(64 FR 19791)

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****Conducting Successful Clinical Trials Under Good Clinical Practice Regulations to Facilitate the Product Approval Process; Public Workshop**

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of workshop.

The Food and Drug Administration (FDA), Los Angeles District Office, in cooperation with the Southern California Pharmaceutical Discussion Group (SCPDG) and the Association of Clinical Research Professionals, is announcing a workshop intended to give clinical investigators and clinical research staff an opportunity to learn

and discuss requirements and expectations for clinical research intended to support new product applications to FDA.

Date and Time: See Table 1 following the "Location" section of this document.

Location: See Table 1 below.

TABLE 1.

Meeting Address	Date and Local Time	FDA Contact Person
SAN DIEGO: Marriott Mission Valley Inn, 8757 Rio San Diego Dr., San Diego, CA, 619-692-3800	Monday, May 10, 1999, 8 a.m. to 5:30 p.m.	Sandi R. Velez
LOS ANGELES: Westin Bonaventure Hotel, 404 South Figueroa St., Los Angeles, CA, 213-624-1000	Wednesday, May 12, 1999, 8 a.m. to 5:30 p.m.	Do.
TUSCON: Plaza Hotel and Conference Center, 1900 East Speedway Blvd., Tucson, AZ, 520-327-7341	Friday, May 14, 1999, 8 a.m. to 5:30 p.m.	Do.

Contact: Sandi R. Velez, Los Angeles District Office, Office of the District Director (HFR-PA200), 19900 MacArthur Blvd., Irvine, CA 92612-2445, 949-798-7698, FAX 949-798-7715.

Registration: Space is limited. Preregistration and confirmation are required by April 28, 1999. Registration forms may be obtained from the contact listed previously. There is a \$150 registration fee payable to SCPDG. The registration fee and form should be sent to Eileen Ohlander at 2525 Dupont Dr., RD-3C, Irvine, CA 92613, FAX 714-246-6220. The registration fee will cover actual expenses including refreshments, lunch, materials, and some speaker expenses. Parking fees are not included in the registration fee. Walk-ins will be accepted, provided space is available. Walk-in registration for each workshop is scheduled between 7:30 a.m. and 8 a.m. on the morning of each workshop.

If you need special accommodations due to a disability, please contact Sandi R. Velez at least 7 days in advance.

Dated: April 16, 1999.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 99-10012 Filed 4-21-99; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****Pharmacy Compounding Advisory Committee; Notice of Meeting**

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Pharmacy Compounding Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on May 6 and 7, 1999, 8:30 a.m. to 5 p.m.

Location: CDER Advisory Committee Conference Room 1066, 5630 Fishers Lane, Rockville, MD.

Contact Person: Igor Cerny, or Tony Slater, Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7001, or by e-mail at CERNY@CDER.FDA.GOV, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12440. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committee will discuss and provide FDA with advice about the agency's development and publication of a list of bulk drug substances that may be used in pharmacy compounding that do not have a United States Pharmacopeia or National Formulary monograph and are not components of FDA-approved drugs. Specifically, the committee is likely to address the following drug substances as candidates for the bulk drugs list: 4-aminopyridine, 3,4-diaminopyridine, betahistine dihydrochloride, chloramine-T, cyclandelate, dinitrochlorobenzene, diphenylcyclopropenone, hydrazine sulfate, mild silver protein, monosodium aspartate, pentylenetetrazole, peruvian balsam, and squaric acid dibutyl ester.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by April 23, 1999. Oral presentations from the public will be scheduled between approximately 10:30 a.m. to 11 a.m. for dinitrochlorobenzene, diphenylcyclopropenone, and squaric acid dibutyl ester, and between approximately 2:45 p.m. and 3:15 p.m. for 4-aminopyridine, 3,4-diaminopyridine, and betahistine dihydrochloride on May 6, 1999; and between approximately 10:15 a.m. and 10:45 a.m. for mild silver protein, cyclandelate, and monosodium aspartate, and between approximately

2:45 p.m. and 3:15 p.m. for hydrazine sulfate on May 7, 1999. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before April 23, 1999, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: April 16, 1999.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 99-10076 Filed 4-19-99; 11:05 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98D-1266]

Draft Guidance for Industry on Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling; Availability; Reopening of Comment Period

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; reopening of comment period.

SUMMARY: The Food and Drug Administration (FDA) is reopening until June 21, 1999, the comment period for the draft guidance for industry entitled "Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling" that appeared in the **Federal Register** of January 28, 1999 (64 FR 4434). FDA is taking this action in response to several requests for an extension and to allow interested parties additional time to submit comments.

DATES: Written comments may be submitted by June 21, 1999. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Copies of the draft guidance for industry are available on the Internet at "<http://www.fda.gov/cder/guidance/index.htm>". Submit written requests for single copies of the draft guidance to the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the draft

guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Comments are to be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Jerry Phillips, Center for Drug Evaluation and Research (HFD-730), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-3225.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 28, 1999, FDA published a notice announcing the availability of a draft guidance for industry entitled "Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling." The draft guidance is intended to clarify for prescription drug manufacturers, relabelers, and distributors FDA's position regarding placing the therapeutic equivalence code on approved FDA product labels and labeling. The January 28, 1999, notice invited interested persons to submit written comments on the draft guidance within 60 days.

The agency has received several requests to extend the comment period on the draft guidance. The agency has decided to reopen the comment period on the draft guidance until June 21, 1999, to allow the public more time to review and comment on its contents.

Interested persons may, on or before June 21, 1999, submit to the Dockets Management Branch (address above) written comments on the draft guidance. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: April 15, 1999.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 99-10010 Filed 4-21-99; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice

is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The contract proposals and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the contract proposals, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Cancer Institute Special Emphasis Panel, Innovative Approaches to Clinical Trials Informatics.

Date: April 19, 1999.

Time: 1:00 PM to 3:00 PM.

Agenda: To review and evaluate contract proposals.

Place: 6130 Executive Boulevard, Rockville, MD 20852, (Telephone Conference Call).

Contact Person: Wilna A. Woods, PHD, Deputy Chief, Special Review, Referral and Research Branch, Division of Extramural Activities, National Cancer Institute, National Institutes of Health, Rockville, MD 20852, (301) 496-7903.

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research; 93.394, Cancer Detection and Diagnosis Research; 93.395, Cancer Treatment Research; 93.396, Cancer Biology Research; 93.397, Cancer Centers Support; 93.398, Cancer Research Manpower; 93.399, Cancer Control, National Institutes of Health, HHS)

Dated: April 15, 1999.

LaVerne Y. Stringfield,

Committee Management Officer, NIH.

[FR Doc. 99-10057 Filed 4-21-99; 8:45 am]

BILLING CODE 4140-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Amended Notice of Meeting

Notice is hereby given of a change in the meeting of the National Cancer Institute Director's Consumer Liaison Group, April 19, 1999, 9:00 AM to April 29, 1999, 5:00 PM, Natcher Building, Conference Room B, 45 Center Drive, Bethesda, MD, 20892 which was published in the **Federal Register** on April 13, 1999, 64 FR 18036.

The meeting will be held from April 19, 1999, 8:30 AM to April 20, 1999,

Tab 74

Federal Register of December 4, 2013
(78 FR 72841)

accordance with all applicable conditions that are necessary to prevent the drug or category of drugs from presenting such demonstrable difficulties (see section 503B(a)(6)(A) and (a)(6)(B) of the FD&C Act). Section 503B(c)(2) of the FD&C Act requires that before issuing regulations to implement section 503B(a)(6) of the FD&C Act, an advisory committee on compounding be convened and consulted.

FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded and still qualify for any of the exemptions set forth in sections 503A and 503B because they present demonstrable difficulties for compounding.

II. Request for Nominations

To identify candidates for the difficult-to-compound list, FDA is seeking public input in the form of specific drug products or categories of drug products that are difficult to compound. Interested groups and individuals may nominate drug products or categories of drug products that are difficult to compound for inclusion on the list. After evaluating the nominations and, as required by Congress, consulting with the Pharmacy Compounding Advisory Committee (see sections 503A(d)(1) and 503B(c)(2) of the FD&C Act), FDA will issue the list as a regulation under notice-and-comment rulemaking procedures.

Nominations should include the following for each drug product or drug product category nominated, and any other relevant additional information available:

- Name of drug product or drug product category;
- Reason why the drug product or drug product category should be included on the list, taking into account the risks and benefits to patients.

Reasons may include but are not limited to:

- The potential effect of compounding on the potency, purity, and quality of a drug product, which could affect the safety and effectiveness of the drug product. Factors that may be relevant to this determination include:

1. Drug Delivery System

- Is a sophisticated drug delivery system required to ensure dosing accuracy and/or reproducibility?
- Is the safety or efficacy of the product a concern if there is product-to-product variability?

2. Drug Formulation and Consistency

- Is a sophisticated formulation of the drug product required to ensure dosing accuracy and/or reproducibility?
- Because of the sophisticated formulation, is product-to-product uniformity of the drug product often difficult to achieve?
- Is the safety or efficacy of the product a concern if there is product-to-product variability?

3. Bioavailability

- Is it difficult to achieve and maintain a uniformly bioavailable dosage form?
- Is the safety or effectiveness of the product a concern if the bioavailability varies?

4. Complexity of Compounding

- Is the compounding of the drug product complex?
- Are there multiple, complicated, or interrelated steps?
- Is there a significant potential for error in one or more of the steps that could affect drug safety or effectiveness?

5. Facilities and Equipment

- Are sophisticated facilities and/or equipment required to ensure proper compounding of the drug product?
- Is there a significant potential for error in the use of the facilities or equipment that could affect drug safety or effectiveness?

6. Training

- Is specialized, highly technical training essential to ensure proper compounding of the drug product?

7. Testing and Quality Assurance

- Is sophisticated, difficult-to-perform testing of the compounded drug product required to ensure potency, purity, performance characteristics, or other important characteristics prior to dispensing?
- Is there a significant potential for harm if the product is compounded without proper quality assurance procedures and end-product testing?
 - Adverse effects that could result when the drug product or drug product category is not made according to appropriate conditions.

FDA cannot guarantee that all drug products or drug product categories nominated during the nomination period will be considered for inclusion on the next published difficult to compound list. Nominations received during the comment period that are supported by the most complete and relevant information will likely be evaluated first. Nominations that are not evaluated during this first phase will

receive consideration for list amendments, because the development of this list will be an ongoing process. Individuals and organizations also will be able to petition FDA to make additional list amendments after the list is published.

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set comments. Identify comments with the docket number found in the brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Dated: November 27, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-28980 Filed 12-2-13; 11:15 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Chapter I

[Docket No. FDA-2013-N-1525]

List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Withdrawal of proposed rule; request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is withdrawing the proposed rule to list bulk drug substances used in pharmacy compounding and preparing to develop a list of bulk drug substances (bulk drugs) that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. To identify candidates for this bulk drugs list, interested groups and individuals may nominate specific bulk drug substances, and FDA is describing the information that should be provided to the Agency in support of each nomination.

DATES: FDA is withdrawing the proposed rule published January 7, 1999 (64 FR 996), as of December 4, 2013.

Submit written or electronic nominations for the bulk drug substances list by March 4, 2014.

ADDRESSES: You may submit nominations, identified by Docket No. FDA-2013-N-1525, by any of the following methods.

Electronic Submissions

Submit electronic nominations in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting “comments.”

Written Submissions

Submit written nominations in the following ways:

- *Mail/Hand delivery/Courier (for paper submissions):* Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and docket number FDA-2013-N-1525 for this request for nominations. All nominations received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting nominations, see the “Request for Nominations” heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or nominations received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Marissa Chaet Brykman, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, suite 5100, Silver Spring, MD 20993-0002, 301-796-3110.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a) describes the conditions under which a human drug product compounded for an identified individual patient based on a prescription is entitled to an exemption from three sections of the FD&C Act: (1) section 501(a)(2)(B) (21 U.S.C.

351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) for drugs); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (21 U.S.C. 355) (concerning the approval of human drug products under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).

One of the conditions for such an exemption is that a drug product may be compounded if the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that: “(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding; (II) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or (III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d) [of Section 503A]” (section 503A(b)(1)(A)(i) of the FD&C Act).

Section 503A refers to the definition of “bulk drug substance” in FDA regulations at 21 CFR 207.3(a)(4): “any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.” See section 503A(b)(1)(A) of the FD&C Act.

Section 503A(d)(1) of the FD&C Act requires that, before issuing regulations to implement section 503A(b)(1)(A)(i)(III) of the FD&C Act, an advisory committee on compounding be convened and consulted “unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health” (section 503A(d)(1) of the FD&C Act).

As described in more detail below, in 1998, FDA began to develop a list of bulk drug substances that may be used in compounding, but before a final rule was published, the constitutionality of section 503A was challenged in court because it included restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug and the solicitation of prescriptions for compounded drugs. These provisions were held unconstitutional by the U.S.

Supreme Court in 2002.¹ After the court decision, FDA suspended its efforts to develop the list of bulk drug substances that could be used in compounding.

The Drug Quality and Security Act (DQSA) removes from section 503A of the FD&C Act the provisions that had been held unconstitutional by the U.S. Supreme Court in 2002.² By removing these provisions, the new law removes uncertainty regarding the validity of section 503A, clarifying that it applies nationwide. Therefore, FDA is reinitiating its efforts to develop a list of bulk drug substances that may be used in compounding under section 503A.

II. Previous Efforts To Develop the List of Bulk Drug Substances Under Section 503A of the FD&C Act

In the **Federal Register** of April 7, 1998 (63 FR 17011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the list of bulk drug substances that may be used in compounding under section 503A. In total, FDA received nominations for 41 different drug substances. After evaluating the nominated drugs and consulting with the Pharmacy Compounding Advisory Committee as required by section 503A, FDA published a proposed rule proposing to list 20 drugs on the section 503A bulk drugs list in January 1999 (64 FR 996, January 7, 1999). The proposed rule also discussed 10 nominated drug substances that were still under consideration for the bulk drugs list. The Pharmacy Compounding Advisory Committee reconvened in May 1999 to discuss drugs included in the proposed rule, in addition to other bulk drug substances (see 64 FR 19791 (April 22, 1999)). However, as explained previously (see the “Background” section), after the 2002 U.S. Supreme Court decision, the Agency suspended its efforts to develop the bulk drugs list under section 503A.

FDA intends to reconsider the bulk drug substances that were proposed for inclusion on the list and that neither have an applicable USP or NF monograph nor are components of an FDA-approved drug due to the time

¹ See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).

² The DQSA also adds a new section 503B to the FD&C Act (21 U.S.C. 353b) that creates a new category of “outsourcing facilities.” For additional information concerning bulk drug substances that may be used to compound drug products in accordance with section 503B, see the notice, “Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance with Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations” published in this issue of the **Federal Register**.

lapse since the last proposal. Therefore, the Agency withdraws the proposed rule, "List of Bulk Drug Substances That May Be Used in Pharmacy Compounding," published in the **Federal Register** of January 7, 1999 (64 FR 996).

III. Request for Nominations

To identify candidates for this list, FDA is seeking public input in the form of specific bulk drug nominations. All interested groups and individuals may nominate specific bulk drug substances for inclusion on the list. After evaluating the nominations and, as required by section 503A, consulting with the USP and the Pharmacy Compounding Advisory Committee, FDA will issue the list as a regulation under notice-and-comment rulemaking procedures.

Nominations should include the following information about the bulk drug substance being nominated and the product(s) that will be compounded using such substance, and any other relevant information available. If the information requested is unknown or unavailable, that fact should be noted accordingly.

Bulk Drug Substance

- Ingredient name;
- Chemical name;
- Common name(s);
- Chemical grade or description of the strength, quality, and purity of the ingredient;
- Information about how the ingredient is supplied (e.g., powder, liquid);
- Information about recognition of the substance in foreign pharmacopeias and the status of its registration(s) in other countries, including whether information has been submitted to USP for consideration of monograph development; and
- A bibliography of available safety and efficacy data,³ including any relevant peer-reviewed medical literature.

Compounded Product

- Information about the dosage form(s) into which the drug substance will be compounded (including formulations);
- Information about the strength(s) of the compounded product(s);
- Information about the anticipated route(s) of administration of the compounded product(s);

- Information about the past and proposed use(s) of the compounded product(s), including the rationale for its use or why the compounded product(s), as opposed to an FDA-approved product, is necessary; and
- Available stability data for the compounded product(s).

FDA cannot guarantee that all drugs nominated during the nomination period will be considered for inclusion on the next published bulk drugs list. Nominations received during the nomination period that are supported by the most complete and relevant information will likely be evaluated first. Nominations that are not evaluated during this first phase will receive consideration for list amendments, as the development of this list will be an ongoing process. Individuals and organizations also will be able to petition FDA to make additional list amendments after the list is published.

Interested persons may submit either electronic nominations to <http://www.regulations.gov> or written nominations to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of nominations. Identify nominations with the docket number found in the brackets in the heading of this document. Received nominations may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Dated: November 27, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-28979 Filed 12-2-13; 11:15 am]

BILLING CODE 4160-01-P

OVERSEAS PRIVATE INVESTMENT CORPORATION

22 CFR Part 706

[No. FOIA-2013]

RIN 3420-ZA00

Freedom of Information

AGENCY: Overseas Private Investment Corporation.

ACTION: Notice of Proposed Rulemaking.

SUMMARY: This rule proposes revisions to the Overseas Private Investment Corporation's ("OPIC") Freedom of Information Act (FOIA) regulations by making substantive and administrative changes. These revisions are intended to supersede OPIC's current FOIA regulations, located at this Part. The

proposed rule incorporates the FOIA revisions contained in the Openness Promotes Effectiveness in our National Government Act of 2007 ("OPEN Government Act"), makes administrative changes to reflect OPIC's cost, and organizes the regulations to more closely match those of other agencies for ease of reference. The proposed rule also reflects the disclosure principles established by President Barack Obama and Attorney General Eric Holder in their FOIA Policy Memoranda issued on January 12, 2009 and March 19, 2009, respectively.

DATES: Written comments must be postmarked and electronic comments must be submitted on or before January 3, 2014.

ADDRESSES: You may submit comments, identified by Docket Number FOIA-2013, by one of the following methods:

- *Email:* foia@opic.gov. Include docket number FOIA-2013 in the subject line of the message.
- *Mail:* Nichole Cadiente, Administrative Counsel, Overseas Private Investment Corporation, 1100 New York Avenue NW., Washington, DC 20527. Include docket number FOIA-2013 on both the envelope and the letter.

FOR FURTHER INFORMATION CONTACT: Nichole Cadiente, Administrative Counsel, (202) 336-8400, or foia@opic.gov.

SUPPLEMENTARY INFORMATION: The revision of Part 706 incorporates changes to the language and structure of the regulations and adds new provisions to implement the OPEN Government Act. OPIC is already complying with these changes and this proposed revision serves as OPIC's formal codification of the applicable law and its practice.

The most significant change in this proposed rule revision is the treatment of business submitters. This section will define confidential commercial information more concisely and provide a default expiration date for confidentiality labels. This will enable OPIC to more efficiently process requests for commercial information, which compose the majority of OPIC's FOIA requests. Among other substantive changes: the search date is now the responsive record cutoff date, the information OPIC posts online has been clarified, there is more detail on how to request records about an individual, and illustrative examples have been added.

In general, comments received, including attachments and other supporting materials, are part of the

³ FDA recognizes that the available safety and efficacy data supporting consideration of a bulk drug substance for inclusion on the list may not be of the same type, amount, or quality as is required to support an NDA.

Tab 75

Federal Register of July 2, 2014
(79 FR 37747)

TABLE 3—ESTIMATED ANNUAL REPORTING BURDEN¹

Type of reporting & proposed 21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Notification to FDA that a compounded drug product fails to meet a sterility criterion	10	1	10	5	50

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

V. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <http://www.regulations.gov>.

Dated: June 25, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-15370 Filed 7-1-14; 8:45 am]

BILLING CODE 4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-1525]

Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; revised request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is preparing to develop a list of bulk drug substances (active ingredients) that may be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. In response to a notice published in the **Federal Register** of December 4, 2013, interested groups and individuals previously nominated a wide variety of substances for this list. However, many of those nominations either were for a substance that is already the subject of a USP monograph or a component of an FDA-approved drug, were not for bulk drug substances used in compounding as active ingredients, or did not include sufficient information to justify inclusion of the nominated substance on the list. To improve the efficiency of the process for developing the list of bulk

drug substances that may be used to compound drug products under section 503A, FDA is providing more detailed information on what it needs to evaluate a nomination. Because the deadline for nominations has passed, FDA is reopening the nomination process so that interested persons can submit nominations of bulk drug substances that are not the subject of a USP or NF monograph or a component of an FDA-approved drug. Interested persons will also have the opportunity to provide adequate support to justify placement of the substances on the list. Bulk drug substances that were previously nominated will not be further considered unless they are renominated and those nominations are adequately supported. Substances that are already eligible for use in compounding or that are not adequately supported will not be placed on the list.

DATES: Submit written or electronic nominations for the bulk drug substances list by September 30, 2014.

ADDRESSES: You may submit nominations, identified by Docket No. FDA-2013-N-1525, by any of the following methods.

Electronic Submissions

Submit electronic nominations in the following way:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the instructions for submitting “comments.”

Written Submissions

Submit written nominations in the following ways:

- *Mail/Hand delivery/Courier (for paper submissions):* Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2013-N-1525 for this request for nominations. All nominations received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting nominations, see the “Request for Nominations” heading of the

SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or nominations received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Emily Helms Williams, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6280, Silver Spring, MD 20993-0002, 301-796-3381.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions under which a compounded drug product may be entitled to an exemption from certain sections of the FD&C Act. Those conditions include that the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that (1) comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A. See section 503A(b)(1)(A)(i) of the FD&C Act. Under section 503A(c)(2), the criteria for determining which substances should appear on the 503A bulk drugs list “shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.”

Section 503A refers to the definition of “bulk drug substance” in FDA regulations at § 207.3(a)(4) (21 CFR 207.3(a)(4)). See section 503A(b)(1)(A) of the FD&C Act. As defined in

§ 207.3(a)(4), a “bulk drug substance” is any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.

An “active ingredient” is any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect. See 21 CFR 210.3(b)(7).

Any component other than an active ingredient is an “inactive ingredient.” See 21 CFR 210.3(b)(8). Inactive ingredients used in compounded drug products, which commonly include flavorings, dyes, diluents, or other excipients, need not appear on the Secretary’s list of bulk drug substances to be eligible for use in compounding drug products and will not be included on the list.

In a notice dated November 27, 2013 (the November 27, 2013, notice), published in the **Federal Register** of December 4, 2013 (78 FR 72841), FDA requested nominations for specific bulk drug substances for the Agency to consider placing on the list. In response to that request, 115 comments were submitted to the docket, most of which nominated substances for inclusion on the bulk drug substances list. Some comments nominated several hundred substances, and approximately 10 comments nominated thousands of substances, including en bloc nominations of substances listed in the British Pharmacopeia, the European Pharmacopeia, the Japanese Pharmacopeia, the Food Chemicals Codex, the Homeopathic Pharmacopeia of the United States, and the USP Dietary Supplements Compendium. Several submissions referenced a spreadsheet entitled “OTC Active Ingredients,” available on FDA’s Web site at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf>. Those submissions nominated all of the ingredients on the spreadsheet, which numbered over 1,700 entries.¹

¹ The total number of unique ingredients on the spreadsheet available on FDA’s Web site and the nominations that mirrored that document is lower

However, many of the nominated substances are typically inactive ingredients or foods. Some commonly used inactive ingredients are occasionally used as the active ingredient in a drug product. See 55 FR 46914 at 46916, November 7, 1990 (noting that 21 CFR 310.545 only affects the use of the listed ingredients as active ingredients for the specific indications, and that some of the ingredients listed in the rule, such as sorbitol, sugars, and eucalyptol, have valid uses as inactive ingredients). Ingredients commonly used as inactive ingredients in compounded drug products, such as flavorings, dyes, diluents, or other excipients, need not appear on the Secretary’s list of bulk drug substances to be eligible for use as an inactive ingredient in compounded drug products, should not be nominated, and will not be included on the list. All nominations must demonstrate how the ingredient is used as an active ingredient in a particular compounded drug product.

Additionally, many of the nominated substances are already eligible for use in compounded drug products, namely, those that are components of approved products or are the subject of a USP or NF monograph. Substances that are in one of those two categories need not appear on the list of bulk drug substances to be used in compounded drug products.

Further, many of the nominations did not include sufficient information for the Agency to evaluate whether the substance is appropriate for use in compounded drug products. As stated previously, under section 503A(c)(2) of the FD&C Act, the criteria for determining which substances should appear on the 503A bulk drugs list shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify. Based on this statutory language and prior consultations with the USP and the Pharmacy Compounding Advisory Committee,² FDA is proposing to examine the following four criteria when determining whether a bulk drug substance is appropriate for use in compounded drug products: (1) The physical and chemical characterization of the substance; (2) any safety issues

than this total because the same substances were listed separately for different indications, according to how they are listed in the over-the-counter (OTC) monographs and regulations.

² See 64 FR 996, January 7, 1999 (proposed rule listing bulk drug substances that may be used in pharmacy compounding). This proposed rule was withdrawn in the November 27, 2013, notice but sets forth additional background about the criteria used in the evaluation of nominated bulk drug substances.

raised by the use of the substance in compounded drug products; (3) historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature; and (4) the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists. Therefore, to qualify for placement on the list, it is necessary to identify this information about the nominated substances. FDA will evaluate the nominated substances in consultation with the Pharmacy Compounding Advisory Committee.

The November 27, 2013, notice requested that nominations include “[i]nformation about the past and proposed use(s) of the compounded product(s), including the rationale for its use or why the compounded product(s), as opposed to an FDA-approved product, is necessary.” However, many comments to the docket did not provide any information in response to this request. The nominators of the en bloc submissions provided no justification for listing any of the specific substances on the list. To the extent information about the rationale for compounding with a bulk drug substance was provided in individual nominations, many of the comments to the docket included only a brief statement about the use of the compounded drug product and a statement that the product is not available as a commercially made drug. Such statements do not provide sufficient information for FDA to determine whether the nominated bulk drug substance is appropriate for use in compounded drug products. Because the information submitted with previous nominations was insufficient, FDA is unable to determine whether those substances should be included on the list.

To improve the efficiency of the process for developing the list of bulk drug substances that may be used to compound drug products under section 503A, and because the deadline for submitting nominations has passed, FDA is reopening the nomination process so that interested persons have the opportunity to submit nominations of bulk drug substances and provide adequate support for placing them on the list. FDA will be able to evaluate only those bulk drug substances submitted in response to this notice that are supported with adequate data and information, as described in section II.

Bulk drug substances that were previously nominated will not be

further considered unless they are renominated and adequately supported. Substances that are not adequately supported will not be placed on the list. FDA expects the submissions for each bulk drug substance to provide the information described in section II. For example, nominations must include sufficient information to demonstrate that a particular ingredient meets the definition of "bulk drug substance," as defined in § 207.3(a)(4). See section 503A(b)(1)(A) of the FD&C Act. The identification of an ingredient as an "active ingredient" in a regulation, or on a spreadsheet such as the one listing "OTC Active Ingredients," is not sufficient to demonstrate that a substance is a bulk drug substance for purposes of the 503A list. En bloc nominations of substances listed in compendia, pharmacopeia, or similar reference materials cannot be placed on the list unless the Agency receives adequate information for each bulk drug substance to justify its placement on the list. FDA will only be able to consider bulk drug substances that are supported with the information requested.

In section II, FDA identifies the type of information needed to support a nomination to the 503A list.

II. Request for Nominations

Interested groups and individuals may nominate specific bulk substances for inclusion on the list. Nominations will only be evaluated if they are for specific active ingredients that meet the definition of a bulk drug substance in § 207.3(a)(4), are not for components of approved products, and are not for the subject of a USP or NF monograph. To fully evaluate a bulk drug substance, FDA needs the following information about both the bulk drug substance being nominated and the drug product(s) that will be compounded using such substance:

A. Confirmation That the Nominated Substance Is a Bulk Drug Substance and Is Not Already Eligible for 503A Compounding

- A statement that the nominated substance is an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4), and an explanation of why the substance is

considered an active ingredient when it is used in the identified compounded drug product(s), citing to specific sources that describe the active properties of the substance.

- A statement that the nominator has searched for the active ingredient in all three sections of the Orange Book (for prescription drug products, over-the-counter drug products, and discontinued drug products), available at <http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm>, and the drug substance did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product.

- A statement that the nominator has searched USP and NF monographs, available at <http://www.uspnf.com>, and the drug substance is not the subject of such a monograph.

B. General Background on the Bulk Drug Substance

- Ingredient name;
- Chemical name;
- Common name(s);
- Identifying codes, as available, from FDA's Unique Ingredient Identifiers (UNII) used in the FDA/USP Substance Registration System, available at <http://fdasis.nlm.nih.gov/srs/>. Because substance names can vary, this code, where available, will be used by the Agency to confirm the exact substance nominated and to identify multiple nominations of the same substance so the information can be reviewed together.

- Chemical grade of the ingredient;
- Description of the strength, quality, stability, and purity of the ingredient;
- Information about how the ingredient is supplied (e.g., powder, liquid); and
- Information about recognition of the substance in foreign pharmacopeias and the status of its registration(s) in other countries, including whether information has been submitted to USP for consideration of monograph development.

C. Information on the Drug Product That Will Be Compounded With the Bulk Drug Substance

- Information about the dosage form(s) into which the bulk drug substance will be compounded;

- Information about the strength(s) of the compounded drug product(s);

- Information about the anticipated route(s) of administration of the compounded product(s);

- A bibliography of safety and efficacy data for the drug compounded using the nominated substance, if available,³ including any relevant peer-reviewed medical literature; and

Information about the past and proposed use(s) of the compounded drug product(s), including the rationale for its use and why the compounded product(s), as opposed to an FDA-approved product, is necessary. Information on the rationale for use of the bulk drug substance and why a compounded drug product is necessary must be specific to the compounded drug product at issue. General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

D. Nomination Process

Because the deadline for submitting nominations has passed, FDA is reopening the nomination process so that interested persons can submit nominations of bulk drug substances and have the opportunity to provide adequate support for placing them on the list. Bulk drug substances that were previously nominated need to be renominated. Nominators are encouraged to submit as much of the information identified in this document as possible. Unless adequate supporting data is received for a bulk drug substance, FDA will be unable to consider it further for inclusion on the list. Individuals and organizations will be able to comment on nominated substances after the nomination period has closed or petition FDA to make additional list amendments after the list is published, in accordance with 21 CFR 10.30.

For efficient consolidation and review of nominations, nominators are encouraged to submit their nominations in an editable Excel file. Specifically, nominators are encouraged to format their nominations as follows:

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient? Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?	Provide the ingredient name. Provide an explanation for why it is considered an active ingredient when it is used in specific compounded drug products, and provide citations to specific sources that describe its active properties.

³ FDA recognizes that the available safety and efficacy data supporting consideration of a bulk

drug substance for inclusion on the list may not be

of the same type, amount, or quality as is required to support a new drug application.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
Is the ingredient listed in any of the three sections of the Orange Book?	Confirm whether the ingredient is a component of an FDA-approved product.
Were any monographs for the ingredient found in the USP or NF monographs?	Confirm whether the ingredient is the subject of a USP or NF monograph.
What is the chemical name of the substance?	Chemical name.
What is the common name of the substance?	Common name.
Does the substance have a UNII Code?	UNII code.
What is the chemical grade of the substance?	Provide the chemical grade.
What is the strength, quality, stability, and purity of the ingredient?	Provide the strength, quality, stability, and purity information.
How is the ingredient supplied?	Describe how the ingredient is supplied (e.g., powder, liquid).
Is the substance recognized in foreign pharmacopeias or registered in other countries?	List the foreign pharmacopeias or other countries in which it is registered.
Has information been submitted about the substance to the USP for consideration of monograph development?	Put yes, no, or unknown. If yes, state the status of the monograph, if known.
What dosage form(s) will be compounded using the bulk drug substance?	State the dosage form(s).
What strength(s) will be compounded from the nominated substance?	List the strength(s) of the drug product(s) that will be compounded from the nominated substance, or a range of strengths, if known.
What are the anticipated route(s) of administration of the compounded drug product(s)?	List the route(s) of administration of the compounded drug product(s).
Are there safety and efficacy data on compounded drugs using the nominated substance?	Provide a bibliography of safety and efficacy data for the drug compounded using the nominated substance, if available, including any relevant peer-reviewed medical literature.
Has the bulk drug substance been used previously to compound drug product(s)?	Describe past uses of the bulk drug substance in compounding.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Provide information on the proposed use of the compounded drug product.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	Provide a rationale for the use of a compounded drug product.
Is there any other relevant information?	Provide any other information you would like FDA to consider in evaluating the nomination.

Interested persons may submit either electronic nominations to <http://www.regulations.gov> or written nominations to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of nominations. Identify nominations with the docket number found in the brackets in the heading of this document. Received nominations may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Dated: June 25, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-15367 Filed 7-1-14; 8:45 am]

BILLING CODE 4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-1524]

Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Revised Request for Nominations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; revised request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is preparing to develop a list of bulk drug substances (active ingredients) that may be used to compound drug products in accordance with section 503B of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) concerning outsourcing facilities. In response to a notice published in the **Federal Register** of December 4, 2013, interested groups and individuals previously nominated a wide variety of substances for this list. However, many of those nominations were not for bulk drug substances used in compounding as active ingredients, and none included sufficient information to justify inclusion of the

nominated substances on the list. To improve the efficiency of the process for developing the list of bulk drug substances that may be used to compound drug products under section 503B of the FD&C Act, FDA is providing more detailed information on what it needs to evaluate a nomination. Because the deadline for nominations has passed, FDA is reopening the nomination process so that interested persons can submit nominations of bulk drug substances and provide adequate support to justify placing the substances on the list. Bulk drug substances that were previously nominated will not be further considered unless they are renominated and adequately supported. Substances that are not adequately supported will not be placed on the list.

DATES: Submit written or electronic nominations for the bulk drug substances list by September 30, 2014.

ADDRESSES: You may submit nominations, identified by Docket No. FDA-2013-N-1524, by any of the following methods.

Electronic Submissions

Submit electronic nominations in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Tab 76

Thymol Iodide Nominations



September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA's request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS

Corporate Offices: 4638 Riverstone Blvd. | Missouri City, Texas 77459 | 281.933.8400
Washington DC Offices: 1321 Duke Street, Suite 200 | Alexandria VA 22314 | 703.299.0796

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created an series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency's activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee prior to the implementation and issuance of regulations including the creation of the bulk ingredient list.

(2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

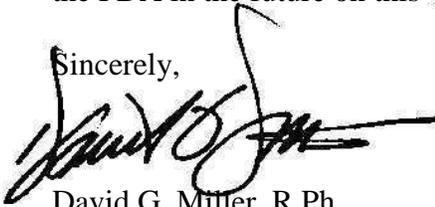
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

A handwritten signature in black ink, appearing to read 'David G. Miller', with a stylized flourish extending to the right.

David G. Miller, R.Ph.
Executive Vice President & CEO



Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Thymol iodide
Chemical/Common Name	Dithymol Diiodide
Identifying Codes	552-22-7
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	USP has Thymol CAS 89-83-8

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	Federal Register 1999

Past and Proposed Use The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.



Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	thymol iodide
Chemical/Common Name	thymol iodide
Identifying Codes	3J50XA376E
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	Not Listed in USP/NF/NF Listed

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	relief of oral discomfort FDA. OTC Active Ingredients List. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf Accessed 2-10-2014, last updated April 7, 2010

Past and Proposed Use	The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.
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September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: FDA-2013-D-1525; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act, Revised Request for Nominations

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit comments to the Food and Drug Administration (FDA) on bulk drug substances that may be used to compound drug products. Nominations for this list were originally announced in the Federal Register on December 4, 2013.¹ A revision to this notification was published on July 2, 2014.² This list would fulfill Section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act) which regulates entities that compound drugs. On November 27, 2013, the Drug Quality and Security Act (DQSA) was signed into law [P.L. 113-54]. The DQSA removed several parts of Section 503A that were declared unconstitutional by the U. S. Supreme Court in 2002. The law requires the FDA to go through the rulemaking process to implement several parts of Section 503A, including a requirement to establish a list of bulk drug substances that may be used in compounding for which there is no applicable USP or NF monograph nor are they components of an FDA-Approved drug.

ASHP represents pharmacists who serve as patient care providers in acute and ambulatory settings. The organization's more than 40,000 members include pharmacists, student pharmacists and pharmacy technicians. For over 70 years, ASHP has been on the forefront of efforts to improve medication use and enhance patient safety. As you are well aware, ASHP was

¹ Federal Register, Volume 78, No. 233. Pages 72841 – 72843

² Federal Register, Volume 79, No. 127. Pages 37747– 37750

actively engaged with the FDA and Federal lawmakers from the onset of the meningitis outbreak in the Fall of 2012. In the aftermath of the incident, ASHP has worked with policymakers, practitioners, and nationally recognized experts in compounding and manufacturing to develop new approaches to protect patients from preventable harm, and to give practitioners and organizations confidence that compounding outsourcers are appropriately regulated and inspected, and that the products they produce are safe.

ASHP understands that the FDA received thousands of nominations for substances to be included on the bulk list, but that the overwhelming majority of nominations did not meet the basic definition of “active ingredient,” and will therefore not be considered by the FDA. Further, the Agency states “Bulk substances that were previously nominated will not be further considered unless they are renominated and adequately supported.” ASHP previously submitted comments to the FDA under the original solicitation for bulk substances and we are again nominating three chemicals – diphenylcyclopropenone, squaric acid dibutyl ester, and thymol iodide – for consideration by the FDA. Please see the accompanying excel file which contains a worksheet for each of the drugs with the information outlined by the FDA.

ASHP appreciates the opportunity to comment as the FDA develops a list of bulk drug substances that may be used in compounding. Please contact me if you have any questions or wish to discuss our comments further. I can be reached by telephone at 301-664-8806, or by e-mail at ctopoleski@ashp.org.

Sincerely,

A handwritten signature in black ink, appearing to read "Christopher J. Topoleski". The signature is fluid and cursive, with a large initial "C" and "T".

Christopher J. Topoleski
Director, Federal Regulatory Affairs.

Column A—What information is requested?	Column B—put data specific to the nominated substance	References
What is the name of the nominated ingredient?	THYMOL IODIDE	
Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?	Yes	
What is the chemical name of the substance?	4,4'-Bis(iodoxy)-2,2'-dimethyl-5,5'-bis(1-methylethyl)-1,1'-biphenyl	http://chem.sis.nlm.nih.gov/chemidplus/unii/A51HJM3XSU
What is the common name of the substance?	THYMOL IODIDE	http://chem.sis.nlm.nih.gov/chemidplus/unii/A51HJM3XSU
Does the substance have a UNII Code?	A51HJM3XSU	http://fdasis.nlm.nih.gov/srs/ProxyServlet?mergeData=true&objectHandle=DBMaint&APPLICATION_NAME=fdasrs&actionHandle=default&nextPage=jsp/srs/ResultScreen.jsp&XTSUPERLISTID=A51HJM3XSU&QV1=THYMOL+IODIDE
What is the chemical grade of the substance?	Mexico Grade- Slight risk, Grade 1 WHMIS Hazard Class- Non-controlled	http://datasheets.scbt.com/sds/WPNA/EN/sc-215985.pdf
What is the strength, quality, stability, and purity of the ingredient?	No current purity/strength information	http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_02_41-BDL28.pdf http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=T2763&brand=SIGMA&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsigma%2Ft2763%3Flang%3Den

How is the ingredient supplied?	Powder	http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=T2763&brand=SIGMA&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsigma%2Ft2763%3Flang%3Den
Is the substance recognized in foreign pharmacopeias or registered in other countries?	No	
Has information been submitted about the substance to the USP for consideration of monograph development?	Unknown; Thymol [NF] monograph available, but is not the same chemical - Phenol, 5-methyl-2-(1-methylethyl) [C10H14O] vs C20H24I2O2	USP-NF
What medical condition(s) is the drug product compounded with the bulk drug substances intended to treat?	Absorbent and protective agent with antimicrobial properties	http://www.iacprx.org/?876
Are there other drug products approved by FDA to treat the same medical condition?		
If there are FDA-approved drug products that address the same medical condition, why is there a clinical need for a compounded drug product?		
Are there safety and efficacy data on compounded drugs using the nominated substance?	Yes	

<p>If there is an FDA-approved drug product that includes the bulk drug substance nominated, is it necessary to compound a drug product from the bulk drug substance rather than from the FDA-approved drug product?</p>	<p>No</p>	<p>http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>
<p>What dosage form(s) will be compounded using the bulk drug substance?</p>	<p>Topical</p>	
<p>What strength(s) will be compounded from the nominated substance?</p>	<p>Unknown or N/A; used as a stabilizing agent</p>	
<p>What are the anticipated route(s) of administration of the compounded drug product(s)?</p>	<p>Topical</p>	
<p>Has the bulk drug substance been used previously to compound drug product(s)?</p>	<p>Yes, as an antiseptic</p>	<p>http://chem.sis.nlm.nih.gov/chemidplus/unii/A51HJM3XSU</p>
<p>Is there any other relevant information?</p>	<p>Pubmed Search Results:</p>	<p>http://www.ncbi.nlm.nih.gov/pubmed/?term=THYMOL+IODIDE</p>
	<p>MSDS:</p>	<p>http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=T2763&brand=SIGMA&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsigma%2Ft2763%3Flang%3Den</p>
	<p>CAS:</p>	<p>552-22-7</p>



Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

“List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act”

Dear Sir or Madam,

Fagron appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

We hereby nominate the bulk drug substances in the attached spreadsheets for FDA’s consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

None of these items appear on an FDA-published list of drugs that present demonstrable difficulties for compounding. In addition, none are a component of a drug product that has been withdrawn or removed from the market because the drug or components of the drug have been found to be unsafe or not effective.

We include references in support of this nomination for your consideration.

Thank you for your consideration. If Fagron can answer any questions, please contact me (j.letwat@fagron.com; 847-207-6100).

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs



Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlsx file)

7-Keto Dehydroepiandrosterone
Acetyl-D-Glucosamine
Aloe Vera 200:1 Freeze Dried
Astragalus Extract 10:1
Beta Glucan (1,3/1,4 –D)
Boswellia Serrata Extract
Bromelain
Cantharidin
Cetyl Myristoleate Oil
Cetyl Myristoleate 20% Powder
Chrysin
Citrulline
Dehydroepiandrosterone
Deoxy-D-Glucose (2)
Diindolylmethane
Domperidone
EGCg
Ferric Subsulfate
Glycolic Acid
Glycosaminoglycans
Hydroxocobalamin Hydrochloride
Kojic Acid
Methylcobalamin
Nicotinamide Adenine Dinucleotide
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)
Ornithine Hydrochloride
Phosphatidyl Serine
Pregnenolone
Pyridoxal 5-Phosphate Monohydrate
Pyruvic Acid
Quercetin
Quinacrine Hydrochloride
Ribose (D)
Silver Protein Mild
Squaric Acid Di-N-Butyl Ester
Thymol Iodide
Tranilast
Trichloroacetic Acid
Ubiquinol 30% Powder

Fagron

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What is the name of the nominated ingredient?	Thymol iodide
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?	<p>Yes, Thymol Iodide is an active ingredient as defined in 207.3(a)(4) because when added to a pharmacologic dosage form it produces a pharmacological effect.</p> <p>Kennedy, L., & Sahn, S. A. (1994). Talc pleurodesis for the treatment of pneumothorax and pleural effusion. CHEST Journal, 106(4), 1215-1222. http://www.yskyeung.com/public/tmp/talc../papers/talc%20is%20effective.pdf</p> <p>Davies, S. C., & Oni, L. (1997). Management of patients with sickle cell disease. BMJ: British Medical Journal, 315(7109), 656. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2127468/pdf/9310570.pdf</p> <p>BAKER, THOMAS J. "Chemical face peeling and rhytidectomy: A combined approach for facial rejuvenation." Plastic and Reconstructive Surgery 29.2 (1962): 199-207. http://journals.lww.com/plasreconsurg/Abstract/1962/02000/CHEMICAL_FACE_PEELING_AND_RHYTIDECTOMY__A_Combined.7.aspx</p>
Is the ingredient listed in any of the three sections of the Orange Book?	The nominated substance was searched for in all three sections of the Orange Book located at http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm . The nominated substance does not appear in any section searches of the Orange Book.
Were any monographs for the ingredient found in the USP or NF monographs?	The nominated substance was searched for at http://www.uspnf.com . The nominated substance is not the subject of a USP or NF monograph.
What is the chemical name of the substance?	Thymol Iodide
What is the common name of the substance?	iosol;iodosol; ARISTOL; iodistol; iothymol ;lothymol ;thymide; thymodin; annidalin ;thymiodol
Does the substance have a UNII Code?	A51HJM3XSU
What is the chemical grade of the substance?	no grade

Nomination from Fagron, September 30, 2014

What is the strength, quality, stability, and purity of the ingredient?	Description: Yellow colored powder with a slight aromatic odor Solubility: Slightly soluble ethanol; freely soluble chloroform Identification (IR): Conforms Identification (100 mg/H ₂ SO ₄): Conforms Alkalinity: Conforms Loss on Drying: <= 2.0% Residue on Ignition: <=1.5% Iodine: Conforms Soluble Halides: Conforms Assay: >= 42.0%
How is the ingredient supplied?	powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	no
Has information been submitted about the substance to the USP for consideration of monograph development?	No USP Monograph Submission found.
What dosage form(s) will be compounded using the bulk drug substance?	Powder / Spray / Ointment
What strength(s) will be compounded from the nominated substance?	5-10%
What are the anticipated route(s) of administration of the compounded drug product(s)?	Topical
Are there safety and efficacy data on compounded drugs using the nominated substance?	BAKER, THOMAS J. "Chemical face peeling and rhytidectomy: A combined approach for facial rejuvenation." Plastic and Reconstructive Surgery 29.2 (1962): 199-207. http://journals.lww.com/plasreconsurg/Abstract/1962/02000/CHEMICAL_FACE_PEELING_AND_RHYTIDECTOMY__A_Combined.7.aspx
Has the bulk drug substance been used previously to compound drug product(s)?	Yes, used in the topical treatment of ulcerations and various skin infections Remington 13th edition page 1251-1252
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	used in the topical treatment of ulcerations and various skin infections
What is the reason for use of a compounded drug product rather than an FDA-approved product?	No FDA approved preparation for thymol iodide

Nomination from Fagron, September 30, 2014

Is there any other relevant information?	
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Submitted electronically via www.regulations.gov

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No.: FDA-2013-N-1525: *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations*

Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

A handwritten signature in black ink, appearing to read 'Steve Pfister', with a long horizontal flourish extending to the right.

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Nomination from National Community Pharmacists Association, September 30, 2014

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format (s)	Recognition in Pharmacopias	Final Compounded Formulation Dosage Form	Final Compounded Formulation Strength	Final Compounded Formulation Route(s) of Admin	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
Thymol iodide	dithymol diiodide; 4,4'-bis(iodoxy)-2,2'-dimethyl-5,5'-bis(1-methylethyl)-1,1'-biphenyl	Thymol iodide	3J50XA376E (Thymol), A51HJM3XSU	From PCCA Database MSDS: Product is 100% by weight. Heat will contribute to instability and discolors on exposure to light. Should be protected from strong oxidizing agents.	Powder	USP has Thymol CAS 89-83-8	Various	Various	Various, Topical	Federal Register 1999, FDA. OTC Active Ingredients List. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf Accessed 2-10-2014, last updated April 7, 2010	Topical absorbent and protective agent with antimicrobial properties, oral health care, relief of oral discomfort Thymol iodide is well characterize chemically. It has been used as a topical agent for its absorbent, protective, and antimicrobial properties. At doses reported in the literature for these indications, thyme iodide appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of thymol iodide's effectiveness for these indications is also reported in the literature. FDA notes, however, that it was able to identify only two relevant articles concerning this substance. Because the literature is limited to the topical use of thymol iodide, FDA is proposing to include it on the bulk drugs list for topical use only.

Tab 77

FDA Review of Thymol Iodide



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: February 4, 2015

FROM: Patricia Brown
Medical Officer, Division of Dermatology and Dental Products

Jill Merrill
Toxicologist (Pharmacology Reviewer), Division of Dermatology and Dental Products

David Lewis
Chemist (CMC Reviewer), Office of Lifecycle Drug Products, Office of Pharmaceutical Quality

THROUGH: Julie Beitz
Director, Office of Drug Evaluation III

Kendall Marcus
Director, Division of Dermatology and Dental Products

Gordana Diglisic
Clinical Team Leader, Division of Dermatology and Dental Products

Barbara Hill
Supervisory Pharmacologist, Division of Dermatology and Dental Products

Doanh Tran
Clinical Pharmacology Team Leader, Office of Clinical Pharmacology

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Thymol Iodide for Inclusion on the 503A Bulk Drug Substances List

I. Introduction

Thymol iodide has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Indications identified in the nominations include as an absorbent and protective agent with antimicrobial properties and for topical treatment of ulcerations and various skin infections. FDA reviewed this substance in 1998, and it was included on a proposed list of bulk drug substances published in January 1999. The background materials from the prior review are attached. This substance is now being reevaluated.

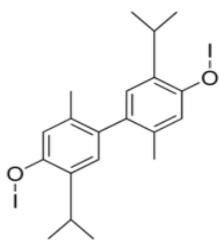
We have reviewed the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. Based on those factors, for the reasons

discussed below, we recommend that thymol iodide be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?

Thymol iodide: CAS-552-22-7, C₂₀H₂₄I₂O₂, 550.21 g/mol, also known as dithymol diiodide



Thymol iodide is available from multiple sources world-wide. A Sigma-Aldrich specification¹ is as follows:

TEST	Specification
Appearance (Color)	Yellow to Tan
Appearance (Form)	Powder
Infrared spectrum	Conforms to Structure
Loss on Drying	≤ 5.0 %
Titration by AgNO ₃	41 - 46 %
UV-Vis Spectrum	≥ 320
E1% in CHCl ₃	
Wavelength	241 - 246 nm
UV-Vis Spectrum	
Recommended Retest Period	-----
9 Years	

1. *Stability of the API and likely dosage forms*

The retest period for thymol iodide, as supplied by Sigma-Aldrich is 9 years, which indicates that thymol iodide, if stored in the original sealed container (and protected from the environment) is stable. The Chemical Book entry for thymol iodide indicates that the

¹ Sigma-Aldrich manufactures chemicals for use in scientific research, biotechnology, and pharmaceutical development. According to its website, a Sigma-Aldrich specification is “a list of test methods, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use.” See <http://www.sigmaaldrich.com/united-kingdom/technical-services/specifications.html>.

substance is sensitive to light and to strong oxidizing agents. The MSDS states that thymol iodide may decompose so that corrosive iodine/iodide fumes are emitted, which indicates that the oxygen-iodine bonds are susceptible to cleavage with subsequent release of iodine. The stability of thymol iodide, when incorporated into a dosage form, is unknown.

2. *Probable routes of API synthesis*

According to older literature (US Dispensatory, 1918) thymol iodide is prepared via treatment of a solution of thymol with iodine and potassium iodide. All cited synthesis started with thymol and iodine.

3. *Likely impurities*

Likely impurities would include thymol (starting material, a synthesis by-product), iodine (from cleavage of the oxygen-iodine bond, a degradation product), and dithymol (a degradation product, produced via loss of iodine from thymol iodide).

4. *Toxicity of those likely impurities*

Iodine is corrosive (by the inhalation route). The toxicity profile of thymol is well-characterized, since thymol is subject to a USP monograph.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

Thymol iodide is described as being soluble in organic solvents (chloroform, ether), slightly soluble in alcohol, and insoluble in water and alkaline aqueous media. Thymol iodide is described as a powder, and also as crystalline. No information on morphology or particle size was located. The non-aqueous solubility of thymol iodide could impact the type of vehicle used to compound topical products.

6. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

The API is neither poorly characterized nor difficult to characterize.

Conclusions: Thymol iodide appears to be well-characterized and easily identified. Thymol iodide is available from multiple sources world-wide, and has appeared in scientific/chemical literature for over 100 years. Suppliers of thymol iodide (including Sigma-Aldrich) include a certificate of analysis with shipped bulk, which includes assay, identification (IR, UV), and appearance. The synthesis for thymol iodide is logical and involves condensation of thymol and iodine/iodide. Thymol iodide is stable when stored in sealed containers, but is labile to heat, light, and oxidation; the substance is not aqueous-soluble. Thymol iodide is well-characterized, physically and chemically, such that it is appropriate for use in compounding.

B. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

The following information is summarized from review of Hazardous Substances Data Bank (HSDB), Chemical Abstracts Service (CAPLUS), and Excerpta Medica dataBASE (EMBASE).

a. Pharmacology of the drug substance

Thymol iodide (1% aqueous solution of the iodophore iodisol CAS# 552-22-7) is an effective in vitro antiseptic for vegetative forms of both gram positive and gram negative microorganisms (Podstatova and Podstata 1978).

b. Safety pharmacology

No information available.

c. Acute toxicity

No information available.

d. Repeat dose toxicity

No information available.

e. Mutagenicity

Thymol iodide (5000 µg/plate) was not mutagenic when tested in a reverse gene mutation test conducted with *Salmonella typhimurium* strains TA 98 and TA 100 in either the absence or presence of metabolic activation (Orstavik and Hongslo, 1985). No genotoxicity testing is available to assess the clastogenic potential of thymol iodide.

f. Developmental and reproductive toxicity

No information available.

g. Carcinogenicity

No component of thymol iodide at levels greater than or equal to 0.1% has been identified as a carcinogen by IARC, ACGIH, NTP, or OSHA.

h. Toxicokinetics

No information available.

Conclusions: Although the available nonclinical information is consistent with inclusion on the 503A list for topical drug products, the toxicity of thymol iodide has not been adequately evaluated.

2. *Human Safety*

a. Reported adverse reactions

An extensive literature search involving multiple databases, including PubMed, Embase, Web of Science, Scifinder, Pharmapendium, and DIOGENES Regulatory Updates database on ProQuestDocuments, revealed only limited information regarding thymol iodide with much of it dating from before 1990. In addition, the literature search retrieved no articles regarding antimicrobial properties or dental uses.

“The Practice of Pharmacy” by Joseph Price Remington (1936 edition) reports that thymol iodide was used in antiseptic surgery as a substitute for iodoform and as an external application to ulcerations in various skin conditions. One case of dermatitis from aristol (thymol iodide) is reported by Amsden (1910). A 27-year-old woman delivered a healthy child, and there was a superficial laceration of the perineum, closed by silkworm-gut suture. Aristol was used as adusting powder and 24 hours later a maculo-papular eruption appeared affecting primarily the extensor surfaces of the knees and elbows, thighs and lower back, accompanied by intense itching. The author states that the eruption promptly subsided on withdrawal of the aristol and no other probable cause could be assigned for the appearance of the eruption. The author concludes that the common use of this preparation as a local application might infrequently be followed by dermatitis in susceptible individuals.

Steingart (1992) reports empiric measures used in early attempts to treat sickle cell anemia including the administration of iodide, arsenic, thymol and the application of boric acid ointment of leg ulcers. No information is provided regarding adverse events.

Litton et al., (1973) report the application of thymol iodide powder by plastic surgeons after face peeling. Tape is applied after the peel then after tape removal thymol iodide powder is applied. This is described as an accepted procedure as of the date of the article in 1973. No information is provided regarding adverse events. Articles by Baker (1962) and Ludin (1974) report on a similar practice. No information is provided regarding adverse events.

Talc has been used for pleurodesis, which is obliteration of the pleural cavity by inducing adherence of the visceral and parietal pleural layers (as by the use of sclerosing agents or surgical abrasion) especially to treat pleural effusion, pneumothorax, and chylothorax. Iodine is occasionally included when talc pleurodesis is performed. A paper by Kennedy and Sahn (1994) includes a report of an allergic reaction following the use of iodinated talc for pleurodesis. The composition of the iodized talc is not reported. Iodized talc may or may not contain thymol iodide. When papers are discussed in this review it will be made clear whether the iodized talc includes thymol iodide. Webb et al., (1992) report

a series of 34 patients who underwent iodized talc pleurodesis. The slurry used contained 50 ml saline, 20 ml of 1% lidocaine, 5 grams of talc, and 3 grams of thymol iodide powder. The authors reported no adverse events related specifically to the pleurodesis agent used.

Additional information:

NDA's approved between January 1939 and April 1940

Records were retrieved on 5 NDA's, which required a showing of safety for approval:

1. NDA 2146 for "A.B.S. Professional Foot Powder" with active ingredients thymol iodide 20GR/3OZ, boric acid 120GR/3OZ, and alum 240GR/3OZ. Approved March 13, 1940. Applicant: A. B. Salander. Indication from labeling: "Relieves that distressing condition of excessive perspiration of the feet, accompanied by offensive odor. It is soothing and tends to alleviate minor irritations caused by the above condition."
2. NDA 1310 for "Pop Eckler's Majik Foot Powder," which contains menthol 1%, thymol iodide 5%, salicylic acid 2%, benzoic acid 2%, boric acid 10%, and fuller's earth. Approved solely with respect to safety September 6, 1939. Applicant Garner L. Eckler. Indication from labeling: "Aids to Relieve: Athlete Foot, Ringworm, Itching, Tired Burning, Aching Perspiring Feet. Cooling – Refreshing, Stops Odor" However, FDA stated at the time that the references to tired or aching feet should be deleted from labeling.
3. NDA 962 for "Duleet Powder," which contains soda bicarbonate, alum, menthol, thymol iodide, formaldehyde, soda benzoate, calcium carbonate, and talcum. Approved June 17, 1939. Applicant: R.G. Dunwody & Sons, Inc. Indication from labeling: "For relief of odors and irritation due to perspiring feet."
4. NDA 364 for "Pellisan Antiseptic Powder," which contains paraformaldehyde, benzocaine 5%, thymol iodide 10%, benzoic acid 10%, boric acid 20%, zinc stearate, zinc oxide 5%, and bismuth subnitrate 5%. Approved January 21, 1939. Applicant: Logan Laboratories, Inc. Indication from labeling: "For controlling the symptoms of certain forms of Athlete's Foot" "Promotes healing of minor cuts, scratches, heat rash & chafing,"
5. NDA 260 for "Surg-O," which contains benzocaine 5 gr/oz, thymol iodide 1 dr, guaiacol 5 minims, phenol 1/2%, clove oil, and anhydrous lanolin. Approved January 7, 1939. Applicant: Kay Specialty Company. Indication from labeling: "Recommended after extraction to protect the socket from the contamination by saliva and to alleviate the irritation of the exposed nerve ends."

Pertaining to thymol and iodide

Thymol: Produces gastric pain, nausea, vomiting, central hyperactivity. occasionally convulsions, coma, cardiac and respiratory collapse (Gosselin et al., 1976,p. II-51)

Iodide salts: 3 = moderately toxic: Probable oral lethal dose (Human), between 1 ounce and 1 pint (or 1 lb) for 70 kg person (150 lb) (Gosselin et al., 1976,p. II-78)

b. Clinical trials assessing safety

Pleurodesis:

Webb et al., (1992) report a series of 34 patients who underwent iodized talc pleurodesis. See Human Safety, B.2, above.

Jacobi et al., (1998) report on a prospective trial wherein talc pleurodesis was performed in 50 patients with recurrent pleural effusions. The pleurodesis agent consisted of 5 mg of talc, 3 mg of thymol iodide, 0.5 ml of 1% xylocaine/kg body weight and 30 ml of 0.9% saline solution. The authors report that talc pleurodesis was well tolerated in all patients. Bilateral chest pain developed in one patient, which was not attributed to the pleurodesis. Postoperative complications, such as infection, respiratory distress syndrome or dyspnea, did not occur in any patient.

Türler et al., (1997) report on a series of 43 patients treated with a suspension of 5 g talc with 3 g thymol iodide via chest tube. The authors state that they used iodized talc to keep the talc sterile. The authors describe the pleurodesis procedure as being well tolerated without major complications in all cases.

Available literature does not describe clinical trials assessing safety of thymol iodide as an antiseptic in surgery or on wounds or ulcers in various skin conditions.

c. Pharmacokinetic data

No human pharmacokinetic information for thymol iodide is reported in the literature.

d. The availability of alternative approved therapies that may be as safe or safer

Regarding use as an antiseptic in surgery and use as an external application to wounds or ulcers in various skin conditions, approved and OTC products are available. Approved products include NDA 21669 2% Pre-Op prep (Chlorhexidine gluconate) (“Helps reduce bacteria that can cause skin infection/skin prep prior to surgery”) and NDA 20832 chlorhexidine gluconate/isopropyl alcohol (“Healthcare antiseptic help to reduce bacteria that can cause skin infection”). OTC products include Polysporin, Neosporin, and Bacitracin ointments. For treatment of malignant pleural effusions, approved therapies include talc (NDA 20587 and NDA 21388) and bleomycin (ANDAs 065031, 065033, 065185).

Conclusions: Based on a review of the literature and the fact that NDAs containing this active ingredient were approved based upon a finding of safety, thymol iodide appears to be relatively safe. Reports indicate that it has been used without major complications. The one adverse event reported did not raise significant safety concerns.

C. Are there concerns about whether a substance is effective for a particular use?

1. Reports of trials demonstrating effectiveness of the bulk drug substance as it is used in drug products

The available literature does not describe controlled clinical trials demonstrating effectiveness of thymol iodide.

2. Any clinical evidence of effectiveness, or lack of effectiveness, of drug products with the bulk drug substance

In the Webb et al., (1992) report referenced above, the authors reported no signs of reaccumulated pleural effusion existed in any of the patients. The authors conclude that in their study, intrapleural instillation of a slurry of iodized talc is a safe, adequate, and effective treatment for control of neoplastic or benign pleural effusions.

In the Türler et al., (1997) report referenced above, the authors state that the success rate among patients who survived more than 1 month was 100% after the 1st month, 97.5% after 2 months, and 92.5% after 3 months. None of the survivors after 3 months developed significant pleural reaccumulations. The authors conclude that iodized talc pleurodesis is an excellent tool in the palliative management of malignant pleural effusions.

Jacobi et al., (1998) report that successful treatment occurred in 31 patients (94%) having malignant effusions. For those having benign effusions, talc pleurodesis was successful in all patients. The authors conclude that pleurodesis with iodized talcum slurry is a simple and inexpensive method with high efficacy in controlling malignant and non-malignant pleural effusions.

Thompson et al., (1998) report a series of 15 patients with malignant pleural effusions treated with an iodized talc slurry. The median follow-up on all patients until death was 6 months (range 1-20). The probability of control of effusion as determined by the method of Kaplan-Meier was 81% (SEM 9.7%). The authors conclude that iodized talc slurry instilled through a small-bore pigtail catheter is a safe, economical and effective treatment for pleural effusions.

3. Any anecdotal reports of effectiveness, or lack of effectiveness, of drug products with the bulk drug substance

See Human Safety, section B.2., above.

4. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

Most of the products compounded with thymol iodide are presumed to be used topically as an antiseptic in surgery and as an external application to ulcerations in various skin conditions. For pleurodesis, iodized talc, which contains thymol iodide, is used to treat malignant and benign pleural effusions. Both malignant and benign effusions reduce the quality of life for patients by pain, dyspnea, cough, and pulmonary dysfunction. Pleural effusions are serious and can be life-threatening.

5. *Whether there are any alternative approved therapies that may be as effective or more effective*

As discussed above, approved products include NDA 21669 2% Pre-Op prep (Chlorhexidine gluconate) (“Helps reduce bacteria that can cause skin infection/skin prep prior to surgery”) and NDA 20832 chlorhexidine gluconate/isopropyl alcohol (“Healthcare antiseptic help to reduce bacteria that can cause skin infection”). OTC products include Polysporin, Neosporin, and Bacitracin ointments.

Pleural effusions have been treated with insertion of a chest tube with and without instillation of various agents, including radioactive, biological, and other chemical substances (Jacobi et al., 1998). Pleurectomy by thoracotomy and thoracoscopy have been performed with varying degrees of efficacy. Pleurectomy is associated with high morbidity. For treatment of malignant pleural effusions, approved therapies include talc (NDA 20587 and NDA 21388) and bleomycin (ANDAs 065031, 065033, 065185).

Conclusions: Clinical data are present suggesting efficacy for the use of thymol iodide in the treatment of pleural effusions. However, there are FDA-approved products, talc and bleomycin, available to treat malignant pleural effusions, and use of an approved product is preferable to using a compounded product about which nothing is known about its safety, efficacy, or quality. Talc is also reported to be used off-label for benign pleural effusions (Kennedy and Sahn, 1994, Sudduth and Sahn, 1992). Data regarding effectiveness for thymol iodide in compounding for use on wounds or ulcers in various skin conditions is limited. Mostly historical, anecdotal uses are reported.

D. Has the substance been used historically in compounding?

1. *Length of time the substance has been used in pharmacy compounding*

Thymol iodide (aristol) has been reported to be on the market as early as the 1890s (Woollett, 1921). Literature describes uses in compounding dating from the 1910s and 1930s (Amsden 1910, Remington 1936).

2. *The medical condition(s) it has been used to treat*

See Human Safety, section B.2. As discussed in the studies referenced in that section, thymol iodide has been used as a substitute for iodoform, as an external application to

ulcerations in various skin conditions, in powder form by plastic surgeons after face peeling, and to treat pleural effusions.

As discussed above, five NDAs for substances that included thymol iodide were approved from 1939 to 1940. Indications included relieving foot odor, perspiration, and irritation, relieving symptoms of athlete's foot and for use in dentistry after tooth extraction to protect the socket from contamination and alleviate irritation of exposed nerve ends.

3. *How widespread its use has been*

The literature suggests that thymol iodide has had some use in compounding. From the literature it is difficult to say how many patients have been using thymol iodide on a yearly basis.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

We found no evidence that thymol iodide is marketed in other countries. Sources examined include: Micromedix with a link to Martindale's, the British, European, Japanese, Chinese (People's Republic), and Indian pharmacopoeias.

Conclusions: Although information on the historical use of thymol iodide in compounding is not extensive, use appears to have been present for application after face peeling, as a dusting powder after surgery, in pleurodesis, and for the relief of symptoms of athlete's foot as well as foot odor and irritation. Thymol iodide also appears to have been used in dentistry after tooth extraction.

RECOMMENDATION

We have reviewed the physiochemical characteristics, safety, effectiveness, and historical use in compounding for thymol iodide. Based on these factors, we recommend that thymol iodide be placed on the list of bulk substances allowed for compounding. Thymol iodide is well-characterized, physically and chemically, such that it is appropriate for use in compounding. Regarding nonclinical information, toxicity is not reported but has not been adequately evaluated. Thymol iodide is not known to be a carcinogen. According to the literature, historical uses of thymol iodide include application after face peeling, as a dusting powder after surgery, and for pleurodesis, among others. Significant adverse events from these uses are not described. Although data for the effectiveness of thymol iodide in compounding are somewhat limited, efficacy is suggested for the use of thymol iodide in treatment of pleural effusions, both benign and malignant. It should be noted that approved products, talc and bleomycin, are available for treatment of malignant pleural effusions, and use of talc has been reported, off-label, in the treatment of benign pleural effusions.

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Nonclinical References

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A. INGREDIENT NAME:

THYMOL IODIDE

B. Chemical Name:

Dithymol Diiodide, Iodothymol

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Specifications)</i>	<i>(Results)</i>
Assay:	43.0% min.	44.08%

E. Information about how the ingredient is supplied:

Reddish-brown, tasteless powder

F. Information about recognition of the substance in foreign pharmacopeias:

Port. and Swiss.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

H. Information about dosage forms used:

It has been used in dusting powders and ointments, and in dental root filling.

I. Information about strength:

J. Information about route of administration:

1998-3454B1-02-41-BDL78

K. Stability data:

Stable

Loses iodine on prolonged exposure to light.

Gives off purple iodine vapors when heated above 100°

L. Formulations:

M. Miscellaneous Information:

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TITLE: Management of patients with sickle cell disease.

AUTHOR: Steingart R

AUTHOR AFFILIATION: Division of Hematology/Oncology, Baystate Medical Center, Springfield, Massachusetts.

SOURCE: Med Clin North Am 1992 May;76(3):669-82

NLM CIT. ID: 92252446

ABSTRACT: The ever-increasing body of information regarding the molecular pathogenesis of sickle cell disease has raised expectations that a specific and effective therapy could be devised to inhibit polymerization of hemoglobin S. Despite an intense international research effort, this goal has not yet been realized. Supportive care continues to be the mainstay in the management of patients with sickle cell anemia. Empiric measures were used in early attempts to treat sickle cell anemia. Herrick reported gratifying improvement after "rest, nourishing food, the administration of iodide, arsenic, thymol and the application of boric ointment to leg ulcers." Many of these suggestions are similar to those of today. Several factors have significantly improved the prognosis of patients with this disease. Improved medical care, genetic counseling, and universal neonatal screening have directly resulted in improved outcome. Molecular biologic techniques have allowed us to approach this disease in a pathophysiologic way. Now we can envision antenatal diagnosis with the use of molecular probes and treatment by gene amplification. Still, however, the most important and challenging link in the chain between the biology of the disease and the clinical sequelae is an astute and interested physician who must remain objective at all times.

MAIN MESH SUBJECTS: Anemia, Sickle Cell/COMPLICATIONS/*DIAGNOSIS/*THERAPY

ADDITIONAL MESH SUBJECTS: Diagnosis, Differential Human

PUBLICATION TYPES: JOURNAL ARTICLE REVIEW REVIEW, TUTORIAL

LANGUAGE: Eng

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TITLE: Iodized talc pleurodesis for the treatment of pleural effusions.

AUTHOR: Webb WR; Ozmen V; Moulder PV; Shabahang B; Breaux J

AUTHOR AFFILIATION: Department of Surgery, Tulane University School of Medicine, New Orleans, LA 70112.

SOURCE: J Thorac Cardiovasc Surg 1992 May;103(5):881-5; discussion 885-6

NLM CIT. ID: 92236136

ABSTRACT: This prospective study was designed to determine the efficacy of iodized talc pleurodesis in patients with pleural effusions. Thirty-four patients underwent this treatment (three bilaterally) between October 1, 1989, and March 31, 1991. All patients had to have complete or nearly complete lung reexpansion after tube thoracostomy with fluid drainage less than 100 ml in 24 hours. A slurry containing 5 gm of talc and 3 gm of thymol iodide was instilled into the pleural space through the chest tube. Chest tubes were removed after complete reexpansion and clearing of the effusions, usually in 3 to 5 days. The patients' ages ranged from 26 to 88 years (average 50 years). Eighteen patients had lung carcinoma, two had mesothelioma, and one each had carcinoma of the ovary, breast, or anorectum, multiple myeloma, schwannoma, or Hodgkin's lymphoma. Two patients had an unknown adenocarcinoma primary and five other patients had acquired immunodeficiency syndrome. One patient had congestive heart failure. Nineteen patients had left, 12 had right, and three had bilateral pleural effusions. The effusion was serosanguineous in 26 and serofibrinous in eight patients. Serial chest radiography showed complete response in all patients. The period of follow-up ranged from 1 to 21 (average 4.9) months, with no recurrences. Twenty-three patients have died during the follow-up period, and there was no sign that reaccumulated pleural effusion existed in any, despite clinical evidence of systemic tumor progression. These observations indicate that intrapleural instillation of a slurry of iodized talc is a safe, adequate, and effective treatment for control of neoplastic or benign pleural effusions.

MAIN MESH SUBJECTS: *Chest Tubes
Pleural Effusion/EPIDEMIOLOGY/ETIOLOGY/*THERAPY
Pleural Effusion, Malignant/EPIDEMIOLOGY/ETIOLOGY/*THERAPY
*Talc

ADDITIONAL MESH SUBJECTS: Acquired Immunodeficiency Syndrome/COMPLICATIONS
Follow-Up Studies
Human
Iodides
Lung Neoplasms/COMPLICATIONS
Middle Age

Prospective Studies

Thymol

Time Factors

PUBLICATION JOURNAL ARTICLE

TYPES:

LANGUAGE: Eng

REGISTRY 0 (Iodides)

NUMBERS: 14807-96-6 (Talc)

89-83-8 (Thymol)

THYMOL IODIDE

Toxicity has not been thoroughly investigated.

May cause irritation to eyes, skin and lungs. May cause CNS hyperactivity and convulsions and coma, cardiac and respiratory collapse. Probable lethal oral dose in human is between 30g and 500 g.

Has been used as an absorbant and protective.

REFERENCES

1. Steingart R. Management of patients with sickle cell disease. *Med Clin North Am* 1992; 76(3):669-82.
2. Webb WR, Ozmen V, Moulder PV, et al. Iodized talc pleurodesis for the treatment of pleural effusions. *J Thorac Cardiovasc Surg* 1992; 103(5):881-5.

Tab 78

Silver Protein Mild Nominations

Submitted electronically via www.regulations.gov

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No.: FDA-2013-N-1525: *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations*

Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

A handwritten signature in black ink, appearing to read 'Steve Pfister', with a long horizontal flourish extending to the right.

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Nomination from National Community Pharmacists Association, September 30, 2014

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format(s)	Recognition in Pharmacopeias	Final Compounded Formulation Dosage Form(s)	Final Compounded Formulation Strength	Final Compounded Formulation Route of Admin	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
Silver protein, Mild (Colloidal silver)	Silver, Colloidal; Silver Nucleate; Mild Protargin	Silver protein; colloidal silver	3M4G523W1G	From PCCA Database MSDS: Product is 19-23% by weight and stable under normal temperatures and pressures. Should be protected from strong oxidizing agents	Powder	Silver sulfadiazine in USP	Various	Various	Various	Federal Register 1999, FDA. OTC Active Ingredients List. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf Accessed 2-10-2014, last updated April 7, 2010	ophthalmic anti-infective Mild silver protein is well characterized chemically. It has been used to treat conjunctivitis and by ophthalmologists as a preoperative chemical preparation of the eye. At doses reported in the literature for these indications, mild silver protein appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. When mild silver protein is administered internally, however, it can cause serious untoward side effects, including agrarian, permanent ashen-gray discoloration of the skin, conjunctiva, and internal organs (see 61 FR 53685, October 15,1996). At this time, FDA is deferring decision on this substance because questions were raised at the inaugural meeting of the Pharmacy Compounding Advisory Committee about its efficacy. FDA is soliciting public input on this issue and any other issues that are relevant to the agency's consideration of mild silver protein for the bulk drugs list. C. Nominated Drug Substances Still Under Consideration for the Bulk Drugs List The following 10 drug substances were nominated for inclusion on the proposed bulk drugs list. However, for the reasons described in section III.C of this document, they are still under review by the agency



Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

“List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act”

Dear Sir or Madam,

Fagron appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

We hereby nominate the bulk drug substances in the attached spreadsheets for FDA’s consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

None of these items appear on an FDA-published list of drugs that present demonstrable difficulties for compounding. In addition, none are a component of a drug product that has been withdrawn or removed from the market because the drug or components of the drug have been found to be unsafe or not effective.

We include references in support of this nomination for your consideration.

Thank you for your consideration. If Fagron can answer any questions, please contact me (j.letwat@fagron.com; 847-207-6100).

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs



Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlsx file)

7-Keto Dehydroepiandrosterone
Acetyl-D-Glucosamine
Aloe Vera 200:1 Freeze Dried
Astragalus Extract 10:1
Beta Glucan (1,3/1,4 -D)
Boswellia Serrata Extract
Bromelain
Cantharidin
Cetyl Myristoleate Oil
Cetyl Myristoleate 20% Powder
Chrysin
Citrulline
Dehydroepiandrosterone
Deoxy-D-Glucose (2)
Diindolylmethane
Domperidone
EGCg
Ferric Subsulfate
Glycolic Acid
Glycosaminoglycans
Hydroxocobalamin Hydrochloride
Kojic Acid
Methylcobalamin
Nicotinamide Adenine Dinucleotide
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)
Ornithine Hydrochloride
Phosphatidyl Serine
Pregnenolone
Pyridoxal 5-Phosphate Monohydrate
Pyruvic Acid
Quercetin
Quinacrine Hydrochloride
Ribose (D)
Silver Protein Mild
Squaric Acid Di-N-Butyl Ester
Thymol Iodide
Tranilast
Trichloroacetic Acid
Ubiquinol 30% Powder

Fagron

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What is the name of the nominated ingredient?	Silver Protein Mild
Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?	<p>Yes, Silver Protein Mild is an active ingredient as defined in 207.3(a)(4) because when added to a pharmacologic dosage form it produces a pharmacological effect.</p> <p>Isenberg, S., Apt, L., & Yoshimuri, R. (1983). Chemical preparation of the eye in ophthalmic surgery: II. Effectiveness of mild silver protein solution. Archives of Ophthalmology, 101(5), 764.</p> <p>Isenberg, S. J., Apt, L., Yoshimori, R., & Khwarg, S. (1985). Chemical preparation of the eye in ophthalmic surgery: IV. Comparison of povidone-iodine on the conjunctiva with a prophylactic antibiotic. Archives of ophthalmology, 103(9), 1340.</p>
Is the ingredient listed in any of the three sections of the Orange Book?	The nominated substance was searched for in all three sections of the Orange Book located at http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm . The nominated substance does not appear in any section searches of the Orange Book.
Were any monographs for the ingredient found in the USP or NF monographs?	The nominated substance was searched for at http://www.uspnf.com . The nominated substance is not the subject of a USP or NF monograph.
What is the chemical name of the substance?	-

Nomination from Fagron, September 30, 2014

What is the common name of the substance?	Albumosesilber;Argent colloidal (colloidal);Argent Colloidal par Voie Chimique (colloidal);Argent, protéinate d';Argentoproteinum;Argentoproteinum Mite (mild);Argentum Colloidale (colloidal);Argentum colloidal (colloidal);Argentum proteicum;Argentum Proteinicum;Argentum Vitellanicum (mild);Collargol (colloidal);Colloidal Silver (colloidal);Hopea, kolloidinen (colloidal);Hopeaproteini;Kolloides Silber (colloidal);Mild Protargin (mild);Mild Silver Protein (mild);Mild Silver Protein (mild);Plata Coloidal (colloidal);Plata coloidal (colloidal);Plata, proteína de;Prata Coloidal (colloidal);Protargolum;Proteína de plata fuerte;Proteína de plata ligera (mild);Proteinato de Plata;Proteinato de Prata;Silver, kolloidalt (colloidal);Silver Nucleinate (mild);Silver Protein;Silver Vitellin (mild);Silverprotein;Srebra proteinicum;Srebro koloidalne (colloidal);Stríbro koloidní (colloidal);Strong Protargin;Strong Protein Silver;Strong Silver Protein;Vitelinato de Plata (mild);Vitelinato de Prata (mild)
Does the substance have a UNII Code?	None found.
What is the chemical grade of the substance?	no grade
What is the strength, quality, stability, and purity of the ingredient?	Description: Borwn or black flakes or granulated powder Solubility: Conforms Identification: Conforms Identification A: Conforms Identification B: Conforms Identification C: Conforms Ionic Silver: Conforms Assay: 12.0 - 23.0%
How is the ingredient supplied?	powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	Aust, Belg, Fr, It Jpn, Pol
Has information been submitted about the substance to the USP for consideration of monograph development?	No USP Monograph Submission found.
What dosage form(s) will be compounded using the bulk drug substance?	Ophthalmic solution
What strength(s) will be compounded from the nominated substance?	1-20%
What are the anticipated route(s) of administration of the compounded drug product(s)?	Ophthalmic

<p>Are there safety and efficacy data on compounded drugs using the nominated substance?</p>	<p>Isenberg, S., Apt, L., & Yoshimori, R. (1983). Chemical preparation of the eye in ophthalmic surgery: II. Effectiveness of mild silver protein solution. Archives of Ophthalmology, 101(5), 764.</p> <p>Isenberg, S. J., Apt, L., Yoshimori, R., & Khwarg, S. (1985). Chemical preparation of the eye in ophthalmic surgery: IV. Comparison of povidone-iodine on the conjunctiva with a prophylactic antibiotic. Archives of ophthalmology, 103(9), 1340.</p>
<p>Has the bulk drug substance been used previously to compound drug product(s)?</p>	<p>Yes, Silver Protein Mild Solution</p> <p>Isenberg, S., Apt, L., & Yoshimori, R. (1983). Chemical preparation of the eye in ophthalmic surgery: II. Effectiveness of mild silver protein solution. Archives of Ophthalmology, 101(5), 764.</p> <p>Isenberg, S. J., Apt, L., Yoshimori, R., & Khwarg, S. (1985). Chemical preparation of the eye in ophthalmic surgery: IV. Comparison of povidone-iodine on the conjunctiva with a prophylactic antibiotic. Archives of ophthalmology, 103(9), 1340.</p> <p>Lansdown, A. B. G. "Silver I: its antibacterial properties and mechanism of action." Journal of wound care 11.4 (2002): 125-130. http://www.internurse.com/cgi-bin/go.pl/library/abstract.html?uid=26389</p> <p>Silver, Simon. "Bacterial silver resistance: molecular biology and uses and misuses of silver compounds." FEMS microbiology reviews 27.2-3 (2003): 341-353. http://onlinelibrary.wiley.com/doi/10.1016/S0168-6445(03)00047-0/full</p> <p>Fung, Man C., and Debra L. Bowen. "Silver products for medical indications: risk-benefit assessment." Clinical Toxicology 34.1 (1996): 119-126. http://informahealthcare.com/doi/abs/10.3109/15563659609020246 Lansdown, A. "Silver in health care: antimicrobial effects and safety in use." (2006): 17-34. http://www.karger.com/Article/Abstract/93928</p>
<p>What is the proposed use for the drug product(s) to be compounded with the nominated substance?</p>	<p>Used as an antibacterial for the eye</p>

Nomination from Fagron, September 30, 2014

What is the reason for use of a compounded drug product rather than an FDA-approved product?	There are FDA approved antibiotic preparations that can be used for ophthalmic surgeries. However, antibiotics are subject to bacterial resistance. Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections. (http://www.cdc.gov/drugresistance/) There are Each year, 3 million Americans that undergo cataracts surgery [Source: "Cataract Statistics." Statistic Brain RSS. N. p., n. d. Web. 27 Aug. 2014.] This leads to elevated exposure to antibiotics and increased chance for resistance. Silver protein offers an option that is resistance free.
Is there any other relevant information?	All relevant information was expressed in the above questions



September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA's request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS

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Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created a series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency's activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee prior to the implementation and issuance of regulations including the creation of the bulk ingredient list.

(2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

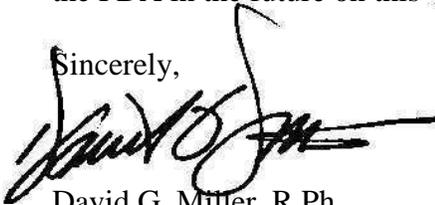
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

A handwritten signature in black ink, appearing to read "David G. Miller", with a large, stylized flourish extending upwards and to the right.

David G. Miller, R.Ph.
Executive Vice President & CEO



Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Silver protein mild
Chemical/Common Name	Silver, Colloidal; Silver Nucleate; Mild Protargin
Identifying Codes	9015-51-4
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	Silver sulfadiazine in USP

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	Federal Register 1999

Past and Proposed Use The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.

Tab 79

FDA Review of Silver Protein Mild



DATE: February 4, 2015

FROM: David Lewis, PhD
Chemist (CMC Reviewer), Office of New Drug Quality Assessment

Aaron Ruhland, PhD
Toxicologist (Pharmacology Reviewer), Division of Transplant and
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THROUGH: Lori Kotch, PhD
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William Boyd, MD
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Renata Albrecht, MD
Director, Division of Transplant and Ophthalmology Products, Office of
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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Silver Protein Mild for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

Silver protein mild, more commonly known as Mild silver protein, was nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic (FD&C) Act. Silver protein mild is identified in the nominations as an anti-infective agent for ophthalmic use.

The term *silver protein mild* describes a variety of preparations. The most famous commercial product described as silver protein mild was Argyrol, which was the trademark for a compounded solution comprising denatured pharmaceutical-grade protein and elemental silver, used for ophthalmic purposes. Argyrol was introduced to the market in 1902 and was widely

available for many decades. The original Argryol was manufactured and distributed by Barnes and Hille and later by Mulford and Company. While Argryol was being marketed, it was essentially the only silver protein mild available and the only preparation in use for ophthalmic indications. By 1996, the original Argryol product was no longer manufactured or distributed. A current online search suggests there are many currently available preparations purported to contain silver-protein adducts, some of which are marketed using the name Argryol; Argryol S.S. Mild silver protein, silver protein mild and Colloidal Silver.¹

We have reviewed the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. Based on those factors, for the reasons discussed below, we recommend that Silver Protein Mild *not* be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?

During its 1999 review of products used in compounding, FDA reviewed the product Argryol. At the time, this specific product was considered well characterized. In 1999, Argryol had only recently ceased marketing and had essentially been the only silver protein mild product marketed for ocular use during the 20th century. Today Argryol remains unmarketed, and the term *silver protein mild* is being used to describe a wide range of products.

1. *Stability of the API and likely dosage forms*

Unknown, because *silver protein mild* is being used for a variety of products. The nomination of this product identifies the dosage form as “various,” the strength as “various” and the route of administration as “various.”

2. *Probable routes of API synthesis*

Unknown, because *silver protein mild* is being used for a variety of products. The nomination of this product identifies the dosage form as “various,” the strength as “various” and the route of administration as “various.”

3. *Likely impurities*

Unknown, because *silver protein mild* is being used for a variety of products.

4. *Toxicity of those likely impurities*

Unknown, because *silver protein mild* is being used for a variety of products.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism;*

The preparations advertised as *silver protein mild*, Argyrol, Protargol, etc. list physicochemical claims regarding material purity, particle size, water quality, etc., but we do not have sufficient information to evaluate these claims.

Conclusions: The bulk substance designated *silver protein mild* cannot be considered to be well identified, well characterized, or controlled in any consistent manner because the name is not sufficiently precise, and many products could fit the common definition of *silver protein mild*. Any products containing elemental silver and a natural substance designated as a protein (representative descriptions are albumin, gelatin, and casein) can be considered to be silver protein mild.

B. Are there concerns about the safety of the substance for use in compounding?

1. *Nonclinical Assessment*

The nomination has not identified any nonclinical pharmacology or toxicology studies of silver protein mild, nor have any been identified in an on-line literature search of silver protein mild or Argyrol. In the absence of specific product identification, the following nonclinical review focuses on silver ions.

Pharmacology: The antimicrobial properties of silver ion on pathogenic organisms are dependent on release of biologically active silver ion (Ag^+) from metallic silver, silver nitrate, silver sulfadiazine, silver protein complexes, and other silver compounds, formulations, and devices. Silver ion denatures DNA, RNA and proteins, disrupts membranes, and can inactivate enzymes through binding with sulfhydryl, amino, carboxyl, phosphate, and imidazole groups. It is also thought that silver nanoparticles may directly interact with cellular membranes.

Safety Pharmacology: No formal safety pharmacology studies of silver protein mild or silver were provided in the nomination and none were found in the literature. Information was not found about cardiovascular safety pharmacology, respiratory safety pharmacology or neurobehavioral safety pharmacology.

In animal studies, deposition of granules that may contain silver were reported in tissues of the central nervous system and changes in behavior have been reported. Deposition occurred particularly in areas with direct exposure to blood, though no study was found that specifically focused on the distribution of silver throughout the brain. Mice exposed to silver nitrate in drinking water (95 ppm) for 4 months showed deposits in the central nervous system and were less active (hypoactive) than unexposed controls.² Granular deposits were found in areas involved in motor control (i.e., red nucleus, deep cerebellar nuclei, motor nuclei of the brainstem), with lesser amounts in the basal ganglia, the anterior olfactory nucleus, and in the cortex in general. The decrease in activity could be attributable to factors unrelated to central nervous system function (such as loss of

appetite due to gastric effects, or general malaise). Exposure to silver as subcutaneously injected silver lactate (0.137 mg silver/kg/day) reduced overall volume of hippocampal cell groups within the brain of rats exposed during the first 4 weeks of life.³ To date, no conclusions have been made regarding a direct neurotoxic effect upon silver exposure.

Toxicity in vitro: Nanocrystalline silver particles were found to be cytotoxic to cultured keratinocytes and fibroblasts. Inhibition of cellular proliferation, changes in cellular morphology and induction of apoptosis were observed.⁴ In a fibroblast cell line, signs of oxidative stress were suggested by decreased glutathione (GSH) and super oxide dismutase (SOD) as well as increased lipid peroxidation.⁵ A study concluded that the in vitro hemolytic potential of unbound silver particles in human blood observed with nanoparticles compared with micron-sized particles may be related to their greater surface area, increased silver ion release, and direct interaction with RBCs.⁶

Acute toxicity (oral administration): In ICR mice orally administered colloidal silver nanoparticles at 5,000 mg/kg, no deaths, changes in general appearance, weight gain, water/food consumption, hematological analysis or any of the biochemical parameters examined were attributed to silver administration. Results indicated that the LD₅₀ of the colloidal silver nanoparticles was greater than 5,000 mg/kg.⁷

Acute toxicity (ocular administration): Single topical ocular administration of colloidal silver nanoparticles at up to 5,000 ppm did not induce any acute toxicological effects. Transient mild conjunctival irritation (Grade 1 conjunctivae irritation with hyperemia of some blood vessels in the conjunctivae) was reported in some animals treated with 5,000 ppm at 24 hours post-exposure. However, no ocular reaction was found after 48 hours post-exposure. Histopathology assessments were not made. Toxicokinetic data was not collected.⁷

Repeat dose oral toxicity: A 28-day study of silver nanoparticles in rats showed that doses of ≥ 300 mg/kg/day resulted in significantly increased alkaline phosphatase and cholesterol suggesting liver toxicity.⁸ Bile duct hyperplasia in response to oral silver administration has been reported. In another study, when administered as 222.2 mg/kg/day in drinking water for 37 weeks, silver nitrate decreased weight gain in rats. Weight loss first appeared at about 23 weeks with several animals reported to have lost weight rapidly and died. Body weight in the surviving animals was approximately 50% less than that of control rats drinking only distilled water. Deposition of silver within Bruch's membrane, the basement membranes of the choriocapillaris and the ciliary processes, and the stroma of the choroid and ciliary processes was also observed in these animals.⁹

In rats at an oral dose of 88.9 mg silver/kg/day, dose/duration dependent enlargement of the left ventricle increased over 9-29 months. Left ventricle size (expressed as a ratio of ventricle weight to body weight). Gross and histopathological examination revealed few scattered granular deposits in the heart. The authors suggest that the increase in ventricle size could be caused by hypertension.¹⁰

Repeat dose topical ophthalmic: Repeat-dose, topical, ocular toxicity studies in non-human animals were not found.

Mutagenicity / Genotoxicity: Studies have shown that silver nanoparticles (1, 25 or 100 µg/ml) create oxidative damage to DNA (8-oxo-7,8-dihydroguanine or 8-oxoG). Silver was not mutagenic in bacteria including several reference strains of Salmonella and E. coli.¹⁰ Studies demonstrated that silver induced DNA strand breaks in Chinese hamster ovary cells (10 µg/mL) and enhanced viral transformation of Syrian Hamster Embryo cells (0.06 mM).^{11,12} In rats, no differences in micronucleated polychromatic erythrocytes occurred after 1000 mg/kg/day silver nanoparticle exposure compared with controls.¹³ However, another study concluded that silver (30 µg/mL) demonstrated a weak positive response in an in vitro micronucleus test.¹⁰

Developmental and reproductive toxicity: Data on the effect of silver on fertility and fetal development were scarce. One study found that 88.9 mg silver/kg/day for 2 years as silver nitrate or silver chloride in drinking water had no effect on fertility in male rats.¹⁴ Another study in male rats found that single subcutaneous injections of 0.04 millimole/kg silver nitrate caused temporary histopathological damage to testicular tissue characterized as shrinkage, edema, and deformation of the epididymal tubules. Gradual recovery following the initial injection was reported even though daily injections continued. After 30-days, no effect on spermatogenesis was reported, though spermatozoa were observed with separated and pyknotic heads.¹⁵ In female rats orally administered 50 mg silver chloride on Days 1 – 20 of gestation, post-implantation lethality increased as well as the incidence of visceral abnormalities in the offspring. All newborns died within 24 hours of birth.

Carcinogenicity: Fibrosarcomas have been induced in rats following subcutaneous imbedding of silver foil. In this study, imbedded silver metal foils appeared to produce fibrosarcomas earlier and more frequently than other metal foils (steel, tantalum, tin, and vitallium) tested.¹⁶ Both positive and negative results for tumorigenesis have been reported following subcutaneous and intramuscular injection, respectively, of colloidal silver in rats.^{17,18}

Oral Pharmacokinetics: Silver compounds are absorbed readily by the inhalation and oral routes. The extent of oral absorption has been associated with transit time through the gastrointestinal tract. An oral dose of silver, following absorption, undergoes a first pass effect through the liver resulting in excretion into the bile, thereby reducing systemic distribution to body tissues. Rats, mice, and monkeys given silver nitrate in drinking water absorb less than 1% of the silver administered within 1 week, whereas in dogs up to 10% may be absorbed. In blood, silver ion may bind with albumins and macroglobulins. Histopathologic analysis of animals exposed to silver demonstrate preferential distribution within certain tissues of the body (liver, kidney, pancreas, skin, spleen, conjunctiva of the eyes, and, to a lesser degree, certain brain areas and muscle). Silver is deposited in the form of granules visible by light microscope. Within these tissues advanced accumulation of silver particles was found in the basement membrane of the glomeruli, the walls of blood vessels between the kidney tubules, the portal vein and

other parts of the liver, the choroid plexus of the brain, the choroid layer of the eye, and in the thyroid gland. The deposition of silver in tissues is the result of the precipitation of insoluble silver salts, such as silver chloride and silver phosphate.

Silver is eliminated from the body through the urine and feces. Some research suggests that silver is chelated and removed slowly by metallothioneins. It is thought that if this removal process is overwhelmed or impeded, argyria can result. Granules observed in the eyes and other tissues of rats exposed to silver nitrate in drinking water were dependent on the duration of exposure.

Conclusions: Silver protein mild has not been adequately characterized in formal nonclinical studies. Silver protein mild may be absorbed as nanoparticulate silver or as silver ion. Upon exposure to ionized silver, existing data suggest potential for cytotoxicity, hepatobiliary toxicity and neurotoxicity. Argyria and argyrosis of the ocular tissues as described in humans following administration of silver mild protein has not been adequately characterized in a nonclinical model.

2. *Human Safety*

a. Adverse reactions

Numerous articles and books have been written describing silver deposition of the conjunctiva, lacrimal sac, cornea and lens following administration of silver protein mild. The conjunctival deposits under the light microscopic are extracellular silver deposits in the connective tissue cells of the submucosa.¹⁹ The silver deposits in the cornea are located in Descemet's membrane¹⁹ and may occur with conjunctival involvement.²⁰ In the lacrimal sac, the silver is deposited in the mucosal epithelium²¹ In the lens, it may cause anterior subcapsular discoloration or in the nucleus.²² Most reported cases of argyrosis have occurred following at least 2 months of instillation.²³ However, Karcioğlu and Caldwell reported a case of ocular argyrosis after only one treatment with Argyrol eye drops.²⁴

Argyrosis is generally permanent and although it is not usually known to impair visual acuity, it has been associated with decreased night vision.²⁵ Decreased night vision has been correlated with increased levels of silver in both the conjunctiva and the cornea.

b. Alternative approved therapies

There are multiple alternative approved products on the market proposed for anti-infective agent for ophthalmic use.

Povidone iodine ophthalmic solution, 5%
Gentamicin ophthalmic solution, 0.3%
Gentamicin ophthalmic ointment, 0.3%
Tobramycin ophthalmic solution, 0.3%
Tobramycin ophthalmic ointment, 0.3%

Sulfacetamide sodium ophthalmic solution, 10%
 Neomycin, polymyxin B sulfate and gramicidin ophthalmic solution
 Trimethoprim sulfate and polymyxin B Sulfate ophthalmic solution
 Bacitracin and Polymyxin B ophthalmic ointment
 Chloramphenicol ophthalmic solution
 Chloramphenicol ophthalmic ointment
 Ciprofloxacin ophthalmic solution, 0.3%
 Ciprofloxacin ophthalmic ointment, 0.3%
 Norfloxacin ophthalmic solution, 0.3%
 Ofloxacin ophthalmic solution, 0.3%
 Levofloxacin ophthalmic solution, 0.5%, 1.5%
 Moxifloxacin ophthalmic solution, 0.5%
 Gatifloxacin ophthalmic solution, 0.5%
 Besifloxacin ophthalmic solution,
 Erythromycin ophthalmic ointment
 Azithromycin ophthalmic solution

Conclusions: Silver protein mild administered to the eye causes deposition of silver in multiple ocular structures. In addition to the discoloration, decreased night vision has been positively correlated with increasing amounts of silver deposited in the cornea and conjunctiva. There are multiple alternative approved products on the market without these adverse reactions.

C. Are there concerns about whether the substance is effective for a particular use?

Silver protein mild has been studied in two controlled studies as described below. In one study, silver protein mild was found to be numerically, although not statistically, inferior to having no treatment at all. In the second study, silver protein mild was found to be inferior to povidone iodine.

In 1983, Isenberg et al.,²⁶ published a study of 32 patients undergoing ophthalmic surgery. No patient had received pre-operative antibiotic therapy or had an infection at the time of surgery. Twenty microliters (1 drop) of 20% mild silver protein solution was instilled in the inferior conjunctival fornix of one randomly selected eye. The other eye was untreated. Hexachlorophene soap was applied equally to both eyelids, and to eyelid margins, cheeks, nose, eyebrow, and forehead. The inferior fornix of the eye into which the mild silver protein solution had been instilled was then irrigated with a normal saline solution, while the other eye had no irrigation.

		Mean±SD	
		Before preparation	After Eye Operation
Colonies	Untreated	183 ± 425	284 ± 571
	Mild silver protein	231 ± 687	323 ± 750
Species	Untreated	1.06 ± .83	1.41 ± .86
	Mild silver protein	1.06 ± .75	1.31 ± .77
Number of Eyes in which Culture was Sterile	Untreated	8	4
	Mild silver protein	7	5

"Although the number of colonies and species were greater after the preparation than before in both mild silver protein solution-treated and untreated eyes, in no case was the increase of actual numbers significant at the 5% level by Student's t test. The difference in the amount of increase of actual number in the untreated eye as opposed to the mild silver protein solution-treated eye also was not found to be significant at the 5% level. The pattern of sterile cultures before and after chemical preparation of the eye is given [above]. Of all the eyes in this study, only three of the 15 that were sterile before preparation remained sterile after preparation. The organisms cultured were diphtheroids, Staphylococcus epidermidis, Propionibacterium acnes, Candida albicans, and Klebsiella sp."

In 1991, Speaker and Menikoff published a study comparing protein silver mild and povidone iodine in patients scheduled to undergo cataract surgery. The study was an open-label, non-randomized, parallel trial comparing topical preoperative application of povidone-iodine versus silver protein mild (Argyrol) in the reduction of the incidence of endophthalmitis after intraocular surgery. During an 11-month period, topical 5% povidone-iodine was used to prepare the conjunctiva in 1 set of 5 operating rooms while silver protein solution was used in another set of 5 rooms. In all cases, surgeons continued to use their customary prophylactic antibiotics. A significantly lower incidence of culture-positive endophthalmitis ($p < 0.03$) was observed in the operating rooms using povidone-iodine (2 of 3489 or 0.06%) compared with those using silver protein solution (11 of 4594 or 0.24%).

Conclusions: Clinical trials fail to demonstrate efficacy of silver protein mild. In comparison to povidone-iodine, silver protein mild appears to be inferior. The nomination included by reference the article by Isenberg listed above. None of the other references identified in the nomination contained any clinical data. A literature search failed to identify any clinical trials demonstrating efficacy of silver protein mild.

D. Has the substance been used historically in compounding?

1. *Length of time the substance has been used in pharmacy compounding*

Silver protein mild, with the trademark Argyrol, was marketed from 1902 until 1996. It was introduced into the market prior to the enactment of the FD&C Act and sold with instructions to be administered topically to the eyes. It was never the subject of a new drug application.

2. *The medical condition(s) it has been used to treat*

Silver protein mild was used predominately for prophylaxis of potential ocular infections including pre-operatively.

3. *How widespread its use has been*

Silver protein mild was used widely until the introduction of antibiotics and other anti-infective agents for the eye. Its use declined precipitously following the introduction of ocular anti-infectives.

Conclusions: Silver protein mild was used widely for potential prophylaxis of ocular infections until the introduction of antibiotics and other anti-infective agents for the eye. Its use declined precipitously following the introduction of ocular anti-infectives.

RECOMMENDATION

Silver protein mild is **not recommended** to be included on the list of bulk drug substances allowed for use in compounding under section 503A. Although there is evidence of historic use of this substance silver protein mild is not well characterized, it was not effective in clinical trials, and chronic use may result in permanent discoloration of the conjunctiva, cornea, and/or lens.

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Mild Silver Protein

Alternative names: Argyrol, Protargol

Formulations:

OTC: 10% solution in 15 and 30 mL containers
Rx: 20% solution with EDTA in 1 mL dropperettes

Previous manufacturers:

Cooper Laboratories
IOLAB

Marketed Indications:¹ (Note: None of the indications have been "Approved indications")

1. Treatment of eye infections
2. Preoperatively in eye surgery.
3. Dye before surgical scrub as indicator of the adequacy of preparation.

Drug Interactions:

Sulfacetamide preparations are incompatible with silver preparations

Dosage and Administration:

Preoperatively: Instill 2 or 3 drops into eye(s). Rinse out with sterile irrigating solution.

Infections: Instill 1 to 3 drops into eye(s) every 3 or 4 hours for several days.

Packaging:

Tight, light-resistant containers.

Alternative Medications:

Gentamicin ophthalmic solution, 0.3%
Tobramycin ophthalmic solution, 0.3%
Sulfacetamide sodium ophthalmic solution, 10%
Neomycin, polymyxin B sulfate and gramicidin ophthalmic solution
Trimethoprim sulfate and polymyxin B Sulfate ophthalmic solution
Chloramphenicol ophthalmic solution, 0.5%
Ciprofloxacin ophthalmic solution, 0.3%
Norfloxacin ophthalmic solution, 0.3%
Ofloxacin ophthalmic solution, 0.3%

¹ Ophthalmic Drug Facts. Facts and Comparisons, St. Louis, MO. 1992. pp.106-107.

Regulatory History:

Mild Silver Protein (Argyrol) has been marketed since approximately 1910 and as such is not the subject of an approved New Drug Application (NDA). It was the subject of submissions by Cooper Laboratories, Inc. as part of the Ophthalmic Drug Products for Over-the-Counter Human Use Panel Review and subsequent rule-making.² Subsequent to the finding that there was insufficient data available to determine that mild silver protein was effective as an ophthalmic anti-infective, marketing was discontinued.

Background:

Therapeutic properties of silver and its salts were recognized as early as the Roman Empire period. Jabir ibn Hayyan Gegber, an Arabian physician of the eighth century, initiated the use of silver nitrate on the eye. The ability of silver ions to kill microorganisms is the basis for their ophthalmic use. Silver nitrate was found to occasionally cause necrosis of conjunctival epithelial cells and a gray-black color when light reduced the salt to its metallic state. In addition, irritation, scarring of the conjunctiva, corneal opacification, and symblepharon occurred. In an attempt to reduce these problems, Albert C. Barnes, MD and Hermann Hille, in 1902, developed a combination of silver nitrate and grain protein (Argyrol). This mild silver protein solution originally was intended to be an antimicrobial agent. The colloidal suspension liberates silver ions that alter the protein in the bacterial cell wall. It also has been suggested that silver interferes with essential metabolic activity of bacteria. The silver in this mild silver protein solution ionizes poorly, and thus causes less irritation than silver nitrate. However, its germicidal effectiveness is also decreased and the adverse experiences were not eliminated.

The 10% and 20% mild silver protein solutions have been available for topical ocular use in the United States as a silver nitrate and gelatin colloid. The drug was available also abroad under a variety of proprietary names and formulations. It is classified in pharmacy textbooks as a local anti-infective agent. The antimicrobial properties of this mild silver protein solution have been questioned for years.

² 45 FR 30002-30050. Ophthalmic Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Proposed Rulemaking, May 6, 1980.

Safety

In most cases, mild silver protein has been administered safely with minimal adverse experiences. Numerous articles and books have been written concerning silver deposition of the conjunctiva, lacrimal sac, cornea and lens following administration of mild silver protein. The conjunctival deposits under the light microscopic are extracellular silver deposits in the connective tissue cells of the submucosa.³ The silver deposits in the cornea are located in Descemet's membrane³ and may occur with clinical conjunctival involvement.⁴ In the lacrimal sac, the silver is deposited in the mucosal epithelium.⁵ In the lens, it may cause anterior subcapsular discoloration or in the nucleus.⁶

Most reported cases of argyrosis have occurred following at least 2 months of instillation,⁷ however, Karcioğlu and Caldwell reported a case of ocular argyrosis after only one treatment with Argyrol eye drops.⁸ The conjunctival, corneal and lens manifestations are shown below.^{3,9}

Argyrosis is generally permanent and although not usually known to impair visual acuity, has been associated with decreased night vision¹⁰. Decreased night vision has been correlated with increased levels of silver in both the conjunctiva and the cornea.



³ Hanna C, Fraunfelder FT, Sanchez J. Ultrastructural Study of Argyrosis of the Cornea and Conjunctiva. *Arch Ophthalmol.* 1974;92:18-22.

⁴ Gutman FA, Crosswell HH. Argyrosis of the Cornea with Clinical Conjunctival Involvement. *Am J Ophthalmol.* 1968;65:183-4.

⁵ Yanoff M, Scheie HG. Argyrosis of the Conjunctiva and Lacrimal Sac. *Arch Ophthalmol.* 1964;72:57-8.

⁶ Bartlett RE. Generalized Argyrosis with Lens Involvement. *Am J Ophthalmol.* 1954;38:402-3.

⁷ Loeffler KU, Lee WR. Argyrosis of the lacrimal sac. *Graefes Arch Clin Exp Ophthalmol.* 1987;225(2):146-50.

⁸ Karcioğlu ZA, Caldwell DR. Corneal argyrosis: histologic, ultrastructural and microanalytic study. *Can J Ophthalmol.* 1985 Dec;20(7):257-60.

⁹ The Cornea. Gilbert Smolin and Richard Thoft editors. Little, Brown and Company. Boston 1983. p. 386.

¹⁰ Moss AP, et al. The Ocular Manifestations and Functional Effects of Occupational Argyrosis. *Arch Ophthalmol* 1979;97:906-908.



Staining of lacrimal sac



Staining within the cornea



Silver impregnation of epithelial basement membrane¹¹



Involvement of Descemet's membrane

¹¹ Diseases of the Cornea. 2nd Edition. Merrill Grayson editor. C.V. Mosby Co. St. Louis 1983. pp. 576-578.

Efficacy

In vitro Studies

1. **Thompson R, Isaacs ML, Khorazo D. *Am J Ophthalmol* 20:1087, 1937 copied with permission in Havener's Ocular Pharmacology. 6th edition. Mosby 1994.**

Bacterial Effect of Nonirritating Concentrations of Antiseptics

Antiseptic	Maximum Nonirritating Concentration (%)	Number of Organisms Surviving (%) - <i>Staphylococcus aureus</i>	
		After 1 minute	After 10 minutes
Merthiolate	0.1	84.7	70.9
Argyrol	50 (12.5 used)	55.2	19.8
Phenyl mercuric nitrate	0.01	53.3	2.9
Gentian violet	0.01	45.4	0.01
Chlorazene	0.1	22.8	2.3
Acriflavine	0.05	19.8	0.46
Mercurochrome	2	6.5	0.25
Silver nitrate	0.25	5.5	5.5
Iodine	0.025	1	0.39
Alba	0.04	0	

Comment: *Mild silver protein (Argyrol) was among the least effective of the antiseptics tested.*

2. **Peeters M, Vanden Berghe D, Meheus A. Antimicrobial activity of seven metallic compounds against penicillinase producing and non-penicillinase producing strains of *Neisseria gonorrhoeae*. *Genitourin Med* 1986 Jun;62(3):163-5.**

The in vitro activity of seven metallic compounds was tested against penicillinase (beta lactamase) producing strains of *Neisseria gonorrhoeae* (PPNG) and non-PPNG strains. On a weight basis, the mercurials showed the greatest in vitro activity.

	MIC90 Concentration at which 90% of all strains were inhibited (mg/L)
Phenylmercuric borate	5
Thiomersal	5
Mercuric chloride	20
Silver nitrate	80
Mild silver protein	200

Comment: *Mild silver protein (Argyrol) was among the least effective of the antiseptics tested.*

Controlled Clinical Studies

3. **Isenberg S, Apt L, Yoshimuri R. Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution. *Arch Ophthalmol* 1983;101(5):764-5.**

32 patients undergoing ophthalmic surgery were studied. No patient had received pre-operative antibiotic therapy or had an infection at the time of surgery. Twenty microliters (1 drop) of 20% mild silver protein solution was instilled in the inferior conjunctival fornix of one randomly selected eye. Hexachlorophene soap was applied equally to both eyelids, eyelid margins, cheeks, nose, eyebrow, and forehead. The inferior fornix of the eye into which the mild silver protein solution had been instilled was then irrigated with a normal saline solution, while the other eye had no irrigation.

		Mean \pm SD	
		Before preparation	After preparation
Colonies	Untreated	183 \pm 425	284 \pm 571
	Mild silver protein	231 \pm 687	323 \pm 750
Species	Untreated	1.06 \pm .83	1.41 \pm .86
	Mild silver protein	1.06 \pm .75	1.31 \pm .77
Number of Eyes in which Culture was Sterile	Untreated	8	4
	Mild silver protein	7	5

“Although the number of colonies and species were greater after the preparation than before in both mild silver protein solution-treated and untreated eyes, in no case was the increase of actual numbers significant at the 5% level by Student's *t* test. The difference in the amount of increase of actual number in the untreated eye as opposed to the mild silver protein solution-treated eye also was not found to be significant at the 5% level. The pattern of sterile cultures before and after chemical preparation of the eye is given [above]. Of all the eyes in this study, only three of the 15 that were sterile before preparation remained sterile after preparation. The organisms cultured were diphtheroids, *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Candida albicans*, and *Klebsiella sp.*”

Comments: *There was no statistically significant difference between groups.*

4. **Speaker MG, Menikoff JA. Prophylaxis of endophthalmitis with topical povidone-iodine. *Ophthalmology* 1991 Dec;98(12):1769-75.**

Open-label, non-randomized parallel trial comparing the preoperative application of povidone-iodine to the ocular surface versus mild silver protein (Argyrol) in the reduction of the incidence of endophthalmitis after intraocular surgery. During an 11-month period, topical 5% povidone-iodine was used to prepare the conjunctiva in 1 set of 5 operating rooms, while silver protein solution was used in another set of 5 rooms. In all cases, surgeons continued to use their customary prophylactic antibiotics. A significantly lower incidence of culture-positive endophthalmitis ($p < 0.03$) was observed in the operating rooms using povidone-iodine (2 of 3489 or 0.06%) compared with those using silver protein solution (11 of 4594 or 0.24%).

Comment: *Povidone-iodine was superior to mild silver protein.*

OTC Review Panel 1973-1979¹²

Evaluated: Marketed mild silver protein products containing either 20 or 40 mg of silver per mL of solution.

Panel Conclusions:

Safety: The Panel concluded that there were no toxicity concerns from the use of mild silver protein and that it was safe for OTC use as an anti-infective, provided that the labeling contained a statement warning of the argyria side effect with prolonged use.

Efficacy: Mild silver protein's effectiveness as an ocular anti-infective has not been documented.

Overall: The claim that mild silver protein is useful in the OTC treatment of minor eye infections requires clinical studies.

¹² Ophthalmic Drug Products for Over-the-Counter Human Use
45 FR 30002-30050 May 6, 1980 Proposed Monograph
48 FR 29788-29800 June 28, 1983 Tentative Final Monograph
53 FR 7076-7093 March 4, 1988 Final Monograph
57 FR 60416 December 18, 1992 Final Rule

Literature Summaries:

Goodman & Gilman¹³

“Mild silver protein (19 to 23% silver) is still marketed. It is mostly bacteriostatic. It is nonirritating, even mildly demulcent. Claims that mild silver protein penetrates tissue at the site of application because chloride ion does not precipitate the silver are misleading. The large carrier protein molecule penetrates poorly. Fortunately, the colloidal silver preparations are now in a deserved oblivion.”

Havener's Ocular Pharmacology¹⁴

“Aseptic preparation of the eye before surgery is important in reducing endophthamitis postoperatively. Silver protein solution has been used during the preoperative preparation of the eye but has been shown to have little to no antimicrobial effect. It is useful in staining mucus and therefore ensuring adequate irrigation at the end of the preparation.”

“Preantibiotic treatment of surface infections has included application of a variety of metallic salts, dyes, and so forth. Most of these medications do, indeed, have bacteriostatic or bactericidal activity, but their use on the eye is limited by ocular tolerance. Topical use of most of these medications is now obsolete.”

“Not only are the antiseptic solutions used in ophthalmology before the introduction of antibiotics relatively ineffective germicides, but they actually greatly delay healing of corneal epithelial defects and in most instances may cause permanent corneal opacity. Such drugs include 10% (mild) silver protein, 2% merbromin (Mercurochrome), 0.5% zinc sulfate, 1:3,000 benzalkonium chloride (Zephiran), 1:1,000 acriflavin (Neutroflavin), 1:2,500 nitroersol (Metaphen), 1:2,500 thimerosal (Merthiolate), and 1:5,000 mercuric oxycyanide.”

“Tragic results may follow confusion of 10% silver protein solutions (Argyrol) with 10% silver nitrate solutions, which may blind a child. A survey of 85 ophthalmologists in 1952 disclosed 17 who had encountered blindness that had resulted from use of excessively strong solutions of silver nitrate. This is largely of historic interest in the 1990s when silver nitrate solution is limited largely to use in some cases of superior limbic keratoconjunctivitis.”

¹³ Goodman and Gilman's The Pharmacological Basis of Therapeutics. 6th Edition. MacMillan Publishing Co., Inc. New York. pp. 977.

¹⁴ Havener's Ocular Pharmacology. 6th Edition. Mosby. New York. pp. 239, 463-4, 475-6, 484-7.

A. INGREDIENT NAME:

SILVER PROTEIN MILD NF

B. Chemical Name:

C. Common Name:

Argentum Crede, Collargol (9CI), Colloidal Silver, Stillargol, Vitargénol, Aust.:
Coldargan, Fr.: Pastaba, Ger.: Coldargan, Ital.: Arscolloid, Bio-Arscolloid, Corti-
Ascolloid, Rikosilver, Rinatipiol, Rinovit Nube.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Specifications)</i>	<i>(Results)</i>
Assay: (after ignition)	19.0-23.0%	19.74%

E. Information about how the ingredient is supplied:

Brown, Dark-Brown, or almost black, odorless, lustrous scales or granules, somewhat hygroscopic, and is affected by light.

F. Information about recognition of the substance in foreign pharmacopeias:

Aust., Belg., Cz., Fr., Hung., It., and Jpn.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Isenberg, S., Apt, L., and Yoshimuri. Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution. *Archives of Ophthalmology*, 1983; 101(5): 764-765.

Apt, L. and Isenberg, S. Chemical preparation of skin and eye in ophthalmic surgery: an international survey. *Ophthalmic Surgery*, 1982; 13(12): 1026-1029.

H. Information about dosage forms used:

Liquid

I. Information about strength:

1-20%

J. Information about route of administration:

Nasal

Ophthalmic

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-1263
51149

PRODUCT: SILVER PROTEIN MILD
RELEASE #: N

LOT # :B61695G18

GRADE:NFXIII
CODE:D5785

	<u>SPECIFICATIONS</u>	<u>RESULT</u>
1. DESCRIPTION	Black granules	Conforms
2. Identification	To pass test	Passes test
3. Solubility	To pass test	Passes test
4. Assay (after ignition) <i>D</i>	<u>19.0 - 23.0%</u>	<u>19.74%</u>
5. Ionic silver	No turbidity	Conforms
6. Distinction from strong silver protein	To pass test	Passes test

ATTENTION: TONY HATCHETT

Date :06/23/97

10762

Prepared by : A. HAZARI

Approved by



6/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: SILVER PROTEIN MILD NF *A*

MANUFACTURE LOT NO.: C64051D10

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP ___/BP ___/MERCK ___/NF ___/MART. ___/CO. SPECS. ___.

1) DESCRIPTION.:

E (BROWN, DARK-BROWN, OR ALMOST BLACK, ODORLESS, LUSTROUS SCALES OR GRANULES; SOMEWHAT HYGROSCOPIC, AND IS AFFECTED BY LIGHT.

2) SOLUBILITY.:

FREELY SOLUBLE IN WATER. ALMOST INSOLUBLE IN ALCOHOL, CHLOROFORM AND IN ETHER.

3) MELTING POINT.:

4) SPECIFIC GRAVITY .:

5) IDENTIFICATION.:

A) COMPLIES (B) AS PER NF 10th EDITION 1955.
B) COMPLIES (C) AS PER NF 10th EDITION 1955.

PASSES.: _____

FAILS.: _____

COMMENTS.:

ANALYST SIGNATURE.: _____

DATE.: _____

PREPACK TEST.: _____

DATE.: _____

INITIAL.: _____

RETEST.: _____

DATE.: _____

INITIAL.: _____

Sesame Oil (7368-w)

Castor de Ajonjolii; Benne Oil; Gingelly Oil; Oleum Sesami; Sesam Oil.

Pharmacopoeias. In Aust., Belg., Br., Chin., Eur., Fr., Ger., It., Jpn., Nep., Port., and Switz. Also in USNF.
Standards of Ph. Eur. apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see *Annex*.

The fixed oil obtained from the ripe seeds of *Sesamum indicum* (Pedaliaceae) by expression or extraction and subsequent refining. It is a clear pale yellow oil, almost odourless and with a bland taste with a fatty-acid content consisting mainly of linoleic and oleic acids. It solidifies to a buttery mass at about -1° .

Slightly soluble to practically insoluble in alcohol; miscible with carbon disulphide, chloroform, ether, and petroleum spirit. Store at a temperature not exceeding 40° in well-filled airtight containers. Protect from light.

Sesame oil has been used in the preparation of liniments, plasters, ointments, and soaps. Because it is relatively stable, it is a useful solvent and vehicle for parenteral products. Hypersensitivity reactions have been observed.

Shellac (285-x)

904; Gomme Laque; Lacca; Lacca in Tabuist; Schellack.

Pharmacopoeias. In Fr. and Ger. Also in USNF.

It includes Purified Shellac and White Shellac (Bleached).

Shellac is obtained by purification of the resinous secretion of the insect *Laccifer lacca* Kerr (Coccidae). The USNF describes 4 grades: Orange Shellac is produced by filtration in the molten state or by a hot solvent process, or both; removal of the wax produces Dewaxed Orange Shellac; Regular Bleached (White) Shellac is prepared by dissolving the secretion in aqueous sodium carbonate, bleaching with hypochlorite, and precipitating with sulphuric acid; removal of the wax by filtration during the process produces Refined Bleached Shellac.

Practically insoluble in water; very slowly soluble in alcohol 85% to 95% (w/w); soluble in ether, 13% to 15%, and in aqueous solutions of ethanalamines, alkalis, and borax. Store preferably at a temperature not exceeding 3° .

Shellac is used as an enteric coating for pills and tablets, but its permeation time has been reported to increase markedly on storage.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USNF 18: Pharmaceutical Glaze.

Siam Benzoin (273-c)

Benjoin du Laos; Benzoe Tonkinensis.

Pharmacopoeias. In Aust., Chin., Fr., It., and Switz. Also in many pharmacopoeias under the title benzoin and should not be confused with Sumatra Benzoin. Hung., Jpn. and US allow both Siam benzoin and Sumatra benzoin under the title Benzoin.

A balsamic resin from *Styrax tonkinensis* (Styracaceae) and containing not more than 10% of alcohol (90%) -insoluble matter.

Yellowish-brown to rusty brown compressed pebble-like tears with an agreeable, balsamic, vanilla-like odour. The tears are separate or very slightly agglutinated, milky white on fracture, and brittle at ordinary temperatures, but soften on heating.

Siam benzoin has been used similarly to Sumatra benzoin (see above) and has been used as a preservative and was formerly used in the preparation of benzoinated lard.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USP 23: Compound Tincture; Podoophyllum Resin Topical Solution.

Proprietary Preparations

Multi-ingredient preparations: Aust., Canada, Benzoin Spray; Cold Sore Lotion; Ital., Onda; Spain, Vano Balsamicos.

Silver (5316-w)

8174.

— 107 3682.

— 7440-22-4.

Pharmacopoeias. In Switz.

A pure white, malleable and ductile metal.

Silver possesses antibacterial properties and is used topically either as the metal or as silver salts. It is not absorbed to any great extent and the main problem associated with the metal

is argyria, a general grey discoloration. Silver is used as a colouring agent for some types of confectionery. It is also used as Argentinum Metallicum in homeopathy.

Numerous salts or compounds of silver have been employed for various therapeutic purposes, including silver acetate (p.1751), silver allantoinate and silver zinc allantoinate, silver borate, silver carbonate, silver chloride, silver chromate, silver glycerolate, colloidal silver iodide, silver lactate, silver manganate, silver nitrate (p.1751), silver-nylon polymers, silver protein (p.1751), and silver sulphadiazine (p.1773).

A report of reversible neuropathy associated with the absorption of silver from an arthroplasty cement.¹

1. Vrk H, et al. Neuropathy caused by silver absorption from arthroplasty cement. *Lancet* 1985; ii: 872.

Coating catheters with silver has been reported to reduce the incidence of catheter-associated bacteriuria,² but other studies have reported increased infection.³

1. Lundberg T. Prevention of catheter-associated urinary-tract infections by use of silver-impregnated catheters. *Lancet* 1986; ii: 1031.

2. Johnson JR, et al. Prevention of catheter-associated urinary tract infections with a silver oxide-coated urinary catheter: clinical and microbiologic correlates. *J Infect Dis* 1990; 162: 1145-50.

3. Riley DK, et al. A large randomized clinical trial of a silver-impregnated urinary catheter: lack of efficacy and staphylococcal superinfection. *Am J Med* 1995; 98: 349-56.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Austral.: Micropur; Canad.: Tabamil; Ger.: Dulcargan; Silargentin.

Multi-ingredient preparations. Austral.: Sina-Varix Bandage; Simanite; Fr.: Sterilet T au Cuivre Argent; Ger.: Adorgan; Grane Salbe "Schmidt"; Ital.: Actosorb Plus; Agrippi; Kaoform; Kaoxy; Nova-T; Silver-Nova T; Spain: Argentocromo; UK: Actosorb Plus.

Silver Acetate (5319-p)

Argentum Acetas.

CH₃COOAg = 166.9.

CAS = 563-63-3.

Pharmacopoeias. In Aust. and Hung.

Silver acetate has been used similarly to silver nitrate as a disinfectant. It has also been used in antismoking preparations.

References

1. Jensen EJ, et al. Serum concentrations and accumulation of silver in skin during three months' treatment with an anti-smoking chewing gum containing silver acetate. *Hum Toxicol* 1988; 7: 535-40.

2. Gourlay SG, McNeill JJ. Antismoking products. *Med J Aust* 1990; 153: 699-707.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

UK: Tabmin.

Silver Nitrate (5321-h)

Argentum Nitras; Nitrato de Plata; Nitrato de Plata.

AgNO₃ = 169.9.

CAS = 7761-88-8.

Pharmacopoeias. In Aust., Belg., Br., Cz., Eur., Fr., Ger., Hung., Ital., Jpn., Nep., Port., Switz, and US.

The standards of Ph. Eur. apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see *Annex*.

Colourless or white transparent crystals or crystalline odourless powder. On exposure to light in the presence of organic matter, silver nitrate becomes grey or greyish-black.

Soluble 1 in 0.4 of water and 1 in 30 of alcohol; its solubility is increased in boiling water or alcohol; slightly soluble in ether. A solution in water has a pH of about 5.5.

Silver nitrate is compatible with a range of substances. Although it is unlikely that there will be a need to add any of the interacting substances to silver nitrate solutions considering its current uses, pharmacists should be aware of the potential for incompatibility. Store in airtight non-metallic containers. Protect from light.

The reported yellow-brown discoloration of samples of silver nitrate bladder irrigation (1 in 10 000) probably arose from the reaction of the silver nitrate with alkali released from the glass bottle which appeared to be soda-glass.¹

1. *PSGB Lab Report PN016* 1980.

Adverse Effects

Symptoms of poisoning stem from the corrosive action of silver nitrate and include pain in the mouth, stomatocoe, diarrhoea, vomiting, coma, and convulsions.

A short lived minor conjunctivitis is common in infants given silver nitrate eye drops; repeated use or the use of high concentrations produces severe damage and even blindness.

Chronic application to the conjunctiva, mucous surfaces, or open wounds leads to argyria, which though difficult to treat is considered to be mainly a cosmetic hazard, see under Silver (above).

Absorption of nitrite following reduction of nitrate may cause methaemoglobinemia. There is also a risk of electrolyte disturbances.

Treatment of these adverse effects is symptomatic.

Silver nitrate from a stick containing 75% was applied to the eyes of a newborn infant instead of a 1% solution.¹ After 1 hour there was a thick purulent secretion, the eyelids were red and oedematous, and the conjunctiva markedly injected. The cornea had a blue-grey bedewed appearance with areas of corneal opacification. After treatment by lavage and topical application of antibiotics and homatropine 2% there was a marked improvement and after 1 week topical application of corticosteroids was started. Residual damage was limited to slight corneal opacity.

1. Homblasi A. Silver nitrate ocular damage in newborns. *JAMA* 1975; 231: 245.

Pharmacokinetics

Silver nitrate is not readily absorbed.

Uses and Administration

Silver nitrate possesses disinfectant properties and is used in many countries as a 1% solution for the prophylaxis of gonococcal ophthalmia neonatorum (see Neonatal Conjunctivitis, p.151) when 2 drops are instilled into each conjunctival sac of the neonate. However, as it can cause irritation, other agents are often used.

In sick form it has been used as a caustic to destroy warts and other small skin growths. Compresses soaked in a 0.5% solution of silver nitrate have been applied to severe burns to reduce infection. Solutions have also been used as topical disinfectants and astringents in other conditions.

Silver nitrate (Argentum Nitricum; Argent. Nit.) is used in homeopathic medicine. It is also used in cosmetics to dye eyebrows and eye lashes to a concentration of not more than 4%.

Cystitis. Comment on silver nitrate irrigation having limited value in the management of haemorrhagic cystitis after radiotherapy.

1. Anonymous. Haemorrhagic cystitis after radiotherapy. *Lancet* 1987; ii: 304-6.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USP 23: Silver Nitrate Ophthalmic Solution; Toughened Silver Nitrate.

Proprietary Preparations

Austral.: Howe's Solution; Quitt; Ger.: Nova Nitrat; Pluralane; Spain: Argental.

Multi-ingredient preparations. Austral.: Super Banish; Spain: Argentotamol; Switz.: Grafca; UK: AVOCA.

Silver Protein (5322-m)

Albumosilber; Argentoproteinum; Argentum Proteinicum; Protargolum; Proteinato de Plata; Proteinato de Plata; Strong Protargin; Strong Protein Silver; Strong Silver Protein. CAS = 9007-35-6 (colloidal silver).

NOTE. Synonyms for mild silver protein include: Argentoproteinum Mite; Argentum Vitellinum; Mild Protargin; Mild Silver Protein; Silver Nucleinate; Silver Vitellin; Vitelinato de Plata and Vitelinato de Plata.

Pharmacopoeias. In Aust., Belg., Cz., Fr., Hung., It., and Jpn. Many of these pharmacopoeias include monographs on mild silver protein as well as on colloidal silver.

Silver protein solutions have antibacterial properties, due to the presence of low concentrations of ionised silver, and have been used as eye drops and for application to mucous membranes. The mild form of silver protein is considered to be less irritating, but less active.

Colloidal silver which is also a preparation of silver in combination with protein has also been used topically for its antibacterial activity.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Fr.: Sullargin; Vitarginal.

Multi-ingredient preparations. Aust.: Coldargan; Fr.: Pastaba; Ger.: Coldargan; Ital.: Arscollid; Bio-Arscollid; Corti-Arscollid; Rikosilver; Rinantipol; Rinovit Nue.

Slippery Elm (5458-t)

Elm Bark; Slippery Elm Bark; Ulmus; Ulmus Fuiva.

Pharmacopoeias. In US.

The dried inner bark of *Ulmus fulva* (= *U. rubra*) (Ulmaceae).

Slippery elm contains much mucilage and has been used as a demulcent.

Epidermal necrolysis. Based on the treatment of 10 cases, the following was suggested as treatment for toxic epidermal necrolysis: continuous moist compresses of silver nitrate solution 0.25 to 0.5%, with generous wrapping to prevent excessive cooling; daily electrolyte estimations; and daily debridement; after about the fourth day the compresses could be replaced by dexamethasone/neomycin spray followed byunction of wool alcohol ointment. A penicillin should be given routinely and steroids if vasculitis was present.— P. J. Koolenzer, *Archs Derm.*, 1967, 95, 508.

Herpes simplex. Silver nitrate 1% had little effect *in vitro* or *in vivo* against herpes simplex virus type 2.— V. R. Coleman *et al.*, *Antimicrob. Ag. Chemother.*, 1973, 4, 259. A further study.— F. Shimizu *et al.*, *ibid.*, 1976, 10, 57.

Hydatid cysts. Intrahepatic cysts of *Echinococcus granulosus* were treated with excellent results in 20 patients by freezing the operation area then administering silver nitrate 0.5% to destroy the scoleces.— I. Nazarian and F. Saidi, *Z. Tropenmed. Parasit.*, 1971, 22, 188, per *Trop. Dis. Bull.*, 1971, 68, 1356.

Ophthalmia neonatorum. In a study of the incidence of ophthalmia neonatorum in 220 000 births, it was found that in 92 365 cases where preparations other than silver nitrate were used the frequency of gonococcal ophthalmia neonatorum was 0.07% whereas where silver nitrate was used the rate was 0.1%. Silver nitrate did not always suppress the development of the condition and seemed no more effective than other agents. While a drop of 1% silver nitrate solution did no harm, there was little evidence that it did any good.— *Lancet*, 1949, 1, 313.

Of the 49 states of the USA which had made regulations requiring routine prophylactic treatment of the eyes of newborn infants, 22 had specified silver nitrate applications. No evidence had been found to contra-indicate 1% silver nitrate drops when properly packed, handled, and administered. The increasing incidence of gonorrhoea had rendered continued routine prophylaxis necessary.— P. C. Barsam, *New Engl. J. Med.*, 1966, 274, 731. Fewer local reactions occurred with penicillin than with silver nitrate eye-drops. Penicillin for neonatal prophylaxis should not be abandoned, since it did not appear to sensitise infants.— G. Nathanson (letter), *ibid.*, 275, 280. Eye-drops containing less than 2% of silver nitrate were considered to be ineffective. Treatment was effective if applied early and prophylaxis was advised only in infants whose mothers were known or suspected to be infected.— E. B. Shaw (letter), *ibid.*, 231. See also P. Kober, *Medische Klin.*, 1967, 62, 424.

To prevent gonorrhoeal ophthalmia neonatorum, a 1% solution of silver nitrate was instilled at birth. The chemical conjunctivitis caused by silver nitrate was of short duration.— P. Thygeson, *J. Am. med. Ass.*, 1967, 201, 902.

For reports on the chemical conjunctivitis associated with instillation of silver nitrate eye-drops and recommendations for reduction of the incidence, see Adverse Effects (above).

Pneumothorax. Spontaneous pneumothorax was successfully treated in 132 patients by pleurodesis induced with silver nitrate; repeated pleurodesis was necessary in only 2 patients. It was suggested that this therapy should be used for patients with only small or no blebs visible on thoracoscopy, or with only mild pre-existing lung disease.— I. Anderson and H. Nissen, *Dis. Chest*, 1968, 54, 230, per *J. Am. med. Ass.*, 1968, 206, 581.

Wounds. Silver nitrate solution 0.5% was more effective against Gram-positive than Gram-negative bacteria in the treatment of nonthermal war wounds. The solution did not hinder wound healing or epithelialisation of split thickness skin grafts.— J. P. Connors *et al.*, *Archs Surg.*, Chicago, 1969, 98, 119, per *J. Am. med. Ass.*, 1969, 207, 580.

Preparations

Mitigated Silver Nitrate (B.P.C. 1968). Argenti Nitras Mitigatus; Mitigated Caustic; Argenti Nitras Dilutus. Silver nitrate 1 and potassium nitrate 2, fused together and suitably moulded for application as a caustic to warts and condylomas. Protect from light. A similar preparation is included in several pharmacopoeias.

Silver Nitrate Stain Remover (Univ. of Iowa). Thiourea (NH₂CS.NH₂; = 76.12) 3 g, citric acid monohydrate 3 g, water to 100 ml. It should be freshly prepared.

Toughened Silver-Nitrate (B.P.C. 1968). Argenti Nitras Induratus; Toughened Caustic; Fused Silver Nitrate; Lunar Caustic; Moulded Silver Nitrate; Stylus Argenti Nitrici. Silver nitrate 95 and potassium nitrate 5, fused together and suitably moulded.

White or greyish-white cylindrical rods or cones, which

become grey or greyish-black on exposure to light. Freely soluble in water; sparingly soluble in alcohol. Protect from light.

A similar preparation is included in several pharmacopoeias.

Toughened Silver Nitrate (U.S.P.). Contains not less than 94.5% of AgNO₃, the remainder consisting of silver chloride. Store in airtight containers. Protect from light.

Creams

Silver Nitrate Cream. Silver nitrate, 0.5 or 1%. Xalifin-15 20%, water to 100%. The cream was stable with only slight discoloration when stored for 4 weeks in the dark at room temperature; at 0° to 4° there was no discoloration.— *Pharm. Soc. Lab. Rep.* P/68/15, 1968.

Eye-drops

Oculoguttas Argenti Nitricis pro Neonatis (Dan. Disp.). Silver nitrate 570 mg, potassium nitrate 1.2 g, and Water for Injections, 98.13 g.

A similar preparation is included in *F.N.Belg.*

Silver Nitrate Eye-drops (B.P.C. 1954). Gutt. Argent. Nit. Silver nitrate 0.5% w/v, potassium nitrate 1.33% w/v, in Solution for Eye-drops.

Nord. P. has 1% w/v with potassium nitrate 1% w/v in Water for Injections.

Ointments

Unguentum Argenti Nitricis Compositum. Compound Silver Nitrate Ointment. An ointment with this title is included in several pharmacopoeias. It contains silver nitrate 1% and Peru balsam 5 to 10% usually in a basis of yellow soft paraffin or yellow soft paraffin and wool fat.

Ophthalmic Solutions

Silver Nitrate Ophthalmic Solution (U.S.P.). A solution of silver nitrate 0.95 to 1.05% in an aqueous medium. pH 4.5 to 6. It may contain sodium acetate as a buffer. Store in single-dose containers. Protect from light.

Solutions

Ammoniacal Silver Nitrate Solution (U.S.N.F. XII, 1965). Ammoniacal Silver Nitrate. Howe. A solution of diamminosilver nitrate was prepared from silver nitrate 704 g, water 245 ml, and strong ammonia solution to dissolve all but the last trace of precipitate (about 680 ml). It contains 28.5 to 30.5% w/w of Ag and 9 to 9.7% w/w of NH₃. Store in small glass-stoppered containers or in ampoules. Protect from light.

This solution has been employed in dental surgery to deposit silver in exposed dentine or to fill up small crevices in the teeth. After the solution had been applied to the tooth it was followed by a reducing agent such as a 10% formaldehyde solution or eugenol to cause a deposit of metallic silver. The solution has also been employed in the treatment of fungous infections of the nails.

Solutio Argenti Nitricis cum Tetracaine (Nord. P.). Silver nitrate 200 mg, amethocaine nitrate 100 mg, and water 99.7 g.

Proprietary Names

Heivedstensstifter (Braun, Denm.); Lapis DAK, Denm.; Mova Nitrat Pipette (Lindopharm, Ger.).

5322-m

Silver Protein (B.P.C. 1968). Argentoproteinum; Strong Protein Silver; Strong Protargin; Argentum Proteinicum; Albumosilber; Protargolum; Proteinato de Plata; Proteinato de Plata.

CAS — 9015-51-4.

Pharmacopoeias. In Arg., Aust., Belg., Cz., Fr., Hung., Ind., It., Jap., Pol., Port., Roum., Span., and Turk.

A brown odourless hygroscopic powder containing 7.5 to 8.5% of Ag. Slowly soluble in 2 of water; very slightly soluble in alcohol, chloroform, and ether. A solution in water is neutral to litmus. Solutions may be prepared by shaking the powder over the surface of cold water and allowing it to dissolve slowly, or by triturating the powder to a cream with water and diluting. Solutions are transparent and not coagulated by heat, nor precipitated by the addition of alkali, alkali sulphides, alkali salts, or albumin; they are relatively non-staining. Store in airtight containers. Protect from light.

Adverse Effects. As for Silver (above).

Uses. Silver protein solutions have antibacterial properties. Due to the presence of low concentrations of ionised silver, and are used as eye-drops in the treatment of conjunctivitis. Solutions are relatively non-irritant unless they contain more than 10% of silver protein.

Preparations

Silver Protein Eye-drops (B.P.C. 1963). Gutt. Prot. A solution of silver protein 5%, with phenylmercuric acetate or nitrate 0.002%, in water. Prepared aseptically, the silver protein is in a sterile solution of phenylmercuric acetate or nitrate referring to the final sterilised container. They must be freshly prepared. They are adversely affected by alkali. Protect from light.

Proprietary Names

Stüllargol (Mayoly-Spindler, Fr.).

5323-b

Mild Silver Protein (B.P.C. 1968). Argentoprot. Mit. Argentum Vitellanicum; Mild Silver Protein; Silver Nuclienate; Silver Vitellin; Mild Proteinato de Plata; Vitelinato de Plata.

NOTE. The name Mild Silver Protein is used for this compound because it is less bactericidal and less than Silver Protein, though it contains more silver.

Pharmacopoeias. In Arg., Belg., Fr., Ind., It., Jap., Roum., Span., Swiss, and Turk.

A hygroscopic brown powder or nearly black granules with a slight odour and taste, containing 23% of Ag.

Soluble slowly but completely in water, and also soluble in alcohol, chloroform, and ether. After exposure to light it is incompletely soluble in water. A solution in water is iso-osmotic with serum, but with cocaine hydrochloride, but compatible with atropine sulphate solution. Incompatible with acids, alkalis, tannins, and oxidising agents. Store in airtight containers. Protect from light.

Preservative for eye-drops. Phenylmercuric 0.005% was a suitable preservative for silver protein eye-drops sterilised by heating at 70° for 30 minutes.— M. Van Ootegem, *Pharmazie*, Belg., 1968, 45, 69.

Adverse Effects, Treatment, and Precautions. Silver (above).

Argyria. Argyria developed in an elderly patient on prolonged use of mild silver protein 10% eye-drops. W. A. Parker, *Am. J. Hosp. Pharm.*, 1970, 25, 100.

Uses. Mild silver protein solutions have properties similar to those of silver protein, but they contain even lower concentrations of silver and are consequently less irritant to the eye. Silver protein may be used, therefore, in concentrations than silver protein, particularly in children. It is important to avoid irritation of mucous membranes. Mild silver protein, usually 1 to 5%, is used as drops or as a spray in nasal infections. It has been applied as a 20% solution in conjunctivitis, the prophylaxis of ophthalmia neonatorum and solution to corneal ulcers.

Rhinitis. Mild silver protein (Argyrol) has been used many years in children with chronic rhinitis and has some value in encouraging nose blowing. The main disadvantage is the irreversible staining of kerchiefs and pillows.— D. F. N. Harrison, *J. Pharm. Med.*, 1976, 16, 59.

Preparations

Mild Silver Protein Eye-Drops (B.P.C. 1968). Argentoprot. Mit. A solution of mild silver protein 5%, with phenylmercuric acetate or nitrate 0.002%, in water. Prepared by dissolving aseptically, the silver protein in a sterile 0.002% solution of phenylmercuric acetate or nitrate and transferring to the final container. The eye-drops must be freshly prepared and are adversely affected by alkali. Protect from light. (Mild Silver Protein Eye-Drops) has silver protein 20% and phenylmercuric nitrate 0.002% in Water for Injections.

Silver Protein and Ephedrine Instillation. Argentoprot. Mit. and Ephedrine Nasal Drops. Mild silver protein 5 g, ephedrine 500 mg, phenylmercuric nitrate 0.002 g, freshly boiled and cooled water to 100 ml. It should be recently prepared. Protect from light.

Proprietary Preparations

Argorone (Rona, UK). Contains mild silver protein and ephedrine hydrochloride 0.5% in 2% chloride solution, available as Nasal Drops Ready-Spray nasal spray in plastic atomiser.

Other Proprietary Names

Argincolor (Fr.); Arginol (Spain); Vitargol (Fr.).

ighly with hot 3 per cent hydro-eight of the precipitate so obtained n.
er Iodide in tight, light-resistant

TRATE SOLUTION

Ammoniacal Silver Nitrate, Howe

a solution of silver diammino equivalent of not less than 28.5 and not less than 9.0 Gm. and

.....	704 Gm.
.....	245 ml.
.....	680 ml.
.....	1000 ml.

and dissolve it in the puri-
om temperature and add
all but the last trace of
his last trace of precipitate from

ion is a clear, colorless, almost odorless
ected by light. Its specific gravity is

ite Solution (1 in 10) responds to the
ate, page 683.

Solution add a few drops of formalde-
precipitate is immediately formed (*dis-*
monium nitrates).

Silver Nitrate Solution (1 in 10) add
filter, add 5 ml. of sodium hydroxide
itmus blue.

remains free from even a transient blue

iacal Silver Nitrate Solution add 3 ml.
the clear filtrate tested in a flame on a
of sodium or potassium (*distinction from*

ml. of Ammoniacal Silver Nitrate Solu-
water, 10 ml. of diluted nitric acid, and
rate with 0.1 N ammonium thiocyanate.
is equivalent to 10.79 mg. of Ag.

ut 1 ml. of Ammoniacal Silver Nitrate
e sample to a Kjeldahl distillation flask

with 50 ml. of water, and add sufficient of the water to make a volume of 200 ml.;
add 10 ml. of sodium sulfide T.S. and 20 ml. of a solution of sodium hydroxide (4
in 10). Connect the flask to a condenser, the lower outlet tube of which dips
beneath the surface of 50 ml. of 0.5 N sulfuric acid contained in a receiving flask.
Distil the mixture until about 100 ml. of distillate has been collected, add methyl
red T.S., and titrate the excess acid with 0.5 N sodium hydroxide. Each ml. of
0.5 N sulfuric acid is equivalent to 3.516 mg. of NH₃.

The ratio between the percentage of ammonia and the percentage of silver
closely approximates 1 to 3.16.

Packaging and storage—Preserve Ammoniacal Silver Nitrate Solution in small glass-
stopped, light-resistant containers, or in light-resistant ampuls.

FOR TOPICAL USE—Mix Ammoniacal Silver Nitrate Solution with a re-
ducing agent, such as formaldehyde (1 in 10) or eugenol, to deposit
the metallic silver, in a state of fine subdivision, in the desired area of the
tooth.

CATEGORY—Protective (dental).

Silver Protein, Mild

MILD SILVER PROTEIN

Argentum Proteinicum Mite

Mild Protargin

Mild Silver Protein is silver rendered colloidal by the presence of, or
combination with, protein. It contains not less than 19 per cent and
not more than 23 per cent of Ag.

*Caution: Solutions of Mild Silver Protein should be freshly prepared or
contain a suitable stabilizer, and should be dispensed in amber-colored bottles!*

Description—Mild Silver Protein occurs as dark brown or almost black, shining
scales or granules. It is odorless, is frequently hygroscopic, and is affected by
light.

Solubility—Mild Silver Protein is freely soluble in water, but almost insoluble in
alcohol, in chloroform, and in ether.

Identification—

A: Heat about 100 mg. of Mild Silver Protein in a porcelain crucible until all
carbonaceous matter is burned off, warm the residue with 1 ml. of nitric
acid, dilute with 10 ml. of water, and add a few drops of hydrochloric acid:
a white precipitate is produced which dissolves in ammonia T.S.

B: Ferric chloride T.S. added to a solution of Mild Silver Protein (1 in 100)
discharges the dark color and a precipitate is gradually produced.

C: To 10 ml. of a solution of Mild Silver Protein (1 in 100) add a few drops of
mercury bichloride T.S.: a white precipitate is formed and the super-
natant liquid becomes colorless or nearly so.

Ionic silver—To 10 ml. of a solution of Mild Silver Protein (1 in 100) add 2 ml. of a
solution of sodium chloride (1 in 100): no turbidity is produced.

Distinction from strong silver protein—Dissolve 1 Gm. of Mild Silver Protein in 10
ml. of water. Add, all at once, 7 Gm. of ammonium sulfate, and stir occasionally
for 30 minutes. Filter through quantitative filter paper into a 50-ml. Nessler
tube, returning the first portions of the filtrate to the filter, if necessary, to secure
a clear filtrate, and allow the filter and precipitate to drain. Add to the clear
filtrate 25 ml. of a solution of acacia (1 in 100). In a second 50-ml. Nessler tube
dissolve 7 Gm. of ammonium sulfate in 10 ml. of water, and add to this solution
25 ml. of the solution of acacia and 1.6 ml. of 0.01 N silver nitrate. To each tube

Database: Medline <1966 to present>

<1>

Unique Identifier

83203583

Authors

Isenberg S. Apt L. Yoshimuri R.

Title

Chemical preparation of the eye in ophthalmic surgery. II.
Effectiveness of mild silver protein solution.

Source

Archives of Ophthalmology. 101(5):764-5, 1983 May.

Abstract

Although a mild silver protein solution (Argyrol) has been used for a number of years and is still used by many ophthalmic surgeons, its efficiency as an antibacterial agent on the conjunctiva has not been scientifically evaluated as part of the preoperative chemical preparation of the eye. We studied the effectiveness of a mild silver protein solution on the conjunctival flora of 32 patients in a masked fashion. By bacteriologic analysis, the mild silver protein solution was found to be no more effective in reducing the number of species and colonies in the treated eye than in the untreated eye. While the mild silver protein solution does stain mucus and other debris on the eye to facilitate irrigation, this study did not demonstrate a significant bactericidal effect.

<2>

Unique Identifier

83142687

Authors

Apt L. Isenberg S.

Title

Chemical preparation of skin and eye in ophthalmic surgery:
an international survey.

Source

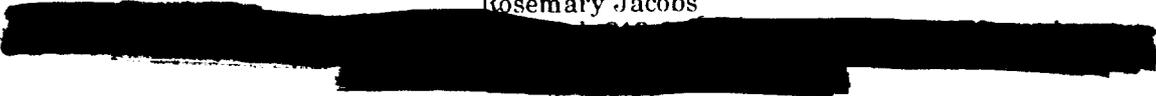
Ophthalmic Surgery. 13(12):1026-9, 1982 Dec.

Abstract

We surveyed 214 ophthalmologists worldwide to learn their methods of preoperative chemical preparation of eye and skin. A 96.8% return rate was achieved. While a wide diversity of agents was reported, povidone-iodine was the most popular agent applied to the skin. The conjunctiva usually was either ignored or rinsed with a saline solution by the respondents. Almost a quarter used mild silver

protein (Argyrol) on the conjunctiva. Most of the preparation is performed by the physician rather than the nurse. Review of the advantages and pitfalls of the agents reported should cause the ophthalmologist to reconsider these agents for their effectiveness, spectrum, and duration of action.

Rosemary Jacobs



Docket # 98N-0182
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
rm. 1061
Rockville, MD 20852

March 8, 1999

Subject: Mild Silver Protein (MSP)

While MSP is well characterized chemically and has a long history of medicinal use, there is also a whole body of evidence indicating that it was neither safe nor effective in any of its historical uses, including as a treatment for conjunctivitis or as a means of sterilizing the eye before surgery.

The best known brand of MSP, Argyrol, was marketed in the US at least until 1996¹. It had been developed and introduced to commerce by Dr. Alfred C. Barnes around 1902². Many silver drugs were fraudulently advertised for decades³. Argyrol in particular has been singled out as one of the most fraudulently advertised^{4,5}. The ingestion of silver causes argyria, gray skin⁶. Look at my photos. I have argyria which I developed about 40 years ago from taking nose drops that contained silver that a doctor in N.Y. prescribed for me. I am not certain, but I believe that the pharmacist compounded the drops since the only label that they ever had was one that he typed out and pasted on. It never showed a brand name. We always referred to them as "the drops".

Every form of silver used therapeutically has caused argyria⁷. Many cases were caused by Argyrol⁸ although that never stopped the company from advertising it as "nontoxic"⁹.

It is well known that MSP put in the eye caused many cases of argyrosis¹⁰, the deposition of silver salts in the conjunctiva, lacrimal sac and cornea. Referring to argyrosis, Hill and Pillsbury state that, "...in severe cases the degree of cosmetic disfigurement may be marked. The color varies from light bluish-gray to a brownish-black."¹¹

There is one case report in the literature that is unusual because just one use of Argyrol drops (1% solution MSP) resulted in argyrosis¹².

In 1928 the Council on Pharmacy and Chemistry refused to readmit Argyrol onto the list of New and Nonofficial Remedies. The principle reason given was the fraudulent adds the company persisted in making. The Council stated that, "Notwithstanding the clinical popularity of Argyrol, its antiseptic efficiency has been seriously questioned. Bacterial culture tests have given variable results, and in the clinical results it has been impossible to distinguish definitely whether improvement is due to the antiseptic or merely to the protective action." Contrary to the manufacturer's claims ophthalmologists did not find that a 25% solution of Argyrol prevented ophthalmia neonatorum although many thought it useful in the treatment of established ophthalmia.¹³

In 1983 an article reported a study in which the effectiveness of MSP as a chemical preparation of the eye before surgery was studied. Thirty-two patients had one eye treated with it. Bacteriologic analysis found that MSP was ineffective in reducing the number of species and colonies of bacteria found in the eye. It was reported that many surgeons used it merely because it acted as a stain enabling them to see debris and mucus that had not been already washed out. When this happened, the eye was

irrigated again. The authors pointed out that that had to be weighted against the finding that irrigation itself caused an increase in the bacterial flora of the conjunctiva."

SUMMARY:

Based on the evidence that MSP has been shown to be unsafe and ineffective as an ophthalmologic drug and on the potential of its being abused and used to treat systemic illnesses for which it is equally ineffective and far more dangerous, I request that it not be added to the list of bulk drugs.

Rosemary Jacobs,
Private Citizen
Victim of Greed Passed Off As Science
<http://homepages.together.net/~rjstan/>

- ¹ Fung, MC, Bowen, DL Silver Products for Medical Indications: Risk-Benefit Assessment CLINICAL TOXICOLOGY, 34(1), 119-26(1996)
- ² Schack, W. ART AND ARGYROL THE LIFE AND CAREER OF DR. ALBERT C. BARNES Sagamore Press, Inc. NY, 1960 p.51
- ³ <http://homepages.together.net/~rjstan/>
- ⁴ Puckner, WA Council on Pharmacy and Chemistry JAMA March 17, 1928 p.849-51
- ⁵ Gaul, LE, Staud, AH Clinical spectroscopy JAMA April 20, 1935 p.1387-90
- ⁶ Mack, RB Return with Us Now to Those Thrilling Days of Yesteryear Argyrol and Argyria NCMJ Sept. 1988, Vol 49 #9 p. 451-2
- ⁷ Hill, WR, Pillsbury, DM ARGYRIA THE PHARMACOLOGY OF SILVER The Williams & Wilkins Company 1939 p. 130
- ⁸ Hill & Pillsbury p.28
- ⁹ THE EYE, EAR, NOSE & THROAT MONTHLY Vol. XXXI #1 Jan. 1952 p. 24
- ¹⁰ Hill & Pillsbury p. 112-5
- ¹¹ Hill & Pillsbury p. 116
- ¹² Karcioğlu, ZA., Caldwell, DR Corneal argyrosis: histologic, ultrastructural and microanalytic study CAN J OPHTHALMOL vol. 29 #7 1985 p.257-60
- ¹³ Puckner, WA Council on Pharmacy and Chemistry JAMA March 17, 1928 p.849-51
- ¹⁴ Isenberg, S, et.. al. Chemical Preparation of the Eye in Ophthalmic Surgery ARCH OPHTHALMOL Vol. 101, May 1983

Tab 80

Squaric Acid Dibutyl Ester (Dibutyl Squarate) Nominations



September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA's request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS

Corporate Offices: 4638 Riverstone Blvd. | Missouri City, Texas 77459 | 281.933.8400
Washington DC Offices: 1321 Duke Street, Suite 200 | Alexandria VA 22314 | 703.299.0796

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created an series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency's activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee prior to the implementation and issuance of regulations including the creation of the bulk ingredient list.

(2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

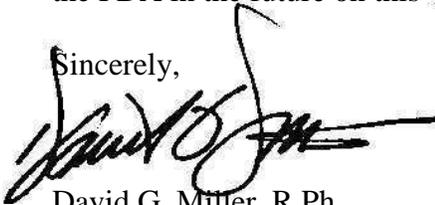
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

A handwritten signature in black ink, appearing to read "David G. Miller", with a large, stylized flourish extending upwards and to the right.

David G. Miller, R.Ph.
Executive Vice President & CEO



Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Squaric acid dibutyl ester
Chemical/Common Name	Squaric Acid Di-N-Butyl Ester (SADBE)?
Identifying Codes	
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	Not Listed in USP/NF for this specific salt/form

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	Federal Register 1999

Past and Proposed Use The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.



Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

“List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act”

Dear Sir or Madam,

Fagron appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

We hereby nominate the bulk drug substances in the attached spreadsheets for FDA’s consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

None of these items appear on an FDA-published list of drugs that present demonstrable difficulties for compounding. In addition, none are a component of a drug product that has been withdrawn or removed from the market because the drug or components of the drug have been found to be unsafe or not effective.

We include references in support of this nomination for your consideration.

Thank you for your consideration. If Fagron can answer any questions, please contact me (j.letwat@fagron.com; 847-207-6100).

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs



Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlsx file)

7-Keto Dehydroepiandrosterone
Acetyl-D-Glucosamine
Aloe Vera 200:1 Freeze Dried
Astragalus Extract 10:1
Beta Glucan (1,3/1,4 -D)
Boswellia Serrata Extract
Bromelain
Cantharidin
Cetyl Myristoleate Oil
Cetyl Myristoleate 20% Powder
Chrysin
Citrulline
Dehydroepiandrosterone
Deoxy-D-Glucose (2)
Diindolylmethane
Domperidone
EGCg
Ferric Subsulfate
Glycolic Acid
Glycosaminoglycans
Hydroxocobalamin Hydrochloride
Kojic Acid
Methylcobalamin
Nicotinamide Adenine Dinucleotide
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)
Ornithine Hydrochloride
Phosphatidyl Serine
Pregnenolone
Pyridoxal 5-Phosphate Monohydrate
Pyruvic Acid
Quercetin
Quinacrine Hydrochloride
Ribose (D)
Silver Protein Mild
Squaric Acid Di-N-Butyl Ester
Thymol Iodide
Tranilast
Trichloroacetic Acid
Ubiquinol 30% Powder

Fagron

2400 Pilot Knob Road
St. Paul, Minnesota 55120 - USA
(800) 423 6967
www.fagron.us



What is the name of the nominated ingredient?	Squaric Acid Di-N-Butyl Ester
--	--------------------------------------

Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?	<p>Yes, Squaric Acid Di-N-Butyl Ester is an active ingredient as defined in 207.3(a)(4) because when added to a pharmacologic dosage form it produces a pharmacological effect.</p> <p>Micali, G., Dall'Oglio, F., Tedeschi, A., Pulvirenti, N., & Nasca, M. R. (2000). Treatment of cutaneous warts with squaric acid dibutylester: a decade of experience. Archives of Dermatology, 136(4), 557. http://archderm.jamanetwork.com/article.aspx?articleid=190091</p> <p>Lee, A. N., & Mallory, S. B. (1999). Contact immunotherapy with squaric acid dibutylester for the treatment of recalcitrant warts. Journal of the American Academy of Dermatology, 41(4), 595-599. http://www.jaad.org/article/S0190-9622(99)80060-7/abstract</p> <p>Kuntz, R. P. (2003). Sensitization Therapy for Warts. International journal of pharmaceutical compounding, 7(4), 266. Happle, R., et al. "Contact allergy as a therapeutic tool for alopecia areata: application of squaric acid dibutylester." Dermatology 161.5 (1980): 289-297. http://www.karger.com/Article/Abstract/250380 Giannetti, A., and G. Orecchid. "Clinical experience on the treatment of alopecia areata with squaric acid dibutyl ester." Dermatology 167.5 (1983): 280-282. http://www.karger.com/Article/Abstract/249797</p> <p>Case, Patrice C., et al. "Topical therapy of alopecia areata with squaric acid dibutylester." Journal of the American Academy of Dermatology 10.3 (1984): 447-451. http://www.sciencedirect.com/science/article/pii/S0190962284800912</p> <p>Orecchia, Giovanni, Piergiorgio Malagoli, and Laura Santagostino. "Treatment of severe alopecia areata with squaric acid dibutylester in pediatric patients." Pediatric dermatology 11.1 (1994): 65-68. http://onlinelibrary.wiley.com/doi/10.1111/j.1525-1470.1994.tb00078.x/abstract</p> <p>Tan, Eileen, Yong-Kwang Tay, and Yoke-Chin Giam. "A clinical study of childhood alopecia areata in Singapore." Pediatric dermatology 19.4 (2002): 298-301. http://onlinelibrary.wiley.com/doi/10.1046/j.1525-1470.2002.00088.x/full</p> <p>Silverberg, Nanette B., et al. "Squaric acid immunotherapy for warts in children." Journal of the American Academy of Dermatology 42.5 (2000): 803-808. http://www.sciencedirect.com/science/article/pii/S0190962200700478</p>
Is the ingredient listed in any of the three sections of the Orange Book?	<p>The nominated substance was searched for in all three sections of the Orange Book located at http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm. The nominated substance does not appear in any section searches of the Orange Book.</p>

Nomination from Fagron, September 30, 2014

Were any monographs for the ingredient found in the USP or NF monographs?	The nominated substance was searched for at http://www.uspnf.com . The nominated substance is not the subject of a USP or NF monograph.
What is the chemical name of the substance?	3,4-Dihydroxycyclobut-3-ene-1,2-dione; The dibutyl ester of 3,4-dihydroxy-3-cyclobutene-1,2-dione
What is the common name of the substance?	Squaric Acid Dibutyl Ester; SADBE; Dibutyl Squarate; Éster dibutílico del ácido escuárico; Quadratic Acid Dibutylester
Does the substance have a UNII Code?	29VT07BGDA
What is the chemical grade of the substance?	no grade
What is the strength, quality, stability, and purity of the ingredient?	Description: Clear to slightly yellow liquid Identification (IR): Conforms Assay: >= 99.0% Water: <= 0.5% Metal cation: <= 0.2% Other Impurities: <= 0.5%
How is the ingredient supplied?	Liquid
Is the substance recognized in foreign pharmacopeias or registered in other countries?	No
Has information been submitted about the substance to the USP for consideration of monograph development?	No USP Monograph Submission found.
What dosage form(s) will be compounded using the bulk drug substance?	Topical Liquid
What strength(s) will be compounded from the nominated substance?	0.03% to 3%
What are the anticipated route(s) of administration of the compounded drug product(s)?	Topical Liquid

Nomination from Fagron, September 30, 2014

Are there safety and efficacy data on compounded drugs using the nominated substance?	Kuntz, R. P. (2003). Sensitization Therapy for Warts. International journal of pharmaceutical compounding, 7(4), 266.
Has the bulk drug substance been used previously to compound drug product(s)?	Yes- used for sensitization therapy for the treatment of warts
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Used in the treatment of warts, alopecia
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There are FDA approved preparations for warts. Imiquimod and OTC freezing preparations. Imiquimod is FDA approved for genital and perianal warts. Imiquimod cream does not cure warts, and new warts may appear during treatment. Squaric acid has been shown eradicate warts from patients with recurrent multiple warts. This treatment has also shown no significant side effects. (G. Mical, M. R. Nasca, A.Tedeschi, F. Dall'oglio, and N. Pulvirenti (2000) Use of Squaric acid Dibutylester (SADBE) for cutaneous warts in children Pediatric dermatol Jul-Aug;17(40):315-8) Imiquimod has not been FDA approved for treatment of patients under the age of twelve. Over the counter freeze preparations, cyrotherapy, only achieve temperatures approximately half of what physicians use in office. This leads to incomplete therapy. Squaric acid has been shown to be a safe effective option for children. (N.B. Silerberg, J. K. Lim, A. S. Paller and A. J. Mancin i(2000) Squaric Acid Immunotherapy for Warts in children May;42(5 Pt1):803-8)
Is there any other relevant information?	All relevant information was expressed in the above questions



September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: FDA-2013-D-1525; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act, Revised Request for Nominations

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit comments to the Food and Drug Administration (FDA) on bulk drug substances that may be used to compound drug products. Nominations for this list were originally announced in the Federal Register on December 4, 2013.¹ A revision to this notification was published on July 2, 2014.² This list would fulfill Section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act) which regulates entities that compound drugs. On November 27, 2013, the Drug Quality and Security Act (DQSA) was signed into law [P.L. 113-54]. The DQSA removed several parts of Section 503A that were declared unconstitutional by the U. S. Supreme Court in 2002. The law requires the FDA to go through the rulemaking process to implement several parts of Section 503A, including a requirement to establish a list of bulk drug substances that may be used in compounding for which there is no applicable USP or NF monograph nor are they components of an FDA-Approved drug.

ASHP represents pharmacists who serve as patient care providers in acute and ambulatory settings. The organization's more than 40,000 members include pharmacists, student pharmacists and pharmacy technicians. For over 70 years, ASHP has been on the forefront of efforts to improve medication use and enhance patient safety. As you are well aware, ASHP was

¹ Federal Register, Volume 78, No. 233. Pages 72841 – 72843

² Federal Register, Volume 79, No. 127. Pages 37747– 37750

actively engaged with the FDA and Federal lawmakers from the onset of the meningitis outbreak in the Fall of 2012. In the aftermath of the incident, ASHP has worked with policymakers, practitioners, and nationally recognized experts in compounding and manufacturing to develop new approaches to protect patients from preventable harm, and to give practitioners and organizations confidence that compounding outsourcers are appropriately regulated and inspected, and that the products they produce are safe.

ASHP understands that the FDA received thousands of nominations for substances to be included on the bulk list, but that the overwhelming majority of nominations did not meet the basic definition of “active ingredient,” and will therefore not be considered by the FDA. Further, the Agency states “Bulk substances that were previously nominated will not be further considered unless they are renominated and adequately supported.” ASHP previously submitted comments to the FDA under the original solicitation for bulk substances and we are again nominating three chemicals – diphenylcyclopropenone, squaric acid dibutyl ester, and thymol iodide – for consideration by the FDA. Please see the accompanying excel file which contains a worksheet for each of the drugs with the information outlined by the FDA.

ASHP appreciates the opportunity to comment as the FDA develops a list of bulk drug substances that may be used in compounding. Please contact me if you have any questions or wish to discuss our comments further. I can be reached by telephone at 301-664-8806, or by e-mail at ctopoleski@ashp.org.

Sincerely,

A handwritten signature in black ink, appearing to read "Christopher J. Topoleski". The signature is fluid and cursive, with a large initial "C" and "T".

Christopher J. Topoleski
Director, Federal Regulatory Affairs.

Column A—What information is requested?	Column B—put data specific to the nominated substance	References
	Squaric acid dibutyl ester	http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&cmd_current=Limits&term=Squaric+acid+dibutyl+ester+OR+2892-62-8+%5Bbn%5D
Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?	Yes	
What is the chemical name of the substance?	3,4-Dibutoxy-3-cyclobutene-1,2-dione (C12H18O4)	http://chem.sis.nlm.nih.gov/chemidplus/unii/4RTO57VG65
What is the common name of the substance?	Squaric acid dibutyl ester	http://chem.sis.nlm.nih.gov/chemidplus/unii/4RTO57VG65
Does the substance have a UNII Code?	4RTO57VG65	http://fdasis.nlm.nih.gov/srs/ProxyServlet?mergeData=true&objectHandle=DBMaint&APPLICATION_NAME=fdasrs&actionHandle=default&nextPage=jsp/srs/ResultScreen.jsp&TXTSUPERLISTID=4RTO57VG65&QV1=SQUARIC+ACID+DIBUTYL+ESTER
What is the chemical grade of the substance?	pharmaceutical or research grade	Sigma Aldrich product description
What is the strength, quality, stability, and purity of the ingredient?	99%; 99.9%	at http://www.keratin.com/ad/ad049.shtml
How is the ingredient supplied?	Crystalline or liquid	http://www.sigmaaldrich.com/catalog/product/aldrich/123447?lang=en&region=US
Is the substance recognized in foreign pharmacopeias or registered in other countries?	No	http://crs.edqm.eu/db/4DCGI/web_catalog_CRS http://www.pharmacopoeia.co.uk/pdf/BP_2015_Index.pdf http://www.pmda.go.jp/english/pharmacopoeia/pdf/jpdata/JP16eng.pdf
Has information been submitted about the substance to the USP for consideration of monograph development?	Unknown; no current monograph avail	USP-NF
What medical condition(s) is the drug product compounded with the bulk drug substances intended to treat?	Treatment of extensive alopecia areate and warts	Monograph, Martindale: The Complete Drug Reference

Nomination from American Society of Health-System Pharmacists, September 30, 2014

Are there other drug products approved by FDA to treat the same medical condition?	No	
If there are FDA-approved drug products that address the same medical condition, why is there a clinical need for a compounded drug product?	No currently available topical sensitizer for treatment of alopecia areata	http://www.ncbi.nlm.nih.gov/pubmed/20115946
Are there safety and efficacy data on compounded drugs using the nominated substance?	Yes; limited to conducted studies, best information based on review article	http://www.ncbi.nlm.nih.gov/pubmed/20115946
If there is an FDA-approved drug product that includes the bulk drug substance nominated, is it necessary to compound a drug product from the bulk drug substance rather than from the FDA-approved drug product?	No	http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
What dosage form(s) will be compounded using the bulk drug substance?	Topical Solution	
What strength(s) will be compounded from the nominated substance?	Varies from 2% initially to 0.0001% to 0.001% for maintenance	
What are the anticipated route(s) of administration of the compounded drug product(s)?	Topically	
Has the bulk drug substance been used previously to compound drug product(s)?	Yes, most recently in 2014 as part of a study	http://www.ncbi.nlm.nih.gov/pubmed/25040421
Is there any other relevant information?	Literature search of uses	http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&cmd_current=Limits&term=Squaric+acid+dibutyl+ester+OR+2892-62-8+%5Brn%5D
	MSDS:	https://extranet.fisher.co.uk/chemicalProductData_uk/wercs?itemCode=10125643&lang=EN
	CAS:	2892-62-8



September 30, 2014

Submitted electronically via www.regulations.gov

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

PCCA respectfully submits the following list of nineteen chemicals to be considered for the List of Bulk Drug Substances that may be used in Pharmacy Compounding in accordance with Section 503A.

PCCA provides its more than 3,600 independent community compounding pharmacy members across the United States with drug compounding ingredients, equipment, extensive education, and consulting expertise and assistance.

Regarding the specific nominations, we would like to reference the attached spreadsheet and point out a couple of facts regarding our research. To the best of our knowledge, all items submitted:

- Do not appear in any of the three sections of the Orange Book.
- Do not currently have a USP or NF monograph.
- Meet the criteria of a "bulk drug substance" as defined in § 207.3(a)(4).

In regards to the request for chemical grade information, we would like to point out that many of the items submitted do not currently have a chemical grade. PCCA believes that pharmacists should use the highest grade chemical available on the market for all aspects of pharmaceutical compounding and we continue to actively source graded chemicals from FDA-registered manufacturers. However, in the current marketplace, some graded chemicals cannot be obtained for various reasons. PCCA actively tests all products received to ensure they meet our required standards to ensure our members receive the highest quality chemicals possible.

We would like to echo the concerns, voiced by NCPA and others in our industry, the strong recommendation to formalize the process by which the list is updated and communicated to the pharmacy industry. We also recommend an annual process to ensure understanding and adherence to the list. All submissions and updates to the list should be reviewed by the Pharmacy Compounding Advisory Committee (PCAC) and no changes to the list should occur with input and review by the PCAC.



We are also dismayed in the fact that no appointments have been made to the PCAC despite the call for nominations closing in March 2014. Without these appointments, FDA is unable to consult the Committee regarding this list, as outlined in the Act. PCCA, along with industry partners, strongly recommends that the FDA consult with the PCAC related to every single submission the Agency received in relation to FDA-2013-N-1525.

We appreciate this opportunity to submit this list for consideration and we look forward to continuing to work with the FDA in the future on this and other important issues as they relate to the practice of pharmacy compounding.

Sincerely,

A handwritten signature in black ink, appearing to read 'A. Lopez', with a stylized flourish at the end.

Aaron Lopez
Senior Director of Public Affairs
PCCA

A handwritten signature in black ink, appearing to read 'John Voliva', with a stylized flourish at the end.

John Voliva, R.Ph.
Director of Legislative Relations
PCCA

<i>PCCA Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations</i>	
Ingredient Name	Dibutyl Squarate
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	dibutyl ester of 3,4-dihydroxy-3-cyclobutene-1,2-dione; 3,4-Dibutoxy-3-cyclobutene-1,2-dione
Common Name(s)	SADBE, Squaric acid dibutyl ester, Dibutyl Squarate, Quadratic Acid Dibutylester
UNII Code	4RTO57VG65
Chemical Grade	N/A
Strength, Quality, Stability, and Purity	Assay, Description, Flash Point, Melting Point, Solubility; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Liquid
Recognition in foreign pharmcopeias or registered in other countries	No; None found unless by other name
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Solution
Compounded Strengths	0.1-5%
Anticipated Routes of Administration	Topical
Saftey & Efficacy Data	Rokhsar CK, et al. Efficacy of topical sensitizers in the treatment of alopecia areata. J Am Acad Dermatol. 1998 Nov;39(5 Pt 1):751-61. [http://www.ncbi.nlm.nih.gov/pubmed/9810892]
	Ajith C, et al. Efficacy and safety of the topical sensitizer squaric acid dibutyl ester in Alopecia areata and factors influencing the outcome. J Drugs Dermatol. 2006 Mar;5(3):262-6 [http://www.ncbi.nlm.nih.gov/pubmed/16573260]

	Dall'oglio F, et al. Topical immunomodulator therapy with squaric acid dibutylester (SADBE) is effective treatment for severe alopecia areata (AA): results of an open-label, paired-comparison, clinical trial. J Dermatolog Treat. 2005 Feb;16(1):10-4. [http://www.ncbi.nlm.nih.gov/pubmed/15897160]
	Iijima S, et al. Contact immunotherapy with squaric acid dibutylester for warts [corrected]. Dermatology. 1993;187(2):115-8. [http://www.ncbi.nlm.nih.gov/pubmed/8358098]
	Micali G, et al. Use of squaric acid dibutylester (SADBE) for cutaneous warts in children. Pediatr Dermatol. 2000 Jul-Aug;17(4):315-8. [http://www.ncbi.nlm.nih.gov/pubmed/10990585]
	Micali G, et al. Treatment of alopecia areata with squaric acid dibutylester. Int J Dermatol. 1996 Jan;35(1):52-6. [http://www.ncbi.nlm.nih.gov/pubmed/8838932]
	Safety and Efficacy of Squaric Acid Dibutyl Ester for the Treatment of Herpes Labialis (Squarex) [http://clinicaltrials.gov/show/NCT01971385]
Used Previously to compound drug products	Alopecia areata, alopecia totalis, warts, herpes labialis
Proposed use	Alopecia areata, alopecia totalis, warts, herpes labialis
Reason for use over and FDA-approved product	Treatment failures and/or patient unable to take FDA approved product
Other relevant information - Stability information	2 months: Wilkerson MG, et al. Squaric acid and esters: analysis for contaminants and stability in solvents. J Am Acad Dermatol. 1985 Aug;13(2 Pt 1):229-34. [http://www.ncbi.nlm.nih.gov/pubmed/4044949]

Submitted electronically via www.regulations.gov

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No.: FDA-2013-N-1525: *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations*

Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

A handwritten signature in black ink, appearing to read "Steve Pfister", with a long horizontal flourish extending to the right.

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Nomination from National Community Pharmacists Association, September 30, 2014

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability	Ingredient Format(s)	Recognition in Pharmacopeias	Final Compound Formulation Dosage Form(s)	Final Compound Formulation Strength	Final Compound Formulation Route(s) of Admin	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
Dibutyl squarate	3,4-dibutoxy-3-cyclobutene-1,2-dione	Dibutyl squarate	4RTO57VG65	From PCCA Certificate of Analysis: 96.9% Pure (Pass); From PCCA MSDS: 95% by weight and stable.	Liquid	Not yet submitted to USP	Solution	0.1-5%	Topical	<p>Ajith C, et al. Efficacy and safety of the topical sensitizer squaric acid dibutyl ester in Alopecia areata and factors influencing the outcome. J Drugs Dermatol. 2006 Mar;5(3):262-6; Rokhsar CK, et al. Efficacy of topical sensitizers in the treatment of alopecia areata. J Am Acad Dermatol. 1998 Nov;39(5 Pt 1):751-61. [http://www.ncbi.nlm.nih.gov/pubmed/9810892][http://www.ncbi.nlm.nih.gov/pubmed/16573260]; Iijima S, et al. Contact immunotherapy with squaric acid dibutylester for warts [corrected]. Dermatology. 1993;187(2):115-8. [http://www.ncbi.nlm.nih.gov/pubmed/8358098]</p>	<p>Indicated for alopecia areata, alopecia totalis, warts, herpes labialis; Squaric acid dibutyl ester (quadratic acid dibutyl ester, the dibutyl ester of 3,4,-dihydroxy-3-cyclobutene-1,2-dione, or SADBE) has been studied for the treatment of alopecia areata. More recently, successful treatment of warts using SADBE 0.5% to 5% in acetone under occlusive dressing as an agent of contact immunotherapy has been reported in the literature. In one study, serial dilutions of SADBE in acetone were applied twice weekly to warts in children for 10 weeks. Of the patients who completed the study (148 of 188), 84% of the treated patients "showed complete clinical resolution with no significant side effects." - See more at: http://www.pharmacytimes.com/publications/issue/2004-06-7953/2004-04/2004-04-7848#sthash.5j3K1aXh.dpuf</p>

Tab 81

FDA Review of Squaric Acid Dibutyl Ester
(Dibutyl Squarate)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: February 4, 2015

FROM: Hon-Sum Ko
Medical Officer, Division of Dermatology and Dental Products

Renqin Duan
Toxicologist (Pharmacology Reviewer), Division of Dermatology and
Dental Products

Norman Schmuff
Associate Director for Science and Communication (CMC Reviewer),
Office of Process and Facilities

THROUGH: Julie Beitz
Director, Office of Drug Evaluation III

Kendall Marcus
Director, Division of Dermatology and Dental Products

Jane Liedtka
Acting Clinical Team Leader, Division of Dermatology and Dental
Products

Barbara Hill
Supervisory Pharmacologist, Division of Dermatology and Dental
Products

Doanh Tran
Clinical Pharmacology Team Leader, Office of Clinical Pharmacology

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Squaric Acid Dibutylester for Inclusion on the 503A Bulk Drug
Substances List

I. Introduction

Squaric acid dibutylester (SADBE) has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Indications identified in the nomination include alopecia areata, warts, and herpes labialis. FDA reviewed this substance in 1999, and it is now being reevaluated. The background materials from the prior review are attached.

We have reviewed available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we recommend that SADBE be added to the list of bulk drug substances

that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?

1. Stability of the API and likely dosage forms

SADBE is rapidly degraded in the presence of water and is hydrolyzed in basic solution at a much higher rate than at acidic or neutral pH (Wilkerson et al., 1985). No thermal instability has been reported. The photochemical reactivity and stability traits of SADBE have not been reported in the literature; however, it is likely to be photochemically reactive based on the molecular structure.

2. Probable routes of API synthesis

Identity

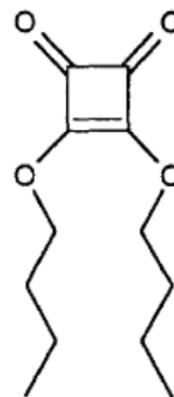
3,4-Dibutoxy-3-cyclobutene-1,2-dione

Dibutyl Squarate

Squaric Acid Dibutyl Ester

SADBE

CAS #	2892-62-8
Molecular Weight	226.27
Molecular Formula	$C_{12}H_{18}O_4$
Appearance	Colorless to slightly yellow oily liquid
Density	0.9650 g/mL
Refr. Index	1.4943
Boiling Point	148-150° C @ 0.6 torr; 121-122° C @ 0.2 torr
Flash Point	>110 C
Storage Precautions:	Keep cold and away from moisture, protect from light



Several methods of preparation have been reported in the chemical literature (Cohen and Cohen, 1966, Liu et al., 1997). A practical method amenable to large-scale synthesis was published in 1997 (Liu et al., 1997). It involves the reactions of squaric acid with the desired alcohol in the presence of an orthoformate.

3. Likely impurities

The likely impurities are unreacted starting materials and degradation products, squaric acid and n-butanol. As an oil, SADBE is more difficult to purify than crystalline solids.

4. *Toxicity of those likely impurities*

There appear to be no structural alerts for mutagenicity for the likely impurities. Other toxicity aspects are addressed in section “B” below.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

As SADBE is used in solution, there are no concerns related to particle size or polymorphism.

6. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

The physical and spectroscopic properties of SADBE have been well characterized.

Conclusions: We concur with FDA’s 1999 assessment, which stated, “Although squaric acid dibutyl ester is well characterized, it hydrolyzes readily in the presence of water. Since it is exquisitely sensitive to water, it should only be compounded in media in which there is no water. The impurity profile of SADBE may differ depending on the route of synthesis. SADBE used in compounding could vary significantly from SADBE used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.”

B. Are there concerns about the safety of the substance for use in compounding?

1. *Nonclinical Assessment*

The following information is summarized from the references listed below, which are the results from the search on Google, EmBase, PubMed, and TOXNET that links to multiple databases such as ChEBI, DrugPortal, EMIC, EPA ACToR, MeSH, NIST, PubChem, TOXLINE, and PubMed including PubMed AIDS, PubMed Cancer and PubMed Toxicology.

a. Pharmacology of the drug substance

SADBE is a contact sensitizer, which conjugates with a protein to form an antigen (Sherertz & Sloan, 1988). Guinea pigs have been sensitized to the dibutyl and diethyl ester derivatives of squaric acid by the application of 0.1 to 10% solutions (Noster et al., 1976; Happle et al., 1980; Avalos et al., 1989). The dibutyl ester appears to be more effective at sensitizing than the diethyl ester. Induction of an allergic contact dermatitis (ACD) by SADBE with a dose-response curve was observed in a murine local lymph node assay and modeling (Scott et al., 2002).

Treatment of alopecia areata-like hair loss with SADBE was investigated in C3H/HeJ mice (Freyschmidt-Paul et al., 1999; Gardner et al., 2000). Hair regrowth was observed on the treated side only in nine of twelve (Freyschmidt-Paul et al., 1999) or nine of eleven experimental mice (Gardner et al., 2000). The mechanism of action of topical

immunotherapy with a contact sensitizer such as SADBE still needs to be elucidated although an altered immune milieu is suspected.

No nonclinical pharmacology data were found for treatment of verruca vulgaris (warts).

b. Safety pharmacology

No information available.

c. Acute toxicity

No information available.

d. Repeat dose toxicity

No information available.

e. Mutagenicity

SADBE is not mutagenic in the Ames assay, nor does it cause the transformation of hamster kidney cells in vitro (Happle et al., 1980; Strobel & Rohrborn 1980).

f. Developmental and reproductive toxicity

Reproductive and developmental toxicity studies have not been conducted with SADBE.

g. Carcinogenicity

Carcinogenicity studies have not been conducted with SADBE. However, its breakdown product, squaric acid, causes a low incidence of tumors at the injection site in rats (van Duuren et al., 1971). Two synthetic precursors and potential contaminants of SADBE, hexachlorobutadiene and tetrachlorocyclobutenedione, show some carcinogenic activity in rats and mice, respectively (van Duuren et al., 1971; Kociba et al., 1977).

h. Toxicokinetics

No information available.

Conclusions: SADBE is not mutagenic in the Ames assay. Mammalian genotoxicity, safety pharmacology, acute and chronic toxicity, reproductive and developmental toxicity, and carcinogenicity studies have not been conducted with SADBE. Available nonclinical data are inadequate to determine whether SADBE would be safe to use in compounding.

2. Human Safety

a. Adverse reactions the substance has caused

There are no randomized controlled trials for SADBE use. Because estimated adverse reaction rates from case reporting and unblinded studies can be misleading, they will not be discussed. Case reporting comes from populations of uncertain size, while bias in unblinded studies cannot be eliminated, making estimation of adverse reaction rates unreliable.

SADBE is a contact sensitizer, and the expected manifestations of contact sensitization have been amply reported, including severe eczematous reactions with potential dissemination, erythema, pruritus, blisters, burning, and even bleeding. There have also been reports of hypopigmentation and lymphadenopathy. These findings were well discussed in FDA’s 1999 review on SADBE.

b. Clinical trials assessing safety

Non-genital Warts

FDA’s review of human safety data on SADBE in 1999 was not specific for cutaneous warts. However, the following table presents clinical data of SADBE in the treatment of warts as summarized by Pandey et al., upon literature review (2014).

Table 1. Previous SADBE Studies on Warts

Reference	Given by	Type of study	SADBE used, %	Type of wart treated	Age, years	Enrolled participants, <i>n</i>	Completed treatment, <i>n</i>	Success rate, %	Adverse effects	Adverse effects leading to discontinuation of treatment
Silverberg et al	Parent	Retrospective	0.20	Verruca vulgaris	5–14	61	59	58	Erythema, pruritus, burning	Burning, florid sensitization reaction
Micali et al	Physician	Retrospective	0.03–3	Verruca plana, verruca vulgaris	2–16	188	148	84	Erythema, pruritus, burning, edema, desquamation	Auto-eczematization
Lee and Mallory	Physician	Retrospective	0.5–5	Verruca vulgaris	1.8–40	29	26	69	Hypopigmentation, pruritus	Acute contact dermatitis and blisters
Hama et al	Physician	Case series	0.01	Verruca vulgaris	31 and 57	2	2	100	Erythema, pruritus	None reported

Alopecia Areata

FDA’s review on human safety data on SADBE in 1999 summarized the available data at that time, citing reports by Foley et al., (1996), Nishioka et al., (1993), and Valsecchi et al., (1984) for disseminated eczema, lymphoplasia, and depigmentation, respectively.

Since that review, there have been more publications containing safety data on SADBE in the treatment of alopecia areata, including an open-label, paired comparison trial (Dall'oglio 2005) enrolling 166 adults and 97 children “with no adverse effects.” In addition, two recent review articles on alopecia areata treatment discussed topical immunotherapy with SADBE and diphenylcyclopropenone without additional adverse reaction items other than those mentioned above in Section II.B.2.a (Tan et al., 2002, Alkhalifah et al., 2010).

Herpes Labialis

No data are available on SADBE in the treatment of herpes labialis.

c. Pharmacokinetic data

There are no reports of human pharmacokinetic studies in vivo. Sheretz and Sloan reported that the flux of 2% SADBE (0.5 mL applied to 7.06 cm² skin surface area, n=2) through human skin in vitro was 400±200 mg/cm².h (SD) with a lag time of 3.1 hours, while the flux was lower with squaric acid itself (Sheretz and Sloan, 1988).

d. The availability of alternative approved therapies that may be as safe or safer

The more common alopecia areata therapies include intralesional corticosteroid injection, topical corticosteroids, minoxidil, anthralin, phototherapy, systemic corticosteroids, cyclosporine, sulfasalazine, and methotrexate. However, the only FDA-approved therapy indicated for the treatment of alopecia areata is intralesional injection of corticosteroid suspensions, including triamcinolone acetonide, triamcinolone hexacetonide, betamethasone acetate and betamethasone sodium phosphate, and methylprednisolone acetate products. This form of treatment carries the risk of permanent skin atrophy with repeated injections.

Contact sensitizer therapy is usually reserved for use on cutaneous warts resistant to more regular treatment modalities. Such warts are frequently treated via initial physical destruction with cryotherapy and paring or excision. Topical salicylic acid in different vehicles has been included in the over-the-counter monograph, Wart Remover Drug Products (21 CFR 358 subpart B). There are no approved therapies for recalcitrant warts not responding to the treatments discussed above (cryotherapy, topical salicylic acid, etc.).

There are several FDA-approved therapies for Herpes labialis – docosanol (Abreva) as an over-the-counter cream preparation, and prescription products that include topical penciclovir cream, as well as famciclovir tablets and valacyclovir hydrochloride tablets. There is no information on SADBE in the treatment of herpes labialis. Thus safety comparisons cannot be made.

For the treatment of genital warts, there are approved drugs (podofilox gel and solution, imiquimod cream, and polyphenon E ointment). Solicitation of a contact dermatitis reaction in the skin of the genital area with sensitizers poses additional challenges for

management, because it may be more difficult to treat the eczematous reaction there, and it may also enhance the risk of secondary infections in this location. This makes the use of SADBE not desirable for the treatment of genital warts.

Conclusions: Although SADBE is not mutagenic in the Ames assay, there are inadequate nonclinical data otherwise to characterize its safety profile. Clinical data accumulated over the past 30 to 40 years, however, show that the adverse effects of SADBE are primarily related to its action as contact sensitizer, and the safety profile is likely no worse than those of available products (regardless of FDA approval) in the management of alopecia areata and warts. Nevertheless, there is a lack of data on the long-term safety of the use of SADBE.

As SADBE is a contact sensitizer, there is a concern that handlers of the substance may become inadvertently sensitized and develop contact dermatitis.

There is also a lack of data on use in specific populations such as pregnant or lactating women. Although systemic absorption of SADBE is probably low, the exposure of and risks to the fetus and neonates being nursed are unknown.

C. Are there concerns about whether a substance is effective for a particular use?

1. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

Non-genital Warts

Reference is made to the chart in Section II.B.2.b above showing response rates of non-genital warts that have been resistant to other forms of therapy, which vary from 58% to 100%. It is noted that three out of the four studies are retrospective, while one was a case series of 2.

Alopecia Areata

Reference is made to FDA's review of effectiveness data on SADBE in the treatment of alopecia areata in 1999, which summarized the available data at that time, citing reports by Tosti et al., (1996), Micali et al., (1996) and Orecchia et al., (1994), which gave response rates between 30% to 64%, and relapse rates between 50% and 70%.

Williams and Bigby's 2014 edition of Evidenced-Based Dermatology states:

- I found no systematic reviews. I found one RCT that involved small numbers of children. Tosti et al., compared SADBE, diphencyprone, minoxidil and placebo, finding a significant relationship between the age of the patients and the results. Complete hair regrowth was seen in 71.3% of adults, but in only 38.9% of children.
- Orecchia and Malagoli treated 28 unresponsive children under the age of 13 years with SADBE for 12 months. Thirty-two percent of the patients achieved

complete or cosmetically acceptable regrowth, and a further 21% achieved significant regrowth.

Delamere's Cochrane review of interventions in alopecia areata cited one study (Picoli 1995) that involved 30 subjects with severe alopecia areata randomly assigned to SADBE, lymphoblastoid interferon (IFN) or a combination of both. Variable treatment durations were used ranging from 12 to 32 weeks. The results at 6 months after discontinuation of therapy showed that 5/10 in the combination group, 2/10 in the SADBE group, and 2/10 in the IFN group achieved scores of 2 or 3 (full recovery with relapse within 6 months, and full/stable recovery with no relapse within 6 month, respectively).

In 2013, Shapiro summarized the literature experience, noting that topical immunotherapy of alopecia areata with SADBE and diphenylcyclopropenone gave similar results: success rate of 50 to 60% with a wide range of 9 to 87%. This is generally dependent on the severity and duration of disease and the heterogeneity of product source, but it is also possible that the variability is related to the compounding with a wide range of strengths used in treatment. Relapse after achieving significant regrowth develops in the majority of patients, with median time to relapse of 2½ years.

Herpes Labialis

There are no available data to support effectiveness of SADBE in the treatment of herpes labialis.

2. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

The proposed indications for product compounded with SADBE include alopecia areata, warts, and herpes labialis. These are not serious or life-threatening conditions.

3. *Whether there are any alternative approved therapies that may be as effective or more effective.*

The only FDA-approved therapy indicated for the treatment of alopecia areata is intralesional injection of corticosteroid suspensions (see above, Section II.B.2.d.). This form of therapy is not practical when the alopecia is widespread, as in the case of alopecia totalis or alopecia universalis, because each injection only produces a tuft of hair regrowth of approximately 0.5 cm². In addition, alopecia areata is also treated off-label with topical corticosteroids, minoxidil, anthralin, phototherapies, systemic corticosteroids, cyclosporine, sulfasalazine, or methotrexate.

There are approved therapies for non-genital cutaneous warts, but the contact sensitizers are generally reserved for the treatment of recalcitrant warts failing other treatment modalities, and as such, there are no approved alternative therapies for recalcitrant warts. In a Cochrane review of non-genital wart treatments by Kwok et al., (2012), it is noted that "none of the other reviewed treatments appeared safer or more effective than SA and

cryotherapy,” and when these two treatments were compared, the “evidence remains more consistent for SA.”

For the treatment of genital warts, there are approved drugs (podofilox gel and solution, imiquimod cream, and polyphenon E ointment), although solicitation of a contact dermatitis reaction in the treatment area with sensitizers poses additional challenges for management, making the use of SADBE not desirable.

There are FDA-approved therapies for the treatment of herpes labialis. Since data on the treatment effect of SADBE for herpes labialis are not available, effectiveness comparisons cannot be made.

Conclusions: Although there are no adequate and well controlled trials on SADBE, there appears to be evidence that this substance used in compounding for the treatment of recalcitrant warts and alopecia areata may be effective in a substantial proportion of patients.

The treatment response of recalcitrant cutaneous warts with SADBE topical immunotherapy is reported to range from 58% to 100%.

For alopecia areata treatment, topical immunotherapy with SADBE provides response rates reported in the order of 50% to 60%, but relapses are reported in the majority of patients. The variability of results is attributed primarily to factors like age, disease duration, and severity, but may also be related to the SADBE source and strengths used in the reports. Responses are lower for patients with a younger age of onset, longer duration of disease, and alopecia totalis/universalis. Because of the amount of evidence accumulated over time, Fitzpatrick’s *Dermatology in General Medicine* (8th edition, 2012) states: “Although not approved by the FDA, topical immunotherapy seems to be the most effective therapeutic option with the best safety profile in the treatment of chronic severe alopecia areata.” Currently the topical immunotherapy commonly used in medical practice for alopecia areata are SADBE and diphenylcyclopropanone.

No evidence is available to support effectiveness of SADBE in the treatment of herpes labialis.

D. Has the substance been used historically in compounding?

1. Length of time the substance has been used in pharmacy compounding

SADBE has been reported for use for over 30 years in pharmacy compounding.

2. The medical condition(s) it has been used to treat

SADBE has been reported for use primarily in the treatment of warts and alopecia areata (including alopecia totalis and alopecia universalis). There is a clinical study under recruitment on the “Safety and Efficacy of Squaric Acid Dibutyl Ester for the Treatment of Herpes Labialis” listed in [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01971385) (NCT01971385).

3. *How widespread its use has been*

SADBE use has been reported in North and South America, Australia, as well as European and Asian countries.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

Although SADBE is recognized globally in many countries, a search did not find this substance listed in the European, British, or Japanese Pharmacopeias.

Conclusions: SADBE has been compounded for use in the treatment of resistant non-genital warts and alopecia areata by practitioners for 30 to 40 years. Reports of its global use for these conditions have accumulated over time. There may also be novel uses such as for herpes labialis, but currently this use is still being studied and may be considered premature.

III. RECOMMENDATION

We recommend that SADBE be placed on the list of bulk drug substances in compounding under section 503A. Despite some concerns about stability and consistency in product quality, as well as lack of adequate nonclinical data, the substance has been in use in compounding for 30 to 40 years and has been adopted globally as a potentially useful form of topical immunotherapy for alopecia areata and recalcitrant warts by medical practitioners. Thus far, the adverse effects reported are related to its primary therapeutic effect as a contact sensitizer. There are some gaps in knowledge about long-term safety and use in specific populations such as pregnant and lactating women. However, given the lack of approved therapies indicated for recalcitrant warts and severe forms of alopecia areata (alopecia totalis and alopecia universalis), not listing SADBE could create obstacles to patient access, unless the drug product is obtained through an IND.

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration, Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540

Date: March 16, 1999

Subject: Review of Squaric Acid Dibutyl Ester, a Candidate for the
Pharmacy Compounding Bulk List, With Selected References

To: Pharmacy Compounding Steering Committee

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HFD-540 Review on Squaric Acid Dibutyl Ester
For the FDA Pharmacy Compounding Advisory Committee

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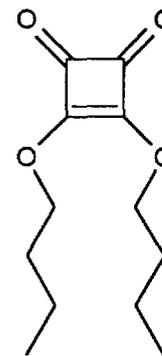
I. Introduction

The Division of Dermatologic and Dental Drug Products (HFD-540) has been charged with the review of squaric acid dibutyl ester (SADBE) for two indications: alopecia areata and verruca vulgaris (warts). Only published literature was used in the preparation of this review.

II. Chemical Characterization of SADBE

Identity

3,4-Dibutoxy-3-cyclobutene-1,2-dione
Dibutyl Squarate
Squaric Acid Dibutyl Ester
SADBE



<i>CAS #</i>	2892-62-8
<i>Molecular Weight</i>	226.27
<i>Molecular Formula</i>	$C_{12}H_{18}O_4$
<i>Appearance</i>	<i>Colorless to slightly yellow oily liquid</i>
<i>Density</i>	0.9650 g/mL
<i>Refr. Index</i>	1.4943
<i>Boiling Point</i>	148-150° C @ 0.6 torr; 121-122° C @ 0.2 torr
<i>Flash Point</i>	>110 C
<i>Storage Precautions:</i>	<i>Keep cold and away from moisture, protect from light</i>

The physical and spectroscopic properties of squaric acid dibutyl ester (SADBE) have been well characterized.

Stability

Squaric acid esters have been shown to be readily hydrolyzed in aqueous solutions, and are hydrolyzed in basic solution at a much higher rate than at acidic or neutral pH. No thermal

instability has been reported. The photochemical reactivity and stability traits of SADBE have not been reported in the literature; however, it is likely to be photochemically reactive based on the molecular structure.

Synthesis and Purity

Squaric acid was first prepared in 1959 by Cohen et al., and its first derivatives, dimethyl squarate and diethyl squarate, were reported in 1966 (Cohen and Cohen, 1966). SADBE is a neutral compound, which contains the unusual unsaturated, dicarbonyl-containing 4-carbon ring, which shows aromatic character. The alkoxy substituents are analogous to carboxylic acid esters, showing similar chemical behavior. Several methods of preparation have been reported in the chemical literature (Cohen and Cohen, 1966), and this material is available from several commercial suppliers, though the methods of production currently are not known. An investigation into the hydrolysis, contaminants, and degradants of this material has been published (Wilkerson et al., 1985).

Several domestic commercial sources of SADBE have been identified: Fisher Scientific (Acros Organics), Frinton Laboratories, Inc., and Sigma-Aldrich Co. Each has confirmed their knowledge of the identity or identities of the actual manufacturing site(s) for SADBE: all but one has declined to make this information public.

Literature on the syntheses of SADBE, refers in general to modern analytical methodology but provide few details as to the actual practices. These reports cite IR spectroscopy, UV spectroscopy, elemental analysis, gas chromatography and GC-mass spectrometry as the determinants of purity. While these are common techniques, they are not established quantitative methods for analysis of this material. The adequacy of these methods for determination of purity and levels of contaminants in SADBE cannot be assessed.

Assessment 1: Although squaric acid dibutyl ester is well characterized, it hydrolyzes readily in the presence of water. Since it is exquisitely sensitive to water, it should only be compounded in media in which there is no water. The impurity profile of SADBE may differ depending on the route of synthesis. SADBE used in compounding could vary significantly from SADBE used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.

III. Safety of SADBE

A. Animal Toxicology

Squaric acid dibutylester is not mutagenic in the Ames assay nor does it cause the transformation of hamster kidney cells *in vitro* (Happle et al., 1980; Strobel & Röhrborn, 1980). The synthetic precursors of squaric acid, hexachlorobutadiene and tetrachlorocyclobutenedione show some carcinogenic activity (van Duuren et al., 1971; Kociba et al., 1977).

The ability of the dibutyl and diethyl esters to penetrate human or mouse skin *in vitro* has been investigated (Sherertz & Sloan, 1988). Diffusion of the diethyl ester was 4.5 fold higher than squaric acid and the dibutyl ester was 24-fold higher than squaric acid.

Guinea pigs have been sensitized to the dibutyl and diethyl ester derivatives of squaric acid by the application of 0.1 to 10% solutions (Noster et al., 1976; Happle et al., 1980; Avalos et al., 1989). The dibutyl ester appears to be more effective at sensitizing than the diethyl ester. The sensitization to the diethyl ester is specific in that animals sensitized to this ester are not sensitized to the other esters as well. In addition, these studies have shown that the dimethoxy (dimethyl), diethoxy (diethyl), diisopropoxy (diisopropyl), dihydroxy and phenylethoxy derivatives of squaric acid are strong irritants.

Assessment 2: SADBE is not mutagenic in the Ames assay. Mammalian genotoxicity, chronic toxicity, reproductive toxicity, and carcinogenicity studies have not been conducted with SADBE. Thus, it is not known what the potential toxicities of SADBE are in humans or whether it is likely to be teratogenic in humans.

B. Human Safety

There are no published reports of studies designed to systematically evaluate the safety of SADBE. In a comprehensive review of immunomodulatory therapy, Naldi et al. (1990) determined that the discussion of side effects was adequate in only half (5 out of 10) trials involving SADBE.

Although not always adequately characterized, the adverse events described in clinical studies reporting the use of SADBE for treatment of alopecia areata and warts have included: burning sensation immediately after application, dermatitis (localized to the application site or generalized), transient perioral burning after application, autoeczematization, persistent contact dermatitis on the primary site of sensitization (rare), severe generalized dermatitis, generalized pruritus without dermatitis, leukoderma, xerosis, scaling, edema of treated skin, scalp folliculitis, and systemic reactions with fever and arthralgias (see review by Rokhsar et al., 1998). Please see Table 1 regarding some of the published reports on side effects.

Table 1 - Side Effects of SADBE

Author	Journal	Year	Side Effect
Foley et al.	Am. J. Contact Derm.	1996	Severe eczematous reaction in 10/14 pts and disseminated reactions in 9/14
Nishioka et al.	Contact Derm.	1993	Benign lymphoplasia
Valsecchi et al.	Contact Derm.	1984	Depigmentation

Physicians and other health care workers, including compounding pharmacists, are at risk for SADBE sensitization. Persons handling the drug should exercise contact precautions and be careful not to inhale these potent sensitizers, as even trace amounts can cause severe allergic reactions. Unwitting exposure and re-exposure can lead to an unwanted adverse reaction that is

Assessment 5: Since its first clinical report in 1980, SADBE has been used as an experimental treatment alternative for alopecia areata and verruca vulgaris. Evidence for current widespread use is not apparent.

V. Available Evidence of Effectiveness

Alopecia areata and warts frequently resolve without any therapeutic intervention. For example, in a study of the natural history of alopecia areata, of 63 alopecia areata patients followed for one year without treatment, hair had regrown in all but 4 patients in one year, and in all but 1 patient after two years. The great majority had recovered by 3 months after their only office visit (Arnold, 1952). Alopecia areata with less than 25% involvement has a high incidence of spontaneous recovery, whereas more severe involvement has a lesser rate of recovery (Moschella and Hurley, 1992). Regarding the natural history of warts, a two-year study showed that two-thirds of warts regressed without treatment (Massing and Epstein, 1963).

Despite the necessity for a placebo arm in evaluating experimental therapies such as SADBE, much of the excitement generated about topical immunomodulators stems from studies that were either uncontrolled or internally controlled. Describing therapy for alopecia areata, Rook et al. state: “The widely conflicting claims for the success of many different measures merely reflect the very great variations in the spontaneous course of the disease.”

Studies that demonstrate a “positive” result, such as regrowth of hair, is more likely to be submitted for publication or published than are studies with “negative” results. Therefore, the published literature may overstate the efficacy of novel therapies. Additionally, most clinical studies lack long-term follow-up, so the lasting treatment benefits cannot be evaluated.

Warts

Warts, caused by cutaneous infection with the human papillomavirus, are another very common dermatological ailment. Aside from cosmetic disfigurement, patients seek treatment for these lesions because plantar (foot) warts may cause pain on walking or interfere with gait, and warts on the fingers may interfere with manual dexterity. As with alopecia areata, therapy is not always effective, although the absence of a control arm precludes any definitive comparisons with other modalities.

Table 2 - Use of SADBE in Human Papillomavirus Infection

Author	Journal	Year	Disease	N	Treatment	Response/ITT
Paller et al.	AAD Academy Summer Meeting	1998	Verruca vulgaris in children	61	Sensitize 2% Treat 2-3X/wk c initial 0.2%	58% complete clearance p average of 7 wks
Iijima et al.	Dermatology	1993	Verruca vulgaris	20	Sensitize 2% Treat q week 0.1 or 0.01 %	60% after avg of 6 applications

Alopecia areata

To make sense of the efficacy of the use of topical sensitizers for the treatment of alopecia areata, Naldi et al., 1990, reviewed 26 papers on “published clinical trials on dinitrochlorobenzene, squaric acid dibutylester, and diphencyprone [DPCP] each published between January 1977 and January 1988.” The authors of the paper stated, “According to our evaluation, the published literature is of limited use in defining the role of topical immunotherapy in alopecia areata. Half the studies examined used informal methods (uncontrolled or historically controlled trials)... In general, the studies that we examined had serious drawbacks in reporting critical procedures such as assessing treatment and selecting and following up patients... In conclusion, a definite role of topical immunotherapy for alopecia areata has yet to be established and this treatment should be offered only as an experimental modality...” To date, there have been at least 14 reports in the peer-reviewed English-language literature on the use of SADBE for treatment of alopecia areata. Three of the most recent studies are presented in Table 3.

Table 3 - Use of SADBE in Alopecia Areata

Author	Journal	Year	Disease	N	Treatment	Response/ITT	Ctrl
Tosti et al.	J. Am. Acad. Dermatol.	1996	Alopecia totalis in children	33		30.3% complete 70% relapse rate	No
Micali et al.	Int. J. Dermatol.	1996	Alopecia areata	144		64% with some regrowth	Yes
Orecchia et al	Pediatr. Dermatol.	1994	Alopecia areata in children <13 years	28	Weekly for 12 months	32.1% complete or acceptable 21.4% partial	No

More recently (in 1998) Rokhsar and his colleagues from the Department of Dermatology at N.Y.U. examined the efficacy of contact sensitizers in alopecia areata in a summary review of the literature. They present a more detailed study of the available literature on the use of SADBE to treat alopecia areata. Their overview of the data in the literature shows a response rate range from 29% to 87%. This includes a sum of both complete and partial responders. The weighted average response rate is 59%, which is similar to the response rate seen in the largest study by Micali et al. Interestingly, a relapse rate of 50-70% was seen in the patients even with continuation of treatment, suggesting that in many patients the response is temporary at best.

A tabular summary of the suggested role of immunomodulators (as gleaned from the leading dermatological textbooks) for the treatment of these disorders is presented in Table 4. There exist many therapeutic alternatives for alopecia areata and warts. The general consensus is that SADBE is currently a potentially useful experimental therapy for patients who fail more conventional therapy. It has shown a modicum of short-term efficacy, but additional well-controlled, long-term studies are needed to evaluate efficacy.

Assessment 6: Taking into account the available information, there is minimal evidence that SADBE is effective in the long-term treatment of alopecia areata or verruca.

Treatment of alopecia areata with SADBE may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped.

Table 4 - Perspectives on use of SADBE for Treatment of Alopecia Areata and for Warts

Reference	Disease	Treatment of Choice	Other Suggested Treatments	Role of SADBE in Therapeutic Armamentarium
<i>Andrews' Diseases of the Skin: Clinical Dermatology</i> , ed. by Arnold et al., Eighth edition (1990) (textbook)	Alopecia Areata—patchy involvement	Intralesional injections of corticosteroid	"None of the other various therapeutic approaches are clearly superior to corticosteroids"	SADBE: not discussed
	Alopecia Areata—totalis/universal is	Systemic (IM) steroids should be "seriously considered".		
	Common/Plantar Warts	Treatment of choice not identified	A, B, C, D, E, F, G, H, I, J, K (not plantar warts), L, M	"It (SADBE) may be worth trying in very large and resistant warts."
<i>Dermatology in General Medicine</i> , ed. by Fitzpatrick et al., Third edition (1987) (textbook)	Alopecia Areata	Treatment of choice not identified	N (little efficacy), P, Q, R	"SADBE (nonmutagenic)...used successfully"; "local discomfort is a problem"
	Warts	Treatment of choice not identified	A, B, C, D, E, F, G, H, I, J, K, T, U, V	SADBE: may be suitable substitute, because it is negative in the Ames mutagenicity assay
<i>Textbook of Dermatology</i> , ed. by Rook et al., Fourth Edition (1986) (textbook)	Alopecia Areata	Treatment of choice not identified	O (unclear if regrowth is maintained), P (not helpful in alopecia totalis—except for eyebrows), W, X, Y, Z	Possible teratogenicity of DNCB (another topical sensitizer) led to SADBE substitution
	Warts	Treatment of choice not identified	B, C, D, L, L', E, H, I, J, T, A', B', ; avoid A,U (risk of scarring)	SADBE: not mentioned
<i>Pediatric Dermatology</i> , ed. by Schachner and Hansen, (1988) (textbook)	Alopecia Areata	Topical corticosteroids, alone or under occlusion; Intralesional corticosteroids	O (for severe involvement, unresponsive to topical or intralesional treatment)	SADBE: as effective as DNCB. "[SADBE] cannot be regarded as completely safe until extensive toxicologic evaluation has been completed."
	Warts	Treatment of choice not identified	A, B, C, G, K	

A: Electrodesiccation and curettage; B: Cryotherapy; C: Salicylic Acid; D: Lactic Acid; E: Trichloroacetic/ other caustic acids; F: Podophyllin; G: laser; H: 5-Fluoro-uracil; I: Retinoids; J: Interferon; K: Cantharin; L: Formalin; L': Glutaraldehyde; M: Bleomycin; N: Topical corticosteroids; O: Systemic corticosteroids; P: Intralesional corticosteroids; Q: Anthralin; R: PUVA (Psoralen and UV-A); S: Inosiplex; T: Bleomycin; U: Surgical excision; V: Vaccination with autogenous-wart extracts; W: Ultraviolet radiation; X: Minoxidil; Y: Dithranol; Z: Zinc sulfate; A': Levamisole; B': Photodynamic inactivation; C': Psychological methods (hypnosis)

VI. Conclusions

Assessment 1: Although squaric acid dibutyl ester is well characterized, it is also known to hydrolyze readily in the presence of water. Since it is so exquisitely sensitive to even small amounts of water, it should only be compounded in media in which there is no water. The impurity profile of SADBE may differ depending on the route of synthesis. SADBE used in compounding could vary significantly from SADBE used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.

Assessment 2: SADBE is not mutagenic in the Ames assay. Mammalian genotoxicity, chronic toxicity, reproductive toxicity, and carcinogenicity studies have not been conducted with SADBE. Thus, it is not known what the potential toxicities of SADBE are in humans or whether it is likely to be teratogenic in humans.

Assessment 3: There is limited characterization of the human safety profile. Adverse side effects from exposure to SADBE include severe eczematous dermatitis, blistering, lymphoplasia and skin pigmentation changes.

Assessment 4: Many approved products are available for the treatment of verruca and alopecia areata.

Assessment 5: Since its first clinical report in 1980, SADBE has been used as an experimental treatment alternative for alopecia areata and verruca vulgaris. Evidence for current widespread use is not apparent.

Assessment 6: Taking into account the available information, there is minimal evidence that SADBE is effective in the long-term treatment of alopecia areata. Treatment of alopecia areata with SADBE may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped. SADBE is potentially a second or third-line treatment alternative for verruca vulgaris.

VII. Recommendation

Four criteria have been used to evaluate SADBE for inclusion on the bulk drug compounding list: (1) the chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness. Our evaluation of SADBE, based on a balanced assessment of each criterion in the context of the others, leads to our recommendation that it is not appropriate for SADBE to be included on the list.

The nonclinical studies conducted to date minimally evaluate the safety of squaric acid dibutylester. The studies do not characterize the potential toxicity to internal tissues nor do they characterize the dermal toxicity from long term topical application. Conclusions about the safety of SADBE cannot be made before such studies are done.

The evidence from historical use suggests that SADBE may be useful as second or third line therapy for warts and possibly as a therapy for alopecia areata. It is our impression that SADBE has become more commonly used as a topical sensitizer than dinitrochlorobenzene (DNCB), largely because the latter compound, available for toxicologic evaluation for more than 20 years, has well-established toxicities. The notion seems to be that the known toxicities of DNCB make it less attractive than the unknown toxicities of SADBE.

If SADBE is not placed on the list of bulk drug substances for compounding, a physician/investigator could still file an investigational new drug application (IND) for use of SADBE in humans. Pursuing this route would provide important and clinically relevant information about: (1) the chemistry of SADBE (i.e., its stability, its comparative solubility in different vehicles), (2) the safety profile – pharmacology/toxicology of SADBE (i.e., safety information about long-term dermal usage), and (3) the clinical side effect profile (i.e., risk of pigmentary and eczematous reactions).

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Tab 82

Diphenylcyclopropenone Nominations



September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: FDA-2013-D-1525; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act, Revised Request for Nominations

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit comments to the Food and Drug Administration (FDA) on bulk drug substances that may be used to compound drug products. Nominations for this list were originally announced in the Federal Register on December 4, 2013.¹ A revision to this notification was published on July 2, 2014.² This list would fulfill Section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act) which regulates entities that compound drugs. On November 27, 2013, the Drug Quality and Security Act (DQSA) was signed into law [P.L. 113-54]. The DQSA removed several parts of Section 503A that were declared unconstitutional by the U. S. Supreme Court in 2002. The law requires the FDA to go through the rulemaking process to implement several parts of Section 503A, including a requirement to establish a list of bulk drug substances that may be used in compounding for which there is no applicable USP or NF monograph nor are they components of an FDA-Approved drug.

ASHP represents pharmacists who serve as patient care providers in acute and ambulatory settings. The organization's more than 40,000 members include pharmacists, student pharmacists and pharmacy technicians. For over 70 years, ASHP has been on the forefront of efforts to improve medication use and enhance patient safety. As you are well aware, ASHP was

¹ Federal Register, Volume 78, No. 233. Pages 72841 – 72843

² Federal Register, Volume 79, No. 127. Pages 37747– 37750

actively engaged with the FDA and Federal lawmakers from the onset of the meningitis outbreak in the Fall of 2012. In the aftermath of the incident, ASHP has worked with policymakers, practitioners, and nationally recognized experts in compounding and manufacturing to develop new approaches to protect patients from preventable harm, and to give practitioners and organizations confidence that compounding outsourcers are appropriately regulated and inspected, and that the products they produce are safe.

ASHP understands that the FDA received thousands of nominations for substances to be included on the bulk list, but that the overwhelming majority of nominations did not meet the basic definition of “active ingredient,” and will therefore not be considered by the FDA. Further, the Agency states “Bulk substances that were previously nominated will not be further considered unless they are renominated and adequately supported.” ASHP previously submitted comments to the FDA under the original solicitation for bulk substances and we are again nominating three chemicals – diphenylcyclopropenone, squaric acid dibutyl ester, and thymol iodide – for consideration by the FDA. Please see the accompanying excel file which contains a worksheet for each of the drugs with the information outlined by the FDA.

ASHP appreciates the opportunity to comment as the FDA develops a list of bulk drug substances that may be used in compounding. Please contact me if you have any questions or wish to discuss our comments further. I can be reached by telephone at 301-664-8806, or by e-mail at ctopoleski@ashp.org.

Sincerely,

A handwritten signature in black ink, appearing to read "Christopher J. Topoleski". The signature is fluid and cursive, with a large initial "C" and "T".

Christopher J. Topoleski
Director, Federal Regulatory Affairs.

Column A—What information is requested?	Column B—put data specific to the nominated substance	References
What is the name of the nominated ingredient?	Diphenylcyclopropenone	http://crs.edqm.eu/db/4DCGI/web_catalog_CRS http://crs.edqm.eu/
Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?	Yes	
What is the chemical name of the substance?	2,3-DIPHENYL-2-CYCLOPROPEN-1-ONE (C15H10O)	http://fdasis.nlm.nih.gov/srs/ProxyServlet?mergeData=true&objectHandle=DBMaint&APPLICATION_NAME=fdasrs&actionHandle=default&nextPage=jsp/srs/ResultScreen.jsp&TXTSUPERLISTID=I7G14NW5EC&QV1=DIPHENYLCYCLOPROPENONE
What is the common name of the substance?	DIPHENCYPRONE	http://fdasis.nlm.nih.gov/srs/ProxyServlet?mergeData=true&objectHandle=DBMaint&APPLICATION_NAME=fdasrs&actionHandle=default&nextPage=jsp/srs/ResultScreen.jsp&TXTSUPERLISTID=I7G14NW5EC&QV1=DIPHENYLCYCLOPROPENONE
Does the substance have a UNII Code?	I7G14NW5EC	http://fdasis.nlm.nih.gov/srs/ProxyServlet?mergeData=true&objectHandle=DBMaint&APPLICATION_NAME=fdasrs&actionHandle=default&nextPage=jsp/srs/ResultScreen.jsp&TXTSUPERLISTID=I7G14NW5EC&QV1=DIPHENYLCYCLOPROPENONE
What is the chemical grade of the substance?	Description, melting point, purity meets technical grade standards	http://datasheets.scbt.com/sds/WPNA/EN/sc-255115.pdf

<p>What is the strength, quality, stability, and purity of the ingredient?</p>	<p>Varies - Ex: 1 gm and 5gm in glass bottle; 98% purity; stable if stored in dry, well-ventilated place</p>	<p>http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=177377&brand=ALDRICH&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F177377%3Flang%3Den</p>
<p>How is the ingredient supplied?</p>	<p>Crystalline Powder, Powder or Crystals</p>	<p>http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=177377&brand=ALDRICH&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F177377%3Flang%3Den</p>
<p>Is the substance recognized in foreign pharmacopeias or registered in other countries?</p>	<p>No</p>	<p>http://crs.edqm.eu/db/4DCGI/web_catalog_CRS http://www.pharmacopoeia.co.uk/pdf/BP_2015_Index.pdf http://www.pmda.go.jp/english/pharmacopoeia/pdf/jpdata/JP16eng.pdf</p>
<p>Has information been submitted about the substance to the USP for consideration of monograph development?</p>	<p>Unknown; no current monograph available</p>	<p>USP-NF</p>
<p>What medical condition(s) is the drug product compounded with the bulk drug substances intended to treat?</p>	<p>Treatment of extensive alopecia areate</p>	<p>https://www.medicinescomplete.com/mc/martindale/current/4896-w.htm?q=diphenylcyclopropenone&=search&ss=text&p=1#_hit</p>
<p>Are there other drug products approved by FDA to treat the same medical condition?</p>	<p>Yes</p>	

Nomination from American Society of Health-System Pharmacists, September 30, 2014

<p>If there are FDA-approved drug products that address the same medical condition, why is there a clinical need for a compounded drug product?</p>	<p>Possibly due to limited topical options in treating alopecia aerate</p>	<p>http://www.ncbi.nlm.nih.gov/pubmed/20115946</p>
<p>Are there safety and efficacy data on compounded drugs using the nominated substance?</p>	<p>Yes; limited to conducted studies, best information based on review article</p>	<p>http://www.ncbi.nlm.nih.gov/pubmed/20115946</p>
<p>If there is an FDA-approved drug product that includes the bulk drug substance nominated, is it necessary to compound a drug product from the bulk drug substance rather than from the FDA-approved drug product?</p>	<p>No</p>	<p>http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>
<p>What dosage form(s) will be compounded using the bulk drug substance?</p>	<p>Topical Solution</p>	
<p>What strength(s) will be compounded from the nominated substance?</p>	<p>Varies; usually 2%</p>	<p>Journal of the American Academy of Dermatology; Volume 44, Issue 1, January 2001, Pages 73–76</p>
<p>What are the anticipated route(s) of administration of the compounded drug product(s)?</p>	<p>Topically</p>	
<p>Has the bulk drug substance been used previously to compound drug product(s)?</p>	<p>Yes</p>	
<p>Is there any other relevant information?</p>	<p>Pubmed Search Results:</p>	<p>http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&cmd_current=Limits&term=Diphenylcyclopropanone+OR+886-38-4+%5Brn%5D</p>
	<p>MSDS:</p>	<p>http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=177377&brand=ALDRICH&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F177377%3Flang%3Den</p>

Nomination from American Society of Health-System Pharmacists, September 30, 2014

	CAS:	886-38-4
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September 30, 2014

Submitted electronically via www.regulations.gov

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

PCCA respectfully submits the following list of nineteen chemicals to be considered for the List of Bulk Drug Substances that may be used in Pharmacy Compounding in accordance with Section 503A.

PCCA provides its more than 3,600 independent community compounding pharmacy members across the United States with drug compounding ingredients, equipment, extensive education, and consulting expertise and assistance.

Regarding the specific nominations, we would like to reference the attached spreadsheet and point out a couple of facts regarding our research. To the best of our knowledge, all items submitted:

- Do not appear in any of the three sections of the Orange Book.
- Do not currently have a USP or NF monograph.
- Meet the criteria of a “bulk drug substance” as defined in § 207.3(a)(4).

In regards to the request for chemical grade information, we would like to point out that many of the items submitted do not currently have a chemical grade. PCCA believes that pharmacists should use the highest grade chemical available on the market for all aspects of pharmaceutical compounding and we continue to actively source graded chemicals from FDA-registered manufacturers. However, in the current marketplace, some graded chemicals cannot be obtained for various reasons. PCCA actively tests all products received to ensure they meet our required standards to ensure our members receive the highest quality chemicals possible.

We would like to echo the concerns, voiced by NCPA and others in our industry, the strong recommendation to formalize the process by which the list is updated and communicated to the pharmacy industry. We also recommend an annual process to ensure understanding and adherence to the list. All submissions and updates to the list should be reviewed by the Pharmacy Compounding Advisory Committee (PCAC) and no changes to the list should occur with input and review by the PCAC.



We are also dismayed in the fact that no appointments have been made to the PCAC despite the call for nominations closing in March 2014. Without these appointments, FDA is unable to consult the Committee regarding this list, as outlined in the Act. PCCA, along with industry partners, strongly recommends that the FDA consult with the PCAC related to every single submission the Agency received in relation to FDA-2013-N-1525.

We appreciate this opportunity to submit this list for consideration and we look forward to continuing to work with the FDA in the future on this and other important issues as they relate to the practice of pharmacy compounding.

Sincerely,

A handwritten signature in black ink, appearing to read 'A. Lopez', with a stylized flourish at the end.

Aaron Lopez
Senior Director of Public Affairs
PCCA

A handwritten signature in black ink, appearing to read 'John Voliva', with a stylized flourish at the end.

John Voliva, R.Ph.
Director of Legislative Relations
PCCA

<i>PCCA Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations</i>	
Ingredient Name	Diphenylcyclopropenone
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	2,3-Diphenylcyclopropenone-1
Common Name(s)	Diphencyprone; DPCP
UNII Code	I7G14NW5EC
Chemical Grade	N/A
Strength, Quality, Stability, and Purity	Description, Melting Point, Purity; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmcopeias or registered in other countries	No; None found unless by other name
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Solution, Stick
Compounded Strengths	0.01 - 2%
Anticipated Routes of Administration	Topical
Safety & Efficacy Data	Choi Y, et al. Topical immunotherapy with diphenylcyclopropenone is effective and preferred in the treatment of periungual warts. Ann Dermatol. 2013 Nov;25(4):434-9. [http://www.ncbi.nlm.nih.gov/pubmed/24371390]
	Salsberg JM, et al. The safety and efficacy of diphencyprone for the treatment of alopecia areata in children. Arch Dermatol. 2012 Sep;148(9):1084-5. [http://archderm.jamanetwork.com/article.aspx?articleid=1359490]

Nomination from PCCA, September 30, 2014

	Choi JW, et al. Does immunotherapy of viral warts provide beneficial effects when it is combined with conventional therapy? <i>Ann Dermatol.</i> 2011 Aug;23(3):282-7. [http://www.ncbi.nlm.nih.gov/pubmed/21909196]
	El Khoury J, et al. Topical immunomodulation with diphenylcyclopropenone for alopecia areata: the Lebanese experience. <i>Int J Dermatol.</i> 2013 Dec;52(12):1551-6. [http://www.ncbi.nlm.nih.gov/pubmed/24134785]
	Sotiriadis D, et al. Topical immunotherapy with diphenylcyclopropenone in the treatment of chronic extensive alopecia areata. <i>Clin Exp Dermatol.</i> 2007 Jan;32(1):48-51. [http://www.ncbi.nlm.nih.gov/pubmed/17004987]
	Upitis JA, et al. The use of diphenylcyclopropenone in the treatment of recalcitrant warts. <i>J Cutan Med Surg.</i> 2002 May-Jun;6(3):214-7. [http://www.ncbi.nlm.nih.gov/pubmed/11951129]
Used Previously to compound drug products	Alopecia areata, alopecia totalis, warts
Proposed use	Alopecia areata, alopecia totalis, warts
Reason for use over and FDA-approved product	Treatment failures and/or patient unable to take FDA approved product

Nomination from PCCA, September 30, 2014

Other relevant information - Stability information	Unless other studies performed / found: USP <795> recommendation of BUD for nonaqueous formulations – “no later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.
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Submitted electronically via www.regulations.gov

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No.: FDA-2013-N-1525: *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations*

Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

A handwritten signature in black ink, appearing to read "Steve Pfister", with a long horizontal flourish extending to the right.

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Nomination from National Community Pharmacists Association, September 30, 2014

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format(s)	Recognition in Pharmacopias	Final Compounded Formulation Dosage Form(s)	Final Compounded Formulation Strength	Final Compounded Formulation Route of Admin	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
Diphenylcyclopropenone	2,3-diphenyl-2-cyclopropen-1-one	Diphenylcyclopropenone, DPCP	17G14NW5EC	From PCCA Certificate of Analysis: 99.5% Pure; From PCCA MSDS: >95% by weight and stable.	Powder	Not yet submitted to USP	Solution, stick	0.01-2%	Topical	<p>Choi Y, et al. Topical immunotherapy with diphenylcyclopropenone is effective and preferred in the treatment of periungual warts. <i>Ann Dermatol.</i> 2013 Nov;25(4):434-9. [http://www.ncbi.nlm.nih.gov/pubmed/24371390]; Salsberg JM, et al. The safety and efficacy of diphenylcyclopropenone for the treatment of alopecia areata in children. <i>Arch Dermatol.</i> 2012 Sep;148(9):1084-5. [http://archderm.jamanetwork.com/article.aspx?articleid=1359490]; Sotiriadis D, et al. Topical immunotherapy with diphenylcyclopropenone in the treatment of chronic extensive alopecia areata. <i>Clin Exp Dermatol.</i> 2007 Jan;32(1):48-51. [http://www.ncbi.nlm.nih.gov/pubmed/17004987]; Upitis JA, et al. The use of diphenylcyclopropenone in the treatment of recalcitrant warts. <i>J Cutan Med Surg.</i> 2002 May-Jun;6(3):214-7. [http://www.ncbi.nlm.nih.gov/pubmed/11951129]</p>	<p>API mixed in Acetone; Allergic contact sensitizer; indicated for topical immunotherapy for alopecia areata, alopecia totalis, recalcitrant and plantar warts; Diphenylcyclopropenone, which is well characterized chemically, has been used for the topical treatment of extensive alopecia areata. The nomination of this substance was not received by FDA in time to permit a full discussion of it at the October 1998 meeting of the Pharmacy Compounding Advisory Committee. A decision about this substance is therefore being deferred until after FDA has had an opportunity to consult the Pharmacy Compounding Advisory Committee about it at a future meeting. C. Nominated Drug Substances Still Under Consideration for the Bulk Drugs List The following 10 drug substances were nominated for inclusion on the proposed bulk drugs list. However, for the reasons described in section III.C of this document, they are still under review by the agency.</p>

Tab 83

FDA Review of Diphenylcyclopropenone



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: February 4, 2015

FROM: Hon-Sum Ko
Medical Officer, Division of Dermatology and Dental Products

Norman See
Toxicologist (Pharmacology Reviewer), Division of Dermatology and
Dental Products

Norman Schmuff
Associate Director for Science and Communication (CMC Reviewer),
Office of Process and Facilities

THROUGH: Julie Betiz
Director, Office of Drug Evaluation III

Kendall Marcus
Director, Division of Dermatology and Dental Products

Jane Liedtka
Acting Clinical Team Leader, Division of Dermatology and Dental
Products

Barbara Hill
Supervisory Pharmacologist, Division of Dermatology and Dental
Products

Doanh Tran
Clinical Pharmacology Team Leader, Office of Clinical Pharmacology

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Diphenylcyclopropanone for Inclusion on the 503A Bulk Drug
Substances List

I. Introduction

Diphenylcyclopropanone (DPCP) has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Indications identified in the nomination include the treatment of non-genital warts and alopecia areata. FDA reviewed this substance in 1999, and it is now being reevaluated. The background materials from the prior review are attached.

We have reviewed the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. Based on those factors, for the reasons discussed below, we recommend that DPCP be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

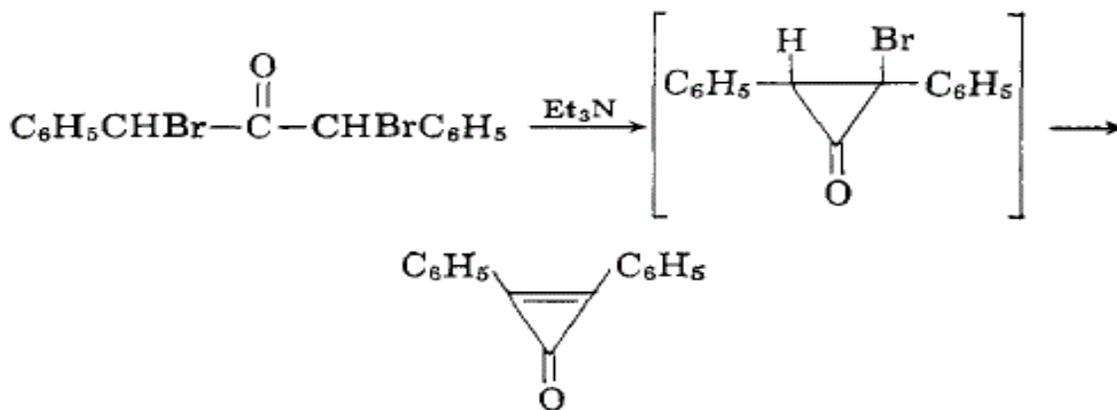
II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?

1. Stability of the API and likely dosage forms

According to FDA's 1999 assessment, attached, "The physical and spectroscopic properties of DPCP are well-characterized. DPCP is insoluble in water, soluble in alcohols and other organic solvents, and is rapidly hydrolyzed in dilute alcoholic base. DPCP reacts with nucleophiles, such as pyridine and hydroxylamine, to form a variety of unidentified products. Thermal instability has been reported. Heating this material above its melting point results in decomposition to diphenylacetylene and carbon monoxide. DPCP reacts photochemically to ultraviolet (UV-A and UV-B), fluorescent, and incandescent lights, as well as natural sunlight. There are no published quantitative methods for analysis of this material. The adequacy of the methods for determination of purity and levels of contaminants cannot be assessed."

DPCP has been found "to decompose, forming diphenylacetylene on exposure to both sunlight and fluorescent light in less than 2 weeks. Samples shielded from the light at -70°C and at room temperature were stable over a 4-week period. The extent of decomposition was the same in both ethanol and cyclohexane. It is possible that DPCP may act as a prosensitizer with the actual sensitizer liberated by a photoactivated intermediate (stable, metastable, or unstable) or a combination of these" (Wilkerson et al., 1984). It has further been reported on the [DermNet NZ website](#) that "DPCP is made up in acetone. It should be stored in a dark glass bottle in a cupboard away from sunlight and kept secure from access by children. The compounded preparation has a shelf-life of around 6 months."

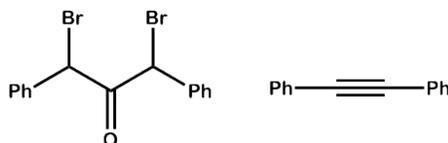


2. *Probable routes of API synthesis*

Breslow reports that “Diphenylcyclopropanone may be synthesized by a variety of methods; the best procedure involves elimination of HBr from α,α' -dibromodibenzyl ketone,…” (Breslow et al., 1965).

3. *Likely impurities*

The likely impurities are the starting material, α,α' -dibromodibenzyl ketone, and the degradation product diphenylacetylene.



Breslow reports that DPCP is a crystalline solid with a melting point of 119° to 120° C. If the material is purified by recrystallization to this melting point, it is likely that the starting α,α' -dibromodibenzyl ketone is present in no more than a few tenths of a percent. (Breslow et al., 1965).

4. *Toxicity of those likely impurities*

Note that α,α' -dibromodibenzyl ketone contains a structural alert for mutagenicity. It is reported on the [DermNet NZ website](#) that “[a]lthough DPCP is non-mutagenic in the Ames test, its precursor and possible contaminant during commercial production, α,α' -dibromodibenzyl ketone, can be mutagenic.”

However, Wilkerson found no detectable contaminants in their analysis of commercial DPCP (Wilkerson et al., 1984).

Specific toxicity concerns are addressed below in the **Nonclinical Assessment** section.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

As DPCP is used in solution, there are no concerns related to particle size or polymorphism.

Conclusions: We concur with FDA’s 1999 assessment that “[a]lthough DPCP is well characterized, it degrades readily by basic hydrolysis or exposure to light. The degradation products [other than diphenylacetylene] have not been identified. DPCP used in compounding

could vary significantly from DPCP used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.”

B. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

a. Pharmacology of the drug substance

DPCP is a hapten that is capable of eliciting contact dermatitis. Following repeated topical applications to the ears of mice, DPCP was found to induce local and systemic immune responses that included immune cell proliferation and altered cytokine activity (Svalgaard et al., 2014).

b. Safety pharmacology

No information available.

c. Acute toxicity

No information available.

d. Repeat dose toxicity

No information available

e. Mutagenicity

DPCP was considered not mutagenic in a reverse mutation assay conducted with bacteria (Wilkerson et al., 1987). Mammalian genotoxicity data have not been located within the public domain.

f. Developmental and reproductive toxicity

No information available.

g. Carcinogenicity

No information available.

h. Toxicokinetics

No information available.

Conclusions: There has been no systematic evaluation of the toxicology of DPCP to support nonclinical safety.

2. *Human Safety*

a. Reported adverse reactions

There are no randomized controlled trials for DPCP use. Since estimated adverse reaction rates from case reporting and unblinded studies can be misleading, they will not be discussed. Case reporting comes from populations of uncertain size while bias in unblinded studies cannot be eliminated, making estimation of adverse reaction rates unreliable.

DPCP is a contact sensitizer, and the expected manifestations of contact sensitization have been amply reported, including, for example, severe local eczematous reactions, erythema, pruritus, blisters, and burning. There have also been reports of hypopigmentation and lymphadenopathy, as well as erythema multiforme-like eruption and contact urticaria. These have been well documented in publications by van der Steen et al., (1991), Perret et al., (1990) and Tosti et al. (1989).

b. Clinical trials assessing safety

The human safety data up to 1999 have been summarized in FDA's review of DPCP for the Pharmacy Compounding Advisory Committee in that year (see attached). The information therein is consistent with the adverse reaction profile described above in Section II.B.2.(a). No clinical trials have been specifically conducted to evaluate the safety of DPCP. The human safety data are derived primarily from uncontrolled studies or case series.

Over the past 15 years (1999 to 2014), there have been additional reports of non-genital wart treatment with DPCP in otherwise healthy and in immunocompromised patients (Upitis and Krol 2002, Boull and Groth 2011, Audrain et al., 2013), with the adverse reaction profile showing primarily contact dermatitis manifestations and no new local or systemic findings. The case is similar with alopecia areata (Avgerinou et al., 2008, Chiang et al., 2014).

c. Pharmacokinetic data

The potential for absorption of DPCP is not clear. Even though in the only reported study (Berth-Jones et al.) DPCP was not detected in the serum or urine, the limit of detection in these biological samples was high; thus there might have been DPCP present at levels below the limit of detection. In addition, it is possible that the DPCP was absorbed and metabolized, thus rendering it not measurable.

In the reported study, Berth-Jones et al., applied a minimum of 0.5 ml (actual volume not described) of a solution containing 1% (w/v) DPCP to the scalp. Single blood samples were obtained from 7 subjects at 30 – 60 minutes after application and complete blood profile (at 15, 30, 60, 90 minutes, 2, 4 and 8 hours after application) was obtained in another 7 subjects; 24-hour urine collections were obtained from 6 subjects. DPCP was

not detected in any serum or urine sample from any subject. The authors noted that at the limit of detection, they should have been able to detect presence of 0.3 – 0.9% of the applied dose if it was excreted in the urine unchanged.

d. The availability of alternative approved therapies that may be as safe or safer

The more common alopecia areata therapies include intralesional corticosteroid injection, topical corticosteroids, minoxidil, anthralin, phototherapy, systemic corticosteroids, cyclosporine, sulfasalazine, and methotrexate. However, the only FDA-approved therapy indicated for the treatment of alopecia areata is intralesional injection of corticosteroid suspensions, including triamcinolone acetonide, triamcinolone hexacetonide, betamethasone acetate and betamethasone sodium phosphate, and methylprednisolone acetate products. This form of treatment carries the risk of permanent skin atrophy with repeated injections.

Contact sensitizer therapy is usually reserved for use on cutaneous warts resistant to more regular treatment modalities. Such warts are frequently treated via initial physical destruction with cryotherapy and paring or excision. Topical salicylic acid in different vehicles has been included in the over-the-counter monograph, Wart Remover Drug Products (21 CFR 358 subpart B). There are no approved therapies for recalcitrant warts not responding to the above (e.g., cryotherapy, topical salicylic acid).

For the treatment of genital warts, approved drugs include podofilox gel and solution, imiquimod cream, and polyphenon E ointment. Solicitation of a contact dermatitis reaction in the skin of the genital area with sensitizers poses additional challenges for management, because it may be more difficult to treat the eczematous reaction there and it may also enhance the risk of secondary infections in this location. This makes the use of DPCP not desirable for the treatment of genital warts.

Conclusions: Although DPCP is not mutagenic in the Ames assay, there are inadequate nonclinical data to otherwise characterize its safety profile. However, much clinical safety data have accumulated over the past 30 to 40 years. They show that the adverse effects of DPCP are primarily related to its action as contact sensitizer, and the safety profile is probably not worse than those of available products (regardless of FDA approval) in the management of alopecia areata and recalcitrant warts. No additional safety issues have been discovered in the past 15 years since the last review by the Committee. Nevertheless, there is a lack of data on the long-term safety in the use of DPCP.

Because DPCP is a contact sensitizer, there is a concern that handlers of the substance may become inadvertently sensitized and develop contact dermatitis.

There is also a lack of data on use in specific populations such as pregnant or lactating women. Although systemic absorption of DPCP is probably low, the exposure of and risks to the fetus and neonates being nursed are unknown. At the University of British Columbia Hair Clinic, six women have become pregnant while on treatment with DPCP despite the fact that they were

warned and signed an informed consent. However, all babies born were apparently normal (Alkhalifah et al., 2010).

C. Are there concerns about whether the substance is effective for a particular use?

1. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

Non-genital Warts

Reference is made to FDA's review on effectiveness data on DPCP in the treatment of cutaneous warts in 1999, which summarized the available data at that time. FDA noted that the largest trial with DPCP on warts was an open-label study in 134 subjects in which 60% of subjects had complete or partial responses after 8 weeks of treatment (Rampen and Steijlen, 1996).

Between 1999 and 2014, there have been many additional reports of the use of DPCP in the treatment of non-genital warts. Although these are not randomized, placebo-controlled, double-blind trials, they do provide evidence from a much larger treated population to support effectiveness of DPCP in recalcitrant warts.

- It appears that the largest series during this period is that from Uptis and Krol (2002) with 211 patients who had recalcitrant warts achieving a complete clearance rate of 88%.
- Boull and Groth's review of cutaneous viral warts in children included 143 patients treated with DPCP showing cure rates of 88% and 63% in two studies (Buckley et al., 1999 [not included in FDA's review of 1999] and Choi et al., 2008 [which also included a cryotherapy control with cure rate of 51%], respectively).
- In 2013, Choi et al., reported a series of 27 DPCP-treated patients with periungual warts showing complete clearance rate of 85% by subject (52% of them being failures with other treatments) and 91% by lesion.
- Audrain and Siddiqui (2013) obtained cure rates for recalcitrant warts of 96% in 28 immunocompetent and 60% in 10 immunosuppressed patients treated with DPCP.

Alopecia Areata

Reference is made to FDA's review on effectiveness data on DPCP in the treatment of alopecia areata in 1999, which summarized the available data at that time, citing reports by Schuttellaar et al., (1996), Gordon et al., (1996), Shapiro et al., (1993), van der Steen et al., (1991) and Berth-Jones et al., (1994), which gave response rates between 9% to 50%.

Williams and Bigby's 2014 edition of Evidenced-Based Dermatology states:

Schuttlelaar et al., treated 26 children with diphencyprone weekly for a period of 3-12 months. Sixteen subjects had alopecia areata totalis, and the others had patchy disease only. Eighty-four percent of the children showed hair regrowth, 32% of the total being cosmetically acceptable. Where treatment failed (0-5% hair growth), it was recommended not to continue treatment for longer than 1 year, as hair growth is not promoted by continued treatment.

In 2013, Shapiro summarized the literature experience, noting that topical immunotherapy of alopecia areata with squaric acid dibutyl ester and DPCP (13 trials and 17 trials, respectively) gave similar results: success rate of 50 to 60% with a wide range of 9 to 87%. This is generally dependent on the severity and duration of disease and the heterogeneity of product source, but it is also possible that the variability is related to the compounding with a wide range of strengths used in treatment. Relapse after achieving significant regrowth develops in the majority of patients, with median time to relapse of 2½ years.

2. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

The intended use of products compounded with DPCP has included treatment of severe forms of alopecia areata and recalcitrant cutaneous warts. These are not serious or life-threatening conditions.

3. *Whether there are any alternative approved therapies that may be as effective or more effective*

The only FDA-approved therapy indicated for the treatment of alopecia areata is intralesional injection of corticosteroid suspensions (see above, Section II.B.2.(d)). This form of therapy is not practical when the alopecia is widespread, as in the case of alopecia totalis or alopecia universalis, because each injection only produces a tuft of hair regrowth of approximately 0.5 cm². In addition, alopecia areata is also treated off-label with topical corticosteroids, minoxidil, anthralin, phototherapies, systemic corticosteroids, cyclosporine, sulfasalazine, or methotrexate.

There are approved therapies for non-genital cutaneous warts, but the contact sensitizers are generally reserved for the treatment of recalcitrant warts failing other treatment modalities, and as such, there are no approved alternative therapies for recalcitrant warts.

For the treatment of genital warts, there are approved drugs (podofilox gel and solution, imiquimod cream, and polyphenon E ointment) while solicitation of a contact dermatitis reaction in the treatment area with sensitizers poses additional challenges for management, making the use of DPCP not desirable (see above, Section II.B.2.(d)).

Conclusions: Although there are no adequate and well-controlled trials on DPCP, there appears to be evidence that this substance used in compounding for the treatment of recalcitrant warts and alopecia areata may be effective in a proportion of patients.

For non-genital cutaneous warts, DPCP treatment of recalcitrant cases is able to achieve cure rates between 60% to over 90%.

For alopecia areata treatment, topical immunotherapy with DPCP provides response rates generally in the order of 50% to 60% but relapses are reported in the majority of patients. The variability of results is attributed primarily to factors like age, disease duration, and severity, but may also be related to the DPCP source and strengths used in the reports. Responses are lower for patients with a younger age of onset, longer duration of disease, and alopecia totalis/universalis.

Because of the amount of evidence accumulated over time, Fitzpatrick's *Dermatology in General Medicine* (8th edition, 2012) has concluded: "Although not approved by the FDA, topical immunotherapy seems to be the most effective therapeutic option with the best safety profile in the treatment of chronic severe alopecia areata." Currently the topical immunotherapy commonly used in medical practice for these conditions are DPCP and squaric acid dibutyl ester.

D. Has the substance been used historically in compounding?

1. *Length of time the substance has been used in pharmacy compounding*

DPCP has been reported for use for over 30 years in pharmacy compounding.

2. *The medical condition(s) it has been used to treat*

DPCP has been reported for use primarily in the treatment of warts and alopecia areata (including alopecia totalis and alopecia universalis). There are also reports for use in oncology indications, such as melanoma metastases.

3. *How widespread its use has been*

Use of DPCP has been reported in North and South America, Australia, and European and Asian countries. In 2006, Europe's Committee for Medicinal Products for Human Use (CHMP) granted DPCP orphan designation for the indications alopecia totalis and alopecia universalis to a French firm, Orfagen. Designation was withdrawn in July 2013 at the firm's request.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

Although DPCP is recognized globally in many countries, a search did not find this substance listed in the European, British, or Japanese Pharmacopeias.

Conclusions: DPCP has been used for compounding to treat resistant non-genital warts and alopecia areata by practitioners for over 30 years. Reports of its global use for these conditions have accumulated over time. There may also be novel uses such as for metastatic melanoma, but this is still under study and considered premature.

III. RECOMMENDATION

We recommend DPCP be placed on the list of bulk drug substances in compounding under section 503A. Despite some concerns about stability and consistency in product quality, as well as lack of adequate nonclinical data, the substance has been in use for compounding for over 30 years and has been adopted globally as a potentially useful form of topical immunotherapy for alopecia areata and recalcitrant warts by medical practitioners. Thus far, the adverse effects reported are related to its primary therapeutic effect as a contact sensitizer.

There are some gaps in knowledge about long-term safety and use in specific populations such as pregnant and lactating women. However, given the lack of approved therapies indicated for recalcitrant warts and severe forms of alopecia areata (alopecia totalis and alopecia universalis), not listing DPCP could create obstacles to patient access, unless the drug product is obtained through an investigational new drug application.

In FDA's review of DPCP in 1999, the primary concern was inadequate safety information, but the reviewers recognized that DPCP might be "useful as second or third line therapy for warts and possibly as a therapy for alopecia areata." Since that time, many more human safety data have been collected, and effectiveness experience in the treatment of severe forms of alopecia areata (alopecia totalis and alopecia universalis) and recalcitrant warts has been gained by clinicians worldwide. This has led to textbooks in dermatology naming this form of therapy as the most effective therapeutic option with the best safety profile in the treatment of such conditions. We believe that it is now appropriate to include DPCP on the 503A bulk drug substances list.

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration, Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540

Date: March 16, 1999

Subject: Review of Diphenacyclopropenone, a Candidate for the
Pharmacy Compounding Bulk List, With Selected References

To: Pharmacy Compounding Steering Committee

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HFD-540 Review on Diphenylcyclopropenone
For the FDA Pharmacy Compounding Advisory Committee

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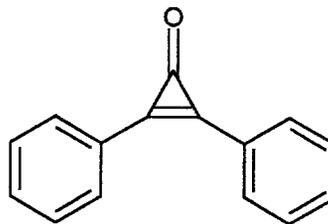
I. Introduction

The Division of Dermatologic and Dental Drug Products (HFD-540) has been charged with the review of diphenylcyclopropenone (DPCP) for two indications: alopecia areata and verruca vulgaris (warts). Only published literature was used in the preparation of this review.

II. Chemical Characterization of DPCP

Identity:

Diphenylcyclopropenone
Diphencyprone
2,3-Diphenyl-2-cyclopropen-1-one
DPCP



CAS #: 886-38-4
Molecular Weight: 206.24
Molecular Formula: C₁₅H₁₀O
Melting Point: 119-121° C (anhydrate); 87-90° C (monohydrate)

The physical and spectroscopic properties of DPCP are well-characterized. DPCP is insoluble in water, soluble in alcohols and other organic solvents, and is rapidly hydrolyzed in dilute alcoholic base. DPCP reacts with nucleophiles, such as pyridine and hydroxylamine, to form a variety of unidentified products. Thermal instability has been reported. Heating this material above its melting point results in decomposition to diphenylacetylene and carbon monoxide. DPCP reacts photochemically to ultraviolet (UV-A and UV-B), fluorescent and incandescent lights, as well as natural sunlight. There are no published quantitative methods for analysis of this material. The adequacy of the methods for determination of purity and levels of contaminants cannot be assessed.

Quality and Stability

DPCP is an off-white to beige crystalline powder and has a melting point of 119-121° C. It is thermally unstable above its melting point, decomposing primarily into diphenylacetylene and a possible dimeric product; this degradant has not been definitively identified. It is insoluble in water, readily hydrolyzed in dilute alkali base ($t_{1/2} < 5$ min. in 0.1N NaOH in ethanol) to cis-1,2-diphenylacrylic acid, and relatively stable to acidic conditions. DPCP reacts readily with strong electrophiles, as well as with nucleophiles such as pyridine and hydroxylamine. The addition products of these reactions have not been fully identified.

DPCP is photochemically reactive. It decomposes during irradiation with both short- and long-wavelength UV (UVB and UVA), fluorescent, incandescent and solar light. The predominant decomposition products appear to be diphenylacetylene and a product which has tentatively been identified as a dimer.

Synthesis and Purity

DPCP was first prepared in 1959 by Breslow (Breslow et al., 1959) and Vol'pin (Vol'pin et al., 1959). Several methods of preparation have been reported in the chemical literature (Breslow et al., 1959, 1963, 1965, 1973; Vol'pin et al., 1959, 1960), only one of which appears amenable to large-scale production (Breslow et al., 1973).

Several domestic commercial sources of DPCP have been identified, including Fisher Scientific (Acros Organics), Spectrum Chemical Co., and Sigma-Aldrich Co. Each has confirmed their knowledge of the identity or identities of the actual manufacturing site(s) for DPCP, but all of them have declined to make this information public.

Literature on the syntheses of DPCP predates modern analytical methodology. These reports cite IR spectroscopy, UV spectroscopy, elemental analysis, and melting point as the determinants of purity. While these methods are common analytical techniques, they are not established quantitative methods for analysis of this material. The adequacy of these methods for determination of the purity and level of contaminants in DPCP can not be assessed.

A monohydrate form of DPCP (melting point 87°-90°C) results from recrystallization in cyclohexane and is probably due to incomplete drying. The reported yield of this synthesis is 44%. The description of the purification indicates the presence of significant amounts of unidentified byproducts (e.g., a "reddish oily impurity"); thus, the impurity profile of this material is unknown.

Assessment 1: Although DPCP is well characterized, it degrades readily by basic hydrolysis or exposure to light. The degradation products have not been identified. DPCP used in compounding could vary significantly from DPCP used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.

III. Safety of DPCP

A. Animal Toxicology

DPCP is not mutagenic in the Ames assay except in the presence of light (Wilkerson et al., 1987). In the presence of light (350 nm) and rat microsomes, DPCP caused a doubling of the mutation rate in one strain of *Salmonella*. Since the photo-conversion products of DPCP were not mutagenic, some short-lived intermediate(s) must cause the mutations. The synthetic precursor to DPCP, α,α -dibromodibenzylketone, is mutagenic in the Ames assay with and without metabolic activation (Wilkerson et al., 1987).

Assessment 2: DPCP is photo-genotoxic. Mammalian genotoxicity, chronic toxicity, reproductive toxicity, and carcinogenicity studies have not been conducted with DPCP. Thus, it is not known what the potential toxicities of DPCP are in humans or whether it is likely to be teratogenic in humans.

B. Human Safety

There are no published reports of studies designed to systematically evaluate the safety of DPCP. The reported side effects are similar to those of other contact sensitizers. Numerous case reports of adverse events are associated with the use of DPCP. Especially notable are reports of vitiligo and pigmentary changes, some of which are permanent. There have been three reports of erythema multiforme (which is characterized by the appearance of purpuric [bruise-like], often blistering, ring-shaped lesions scattered over the body surface, with systemic signs and symptoms including fever and malaise).

DPCP has been shown to elicit eczematous reactions with or without blistering. These reactions may occur at the site of application and other areas of the body. Other reactions include itching and resulting insomnia, urticaria, edema of the scalp, eyelids, and face, lymphadenopathy, and high fever (Rokhsar et al., 1998).

Table 1 - Side Effects of DPCP

Author	Journal	Year	Side Effect
Alam et al.	J. Am. Acad. Dermatol.	1999	Severe urticarial reaction, eczematous dermatitis, and dermographism
Oh et al.	Contact Derm.	1998	Bullous erythema multiforme
Henderson et al.	Br. J. Dermatol.	1995	Vitiligo
Puig et al.	Int. J. Dermatol.	1994	Erythema multiforme-like reaction
Van der Steen et al.	Arch. Dermatol.	1992	Pigmentation changes (4/243 pts) – ‘dyschromia in confetti’
Duhra et al.	Br. J. Dermatol.	1990	Persistent vitiligo
Perret et al.	Dermatologica	1990	Erythema multiforme (3 patients)
Tosti et al.	Contact Derm.	1989	Contact urticaria

In human skin absorption studies, DPCP was not detected in the serum or urine of human subjects treated with 0.5 ml of 1% DPCP in a mixture of denatured alcohol and propylene glycol in a 9:1 ratio for a total dose of 5 mg (Berth-Jones et al., 1994). The limit of detection in this study was 60 ng/ml for serum and 20 ng/ml for urine. The authors note that their results do not eliminate the possibility that DPCP is absorbed and rapidly metabolized.

Topical sensitizers such as DPCP present a particular hazard to those who work with the compounds since, by definition, repeated exposure is likely to elicit an allergic response. There are several published accounts of workers, including pharmacists and nurses, becoming sensitized to DPCP (Sansom et al., 1995; Shah et al., 1996; Adishes et al., 1997).

Assessment 3: There is limited characterization of the human safety profile. With human exposure to DPCP, adverse side effects have been reported in the literature, including erythema multiforme, eczematous dermatitis, urticaria, persistent vitiligo and post-inflammatory pigmentation changes.

Available alternative approved therapies for alopecia areata include intralesional, topical, and systemic corticosteroids.

Available alternative approved therapies for verruca vulgaris (warts) include podophyllin, imiquimod, and salicylic acid. Other well-accepted modalities with excellent safety include ablation using cryotherapy or laser treatment.

Assessment 4: Many approved products are available for the treatment of verruca and alopecia areata.

IV. Historical Use of DPCP in Pharmacy Compounding

DPCP's ability to induce strong allergic reactions was first reported in 1972 (Whittaker, 1972). Clinical use of DPCP for the treatment of alopecia areata was first reported in 1983 (Happle et al., 1983).

Numerous animal and human studies have demonstrated that DPCP is a potent contact sensitizer. It has been investigated for topical immunotherapy of conditions such as warts and alopecia areata. The mechanism by which topical immunotherapy can improve these conditions is not known, however exposure of patients to this agent results in a clinical picture similar to that of exposure to poison ivy.

DPCP is usually applied in a health care provider's office by a physician (usually a dermatologist), podiatrist, or trained staff member. First, patients are sensitized with a 2% DPCP solution in acetone applied to a 10 to 16 cm² area on one side of the scalp, forearm, or back (Rokhsar et al., 1998). If a severe eczematous response does not occur at the initial sensitization site, a 0.0001% solution is applied to one side of the scalp (if the initial reaction is too severe, two

weeks are allowed to elapse between the sensitization and elicitation phases). Caution must be exercised to avoid a severe blistering response.

Assessment 5: Since its first clinical report in 1983, DPCP has been used as an experimental treatment alternative for alopecia areata and verruca vulgaris. Evidence of its widespread use is not apparent.

V. Available Evidence of Effectiveness

Alopecia areata and warts frequently resolve without any therapeutic intervention. For example, in a study of the natural history of alopecia areata, of 63 alopecia areata patients followed for one year without treatment, hair had regrown in all but 4 patients in one year, and in all but 1 patient after two years. The great majority had regrown hair by 3 months after their only office visit (Arnold, 1952). Alopecia areata with less than 25% involvement has a high incidence of spontaneous recovery, whereas more severe involvement has a lesser rate of recovery (Moschella and Hurley, 1992). Regarding the natural history of warts, a two-year study showed that two-thirds of warts regressed without treatment (Massing and Epstein, 1963).

Despite the necessity for a placebo arm in evaluating experimental therapies such as DPCP, much of the putative success of topical immunomodulators stems from studies that were either uncontrolled or internally controlled. Describing therapy for alopecia areata, Rook et al. states, "The widely conflicting claims for the success of many different measures merely reflect the very great variations in the spontaneous course of the disease."

Studies that demonstrate a "positive" result, such as regrowth of hair, are more likely to be submitted for publication or published than are studies with "negative" results. Therefore, the published literature may overstate the efficacy of novel therapies. Additionally, most clinical studies lack long-term follow-up, so the lasting treatment benefits cannot be evaluated.

To date, in the peer-reviewed English-language literature, there have been at least 18 reports of studies using DPCP in alopecia areata and 5 studies on the treatment of warts.

Warts

Warts, caused by cutaneous infection with the human papillomavirus, are a very common dermatological ailment. Aside from cosmetic disfigurement, patients seek treatment because plantar (foot) warts may cause pain on walking or interfere with gait, and warts on the fingers may interfere with manual dexterity. As with alopecia areata, therapy is not always effective.

The largest trial with DPCP on warts was an open study on 134 subjects with palmoplantar and periungual verruca done by Rampen and Steijlen in 1996. After 8 weeks of treatment, 36.6% of subjects exhibited a complete response. The low rate of response is worse than that of other therapeutic modalities for warts, although the absence of a control arm precludes any definitive comparisons with other modalities.

Alopecia areata

Alopecia areata is a nonscarring loss of hair, that, depending upon its severity, can affect patches of scalp, the entire scalp (alopecia totalis), or the entire body (alopecia universalis). The etiology of this illness is unknown. Alopecia areata is a relatively common dermatologic disease that is associated with cosmetic disfigurement and functional impairment, especially if eyebrows or eyelashes are lost.

Table 2 - Use of DPCP in Alopecia Areata

Author	Journal	Year	Disease	N	Treatment	Response/ITT	Ctrl
Schuttelaar et al.	Br. J. Dermatol.	1996	Alopecia areata Children	26	3 mo – 1 yr	30.8% acceptable regrowth	Yes
Gordon et al.	Br. J. Dermatol.	1996	Alopecia areata	48	30.8 months follow-up	38 % “good” regrowth	Yes
Shapiro et al.	J. Am. Acad. Dermatol.	1993	Alopecia areata > 50 % hair loss	15	24 weeks + 5% minoxidil	33.3% marked regrowth	Yes
van der Steen et al	Dermatology	1991	Alopecia areata	139	> 7 months	30.2% complete 20.1% partial	Yes
Berth-Jones et al	Clin. Exp. Dermatol.	1991	Alopecia totalis	22	6 months	9.1% response	Yes

Naldi et al., 1990, assessed the efficacy of topical sensitizers for the treatment of alopecia areata in a review of 26 papers on “published clinical trials on dinitrochlorobenzene, squaric acid dibutylester, and diphenylprone [DPCP] each published between January 1977 and January 1988.” The authors of the paper stated, “According to our evaluation, the published literature is of limited use in defining the role of topical immunotherapy in alopecia areata. Half the studies examined used informal methods (uncontrolled or historically controlled trials)... In general, the studies that we examined had serious drawbacks in reporting critical procedures such as assessing treatment and selecting and following up patients... In conclusion, a definite role of topical immunotherapy for alopecia areata has yet to be established and this treatment should be offered only as an experimental modality...”

In 1998, Rokhsar et al. examined the efficacy of contact sensitizers in alopecia areata in a summary review of the literature. They reported a response rate range from 9% to 85%. This range included the sum of both complete and partial responders. The weighted average response rate was 58%, similar to the response rate seen in the largest study by van der Steen et al. (1998). A relapse rate of about 50% was seen in the patients, even with continuation of treatment, suggesting that in many patients the response is temporary at best.

A tabular summary of the suggested role of immunomodulators (as gleaned from leading dermatological textbooks) for the treatment of alopecia areata and warts is presented in Table 3. Many therapeutic alternatives exist for these conditions.. The consensus is that DPCP is an experimental therapy, with a modicum of short-term efficacy. Additional well-controlled, long-term studies are needed to evaluate efficacy.

Assessment 6: There is little evidence that DPCP is effective in the long-term treatment of alopecia areata or verruca. Treatment of alopecia areata with DPCP may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped.

Table 3 - Perspectives on Treatment for Alopecia Areata and for Warts

Reference	Disease	Treatment of Choice	Other Suggested Treatments	Role of DPCP in Therapeutic Armamentarium
<i>Andrews' Diseases of the Skin: Clinical Dermatology</i> , ed. by Arnold et al., Eighth edition (1990) (textbook)	Alopecia Areata—patchy involvement	Intralesional injections of corticosteroid	"None of the other various therapeutic approaches are clearly superior to corticosteroids"	DPCP: not discussed
	Alopecia Areata—totalis/universalis	Systemic (IM) steroids should be "seriously considered".		
	Common/Plantar Warts	Treatment of choice not identified	A, B, C, D, E, F, G, H, I, J, K (not plantar warts), L, M	DPCP: not discussed
<i>Dermatology in General Medicine</i> , ed. by Fitzpatrick et al., Third edition (1987) (textbook)	Alopecia Areata	Treatment of choice not identified	N (little efficacy), P, Q, R	DPCP: not discussed
	Warts	Treatment of choice not identified	A, B, C, D, E, F, G, H, I, J, K, T, U, V	DPCP: not discussed
<i>Textbook of Dermatology</i> , ed. by Rook et al., Fourth Edition (1986) (textbook)	Alopecia Areata	Treatment of choice not identified	O (unclear if regrowth is maintained), P (not helpful in alopecia totalis—except for eyebrows), W, X, Y, Z	DPCP: not discussed
	Warts	Treatment of choice not identified	B, C, D, L, L', E, H, I, J, T, A', B', ; avoid A,U (risk of scarring)	DPCP: not discussed
<i>Pediatric Dermatology</i> , ed. by Schachner and Hansen, (1988) (textbook)	Alopecia Areata	Topical corticosteroids, alone or under occlusion; Intralesional corticosteroids	O (for severe involvement, unresponsive to topical or intralesional treatment)	DPCP: as effective as DNCB (another topical sensitizer). "Here again these chemicals [DPCP] cannot be regarded as completely safe until extensive toxicologic evaluation has been completed."
	Warts	Treatment of choice not identified	A, B, C, G, K	DPCP: not discussed

A: Electrodesiccation and curettage; B: Cryotherapy; C: Salicylic Acid; D: Lactic Acid; E: Trichloroacetic/ other caustic acids; F: Podophyllin; G: laser; H: 5-Fluoro-uracil; I: Retinoids; J: Interferon; K: Cantharin; L: Formalin; L': Glutaraldehyde; M: Bleomycin; N: Topical corticosteroids; O: Systemic corticosteroids; P: Intralesional corticosteroids; Q: Anthralin; R: PUVA (Psoralen and UV-A); S: Inosiplex; T: Bleomycin; U: Surgical excision; V: Vaccination with autogenous-wart extracts; W: Ultraviolet radiation; X: Minoxidil; Y: Dithranol; Z: Zinc sulfate; A': Levamisole; B': Photodynamic inactivation; C': Psychological methods (hypnosis)

VI. Conclusions

Assessment 1: Although DPCP is well characterized, it degrades readily by basic hydrolysis or exposure to light. The degradation products have not been identified. DPCP used in compounding could vary significantly from DPCP used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.

Assessment 2: DPCP is photo-genotoxic. Mammalian genotoxicity, chronic toxicity, reproductive toxicity, and carcinogenicity studies have not been conducted with DPCP. Thus, it is not known what the potential toxicities of DPCP are in humans or whether it is likely to be teratogenic in humans.

Assessment 3: There is limited characterization of the human safety profile. With human exposure to DPCP, adverse side effects have been reported in the literature, including erythema multiforme, eczematous dermatitis, urticaria, persistent vitiligo and post-inflammatory pigmentation changes.

Assessment 4: Many approved products are available for the treatment of verruca and alopecia areata.

Assessment 5: Since its first clinical report in 1983, DPCP has been used as an experimental treatment alternative for alopecia areata and verruca vulgaris. Evidence of its widespread use is not apparent.

Assessment 6: There is little evidence that DPCP is effective in the long-term treatment of alopecia areata or verruca. Treatment of alopecia areata with DPCP may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped.

VII. Recommendation:

Four criteria have been used to evaluate DPCP for inclusion on the bulk drug compounding list: (1) the chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness. Our evaluation of DPCP, based on a balanced assessment of each criterion in the context of the others, leads to our recommendation that it is not appropriate for DPCP to be included on the list.

The nonclinical studies conducted to date minimally evaluate the safety of diphenylcyclopropanone. The studies do not characterize the potential toxicity to internal tissues nor do they characterize the dermal toxicity from long term topical application. Conclusions about the safety of DPCP cannot be made before such studies are done.

The evidence from historical use suggests that DPCP may be useful as second or third line therapy for warts and possibly as a therapy for alopecia areata. It is our impression that DPCP has become more commonly used as a topical sensitizer than dinitrochlorobenzene (DNCB), largely because the latter compound, available for toxicologic evaluation for more than 20 years, has well-established toxicities. The notion seems to be that the known toxicities of DNCB make it less attractive than the unknown toxicities of DPCP.

If DPCP is not placed on the list of bulk drug substances for compounding, a physician/investigator could still file an investigational new drug application (IND) for use of DPCP in humans. Pursuing this route would provide important and clinically relevant information about: (1) the chemistry of DPCP (i.e., its stability, its comparative solubility in different vehicles), (2) the safety profile – pharmacology/toxicology of DPCP (i.e., safety information about long-term dermal usage), and (3) the clinical side effect profile (i.e., risk of pigmentary and eczematous reactions).

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Tab 84

Cantharidin Nominations

Submitted electronically via www.regulations.gov

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No.: FDA-2013-N-1525: *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations*

Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

A handwritten signature in black ink, appearing to read "Steve Pfister", with a long horizontal flourish extending to the right.

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Nomination from National Community Pharmacists Association, September 30, 2014

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format(s)	Recognition in Pharmacopeias	Final Compounded Formulation Dosage Form(s)	Final Compounded Formulation Strength	Final Compounded Formulation Route(s) of Administration	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
Cantharidin	2,3-dimethyl-7-oxabicyclo(2.2.1)heptane-2,3-dicarboxylic anhydride	Cantharidin	IGL471WQ8P	From PCCA Certificate of Analysis: 98.21% Pure (Pass); From PCCA MSDS: 100% by weight and stable.	Powder, Crystals	Not yet submitted to USP	Topical Solution	0.1-2%	Topical	Federal Register 1999, Moed L, Shwayder TA, Chang MW. Cantharidin Revisited: a blistering defense of an ancient medicine. Arch Dermatol 2001; 137: 1357-1360, de Bengoa Vallejo RB, Iglesias MEL, Gomez Martin B, Gomez RS, Crespo AS. Application of Cantharidin and Podophyllotoxin for the Treatment of Plantar Warts. J Am Podiatr Med Assoc 98(6): 445-450, 2008.	API in Flexible Collodion. Cantharidin, which is well characterized chemically, is a substance obtained from the Chinese blister beetle, among other beetle species, that has been used topically in the treatment of warts and molluscum contagiosum, often in patients with compromised immune systems. Limited anecdotal evidence of cantharidin's effectiveness for these indications is reported in the literature. Although cantharidin is an extremely toxic substance, it is apparently used only in the professional office setting and not dispensed for home use. Because of cantharidin's toxicity, FDA is proposing to include it on the bulk drugs list for topical use in the professional office setting only.



September 30, 2014

Submitted electronically via www.regulations.gov

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

PCCA respectfully submits the following list of nineteen chemicals to be considered for the List of Bulk Drug Substances that may be used in Pharmacy Compounding in accordance with Section 503A.

PCCA provides its more than 3,600 independent community compounding pharmacy members across the United States with drug compounding ingredients, equipment, extensive education, and consulting expertise and assistance.

Regarding the specific nominations, we would like to reference the attached spreadsheet and point out a couple of facts regarding our research. To the best of our knowledge, all items submitted:

- Do not appear in any of the three sections of the Orange Book.
- Do not currently have a USP or NF monograph.
- Meet the criteria of a “bulk drug substance” as defined in § 207.3(a)(4).

In regards to the request for chemical grade information, we would like to point out that many of the items submitted do not currently have a chemical grade. PCCA believes that pharmacists should use the highest grade chemical available on the market for all aspects of pharmaceutical compounding and we continue to actively source graded chemicals from FDA-registered manufacturers. However, in the current marketplace, some graded chemicals cannot be obtained for various reasons. PCCA actively tests all products received to ensure they meet our required standards to ensure our members receive the highest quality chemicals possible.

We would like to echo the concerns, voiced by NCPA and others in our industry, the strong recommendation to formalize the process by which the list is updated and communicated to the pharmacy industry. We also recommend an annual process to ensure understanding and adherence to the list. All submissions and updates to the list should be reviewed by the Pharmacy Compounding Advisory Committee (PCAC) and no changes to the list should occur with input and review by the PCAC.

PCCA USA: 9901 S. Wilcrest Drive Houston, Texas 77099 | 800.331.2498 (t) 800.874.5760 | www.pccarx.com

PCCA Canada: 744 Third Street London, ON Canada N5V 5J2 | 800.668.9453 (t) 800.799.4537 | www.pccarx.ca

PCCA Australia: Unit 1, 73 Beauchamp Road Matraville NSW 2036 Australia | 02.9316.1500 (t) 02.9316.7422 | www.pccarx.com.au



We are also dismayed in the fact that no appointments have been made to the PCAC despite the call for nominations closing in March 2014. Without these appointments, FDA is unable to consult the Committee regarding this list, as outlined in the Act. PCCA, along with industry partners, strongly recommends that the FDA consult with the PCAC related to every single submission the Agency received in relation to FDA-2013-N-1525.

We appreciate this opportunity to submit this list for consideration and we look forward to continuing to work with the FDA in the future on this and other important issues as they relate to the practice of pharmacy compounding.

Sincerely,

A handwritten signature in black ink, appearing to read 'A. Lopez', with a stylized flourish at the end.

Aaron Lopez
Senior Director of Public Affairs
PCCA

A handwritten signature in black ink, appearing to read 'John Voliva', with a stylized flourish at the end.

John Voliva, R.Ph.
Director of Legislative Relations
PCCA

PCCA Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations	
Ingredient Name	Cantharidin
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	Hexahydro-3 α ,7 α -dimethyl-4 β ,7 β -epoxyisobenzofuran-1,3-dione
Common Name(s)	Cantharidin
UNII Code	IGL471WQ8P
Chemical Grade	N/A
Strength, Quality, Stability, and Purity	Assay, Description, Loss on Drying, Melting Point; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmacopeias or registered in other countries	Canthacur (Canada & Turkey); Cantharone (Canada)
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Solution
Compounded Strengths	0.1-2%
Anticipated Routes of Administration	Topical
Safety & Efficacy Data	Kartal Durmazlar SP, et al. Cantharidin treatment for recalcitrant facial flat warts: a preliminary study. J Dermatolog Treat. 2009;20(2):114-9. [http://www.ncbi.nlm.nih.gov/pubmed/18821118]

	<p>Epstein JH, et al. Cantharidin treatment of digital and periungual warts. Calif Med. 1960 Jul;93:11-2. [http://www.ncbi.nlm.nih.gov/pubmed/13820498]</p>
	<p>Coloe Dosal J, et al. Cantharidin for the Treatment of Molluscum Contagiosum: A Prospective, Double-Blinded, Placebo-Controlled Trial. Pediatr Dermatol. 2012 Aug 16. [http://www.ncbi.nlm.nih.gov/pubmed/22897595]</p>
	<p>Moye VA, et al. Safety of Cantharidin: A Retrospective Review of Cantharidin Treatment in 405 Children with Molluscum Contagiosum. Pediatr Dermatol. 2014 Jan 3. [http://www.ncbi.nlm.nih.gov/pubmed/24383663]</p>
	<p>Kadioglu O, et al. Pharmacogenomics of cantharidin in tumor cells. Biochem Pharmacol. 2014 Feb 1;87(3):399-409. [http://www.ncbi.nlm.nih.gov/pubmed/24231507]</p>
	<p>Deng L, et al. Exploiting protein phosphatase inhibitors based on cantharidin analogues for cancer drug discovery. Mini Rev Med Chem. 2013 Jun 1;13(8):1166-76. [http://www.ncbi.nlm.nih.gov/pubmed/23373656]</p>

Nomination from PCCA, September 30, 2014

Used Previously to compound drug products	Warts, Molluscum Contagiosum, Chemotherapy
Proposed use	Warts, Molluscum Contagiosum, Chemotherapy
Reason for use over and FDA-approved product	Treatment failures and/or patient unable to take FDA approved product
Other relevant information - Stability information	USP <795> recommendation of BUD for nonaqueous formulations – “no later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.



September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA's request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS

Corporate Offices: 4638 Riverstone Blvd. | Missouri City, Texas 77459 | 281.933.8400
Washington DC Offices: 1321 Duke Street, Suite 200 | Alexandria VA 22314 | 703.299.0796

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created an series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency's activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee prior to the implementation and issuance of regulations including the creation of the bulk ingredient list.

(2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

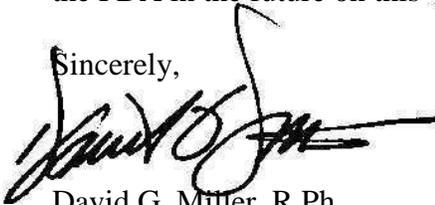
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

A handwritten signature in black ink, appearing to read "David G. Miller", with a stylized flourish extending to the right.

David G. Miller, R.Ph.
Executive Vice President & CEO



Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Cantharidin
Chemical/Common Name	Cantharidin
Identifying Codes	56-25-7
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	Not Listed in USP/NF

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	Federal Register 1999 Moed L, Shwayder TA, Chang MW. Cantharidin Revisited: a blistering defense of an ancient medicine. Arch Dermatol 2001; 137: 1357-1360. de Bengoa Vallejo RB, Iglesias MEL, Gomez-Martin B, Gomez RS, Crespo AS. Application of Cantharidin and Podophyllotoxin for the Treatment of Plantar Warts. J Am Podiatr Med Assoc 98(6): 445-450, 2008.
Past and Proposed Use	The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.



Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

“List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act”

Dear Sir or Madam,

Fagron appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

We hereby nominate the bulk drug substances in the attached spreadsheets for FDA’s consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

None of these items appear on an FDA-published list of drugs that present demonstrable difficulties for compounding. In addition, none are a component of a drug product that has been withdrawn or removed from the market because the drug or components of the drug have been found to be unsafe or not effective.

We include references in support of this nomination for your consideration.

Thank you for your consideration. If Fagron can answer any questions, please contact me (j.letwat@fagron.com; 847-207-6100).

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs



Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlsx file)

7-Keto Dehydroepiandrosterone
Acetyl-D-Glucosamine
Aloe Vera 200:1 Freeze Dried
Astragalus Extract 10:1
Beta Glucan (1,3/1,4 -D)
Boswellia Serrata Extract
Bromelain
Cantharidin
Cetyl Myristoleate Oil
Cetyl Myristoleate 20% Powder
Chrysin
Citrulline
Dehydroepiandrosterone
Deoxy-D-Glucose (2)
Diindolylmethane
Domperidone
EGCg
Ferric Subsulfate
Glycolic Acid
Glycosaminoglycans
Hydroxocobalamin Hydrochloride
Kojic Acid
Methylcobalamin
Nicotinamide Adenine Dinucleotide
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)
Ornithine Hydrochloride
Phosphatidyl Serine
Pregnenolone
Pyridoxal 5-Phosphate Monohydrate
Pyruvic Acid
Quercetin
Quinacrine Hydrochloride
Ribose (D)
Silver Protein Mild
Squaric Acid Di-N-Butyl Ester
Thymol Iodide
Tranilast
Trichloroacetic Acid
Ubiquinol 30% Powder

Fagron

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St. Paul, Minnesota 55120 - USA
(800) 423 6967
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What is the name of the nominated ingredient?	Cantharidin
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?	<p>Yes, Cantharidin is an active ingredient as defined in 207.3(a)(4) because when added to a pharmacologic dosage form it produces a pharmacological effect.</p> <p>Silverberg, Nanette B., Robert Sidbury, and Anthony J. Mancini. "Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients." <i>Journal of the American Academy of Dermatology</i> 43.3 (2000): 503-507.</p> <p>Moed, Lisa, Tor A. Shwayder, and Mary Wu Chang. "Cantharidin revisited: a blistering defense of an ancient medicine." <i>Archives of dermatology</i> 137.10 (2001): 1357-1360.</p> <p>EPSTEIN, WILLIAM L., and ALBERT M. KLIGMAN. "Treatment of warts with cantharidin." <i>AMA archives of dermatology</i> 77.5 (1958): 508-511.</p>
Is the ingredient listed in any of the three sections of the Orange Book?	The nominated substance was searched for in all three sections of the Orange Book located at http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm . The nominated substance does not appear in any section searches of the Orange Book.
Were any monographs for the ingredient found in the USP or NF monographs?	The nominated substance was searched for at http://www.uspnf.com . The nominated substance is not the subject of a USP or NF monograph.
What is the chemical name of the substance?	Hexahydro-3 α ,7 α -dimethyl-4 β ,7 β -epoxyisobenzofuran-1,3-dione
What is the common name of the substance?	Cantharidin
Does the substance have a UNII Code?	IGL471WQ8P
What is the chemical grade of the substance?	No grade

Nomination from Fagron, September 30, 2014

What is the strength, quality, stability, and purity of the ingredient?	Description: Colorless, glistening crystals. Odorless. Solubility: Very slightly soluble in water. Soluble in Alcohol. Identification (Infrared): Conforms Melting range start: $\geq 216^{\circ}\text{C}$ Melting range end: $\leq 218^{\circ}\text{C}$ Residue on Ignition: $\leq 0.1\%$
How is the ingredient supplied?	Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	Registered in Turkey, Canada, Singapore, and China
Has information been submitted about the substance to the USP for consideration of monograph development?	No
What dosage form(s) will be compounded using the bulk drug substance?	Liquid
What strength(s) will be compounded from the nominated substance?	0.1 - 1%
What are the anticipated route(s) of administration of the compounded drug product(s)?	Topical
Are there safety and efficacy data on compounded drugs using the nominated substance?	Silverberg, Nanette B., Robert Sidbury, and Anthony J. Mancini. "Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients." Journal of the American Academy of Dermatology 43.3 (2000): 503-507. Moed, Lisa, Tor A. Shwayder, and Mary Wu Chang. "Cantharidin revisited: a blistering defense of an ancient medicine." Archives of dermatology 137.10 (2001): 1357-1360. EPSTEIN, WILLIAM L., and ALBERT M. KLIGMAN. "Treatment of warts with cantharidin." AMA archives of dermatology 77.5 (1958): 508-511.

Nomination from Fagron, September 30, 2014

Has the bulk drug substance been used previously to compound drug product(s)?	<p>There are FDA approved preparations for warts. Imiquimod and OTC freezing preparations. Imiquimod is FDA approved for genital and perianal warts. Imiquimod cream does not cure warts, and new warts may appear during treatment. Cantharidin is safe an effective alternative to wart therapy.(R. Torbeck, M. Pan, E. DeMoll, and J. Levitt. (2014) Cantharidin:A Comprehensive Review of the Clinical Literature Dermatol Online Jun15:20(6)) Cantaridin has been shown to be more effective them cryotherapy agents in plantar warts. N. Kacar, L.Tasil, S. Korkmaz, S. Ergin, and B.S. Ergogan (2012) Cantharidin-Podophylotoxin-Salicyclic Acid Versus Cryotherapy in the Treatment of plantar Warts: A randomized Prospective Study J. Eur Acad Dermatol Venerol Jul;26(7):889-93.) Imiquimod is FDA not approved for plantar warts</p> <p>Silverberg, Nanette B., Robert Sidbury, and Anthony J. Mancini. "Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients." Journal of the American Academy of Dermatology 43.3 (2000): 503-507.</p> <p>Moed, Lisa, Tor A. Shwayder, and Mary Wu Chang. "Cantharidin revisited: a blistering defense of an ancient medicine." Archives of dermatology 137.10 (2001): 1357-1360.</p> <p>EPSTEIN, WILLIAM L., and ALBERT M. KLIGMAN. "Treatment of warts with cantharidin." AMA archives of dermatology 77.5 (1958): 508-511.</p>
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Used as a blistering agent in the treatment of warts
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There is no FDA-approved product which contains Cantharidin. There are FDA approved wart removal treatments both OTC and RX.
Is there any other relevant information?	All relevant information was expressed in the above questions

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September 30, 2014

BY ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. FDA-2013-N-1524
Docket No. FDA-2013-N-1525

To Whom It May Concern:

On behalf of a client, Hyman, Phelps & McNamara, P.C. submits this comment in response to the Food and Drug Administration's ("FDA's") revised request for nominations to the list of bulk drug substances that may be used to compound drug products (79 Fed. Reg. 37747, July 2, 2014; 79 Fed. Reg. 37750, July 2, 2014). FDA should not include cantharidin as a bulk drug substance that may be used to compound drug products in accordance with section 503B of the Federal Food, Drug, and Cosmetic Act ("FDC Act"). Instead, cantharidin should be identified as a drug product that presents demonstrable difficulties for compounding under sections 503A and 503B of the FDC Act.

1. Statutory and Regulatory Background

Section 503A of the FDC Act describes the conditions under which a human drug product compounded for an identified individual patient based on a prescription is entitled to an exemption from certain sections of the FDC Act. One of the conditions for such an exemption is that the compounded drug product is not a "drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product" (section 503A(b)(3)(A) of the FDC Act). Section 503A(d)(1) of the FDC Act requires that before issuing regulations to implement section

503A(b)(3)(A) of the FDC Act, an advisory committee on compounding be convened and consulted “unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health” (section 503A(d)(1) of the FDC Act). FDA recently published two Federal Register notices reopening the nomination process for developing a list of bulk drug substances that may be used to compound drug products [1, 2].

Section 503B of the FDC Act creates a new category of “outsourcing facilities,” which must meet certain conditions. One of the conditions is that an outsourcing facility must not compound a drug identified on a list published by the Secretary of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug, taking into account the risks and benefits to patients, or the drug is compounded in accordance with certain applicable conditions (*see* sections 503B(a)(6)(A) and (a)(6)(B) of the FDC Act). FDA also recently published a Federal Register notice seeking nominations to a list of drug products that present demonstrable difficulties for compounding [3].

In 1999, FDA issued a proposed rule identifying the bulk drug substances that may be used in pharmacy compounding [4]. At that time, cantharidin was nominated for inclusion on the bulk drug substances list. Although this proposed rule was recently withdrawn [5], we urge FDA to consider the information below as the Agency begins to formulate the new list of bulk drug substances that may be used in pharmacy compounding.

2. Cantharidin Is Not Appropriate for Inclusion on the Bulk Drug Substances List

Cantharidin is a powerful vesicant that causes the detachment of epidermal tissue at very low concentrations. While there is some evidence to support the effectiveness of cantharidin at removing human papilloma virus (“HPV”) mediated *Verruca vulgaris* (common warts) and *Molluscum contagiosum* [6], cantharidin is not appropriate for compounding as a bulk drug substance. Cantharidin is extracted from a variable natural source, is highly toxic and lacks a standardized formulation, dose and treatment schedule, making it unsuitable for inclusion on the bulk drug substances list. In short, including cantharidin on the bulk drug substances list would put patients and healthcare providers at unnecessary risk.

Unlike most compounds on the originally proposed bulk drug substances list [4], cantharidin is obtained from a variable natural source: the blister beetle.¹ Many species of blister beetle produce cantharidin and other cantharides as a means of defense. Synthetic methodologies for producing cantharidin exist, but the requirement of hazardous catalysts or extreme pressures make synthesis commercially unviable. Because of this, every commercially available preparation of cantharidin is extracted from these beetles via a sequence of harvesting, drying, grinding and solvent extraction steps. The species of beetle used and preparative steps involved can vary by manufacturer and can result in cantharidin extracts that vary greatly in overall strength and purity, as well as in the amounts and types of impurities present. Visual and melt point analysis are not comprehensive enough for the chemical characterization of such material as impure cantharidin extracts would still pass visual and melt point inspections. Without a current USP monograph for cantharidin, there is no standard specification that is available for determining if a raw extract is of appropriate purity or safe for human use. Further, because cantharidin extracts originate from a natural source, they may contain pesticides, endotoxins or pathogens.

Cantharidin is an extremely toxic compound that has been reported to be fatal at a dose as low as 10mg [6]. To put this in perspective, a sample weighing just 1/100th of an M&M[®] could be fatal if ingested. While many FDA-approved drugs are equally or even more toxic than cantharidin, these other compounds are highly regulated as FDA-approved drugs and not as bulk substances. The Hazardous Material Identification System lists cantharidin as a Category 4 health hazard indicating that life-threatening or permanent damage may result from a single exposure [7]. It is not appropriate to use a substance with this degree of toxicity for compounding. Drugs with this degree of toxicity must be treated with extreme caution and appropriate controls. For their own safety, pharmacists working with extracted cantharidin should wear respirators and work with the material in chemical hoods using dedicated equipment and materials. Further, pharmacists must account for every milligram of material and ensure that no material is transferred or disposed of improperly. Working with cantharidin in the absence of these rigorous protective measures puts pharmacists, their colleagues, doctors, patients and the public at risk.

Indeed, other international regulatory agencies understand the complications of working with cantharidin. Health Canada, for example, regulates cantharidin as a drug,

¹ Of the 30 drug substances included on FDA's 1999 proposed bulk drugs list or identified as drugs still under consideration by FDA, only one other (myrrh gum tincture) is a natural product.

rather than as a bulk drug substance appropriate for compounding. The Health Canada-approved cantharidin formulations specify the dose, formulation and appropriate indications [8]. Contraindications that accompany the product clearly state that cantharidin is not to be used “near eyes, on mucus membranes [or] in ano-genital areas” or in “diabetics or persons with impaired peripheral circulation.” However, such warnings, recommendations and instructions for use would not be required if included by FDA as a bulk drug substance for compounding.

In the United States, there is no standard formulation, dose or treatment schedule for cantharidin. A review of the published literature shows that cantharidin formulations vary in the amount of active ingredient and the excipients used. Cantharidin plasters and ointments would be compounded if included on the bulk drug substances list, but the most likely formulations would include collodion, which contains a highly flammable solvent, diethyl ether, as a base. Additionally, typical container closure systems (~5-10ml in a glass screw top bottle) provide enough material for hundreds of applications. This large volume is far in excess of what is required to treat a single patient, which increases the likelihood of product expiration as well as cross-inoculation of HPV among patients. Moreover, when cantharidin is combined with volatile solvents like diethyl ether and acetone, the amount of cantharidin becomes more concentrated as the solvent evaporates each time the container is opened. Thus, subsequent patients will be treated with increasingly higher and more concentrated doses. Finally, the clinical protocol in which cantharidin should be used has not been proven or demonstrated in adequate double-blinded studies. Protocols vary in the frequency of application, whether to pare the sites down prior to application and whether to wash or occlude the sites post-application [6, 9, 10, 11].

If included on the bulk drug substances list, cantharidin will be used to treat warts and *Molluscum* in young children and the immunosuppressed, two particularly vulnerable patient populations. The safe dose, concentration, and maximum skin area to be treated have not been established in any population, much less these more sensitive populations, and so it is likely that adverse events will occur. For example, physicians may use cantharidin on immunocompromised patients ineligible for therapy with topical immunomodulators like imiquimod, but there can be no assurance that the material is pathogen-free or that other patients with HPV or *Molluscum* have not used the same material, from the same container, before them.

Drug substances with mild safety profiles that are easy to synthesize and characterize chemically should be included on the list of bulk drug substances for compounding. However, cantharidin is not one of these drug substances. Cantharidin is an extremely toxic compound extracted from a natural source, making it unlike any other

drug substance initially proposed for compounding by FDA in 1999. The lack of consensus on how best to prepare, dose and treat patients with cantharidin is especially worrisome knowing that many of the patients who will get this compounded product are young children. With many other safe therapeutic options available for the treatment of both warts and *Molluscum*, there is no need to put patients at unnecessary risk by including cantharidin as a bulk drug substance for compounding.

As summarized above, cantharidin is more appropriately classified as a drug product that presents demonstrable difficulties for compounding under sections 503A and 503B of the FDC Act. Because cantharidin is obtained from a variable natural source using different methods of manufacture, cantharidin extracts can vary greatly in overall purity as well as in the amounts and types of impurities present. There is no standard specification available for cantharidin, and various solvents (including volatile or flammable solvents) are used to formulate the drug product. All of these factors contribute to a potential negative effect on the potency, purity, and quality of cantharidin products, which could affect the safety and effectiveness of the drug product. Moreover, the product is relatively difficult to compound safely and requires appropriate protective equipment and technical training. Inappropriate compounding may lead to immediate and serious toxic effects, including death, in case of skin or eye contact, ingestion, or inhalation.

Sincerely,



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202-737-7545

References

1. 79 Fed. Reg. 37747 (July 2, 2014).
2. 79 Fed. Reg. 37750 (July 2, 2014).
3. 78 Fed. Reg. 72840 (Dec. 4, 2013).
4. 64 Fed. Reg. 996 (Jan. 7, 1999).
5. 78 Fed. Reg. 72841 (Dec. 4, 2013).
6. Lisa Moed, et al., *Cantharidin Revisited: A Blistering Defense of an Ancient Medicine*, 137 Arch Dermatol 1357-1360 (Oct. 2001).
7. Material Safety Data Sheet for Cantharidin, Science Lab.com, *available at* <http://www.sciencelab.com/msds.php?msdsId=9923293>, last accessed on March 20, 2014.
8. Cantharone Brochure, Dormer Laboratories Inc., *available at* http://www.dormer.ca/PDF/Can_Brochure.pdf, last accessed on March 15, 2014.
9. Jacquelyn Coloe Dosal, et al., *Cantharidin for the Treatment of Molluscum Contagiosum: A Prospective, Double-Blinded, Placebo-Controlled Trial*, Pediatric Dermatology 1-10 (2012).
10. Selda Pelinx Kartal Durmazlar, et al., *Cantharidin treatment for recalcitrant flat warts: a preliminary study*, 20:2 Journal of Dermatological Treatment 114-119 (2009).
11. John H. Epstein and William L. Epstein, *Cantharidin Treatment of Digital and Periungual Warts*, 93:1 California Medicine 11-12 (July 1960).

Reference 1

comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

III. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <http://www.regulations.gov>.

Dated: June 25, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-15372 Filed 7-1-14; 8:45 am]

BILLING CODE 4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-D-0779]

Draft Guidance for Industry on Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug and Cosmetic Act; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled “Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act.” This draft guidance describes FDA’s current expectations regarding compliance with current good manufacturing practice (CGMP) requirements for facilities that compound human drugs and register with FDA as outsourcing facilities under the Federal Food, Drug, and Cosmetic Act (the FD&C Act), in accordance with provisions added by the Drug Quality and Security Act (DQSA). FDA is also soliciting public input on specific potential alternative approaches regarding certain CGMP requirements. These potential approaches are explained in detail in the draft guidance.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency

considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by September 2, 2014.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Brian Hasselbalch, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 4364, Silver Spring, MD 20993-0002, 301-796-3279.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act.” On November 27, 2013, President Obama signed the DQSA (Public Law 113-54), which added section 503B to the FD&C Act (21 U.S.C. 353b). Under section 503B(b) of the FD&C Act, a compounder can register as an outsourcing facility with FDA. Drug products compounded in a registered outsourcing facility can qualify for exemptions from the FDA approval requirements in section 505 of the FD&C Act (21 U.S.C. 355) and the requirement to label products with adequate directions for use under section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) if the requirements in section 503B are met. Outsourcing facilities will be inspected by FDA and must comply with other provisions of the FD&C Act, including CGMP requirements under section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)).

Under section 501(a)(2)(B) of the FD&C Act, a drug is deemed to be adulterated if it is not produced in accordance with CGMP. FDA’s regulations regarding CGMP

requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to issue more specific CGMP regulations for outsourcing facilities. Until final regulations are issued, this draft guidance describes FDA’s expectations regarding outsourcing facilities and the CGMP requirements in parts 210 and 211 during this interim period. This draft guidance reflects FDA’s intent to recognize the differences between compounding outsourcing facilities and conventional drug manufacturers, and to tailor CGMP requirements to the nature of the specific compounding operations conducted by outsourcing facilities while maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products. This draft guidance is only applicable to drugs compounded in accordance with section 503B of the FD&C Act.

FDA intends to focus its inspectional and enforcement efforts on those aspects of compounding operations that pose the highest risk to patient safety. In particular, the primary focus of this draft guidance is on those aspects of part 211 that relate to sterility assurance of sterile drug products and the safety of compounded drug products more generally, with respect to strength (e.g., subpotency, superpotency), and labeling or drug product mix-ups.

II. Specific Request for Comments and Information

In addition to comments on the draft guidance generally, FDA is requesting comments and related supporting information on the following specific issues: (1) alternative approaches that would enable an outsourcing facility to have confidence in the quality of incoming components from sources used by multiple outsourcing facilities without each individual outsourcing facility having to conduct periodic laboratory testing to confirm the information in the third-party supplier’s certificate of analysis and (2) alternative approaches that would minimize the need for outsourcing facilities to establish an in-house laboratory while providing confidence about the accuracy of testing performed by a third party used by more than one outsourcing facility. FDA has described these potential alternative approaches in the draft guidance and is seeking public comment on these and any other alternative approaches.

This draft guidance is being issued consistent with FDA’s good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will

represent the Agency's current thinking on "Current Good Manufacturing Practice-Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act." It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

III. Comments

Interested persons may submit electronic comments regarding this document to <http://www.regulations.gov>, or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

IV. Paperwork Reduction Act of 1995

This draft guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection are given under this section with an estimate of the annual recordkeeping, third-party disclosure, and reporting burdens. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

We invite comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Guidance for Industry, Current Good Manufacturing Practice—Interim Guidance for Human Drug

Compounding Outsourcing Facilities under Section 503B of the FD&C Act.

Description: The draft guidance describes FDA's expectations regarding compliance with CGMP requirements for facilities that register with FDA as outsourcing facilities under section 503B of the FD&C Act. The primary focus of the draft guidance is on sterility assurance of sterile products and the safety of compounded drug products with respect to strength (e.g., subpotency, superpotency), and labeling or drug product mix-ups. OMB has already approved the information collection (recordkeeping) contained in FDA's CGMP regulations in part 211 (OMB control number 0910–0139). FDA believes that much of the recordkeeping burden that would result from the draft guidance is already incurred by outsourcing facilities in the normal course of their business activities. Thus, the burden estimates for these "usual and customary" business practices are not included in the calculation of burden that follows (see 5 CFR 1320.3(b)(2)).

The draft guidance contains the following collections of information under the PRA:

1. Facility Design

The draft guidance describes those elements of facility design of outsourcing facilities that are considered critical to assuring the quality of compounded sterile drug products at those facilities. For example, the draft guidance states that sterile drugs should be produced only in ISO 5 or better air quality, and that the ISO 5 zone or critical area must be qualified (i.e., shown to meet the specifications). In section III.A, the draft guidance lists certain studies and tests which should be successfully performed for outsourcing facilities, and states that the results of these studies and tests should be documented.

We estimate that annually a total of approximately 50 outsourcing facilities¹ ("No. of Recordkeepers" in table 1, row 1) will individually document approximately 20 studies and tests ("Total Annual Records" in table 1, row 1) that are critical to assuring the quality of compounded sterile drug products.

¹ This is an estimate of the number of facilities that will register as outsourcing facilities in fiscal year 2014 (which runs from October 1, 2013 to September 30, 2014). As of April 30, 2014, 40 facilities had registered as outsourcing facilities, and on average, 2 facilities have registered each month for the past 3 months, but these estimates are highly uncertain. Annual establishment fees will be assessed for each outsourcing facility registered on or after October 1, 2014. It is unknown how many facilities will remain as registered outsourcing facilities once these fees take effect.

We also estimate that preparing and maintaining each record as described in the draft guidance will take on average approximately 1.5 hours for each record ("Average Burden per Recordkeeping" in table 1, row 1).

2. Control Systems and Procedures for Maintaining Suitable Facilities

The draft guidance describes certain controls, procedures, and documentation that should be established and followed for maintaining suitable facilities and to prevent contamination and mix-ups during the course of aseptic operations at outsourcing facilities. Procedures must be established that assign responsibility for and describe cleaning schedules, methods, equipment, and materials. In addition, the guidance describes that procedures should ensure recording of instances when there is a loss of positive pressure in the clean room during production.

We estimate that annually a total of approximately 50 outsourcing facilities ("No. of Recordkeepers" in table 1, row 2) will individually establish and maintain approximately 3 records (procedures and documentation) for maintaining suitable outsourcing facilities ("Total Annual Records" in table 1, row 2). We also estimate that preparing and maintaining each record as described in section III.B of the draft guidance will take on average approximately 5 hours for each record ("Average Burden per Recordkeeping" in table 1, row 2).

3. Environmental and Personnel Monitoring

Under the draft guidance, procedures for environmental and personnel monitoring in the aseptic processing area for viable, nonviable, and total particulate matter should be established and followed in outsourcing facilities. The procedures should include establishing the validity of the microbiological media, including the preparation, sterilization, and growth potential of the media used in performing tests.

We estimate that annually a total of approximately 50 outsourcing facilities ("No. of Recordkeepers" in table 1, row 3) will individually establish approximately 1,200 environmental and personnel monitoring procedures and records to document test results ("Total Annual Records" in table 1, row 3) for the aseptic processing areas. We also estimate that preparing and maintaining the environmental and personnel monitoring procedures as described in section III.C of the draft guidance will take on average approximately 0.25

hours for each record (“Average Burden per Recordkeeping” in table 1, row 3).

4. *Equipment, Containers, and Closures*

Procedures and documentation should be established and maintained for testing compounding equipment and containers and closures to ensure the quality of compounded drug products at outsourcing facilities.

We estimate that annually a total of approximately 50 outsourcing facilities (“No. of Recordkeepers” in table 1, row 4) will individually establish and maintain approximately 1,000 procedures and documentation for testing equipment, containers, and closures (“Total Annual Records” in table 1, row 4) in the aseptic processing areas. We also estimate that preparing and maintaining these procedures and documentation as described in section III.D of the draft guidance will take on average approximately 0.25 hours for each record (“Average Burden per Recordkeeping” in table 1, row 4).

5. *Components*

Procedures should be established and records maintained concerning the source and quality of components such as raw materials or ingredients used in producing compounded sterile drug products at outsourcing facilities.

We estimate that annually a total of approximately 50 outsourcing facilities (“No. of Recordkeepers” in table 1, row 5) will individually establish and maintain approximately 240 records of testing to ensure the quality of components used in producing compounded drugs, as recommended in section III.E of the draft guidance (“Total Annual Records” in table 1, row 5). We also estimate that preparing and maintaining these records will take on average approximately 4 hours for each record (“Average Burden per Recordkeeping” in table 1, row 5).

6. *Production and Process Controls*

Production and process documentation and procedures, such as batch records, must be established to assure the quality of compounded sterile drug products at outsourcing facilities. Training on aseptic technique, cleanroom behavior, gowning, and procedures covering aseptic manufacturing area operations must be established. Sterilization validation of operations (e.g., holding vessels, filling equipment, lyophilizer) and periodic verification activities and results must be documented.

We estimate that annually a total of approximately 50 outsourcing facilities (“No. of Recordkeepers” in table 1, row 6) will individually establish and

maintain approximately 5,000 records pertaining to production and process controls, such as validation procedures and training, to assure the quality of compounded sterile drug products (“Total Annual Records” in table 1, row 6). We also estimate that preparing and maintaining these records, as described in section III.F of the draft guidance, will take on average approximately 0.25 hours for each record (“Average Burden per Recordkeeping” in table 1, row 6).

7. *Release Testing*

Compounded drug products produced at outsourcing facilities must be tested to determine whether they meet final product specifications prior to release for distribution, and procedures for final release testing must be established and followed.

We estimate that annually a total of approximately 50 outsourcing facilities (“No. of Recordkeepers” in table 1, row 7) will individually establish and maintain approximately 240 records pertaining to final release testing of compounded drug products, including release testing procedures and documentation (“Total Annual Records” in table 1, row 7). We also estimate that preparing and maintaining these records, as described in section III.G of the draft guidance, will take on average approximately 4 hours for each record (“Average Burden per Recordkeeping” in table 1, row 7).

If sterility testing is not completed prior to release under certain conditions described in section III.G of the draft guidance, procedures must be established that specify that if the product fails to meet a criterion for sterility, all healthcare and other facilities that received the product must be immediately notified of the test results and provided with any appropriate information and recommendations to aid in the treatment of patients; the notification must be documented; and FDA must be notified in writing.

We estimate that annually a total of approximately 10 outsourcing facilities (“No. of Respondents” in table 2, row 1) will individually send approximately 1 notification of test results to all healthcare and other facilities that received the compounded drug product and provide them with any appropriate information and recommendations to aid in the treatment of patients (“Total Annual Disclosures” in table 2, row 1). We also estimate that preparing and sending each notification will take approximately 5 hours (“Average Burden per Disclosure” in table 2, row 1).

We also estimate that annually, a total of approximately 10 outsourcing facilities (“No. of Respondents” in table 3) will individually submit to FDA 1 notification of the test results for any compounded drug product that fails to meet a sterility criterion (“Total Annual Responses” in table 3). Preparing and submitting this information will take approximately 5 hours per notification (“Average Burden per Response” in table 3).

8. *Laboratory Controls*

Each laboratory used to conduct testing of components, in-process materials, and finished drug products for outsourcing facilities must follow written procedures for the conduct of each test and document the results, establish sampling and testing procedures to ensure that components, in-process materials, and drug products conform to the product specifications, and keep complete records of all tests performed to ensure compliance with established specifications and standards, including examinations and assays.

We estimate that annually a total of approximately 50 outsourcing facilities (“No. of Recordkeepers” in table 1, row 8) will individually establish and maintain approximately 1,000 laboratory records as described in section III.H of the draft guidance (“Total Annual Records” in table 1, row 8). We also estimate that preparing and maintaining these records will take on average approximately 0.5 hours for each record (“Average Burden per Recordkeeping” in table 1, row 8).

9. *Stability/Expiration Dating*

Stability testing is used to ensure that a drug product will retain its quality (in particular, strength) and remain sterile through the labeled expiration date. The draft guidance recommends that procedures established by outsourcing facilities for assessing the stability of drug products should include: (1) using stability-indicating test methods that are reliable, meaningful and specific; (2) evaluating samples of the drug product in the same container closure system in which the drug product will be marketed; (3) evaluating samples for stability that are representative of the lot or batch from which they were obtained and are stored under suitable conditions; and (4) testing to evaluate antimicrobial effectiveness (resistance to antimicrobial contamination) for drug products labeled or intended to be multiple dose.

We estimate that annually a total of approximately 50 outsourcing facilities (“No. of Recordkeepers” in table 1, row

9) will individually establish and maintain approximately 90 procedures for stability studies to determine an expiration date ("Total Annual Records" in table 1, row 9) for compounded drug products. We also estimate that preparing and maintaining these procedures as described in section III.I of the draft guidance will take approximately 5 hours for each record ("Average Burden per Recordkeeping" in table 1, row 9).

10. Packaging and Labels

Packaging of sterile drugs must ensure the sterility and integrity of the product until it is administered to a patient, and product labels must contain required information and labeling operations must include controls to prevent mix-ups. Procedures should be established by outsourcing facilities for packaging and labeling operations for compounded sterile drug products, including the following: (1) The container, closure, and packaging systems should provide adequate protection against foreseeable external factors in storage, shipment, and use that can cause contamination or deterioration; (2) packaging records should include specimens of all labels used; procedures should be established for issuance of labels, examination of

issued labels, reconciliation of used labels to prevent mix-ups; (3) there should be physical/spatial separation between different labeling and packaging operations to prevent mix-ups; and (4) controls should be established that assure proper identification of any filled containers of sterile products that are stored unlabeled for any period of time.

We estimate that annually a total of approximately 50 outsourcing facilities ("No. of Recordkeepers" in table 1, row 10) will individually establish and maintain approximately 20 procedures and records for packaging operations and labels ("Total Annual Records" in table 1, row 10) for compounded drug products. We also estimate that preparing and maintaining these procedures and records as described in section III.J of the draft guidance will take approximately 5.5 hours for each record ("Average Burden per Recordkeeping" in table 1, row 10).

11. Quality Assurance Activities

A quality control unit must be established by outsourcing facilities to oversee various aspects of compounded sterile drug production and to monitor quality assurance. The responsibilities of the quality control unit must be

established in procedures and should include investigations and development and oversight of appropriate corrective actions and preventive actions regarding: Rejected lots of finished product, unexpected results or trends, validation and stability failures, and process deviations or equipment malfunctions that involve critical equipment. The quality control unit also is responsible for ensuring that sampling and testing are conducted to ensure that appropriate specifications are met, and for product complaint handling.

We estimate that annually a total of approximately 50 outsourcing facilities ("No. of Recordkeepers" in table 1, row 11) will individually establish approximately 8 procedures on the responsibilities of the quality control unit ("Total Annual Records" in table 1, row 10) as described in section III.K of the draft guidance. We also estimate that preparing and maintaining these procedures will take approximately 3 hours for each record ("Average Burden per Recordkeeping" in table 1, row 11).

The total estimated recordkeeping, third party disclosure, and reporting burdens for the draft guidance are as follows:

TABLE 1—ESTIMATED ANNUAL RECORDKEEPING BURDEN ¹

Type of recordkeeping	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
Facility Design	50	20	1,000	1.5	1,500
Control Systems and Procedures For Maintaining Suitable Facilities.	50	3	150	5	750
Environmental and Personnel Monitoring.	50	1,200	60,000	0.25 (15 minutes)	15,000
Equipment, Containers, and Closures.	50	1,000	50,000	0.25 (15 minutes)	12,500
Components	50	240	12,000	4	48,000
Production and Process Controls	50	5,000	250,000	0.25 (15 minutes)	62,500
Release Testing	50	240	12,000	4	48,000
Laboratory Controls	50	1,000	50,000	0.5 (30 minutes)	25,000
Stability/Expiration Dating	50	90	4,500	5	22,500
Packaging and Labels	50	20	1,000	5.5	5,500
Quality Assurance Activities	50	8	400	3	1,200
Total	50	8,821	441,050	242,450

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 2—ESTIMATED ANNUAL THIRD-PARTY DISCLOSURE BURDEN ¹

Type of disclosure & proposed 21 CFR section	Number of respondents	Frequency per disclosure	Total annual disclosures	Average burden per disclosure	Total hours
Notification that a compounded drug product fails to meet a sterility criterion.	10	1	10	5	50
An expiration date is added to the compounded drug product's label.	50	540	27,000	0.25 (15 minutes)	6,750
Total	6,800				

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 3—ESTIMATED ANNUAL REPORTING BURDEN¹

Type of reporting & proposed 21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Notification to FDA that a compounded drug product fails to meet a sterility criterion	10	1	10	5	50

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

V. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <http://www.regulations.gov>.

Dated: June 25, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014–15370 Filed 7–1–14; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2013–N–1525]

Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; revised request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is preparing to develop a list of bulk drug substances (active ingredients) that may be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. In response to a notice published in the **Federal Register** of December 4, 2013, interested groups and individuals previously nominated a wide variety of substances for this list. However, many of those nominations either were for a substance that is already the subject of a USP monograph or a component of an FDA-approved drug, were not for bulk drug substances used in compounding as active ingredients, or did not include sufficient information to justify inclusion of the nominated substance on the list. To improve the efficiency of the process for developing the list of bulk

drug substances that may be used to compound drug products under section 503A, FDA is providing more detailed information on what it needs to evaluate a nomination. Because the deadline for nominations has passed, FDA is reopening the nomination process so that interested persons can submit nominations of bulk drug substances that are not the subject of a USP or NF monograph or a component of an FDA-approved drug. Interested persons will also have the opportunity to provide adequate support to justify placement of the substances on the list. Bulk drug substances that were previously nominated will not be further considered unless they are renominated and those nominations are adequately supported. Substances that are already eligible for use in compounding or that are not adequately supported will not be placed on the list.

DATES: Submit written or electronic nominations for the bulk drug substances list by September 30, 2014.

ADDRESSES: You may submit nominations, identified by Docket No. FDA–2013–N–1525, by any of the following methods.

Electronic Submissions

Submit electronic nominations in the following way:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the instructions for submitting “comments.”

Written Submissions

Submit written nominations in the following ways:

- *Mail/Hand delivery/Courier (for paper submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA–2013–N–1525 for this request for nominations. All nominations received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting nominations, see the “Request for Nominations” heading of the

SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or nominations received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Emily Helms Williams, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6280, Silver Spring, MD 20993–0002, 301–796–3381.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions under which a compounded drug product may be entitled to an exemption from certain sections of the FD&C Act. Those conditions include that the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that (1) comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A. See section 503A(b)(1)(A)(i) of the FD&C Act. Under section 503A(c)(2), the criteria for determining which substances should appear on the 503A bulk drugs list “shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.”

Section 503A refers to the definition of “bulk drug substance” in FDA regulations at § 207.3(a)(4) (21 CFR 207.3(a)(4)). See section 503A(b)(1)(A) of the FD&C Act. As defined in

Reference 2

Column A—What information is requested?	Column B—Put data specific to the nominated substance
Is the ingredient listed in any of the three sections of the Orange Book?	Confirm whether the ingredient is a component of an FDA-approved product.
Were any monographs for the ingredient found in the USP or NF monographs?	Confirm whether the ingredient is the subject of a USP or NF monograph.
What is the chemical name of the substance?	Chemical name.
What is the common name of the substance?	Common name.
Does the substance have a UNII Code?	UNII code.
What is the chemical grade of the substance?	Provide the chemical grade.
What is the strength, quality, stability, and purity of the ingredient?	Provide the strength, quality, stability, and purity information.
How is the ingredient supplied?	Describe how the ingredient is supplied (e.g., powder, liquid).
Is the substance recognized in foreign pharmacopeias or registered in other countries?	List the foreign pharmacopeias or other countries in which it is registered.
Has information been submitted about the substance to the USP for consideration of monograph development?	Put yes, no, or unknown. If yes, state the status of the monograph, if known.
What dosage form(s) will be compounded using the bulk drug substance?	State the dosage form(s).
What strength(s) will be compounded from the nominated substance?	List the strength(s) of the drug product(s) that will be compounded from the nominated substance, or a range of strengths, if known.
What are the anticipated route(s) of administration of the compounded drug product(s)?	List the route(s) of administration of the compounded drug product(s).
Are there safety and efficacy data on compounded drugs using the nominated substance?	Provide a bibliography of safety and efficacy data for the drug compounded using the nominated substance, if available, including any relevant peer-reviewed medical literature.
Has the bulk drug substance been used previously to compound drug product(s)?	Describe past uses of the bulk drug substance in compounding.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Provide information on the proposed use of the compounded drug product.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	Provide a rationale for the use of a compounded drug product.
Is there any other relevant information?	Provide any other information you would like FDA to consider in evaluating the nomination.

Interested persons may submit either electronic nominations to <http://www.regulations.gov> or written nominations to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of nominations. Identify nominations with the docket number found in the brackets in the heading of this document. Received nominations may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Dated: June 25, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-15367 Filed 7-1-14; 8:45 am]

BILLING CODE 4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-1524]

Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Revised Request for Nominations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; revised request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is preparing to develop a list of bulk drug substances (active ingredients) that may be used to compound drug products in accordance with section 503B of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) concerning outsourcing facilities. In response to a notice published in the **Federal Register** of December 4, 2013, interested groups and individuals previously nominated a wide variety of substances for this list. However, many of those nominations were not for bulk drug substances used in compounding as active ingredients, and none included sufficient information to justify inclusion of the

nominated substances on the list. To improve the efficiency of the process for developing the list of bulk drug substances that may be used to compound drug products under section 503B of the FD&C Act, FDA is providing more detailed information on what it needs to evaluate a nomination. Because the deadline for nominations has passed, FDA is reopening the nomination process so that interested persons can submit nominations of bulk drug substances and provide adequate support to justify placing the substances on the list. Bulk drug substances that were previously nominated will not be further considered unless they are renominated and adequately supported. Substances that are not adequately supported will not be placed on the list.

DATES: Submit written or electronic nominations for the bulk drug substances list by September 30, 2014.

ADDRESSES: You may submit nominations, identified by Docket No. FDA-2013-N-1524, by any of the following methods.

Electronic Submissions

Submit electronic nominations in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written nominations in the following ways:

- Mail/Hand delivery/Courier (for paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2013-N-1524 for this request for nominations. All nominations received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting nominations, see the "Request for Nominations" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or nominations received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Emily Helms Williams, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6280, Silver Spring, MD 20993-0002, 301-796-3381.

SUPPLEMENTARY INFORMATION:

I. Background

I. Background

Under the Drug Quality and Security Act (Pub. L. 113-54), which added section 503B to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b), outsourcing facilities¹ may qualify for certain exemptions from the FD&C Act if the conditions set forth in the statute are satisfied. Those conditions include that an outsourcing facility does not compound drug products using a bulk drug substance unless the bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need (the 503B list), or the drug product compounded from such bulk drug substance appears on the drug shortage list in effect under section 506E of the FD&C Act (21 U.S.C. 356e) (FDA drug shortage list) at the time of compounding, distribution, and dispensing, and each of the following conditions are met: (1) If an applicable

¹ "Outsourcing facilities" are facilities that meet certain conditions described in section 503B of the FD&C Act, including registering with FDA as an outsourcing facility.

monograph exists under the United States Pharmacopeia, the National Formulary, or another compendium or pharmacopeia recognized by the Secretary for purposes of this paragraph, the bulk drug substance complies with the monograph; (2) the bulk drug substance is manufactured by an establishment that is registered under section 510 of the FD&C Act (21 U.S.C. 360); and (3) the bulk drug substance is accompanied by a valid certificate of analysis (see section 503B(a)(2) of the FD&C Act).

Section 503B refers to the definition of "bulk drug substance" in FDA regulations at § 207.3(a)(4) (21 CFR 207.3(a)(4)). See section 503B(a)(2) of the FD&C Act. As defined in § 207.3(a)(4), a "bulk drug substance" is any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.

An "active ingredient" is any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect. See 21 CFR 210.3(b)(7).

Any component other than an active ingredient is an "inactive ingredient." See 21 CFR 210.3(b)(8). Inactive ingredients used in compounded drug products, which commonly include flavorings, dyes, diluents, or other excipients, need not appear on the Secretary's list of bulk drug substances to be eligible for use in compounding drug products and will not be included on the list.

In a notice dated November 27, 2013, published in the **Federal Register** of December 4, 2013 (78 FR 72838), FDA requested nominations for specific bulk drug substances for the Agency to consider for placement on the 503B list. In response to that request, 753 comments were submitted to the docket, most of which nominated substances for inclusion on the bulk drug substances list. Some comments nominated several hundred substances, and approximately 10 comments nominated thousands of substances, including en bloc nominations of substances listed in the United States Pharmacopeia (USP) or

National Formulary, the British Pharmacopeia, the European Pharmacopeia, the Japanese Pharmacopeia, the Food Chemicals Codex, the Homeopathic Pharmacopeia of the United States, and the USP Dietary Supplements Compendium. Several submissions referenced a spreadsheet entitled "OTC Active Ingredients," available on FDA's Web site at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf>. Those submissions nominated all of the ingredients on the spreadsheet, which numbered over 1,700 entries.²

However, many of the nominated substances are typically inactive ingredients or foods. Some commonly used inactive ingredients are occasionally used as the active ingredient in a drug product. See 55 FR 46914 at 46916, November 7, 1990 (noting that 21 CFR 310.545 only affects the use of the listed ingredients as active ingredients for the specific indications and that some of the ingredients listed in the rule, such as sorbitol, sugars, and eucalyptol, have valid uses as inactive ingredients). Ingredients commonly used as inactive ingredients in compounded drug products, such as flavorings, dyes, diluents, or other excipients, need not appear on the Secretary's list of bulk drug substances to be eligible for use as an inactive ingredient in compounded drug products, should not be nominated, and will not be included on the list. All nominations must demonstrate how the ingredient is used as an active ingredient in a particular compounded drug product.

Further, the nominations did not include sufficient information for the Agency to evaluate the clinical need for drug products compounded using the bulk drug substance. As stated previously, section 503B requires FDA to create a list "identifying bulk drug substances for which there is a clinical need" Section 503B(a)(2)(A)(i) of the FD&C Act. Although this language is ambiguous, the Agency has interpreted it to mean that a clinical need to compound with a bulk drug substance exists where there is a clinical need for a specific drug product to be compounded with the nominated bulk drug substance. The Agency believes that this interpretation is consistent with both the language and purpose of

² The total number of unique ingredients on the spreadsheet available on FDA's Web site and the nominations that mirrored that document is lower than this total because the same substances were listed separately for different indications, according to how they are listed in the over-the-counter (OTC) monographs and regulations.

the statute. Therefore, to qualify for placement on the 503B list, it is necessary to identify the compounded drug product for which there is a clinical need and to demonstrate that the nominated bulk drug substance is required to compound that drug product.

The nominators of the en bloc submissions provided no justification for listing any of the specific substances on the list. To the extent information about the clinical need for the use of a bulk drug substance in compounded drug products was provided at all in individual nominations, many of the comments to the docket included a statement about the need for the use of bulk drug substances in compounding generally rather than information about the specific clinical need for drug products compounded using a particular bulk drug substance. For example, many nominations included the following standardized language as the explanation of clinical need for compounding with the bulk drug substance: "Prescribed dosage forms and strengths not available commercially. Manufacturer backorders. Possible patient sensitivities to manufactured product dyes, fillers, preservatives and other excipients." Such statements do not provide sufficient information for FDA to determine that there is a clinical need to compound a particular drug product from the nominated bulk drug substance. Because the information submitted with previous nominations was insufficient, FDA is unable to determine whether those substances should be included on the list.

To improve the efficiency of the process for the development of the list of bulk drug substances that may be used to compound drug products under section 503B of the FD&C Act, and because the deadline for submitting nominations has passed, FDA is reopening the nomination process so that interested persons have the opportunity to submit nominations of bulk drug substances and provide adequate support for placing them on the list. FDA will be able to evaluate only those bulk drug substances submitted in response to this notice that are supported with adequate data and information, as described in section II.

Bulk drug substances that were previously nominated will not be further considered unless they are renominated and adequately supported. Substances that are not adequately supported will not be placed on the list. FDA expects the submissions for each bulk drug substance to provide the information described in section II. For

example, nominations must include sufficient information to demonstrate that a particular ingredient meets the definition of "bulk drug substance," as defined in § 207.3(a)(4). See section 503B(a)(2) of the FD&C Act. The identification of an ingredient as an "active ingredient" in a regulation, or on a spreadsheet such as the one listing "OTC Active Ingredients," is not sufficient to demonstrate that a substance is a bulk drug substance for purposes of the 503B List. En bloc nominations of substances listed in compendia, pharmacopeia, or similar reference materials cannot be placed on the list unless the Agency receives adequate information for each bulk drug substance to justify its placement on the list. FDA will only be able to consider bulk drug substances that are supported with the information requested in section II.

In section II, FDA identifies the type of information needed to support a nomination to the 503B list.

II. Request for Nominations

A. Active Ingredients

Interested groups and individuals may nominate specific bulk substances for inclusion on the list. Nominations will only be evaluated if they are for specific active ingredients that meet the definition of a bulk drug substance in § 207.3(a)(4). Nominated substances that do not meet this definition will not be included on the list.

To fully evaluate a bulk drug substance, FDA needs the following information about both the bulk drug substance being nominated and the drug product(s) that will be compounded using such substance:

1. Confirmation That the Nominated Substance Is a Bulk Drug Substance

A statement that the nominated substance is an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4), and an explanation of why the substance is considered an active ingredient when it is used in compounded drug products, citing to specific sources that describe the active properties of the substance.

2. General Background on the Bulk Drug Substance

- Ingredient name;
- chemical name;
- common name(s); and
- identifying codes, as available, from FDA's Unique Ingredient Identifiers (UNII) used in the FDA/USP Substance Registration System, available at <http://fdasis.nlm.nih.gov/srs/>. Because substance names can vary, this code,

where available, will be used by the Agency to confirm the exact substance nominated and to identify multiple nominations of the same substance so the information can be reviewed together.

- Chemical grade of the ingredient;
- description of the strength, quality, stability, and purity of the ingredient;
- information about how the ingredient is supplied (e.g., powder, liquid); and
- information about recognition of the substance in foreign pharmacopeias and the status of its registration(s) in other countries, including whether information has been submitted to USP for consideration of monograph development.

B. Clinical Need To Compound

For FDA to be able to meaningfully evaluate a substance, the information provided regarding the clinical need for compounding with a bulk drug substance must be specific to the particular substance nominated and drug product to be compounded. A "boilerplate" or general explanation of clinical need for compounding with bulk drug substances will not enable FDA to conduct an adequate review. Prescribers of the compounded drug products who may be in the best position to explain why there is a clinical need for a compounded drug product may provide data in support of a nomination. The following information about clinical need is necessary to provide adequate support for nominations to the 503B list:

- A statement describing the medical condition(s) that the drug product to be compounded with the nominated bulk drug substances is intended to treat (i.e., what patient need is met by the drug product compounded with the bulk drug substance);
- a list of FDA-approved drug products, if any, that address the same medical condition;
- if there are FDA-approved drug products that address the same medical condition, an explanation of why a compounded drug product is necessary (i.e., why the approved drug product is not suitable for a particular patient population);
- if the approved drug product is not suitable for a particular patient population, an estimate of the size of the population that would need a compounded drug product (e.g., for a drug product compounded from bulk because of patient allergies or other intolerances to excipients in FDA-approved drug products, FDA expects the supporting information to include a good faith estimate of the patient

population with the specific medical condition that suffers from the allergy or intolerance, with citations to the literature regarding the incidence of the condition or a statement that a search was conducted and no references were found);³

- a bibliography of safety and efficacy data for the drug compounded using the nominated substance,⁴ if available, including any relevant peer-reviewed medical literature; and

- if there is an FDA-approved drug product that includes the bulk drug substance nominated, an explanation of why the drug product proposed to be compounded must be compounded from bulk rather than with the FDA-approved drug product.

General or boilerplate statements regarding the need to compound from the bulk drug substance or the benefits of compounding generally will not be considered sufficient. Note that the Agency does not consider supply issues, such as backorders, that do not rise to the level of a drug shortage listed on FDA's drug shortage Web site as

evidence of a clinical need for compounding with a bulk drug substance, and section 503B of the FD&C Act already allows compounding from bulk drug substances if the compounded drug product is on the FDA drug shortage list. Similarly, considerations of cost and convenience will not be considered indicators of clinical need.

C. Information on the Drug Product That Will Be Compounded With the Bulk Drug Substance

- Information about the dosage form(s) into which the bulk drug substance will be compounded;
- information about the strength(s) of the compounded drug product(s);
- information about the anticipated route(s) of administration of the compounded drug product(s); and
- information about the previous use(s) of the compounded drug product(s).

D. Nomination Process

Because the deadline for submitting nominations has passed, FDA is

reopening the nomination process so that interested persons can submit nominations of bulk drug substances and have the opportunity to provide adequate support for placing them on the list. Bulk drug substances that were previously nominated need to be renominated. Nominators are encouraged to submit as much of the information identified in this document as possible. Unless adequate supporting data is received for a bulk drug substance, FDA will be unable to consider it further for inclusion on the list.

Individuals and organizations will be able to comment on nominated substances after the nomination period has closed or petition FDA to make additional list amendments after the list is published, in accordance with 21 CFR 10.30.

For efficient consolidation and review of nominations, nominators are encouraged to submit their nominations in an editable Excel file. Specifically, nominators are encouraged to format their nominations as follows:

Column A—What information is requested?	Column B—put data specific to the nominated substance
What is the name of the nominated ingredient? Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?	Provide the ingredient name. Provide an explanation for why it is considered an active ingredient when it is used in specific compounded drug products, and provide citations to specific sources that describe its active properties.
What is the chemical name of the substance?	Chemical name.
What is the common name of the substance?	Common name.
Does the substance have a UNII Code?	UNII code.
What is the chemical grade of the substance?	Provide the chemical grade.
What is the strength, quality, stability, and purity of the ingredient?	Provide the strength, quality, stability, and purity information.
How is the ingredient supplied?	Describe how the ingredient is supplied (e.g., powder, liquid).
Is the substance recognized in foreign pharmacopeias or registered in other countries?	List the foreign pharmacopeias or other countries in which it is registered.
Has information been submitted about the substance to the USP for consideration of monograph development?	Put yes, no, or unknown. If yes, state the status of the monograph, if known.
What medical condition(s) is the drug product compounded with the bulk drug substances intended to treat?	Describe the medical condition(s) that the drug product compounded with the bulk drug substances is intended to treat.
Are there other drug products approved by FDA to treat the same medical condition?	List the other approved treatments.
If there are FDA-approved drug products that address the same medical condition, why is there a clinical need for a compounded drug product?	Provide a justification for clinical need, including an estimate of the size of the population that would need the compounded drug.
Are there safety and efficacy data on compounded drugs using the nominated substance?	Provide a bibliography of safety and efficacy data for the drug compounded using the nominated substance, if available, including any relevant peer-reviewed medical literature.
If there is an FDA-approved drug product that includes the bulk drug substance nominated, is it necessary to compound a drug product from the bulk drug substance rather than from the FDA-approved drug product?	Provide an explanation of why it is necessary to compound from the bulk drug substance.
What dosage form(s) will be compounded using the bulk drug substance?	State the dosage form(s).
What strength(s) will be compounded from the nominated substance?	List the strength(s) of the drug product(s) that will be compounded from the nominated substance, or a range of strengths, if known.
What are the anticipated route(s) of administration of the compounded drug product(s)?	List the route(s) of administration of the compounded drug product(s).

³ For example, if there is a need to compound a drug product from bulk drug substances due to patient sensitivity to a preservative or other excipient in the approved drug product, the supporting data is expected to set forth the number of patients for whom the drug product is prescribed

that are allergic or sensitive to that particular excipient.

⁴ FDA recognizes that the available safety and efficacy data supporting consideration of a bulk drug substance for inclusion on the list may not be of the same type, amount, or quality as is required

to support a new drug application. Note that data regarding safety and efficacy, while relevant, is not indicative of a clinical need for a particular bulk drug substance, and additional information regarding the clinical need must be provided.

Column A—What information is requested?	Column B—put data specific to the nominated substance
Has the bulk drug substance been used previously to compound drug product(s)?	Describe previous uses of the bulk drug substance in compounding.
Is there any other relevant information?	Provide any other information you would like FDA to consider in evaluating the nomination.

Interested persons may submit either electronic nominations to <http://www.regulations.gov> or written nominations to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of nominations. Identify nominations with the docket number found in the brackets in the heading of this document. Received nominations may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Dated: June 25, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014–15373 Filed 7–1–14; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Statement of Organization, Functions and Delegations of Authority

This notice amends Part R of the Statement of Organization, Functions and Delegations of Authority of the Department of Health and Human Services (HHS), Health Resources and Services Administration (HRSA) (60 FR 56605, as amended November 6, 1995; 67 FR 46519, as amended June 11, 2008; 73 FR 33099, as amended September 30, 2009, 78 FR 50227, as last amended January 24, 2013, 78 FR 7436). This Order of Succession supersedes the Order of Succession for the Administrator, HRSA, published at 78 FR 7436, February 1, 2013.

This notice deletes the Bureau of Health Professions; the Bureau of Clinician Recruitment and Services; and Regional Division Directors from the order of succession, and adds the Bureau of Health Workforce and Regional Administrators to HRSA’s hierarchy affecting the Order of Succession. This notice reflects the new Order of Succession for HRSA.

Section R–30, Order of Succession

During the absence or disability of the Administrator, or in the event of a vacancy in the office, the officials

designated below shall act as Administrator in the order in which they are listed:

1. Deputy Administrator;
2. Chief Operating Officer;
3. Associate Administrator, Bureau of Primary Health Care;
4. Associate Administrator, Bureau of Health Workforce;
5. Associate Administrator, HIV/AIDS Bureau;
6. Associate Administrator, Maternal and Child Health Bureau;
7. Associate Administrator, Healthcare Systems Bureau;
8. Associate Administrator, Office of Regional Operations; and
9. HRSA Regional Administrators in the order in which they have received their permanent appointment as such.

Exceptions

(a) No official listed in this section who is serving in acting or temporary capacity shall, by virtue of so serving, act as Administrator pursuant to this section.

(b) Notwithstanding the provisions of this section, during a planned period of absence, the Administrator retains the discretion to specify a different order of succession.

Section R–40, Delegations of Authority

All delegations of authority and re-delegations of authority made to HRSA officials that were in effect immediately prior to this action, and that are consistent with this action, shall continue in effect pending further re-delegation, pending further re-delegation, provided they are consistent with this action.

This document is effective upon date of signature.

Dated: June 25, 2014.

Mary K. Wakefield,

Administrator.

[FR Doc. 2014–15498 Filed 7–1–14; 8:45 am]

BILLING CODE 4165–15–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Submission for OMB Review; 30-Day Comment Request; Population Assessment of Tobacco and Health (PATH) Study

SUMMARY: Under the provisions of Section 3507(a)(1)(D) of the Paperwork Reduction Act of 1995, the National Institute on Drug Abuse (NIDA), the National Institutes of Health (NIH), has submitted to the Office of Management and Budget (OMB) a request for review and approval of the information collection listed below. This proposed information collection was previously published in the **Federal Register** on February 6, 2014, pages 7206–7207, and allowed 60-days for public comment. One public comment was received. The purpose of this notice is to allow an additional 30 days for public comment. The National Institutes of Health may not conduct or sponsor, and the respondent is not required to respond to, an information collection that has been extended, revised, or implemented on or after October 1, 1995, unless it displays a currently valid OMB control number.

Direct Comments to OMB: Written comments and/or suggestions regarding the item(s) contained in this notice, especially regarding the estimated public burden and associated response time, should be directed to the: Office of Management and Budget, Office of Regulatory Affairs, OIRA_Submission@omb.eop.gov or by fax to 202–395–6974, Attention: NIH Desk Officer.

Comment Due Date: Comments regarding this information collection are best assured of having their full effect if received within 30-days of the date of this publication.

FOR FURTHER INFORMATION CONTACT: To obtain a copy of the data collection plans and instruments, submit comments in writing, or request more information on the proposed project contact: Kevin P. Conway, Ph.D., Deputy Director, Division of Epidemiology, Services, and Prevention Research, National Institute on Drug Abuse, 6001 Executive Boulevard., Room 5185; or call non-toll-free number (301)-443–8755; or Email your request,

Reference 3

through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Dated: November 27, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-28978 Filed 12-2-13; 11:15 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Chapter I

[Docket No. FDA-2013-N-1523]

Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Nominations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification; request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is preparing to develop a list of drug products that present demonstrable difficulties for compounding (difficult-to-compound list). To identify candidates for this list, FDA is encouraging interested groups and individuals to nominate specific drug products or categories of drug products and is describing the information that should be provided to the Agency in support of each nomination.

DATES: Submit written or electronic comments by March 4, 2014.

ADDRESSES: You may submit comments, identified by Docket No. FDA-2013-N-1523, by any of the following methods.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- *Mail/Hand delivery/Courier [for paper submissions]:* Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2013-N-1523 for this request for nominations. All comments

received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the “Request for Nominations” heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Marissa Chaet Brykman, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, suite 5100, Silver Spring, MD 20993-0002, 301-796-3110.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a) describes the conditions under which a human drug product compounded for an identified individual patient based on a prescription is entitled to an exemption from three sections of the FD&C Act: (1) Section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice for drugs); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (21 U.S.C. 355) (concerning the approval of human drug products under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).

One of the conditions for such an exemption is that the compounded drug product is not a “drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product” (section 503A(b)(3)(A) of the FD&C Act).

Section 503A(d)(1) of the FD&C Act requires that before issuing regulations to implement section 503A(b)(3)(A) of the FD&C Act, an advisory committee on compounding be convened and consulted “unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health” (section 503A(d)(1) of the FD&C Act).

At a meeting on July 13 and 14, 2000, the Pharmacy Compounding Advisory Committee discussed and provided FDA with advice about the Agency’s efforts to develop a list of drugs that present demonstrable difficulties for compounding. FDA had published a notice of that meeting in the **Federal Register** of June 29, 2000 (65 FR 40104). However, before a list could be developed, the constitutionality of section 503A was challenged in court because it included restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug and the solicitation of prescriptions for compounded drugs. These provisions were held unconstitutional by the U.S. Supreme Court in 2002.¹ After the court decision, FDA suspended its efforts to develop the difficult-to-compound list.

The Drug Quality and Security Act (DQSA) removes from section 503A of the FD&C Act the provisions that had been held unconstitutional by the U.S. Supreme Court in 2002. By removing these provisions, the new law removes uncertainty regarding the validity of section 503A, clarifying that it applies nationwide. Therefore, FDA is reinitiating its efforts to develop a list of drug products that present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.

In addition, the DQSA adds a new section 503B to the FD&C Act (21 U.S.C. 353b) that creates a new category of “outsourcing facilities.” Outsourcing facilities, as defined in section 503B, are facilities that meet certain conditions described in section 503B, including registering with FDA as an outsourcing facility. If these conditions are satisfied, a drug compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility is exempt from two sections of the FD&C Act: (1) Section 502(f)(1) and (2) section 505; but not section 501(a)(2)(B).

One of the conditions in section 503B that must be satisfied to qualify for the exemptions is that an outsourcing facility does not compound a drug identified (directly or as part of a category of drugs) on a list published by the Secretary of drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients, or the drug is compounded in

¹ See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).

accordance with all applicable conditions that are necessary to prevent the drug or category of drugs from presenting such demonstrable difficulties (see section 503B(a)(6)(A) and (a)(6)(B) of the FD&C Act). Section 503B(c)(2) of the FD&C Act requires that before issuing regulations to implement section 503B(a)(6) of the FD&C Act, an advisory committee on compounding be convened and consulted.

FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded and still qualify for any of the exemptions set forth in sections 503A and 503B because they present demonstrable difficulties for compounding.

II. Request for Nominations

To identify candidates for the difficult-to-compound list, FDA is seeking public input in the form of specific drug products or categories of drug products that are difficult to compound. Interested groups and individuals may nominate drug products or categories of drug products that are difficult to compound for inclusion on the list. After evaluating the nominations and, as required by Congress, consulting with the Pharmacy Compounding Advisory Committee (see sections 503A(d)(1) and 503B(c)(2) of the FD&C Act), FDA will issue the list as a regulation under notice-and-comment rulemaking procedures.

Nominations should include the following for each drug product or drug product category nominated, and any other relevant additional information available:

- Name of drug product or drug product category;
- Reason why the drug product or drug product category should be included on the list, taking into account the risks and benefits to patients.

Reasons may include but are not limited to:

- The potential effect of compounding on the potency, purity, and quality of a drug product, which could affect the safety and effectiveness of the drug product. Factors that may be relevant to this determination include:

1. Drug Delivery System

- Is a sophisticated drug delivery system required to ensure dosing accuracy and/or reproducibility?
- Is the safety or efficacy of the product a concern if there is product-to-product variability?

2. Drug Formulation and Consistency

- Is a sophisticated formulation of the drug product required to ensure dosing accuracy and/or reproducibility?
- Because of the sophisticated formulation, is product-to-product uniformity of the drug product often difficult to achieve?
- Is the safety or efficacy of the product a concern if there is product-to-product variability?

3. Bioavailability

- Is it difficult to achieve and maintain a uniformly bioavailable dosage form?
- Is the safety or effectiveness of the product a concern if the bioavailability varies?

4. Complexity of Compounding

- Is the compounding of the drug product complex?
- Are there multiple, complicated, or interrelated steps?
- Is there a significant potential for error in one or more of the steps that could affect drug safety or effectiveness?

5. Facilities and Equipment

- Are sophisticated facilities and/or equipment required to ensure proper compounding of the drug product?
- Is there a significant potential for error in the use of the facilities or equipment that could affect drug safety or effectiveness?

6. Training

- Is specialized, highly technical training essential to ensure proper compounding of the drug product?

7. Testing and Quality Assurance

- Is sophisticated, difficult-to-perform testing of the compounded drug product required to ensure potency, purity, performance characteristics, or other important characteristics prior to dispensing?
- Is there a significant potential for harm if the product is compounded without proper quality assurance procedures and end-product testing?
 - Adverse effects that could result when the drug product or drug product category is not made according to appropriate conditions.

FDA cannot guarantee that all drug products or drug product categories nominated during the nomination period will be considered for inclusion on the next published difficult to compound list. Nominations received during the comment period that are supported by the most complete and relevant information will likely be evaluated first. Nominations that are not evaluated during this first phase will

receive consideration for list amendments, because the development of this list will be an ongoing process. Individuals and organizations also will be able to petition FDA to make additional list amendments after the list is published.

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set comments. Identify comments with the docket number found in the brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Dated: November 27, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-28980 Filed 12-2-13; 11:15 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Chapter I

[Docket No. FDA-2013-N-1525]

List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Withdrawal of proposed rule; request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is withdrawing the proposed rule to list bulk drug substances used in pharmacy compounding and preparing to develop a list of bulk drug substances (bulk drugs) that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. To identify candidates for this bulk drugs list, interested groups and individuals may nominate specific bulk drug substances, and FDA is describing the information that should be provided to the Agency in support of each nomination.

Reference 4

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. 98N-0182]

List of Bulk Drug Substances That May Be Used in Pharmacy Compounding

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing a new regulation which will identify the bulk drug substances that may be used in pharmacy compounding under the exemptions provided by the Federal Food, Drug, and Cosmetic Act (the act) even though such substances are neither the subject of a current United States Pharmacopeia (USP) or National Formulary (NF) monograph nor a component of an FDA-approved drug. FDA's development and publication of this bulk drugs list is statutorily required by the Food and Drug Administration Modernization Act of 1997 (the Modernization Act).

DATES: Submit written comments on or before March 23, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Robert J. Tonelli, Center for Drug Evaluation and Research (HFD-332), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-7295.

SUPPLEMENTARY INFORMATION:

I. Background

President Clinton signed the Modernization Act (Pub. L. 105-115) into law on November 21, 1997. Section 127 of the Modernization Act, which added section 503A to the act (21 U.S.C. 353a), clarifies the status of pharmacy

compounding under Federal law. Under section 503A of the act, drug products that are compounded by a pharmacist or physician on a customized basis for an individual patient may be entitled to exemptions from three key provisions of the act: (1) The adulteration provision of section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning the good manufacturing practice requirements); (2) the misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug or abbreviated new drug applications).

To qualify for these statutory exemptions, a compounded drug product must satisfy several requirements. One of these requirements, found in section 503A(b)(1)(A) of the act, restricts the universe of bulk drug substances that a compounder may use. Section 503A(b)(1)(A) provides, in relevant part, that every bulk drug substance used in compounding: (1) Must comply with an applicable and current USP or NF monograph, if one exists, as well as the current USP chapter on pharmacy compounding; (2) if such a monograph does not exist, the bulk drug substance must be a component of an FDA-approved drug;¹ or (3) if a monograph does not exist and the bulk drug substance is not a component of an FDA-approved drug, it must appear on a list of bulk drug substances that may be used in compounding (i.e., the bulk drugs list being proposed in this rulemaking). The term "bulk drug substance" is defined in FDA regulations at 21 CFR 207.3(a)(4) to mean "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances" (see section 503A(b)(1)(A) of the act).

¹ To identify such FDA-approved drugs, compounders can consult the publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluation," commonly referred to as the "Orange Book."

II. Criteria for Bulk Drug Substances

According to section 503A(d)(2) of the act, the criteria for determining which substances should appear on the bulk drugs list "shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary of Health and Human Services may identify." The FDA, after consulting with the USP and the Pharmacy Compounding Advisory Committee, is proposing to use the following four criteria: (1) The chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists.

In evaluating candidates for the bulk drugs list under these criteria, the agency proposes to use a balancing test. No single one of these criteria will be considered to be dispositive. Rather, the agency will consider each criterion in the context of the others and balance them, on a substance-by-substance basis, in deciding whether a particular substance is appropriate for inclusion on the list.

Under the first criterion, the chemical characterization of the substance, FDA will consider each substance's purity, identity, and quality. Based on attributes such as the substance's chemical formula, melting point, appearance, and solubilities, FDA will determine whether the substance can be identified consistently based on its chemical characteristics. If a substance cannot be well characterized chemically, this criterion will weigh against its inclusion on the proposed bulk drugs list because there can be no assurance that its properties and toxicities when used in compounding would be the same as the properties and toxicities reported in the literature and considered by the agency.

Under the second criterion, FDA will consider the safety issues raised by the use of each substance in general pharmacy compounding. Based on FDA's review of the substances nominated to date, it is unlikely that candidates for the bulk drugs list will have been thoroughly investigated in well-controlled animal toxicology studies, or that there will be well-controlled clinical studies to substantiate their safe use in humans.

Thus, in evaluating list candidates, the agency is likely to have at its disposal either none or very little of the type or quality of information that is ordinarily required and evaluated as part of the drug approval process.

To evaluate the safety of the substances, then, the agency will rely on information about each substance's acute toxicity, repeat dose toxicity, and other reported toxicities, including mutagenicity, teratogenicity, and carcinogenicity. The agency will also rely on reports and abstracts in the literature about adverse reactions the substances have caused in humans. In applying the toxicity criterion, FDA may also consider the availability of alternative approved therapies when the toxicity of a particular substance appears to be significant. The existence of alternative approved therapies is likely to weigh against inclusion on the proposed list because the risks of using a substance with significant toxicities is more likely to outweigh the benefits when approved alternative therapies are available.

Under the third criterion, the historical use of the substance in pharmacy compounding, FDA will consider the length of time the substance has been used in pharmacy compounding, the medical conditions it has been used to treat, and how widespread its use has been. This criterion will weigh in favor of list inclusion for nominated substances that have enjoyed longstanding and widespread use in pharmacy compounding for a particular indication. Evidence of both widespread and longstanding use will be viewed by the agency as indicative of the substance's perceived usefulness and acceptance in the medical community. Fraudulent or "quack" remedies, on the other hand, will be less likely to be included on the list as a result of this criterion because the practice of compounding such drugs is not expected to be sufficiently prevalent and longstanding.

Under the fourth criterion, FDA will consider the available evidence of the substance's effectiveness or lack of effectiveness for a particular use, if any such evidence exists. When drugs go through the new drug approval process, they are required to demonstrate effectiveness under the substantial evidence standard described in section 505(d) of the act. FDA recognizes that few, if any, of the candidates for the bulk drugs list will have been studied in adequate and well-controlled investigations sufficient to satisfy this standard. Thus, in its balancing of the relevant criteria, the agency will take

into account whatever relevant evidence concerning effectiveness is available.

For example, for substances that have been widely used for a long period of time, the literature may include anecdotal reports of effectiveness for a particular use, or reports of one or more trials demonstrating effectiveness. Conversely, the literature may contain anecdotal or clinical evidence that a particular bulk drug substance was shown not to be effective for a particular use (negative effectiveness data).

When evaluating a bulk drug substance used to treat a less serious illness, FDA will generally be more concerned about the safety of the substance than about its effectiveness. Thus, the absence of effectiveness data, or the existence of mere anecdotal reports, will be less likely to preclude inclusion of the substance on the list. However, for a bulk drug substance used to treat a more serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy, particularly when there are alternative approved therapies. In those cases, the absence of effectiveness data, or the presence of negative effectiveness data, will weigh more heavily in FDA's balancing of the relevant criteria.

III. FDA Development of a Bulk Drugs List

A. Methodology

Although the Modernization Act directs FDA to develop a list of bulk drug substances for use in pharmacy compounding, it does not specify how candidates for the list should be identified. In a notice published in the **Federal Register** of April 7, 1998 (63 FR 17011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the list. In response to this request, FDA received nominations for 41 different drug substances. The nominations came from Abbott Laboratories, the American Academy of Dermatology, the Texas Pharmacy Association, the North Carolina Board of Pharmacy, Moss Pharmacy and Nutrition Center, the University of Texas MD Anderson Cancer Center, the International Academy of Compounding Pharmacists, Baxter Healthcare Corp., Scottsdale Skin & Cancer Center Ltd., Dermatology Associates, and Neil Brody, M.D.

Ten of the nominated substances (clotrimazole, fluocinonide, hydrocortisone, hydroquinone, mechlorethamine, pramoxine, quinacrine hydrochloride, salicylic acid, tretinoin, and triamcinolone) are the subject of a USP or NF monograph or

are components of FDA-approved drugs. As such, they already qualify for use in pharmacy compounding under section 503A(b)(1)(A)(i) of the act (assuming they satisfy all other applicable requirements of the act). Therefore, FDA dismissed these substances as list candidates and will not address them further in this proposed rulemaking. An additional substance (sulfadimethoxine) was eliminated as a list candidate after being withdrawn by its sponsor at the inaugural meeting of the Pharmacy Compounding Advisory Committee. It too will not be addressed further in this proposed rulemaking.

The remaining 30 nominations were appropriate list candidates and were evaluated based on a balancing of the four criteria identified in section II of this document: (1) The chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists.²

The information that FDA assessed under each of the evaluation criteria was obtained from journal reports and abstracts from reliable medical sources, including peer reviewed medical literature. This information is available for viewing at the Dockets Management Branch (address above) under Docket No. 98N-0182. Some of this information was submitted in support of the nominations. The remainder FDA gathered through independent searches of medical and pharmaceutical data bases. FDA did not review any raw data.

The nature, quantity, and quality of the information assessed by FDA varied considerably from substance to substance. In some cases there was very little data. For example, the agency found only two relevant journal articles concerning thymol iodide. For other substances, such as taurine and sodium butyrate, reports in the literature were more plentiful and sometimes comprised hundreds of articles. In those cases, the agency reviewed a limited sample of the available literature sources.

Because FDA's assessment of the nominated substances was far less rigorous and far less extensive than the agency's ordinary evaluation of drugs as part of the new drug approval process,

²In making its evaluations, the agency did not consider whether any of the nominated substances are manufactured by an establishment registered under section 510 of the act (see 21 U.S.C. 353a(b)(1)(A)(ii)). This registration requirement is one of a number of other conditions that must be satisfied to qualify for the applicable compounding exemptions.

the inclusion of a drug substance on the proposed bulk drugs list should not, in any way, be equated with an approval, endorsement, or recommendation of the substance by FDA. Nor should it be assumed that substances on the proposed list have been proven to be safe and effective under the standards normally required to receive agency approval. In fact, any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA-approved, or otherwise endorsed by FDA generally or for a particular indication, will cause such drug to be misbranded under section 502(a) of the act.

On October 14 and 15, 1998, FDA consulted with the Pharmacy Compounding Advisory Committee, created under section 503A(d)(1) of the act about the contents of this proposed rule (see 63 FR 47301, September 4, 1998). The discussion included the criteria FDA proposes to use to evaluate candidates for the bulk drugs list and the nominations that FDA has already received.³ In general, the advisory committee agreed with the approach taken by the agency in evaluating the nominated bulk drug substances and the agency's tentative conclusions regarding whether these substances should be included on the bulk drugs list. The agency has taken into consideration all of the advisory committee's recommendations in developing this proposed rule, and the agency intends to continue to consult with the Pharmacy Compounding Advisory Committee in evaluating future candidates for the bulk drugs list.

After evaluating the comments on this proposed rule, FDA is proposing to issue the bulk drugs list as a final rule which will be codified in the Code of Federal Regulations (CFR). The final version of the rule may include all, or only some, of the substances proposed for inclusion on the list in this proposal, depending on the comments received. Individuals and organizations will be able to petition FDA to amend the list (to add or delete bulk drug substances) at any time after the final rule is published. Amendments to the list will be proposed through rulemaking.

With regard to nominated substances discussed in this proposed rulemaking (substances proposed for inclusion on the proposed list and substances that have been nominated but are still under consideration by the agency), FDA intends to exercise its enforcement discretion regarding regulatory action

during the pendency of this proposed rulemaking. For further information on this subject, see the guidance for industry entitled "Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act" (see 63 FR 64723, November 23, 1998).

B. Nominated Drug Substances Being Proposed for Inclusion on the Bulk Drugs List

Under section 503A(d)(2) of the act, FDA is proposing that the following 20 drug substances, which are neither the subject of a current USP or NF monograph nor components of FDA-approved drugs, be included in the list of bulk drug substances that may be used in compounding under the exemptions provided in section 503A of the act (sections 501(a)(2)(B), 502(f)(1), and 505). When a salt or ester of an active moiety is listed, e.g., diloxanide furoate, only that particular salt or ester may be used. Neither the base compound nor other salts or esters of the same active moiety qualify for section 503A of the act's compounding exemptions, unless separately listed.

The following bulk drugs list is being proposed in § 216.23 of title 21 of the CFR. (Section 216.23 will be included in new part 216, which is currently intended to include all FDA regulations whose primary purpose is implementation of the pharmacy compounding provisions found in section 503A of the act):

Bismuth citrate. Bismuth citrate is well characterized chemically. It has been used extensively in compounded products for short-term treatment of several gastrointestinal disorders, including *Helicobacter pylori*-associated ulcers. At doses reported in the literature for these indications, bismuth citrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of bismuth citrate's effectiveness for these indications is also reported in the literature.

Caffeine citrate. Caffeine citrate is well characterized chemically. As a central nervous system stimulant, caffeine citrate has been used extensively and for many years in compounded products to treat apnea in premature infants. At doses reported in the literature for this indication, caffeine citrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of caffeine citrate's effectiveness for this indication is also reported in the literature.

Cantharidin. Cantharidin, which is well characterized chemically, is a substance obtained from the Chinese blister beetle, among other beetle species, that has been used topically in the treatment of warts and molluscum contagiosum, often in patients with compromised immune systems. Limited anecdotal evidence of cantharidin's effectiveness for these indications is reported in the literature. Although cantharidin is an extremely toxic substance, it is apparently used only in the professional office setting and not dispensed for home use. Because of cantharidin's toxicity, FDA is proposing to include it on the bulk drugs list for topical use in the professional office setting only.

Choline bitartrate. Choline bitartrate is well characterized chemically. It has been used to treat Alzheimer's-type dementia. It has also been used to treat infantile colic. At doses reported in the literature for these indications, choline bitartrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of choline bitartrate's effectiveness for these indications is also reported in the literature. Additionally, FDA has previously established that choline bitartrate is generally recognized as safe, as a dietary supplement, when used in accordance with good manufacturing practices (see 21 CFR 182.8250 (45 FR 58837, September 5, 1980)).

Diloxanide furoate. Diloxanide furoate is well characterized chemically. It has been used to treat parasitic diseases such as intestinal amoebiasis. At doses reported in the literature for these indications, diloxanide furoate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of diloxanide furoate's effectiveness for these indications is also reported in the literature.

Dimercapto-1-propanesulfonic acid. Dimercapto-1-propanesulfonic acid (DMPS), a chelating agent, is well characterized chemically. DMPS has been used to treat heavy metal poisoning. At doses reported in the literature for this indication, DMPS appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of DMPS's effectiveness for this indication is also reported in the literature.

³A transcript of the advisory committee meeting may be found at the Dockets Management Branch (address above) under Docket No. 98N-0182.

*Ferric subsulfate.*⁴ Ferric subsulfate is well characterized chemically. It has been used as a topical hemostatic agent to control bleeding associated with minor surgical procedures, biopsies, and minor gynecological surgery involving the cervix. At doses reported in the literature for this indication, ferric subsulfate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of ferric subsulfate's effectiveness for this indication is also reported in the literature. However, because the literature is limited to topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

Ferric sulfate hydrate. Ferric sulfate hydrate is well characterized chemically. It has been used topically as a hemostatic agent to control bleeding from dermatological and dental procedures. At doses reported in the literature for these indications, ferric sulfate hydrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of ferric sulfate hydrate's effectiveness for this indication is also reported in the literature. However, because the literature is limited to topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

Glutamine. Glutamine, the most abundant free amino acid found in the human body, is well characterized chemically. Glutamine is involved in a wide variety of metabolic processes, including regulation of the body's acid-base balance. For years, glutamine has been used in compounding as a supplement in parenteral nutrition regimens in adults. At doses reported in the literature for this use, glutamine appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of glutamine's effectiveness for this indication is also reported in the literature.

Guaiacol. Guaiacol is well characterized chemically. It has been used for decades in compounded products as an expectorant. At doses reported in the literature for this indication, guaiacol appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited

anecdotal evidence of guaiacol's effectiveness for this indication is also reported in the literature.

Iodoform. Iodoform is well characterized chemically. It has been used for the control of acute epistaxis (nosebleeds) and as a paste for dental root fillings. Iodoform has tested positive in in vitro mutagenicity assays and in an in vitro transformational assay in mammalian cells. However, in 2-year bioassays conducted by the National Toxicology Program, iodoform was found to be noncarcinogenic in rats and mice. At doses reported in the literature for these indications, iodoform appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of iodoform's effectiveness for these indications is also reported in the literature. However, because the literature is limited to the topical and intradental use of this substance, FDA is proposing to include it on the bulk drugs list for topical and intradental use only.

Metronidazole benzoate. Metronidazole benzoate, which is well characterized chemically, has been used to treat parasitic diseases such as amoebiasis and giardiasis. The base of this substance (metronidazole) is an FDA-approved drug which has a bitter taste. The benzoate salt apparently renders metronidazole tasteless, however, so metronidazole benzoate is sometimes prescribed instead of the metronidazole base to increase patient compliance, especially in children. Serious adverse reactions associated with the use of metronidazole benzoate have not been commonly reported, and limited anecdotal evidence of its effectiveness is reported in the literature. Although the agency is proposing to include metronidazole benzoate on the bulk drugs list, it is specifically seeking public comment on metronidazole benzoate's solubility and appropriate dosing, as questions about these issues have been raised in the literature.

Myrrh gum tincture. Myrrh is a gum resin obtained from the stem of *Commiphora molmol* and other species of camphora. Myrrh is a mixture of many substances and has not been well characterized chemically. Myrrh has been used in its natural form and as a tincture to treat inflammatory disorders of the mouth and pharynx. The preparation reviewed by FDA is the tincture, which, at doses reported in the literature for those indications, appears to be relatively nontoxic. Serious adverse reactions associated with the use of myrrh gum tincture have not been

commonly reported. Limited anecdotal evidence of myrrh gum tincture's effectiveness for those indications is also reported in the literature. Because the literature is limited to the topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

Phenindamine tartrate. Phenindamine tartrate is well characterized chemically. It is an antihistamine that has been used to treat hypersensitivity reactions including urticaria (hives) and rhinitis (nasal inflammation). At doses reported in the literature for this indication, phenindamine tartrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Additionally, in developing the over-the-counter monograph for antihistamine drug products, FDA previously established that phenindamine tartrate, under the conditions established in the monograph (including particular labeling and dosage limits), is generally recognized as safe and effective for over-the-counter antihistamine use (see 21 CFR 341.12; 57 FR 58356, December 9, 1992). Limited anecdotal evidence of phenindamine tartrate's effectiveness as an antihistamine is reported in the literature.

Phenyltoloxamine dihydrogen citrate. Phenyltoloxamine dihydrogen citrate, a structural isomer of diphenhydramine, is well characterized chemically. It has been used as an antihistamine. At doses reported in the literature for this indication, phenyltoloxamine dihydrogen citrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of phenyltoloxamine dihydrogen citrate's effectiveness as an antihistamine is reported in the literature.

Piracetam. Piracetam, a derivative of the amino acid gamma-amino butyric acid, is well characterized chemically. Piracetam is believed by some to enhance certain cognitive skills, and has been used to treat Down's syndrome, dyslexia, and Alzheimer's disease, among other cognitive disorders. At doses reported in the literature for these indications, piracetam appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of piracetam's effectiveness for these indications is reported in the literature.

Sodium butyrate. Sodium butyrate is a short chain fatty acid that is well characterized chemically. It has been

⁴ Both ferric subsulfate solution and ferric subsulfate powder were nominated for inclusion on the bulk drugs list. FDA combined them under one entry for ferric subsulfate.

used rectally in an enema formulation to treat several inflammatory bowel conditions, including ulcerative colitis and diversion colitis. At doses reported in the literature for these indications, sodium butyrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of sodium butyrate's effectiveness for these indications is also reported in the literature. However, because the literature is limited to the use of sodium butyrate rectally in an enema formulation, FDA is proposing to include it on the bulk drugs list for use in this dosage form and route of administration only.

Taurine. Taurine, an amino acid with several important physiological functions, including a role in bile acid conjugation, is well characterized chemically. It has been used for years in compounding as a component in parenteral nutrition solutions for infants and adult patients. At doses reported in the literature for this use, taurine appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of taurine's effectiveness for this indication is also reported in the literature.

Thymol iodide. Thymol iodide is well characterized chemically. It has been used as a topical agent for its absorbent, protective, and antimicrobial properties. At doses reported in the literature for these indications, thymol iodide appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of thymol iodide's effectiveness for these indications is also reported in the literature. FDA notes, however, that it was able to identify only two relevant articles concerning this substance. Because the literature is limited to the topical use of thymol iodide, FDA is proposing to include it on the bulk drugs list for topical use only.

Tinidazole. Tinidazole is a chemically well-characterized derivative of 5-nitromidazole. It has been used, often in conjunction with diloxanide furoate, which also appears on this proposed list, to treat parasitic diseases such as amoebiasis and giardiasis. At doses reported in the literature for these indications, tinidazole appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of tinidazole's effectiveness for these indications is also reported in the literature.

C. Nominated Drug Substances Still Under Consideration for the Bulk Drugs List

The following 10 drug substances were nominated for inclusion on the proposed bulk drugs list. However, for the reasons described in section III.C of this document, they are still under review by the agency:

4-Aminopyridine. The drug substance 4-Aminopyridine (4-AP), which is well characterized chemically, is a potassium channel blocker that may enhance the release of acetylcholine from nerve terminals. It has been used to treat several neurological disorders, including Lambert-Eaton myasthenic syndrome, multiple sclerosis, and Alzheimer's disease. It also has been used to reverse the effects of nondepolarizing muscle relaxants. At doses reported in the literature, the side effects of 4-AP for most patients do not appear to be serious. However, there have been some reports of seizures associated with the use of 4-AP. FDA would like more information about the historical use, safety, and effectiveness of 4-AP before deciding whether to propose it for inclusion on the bulk drugs list. The Pharmacy Compounding Advisory Committee similarly expressed a desire for more information about 4-AP before making a recommendation about its status to the agency. FDA is soliciting public input on these and any other issues that are relevant to the agency's consideration of this substance for the bulk drugs list.

Betahistine dihydrochloride. Betahistine dihydrochloride is a chemically well characterized histamine analog. Formerly marketed as Serc tablets, betahistine dihydrochloride was approved by FDA to treat the symptoms of vertigo in patients with Meniere's disease. In 1970, however, FDA withdrew approval of the new drug application for Serc tablets because they were found to lack substantial evidence of effectiveness for this approved indication (see 35 FR 17563, November 14, 1970). FDA will consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include betahistine dihydrochloride on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

Cyclandelate. Cyclandelate, which is well characterized chemically, is a vasodilator that was formerly approved by FDA for two indications: (1) Treatment for intermittent claudication caused by arteriosclerosis obliterans, and (2) as a treatment for cognitive dysfunction in patients suffering from senile dementia of the multi-infarct or

Alzheimer's type. Cyclandelate was formerly marketed in Cyclospasmol capsules and tablets, which were removed from the market for lack of effectiveness for these approved indications (see 61 FR 64099, December 3, 1996). FDA will consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include cyclandelate on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

3,4-Diaminopyridine. The drug substance 3,4-Diaminopyridine (DAP), which is well characterized chemically, is a potassium channel blocker that may enhance the release of acetylcholine from nerve terminals. DAP has been used in the treatment of several neuromuscular disorders, including Lambert-Eaton myasthenic syndrome, myasthenia gravis, amyotrophic lateral sclerosis, and multiple sclerosis. At doses reported in the literature, DAP appears to be well tolerated and its toxicity appears to be dose related. There have been reports of seizures with its use, however, and DAP is contraindicated in patients with epilepsy. FDA would like more information about the historical use, safety, and effectiveness of DAP before deciding whether to propose it for inclusion on the bulk drugs list. The Pharmacy Compounding Advisory Committee similarly expressed a desire for more information about DAP before making a recommendation about its status to the agency. FDA is soliciting public input on these and any other issues that are relevant to the agency's consideration of this substance for the bulk drugs list.

Dinitrochlorobenzene. Dinitrochlorobenzene (DNCB), which is well characterized chemically, has been used in the treatment of recurrent melanoma and as a skin sensitizer to estimate immune system competency. It also has been used topically in the treatment of warts. Limited anecdotal evidence of DNCB's effectiveness for these indications is reported in the literature. DNCB is a highly toxic substance that may be fatal if inhaled, swallowed, or absorbed through skin. High concentrations of DNCB are also extremely destructive to tissues of the mucous membranes and upper respiratory tract, eyes, and skin. At the inaugural meeting of the Pharmacy Compounding Advisory Committee, the nominator of this substance withdrew it as a list candidate, but several members of the committee recommended that it still be considered. The Pharmacy Compounding Advisory Committee then voiced concerns about the safety of the

substance and expressed a desire for more information about it before making a recommendation to the agency. FDA agrees and, therefore, is requesting public input about the historical use, safety, and effectiveness of DNCB, as well as any other information that would be relevant to the agency's consideration of DNCB for the bulk drugs list.

Diphenylcyclopropenone.

Diphenylcyclopropenone, which is well characterized chemically, has been used for the topical treatment of extensive alopecia areata. The nomination of this substance was not received by FDA in time to permit a full discussion of it at the October 1998 meeting of the Pharmacy Compounding Advisory Committee. A decision about this substance is therefore being deferred until after FDA has had an opportunity to consult the Pharmacy Compounding Advisory Committee about it at a future meeting.

Hydrazine sulfate. Hydrazine sulfate is well characterized chemically and has been used to treat cachexia in cancer patients. The substance, however, is extremely toxic. Multiple exposures to hydrazine sulfate have caused liver and kidney damage, gastrointestinal damage, convulsions, and coma, among other conditions. Hydrazine sulfate is also considered by the International Agency for Research on Cancer to be a potential carcinogen to humans. In at least two clinical studies, hydrazine sulfate was shown to have no effect, or even a negative effect, on patients who received it. FDA would like more information about the historical use, safety, and effectiveness of hydrazine sulfate before deciding whether to propose it for inclusion on the bulk drugs list. The Pharmacy Compounding Advisory Committee similarly expressed a desire for more information about hydrazine sulfate before making a recommendation about its status to the agency. FDA is soliciting public input on these and any other issues that are relevant to the agency's consideration of this substance for the bulk drugs list.

Pentylentetrazole.

Pentylentetrazole, which is well characterized chemically, was approved by FDA for use in the treatment of senile confusion, depression, psychosis, fatigue, and debilitation, as well as for the relief of dizzy spells, mild behavioral disorders, irritability, and functional memory disorders in elderly patients. Pentylentetrazole was formerly marketed in numerous drug products, all of which were removed from the market for lack of effectiveness for these approved indications (see 47 FR 19208, May 4, 1982). FDA will

consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include pentylentetrazole on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

Silver protein mild. Mild silver protein is well characterized chemically. It has been used to treat conjunctivitis and by ophthalmologists as a preoperative chemical preparation of the eye. At doses reported in the literature for these indications, mild silver protein appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. When mild silver protein is administered internally, however, it can cause serious untoward side effects, including argyria, a permanent ashen-gray discoloration of the skin, conjunctiva, and internal organs (see 61 FR 53685, October 15, 1996). At this time, FDA is deferring a decision on this substance because questions were raised at the inaugural meeting of the Pharmacy Compounding Advisory Committee about its efficacy. FDA is soliciting public input on this issue and any other issues that are relevant to the agency's consideration of mild silver protein for the bulk drugs list.

Squaric acid dibutyl ester. Squaric acid dibutyl ester, which is well characterized chemically, is a contact sensitizer that has been used as a topical treatment for alopecia areata and warts. The nomination of this substance was not received by FDA in time to permit a full discussion of it at the October 1998 meeting of the Pharmacy Compounding Advisory Committee. A decision about this substance is therefore being deferred until after FDA has had an opportunity to consult the Pharmacy Compounding Advisory Committee about it at a future meeting.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select

regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to examine regulatory alternatives for small entities if the proposed rule is expected to have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act requires agencies to prepare an assessment of anticipated costs and benefits before enacting any rule that may result in an expenditure in any 1 year by State, local and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency has reviewed this proposed rule and has determined that it is consistent with the regulatory philosophy and principles identified in the Executive Order and these two statutes. The proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order. As discussed below, the agency certifies that this proposed rule will not have a significant economic impact on a substantial number of small entities. Also, because the rule is not expected to result in any annual expenditures, FDA is not required to prepare a cost/benefit analysis under the Unfunded Mandates Reform Act.

FDA is proposing to amend its regulations to include a list of bulk drugs that may be used in pharmacy compounding under certain conditions even though such substances are neither the subject of a USP or NF monograph nor components of FDA-approved drugs. FDA has requested and received nominations for bulk drugs to be included on this list. Twenty of the nominated substances are being proposed for inclusion, which means they would be eligible for use in pharmacy compounding under the exemptions provided by section 503A of the act. As a result, there would be no loss of any sales, or other economic impact, for compounded drug products containing these 20 substances.

FDA has proposed to include some of these substances on the list with a restriction on their route of administration or a requirement that the resulting compounded drug product be for professional office use only. As FDA is unaware that any of these drug substances are currently used in compounding outside of the proposed restrictions, the agency does not expect these restrictions to result in decreased sales of any compounded drug product.

Further, this regulation is not anticipated to impose any other compliance costs on bulk drug manufacturers or compounding pharmacies.

Ten additional nominated substances, while not being proposed for inclusion on the bulk drugs list, are still under review by the agency. As explained more fully in the guidance for industry entitled "Enforcement Policy During Implementation of section 503A of the Federal Food, Drug, and Cosmetic Act" (see notice of availability, 63 FR 64723, November 23, 1998), FDA intends to exercise its enforcement discretion regarding these 10 substances. In short, FDA does not intend to take regulatory action against a drug product that has been compounded with one of these substances while the substance is being evaluated during the pendency of this rulemaking proceeding, as long as the compounding complies with the other effective requirements in section 503A of the act and does not appear to present a significant safety risk.

Although usage or sales data for the nominated drug substances is limited, the agency further concludes that even if any of the 10 deferred drug substances were, in the future, to be excluded as candidates for the bulk drugs list, the economic impact would not be significant, particularly not for any substantial number of pharmacies or other small entities. The quantity demanded of these 10 drugs appears to be relatively small, especially when compared to the total number of prescription drugs dispensed annually in the United States. In addition, if any of the 10 substances were ultimately excluded from the list, sales of alternatives to the excluded drugs would be expected to reduce the economic impact of such exclusion.

At the October 1998 meeting of the Pharmacy Compounding Advisory Committee, a representative of the International Academy of Compounding Pharmacists (IACP) presented usage and sales data for four of the deferred substances: 3,4-DAP, 4-AP, hydrazine sulfate, and mild silver protein. According to the IACP representative, the drug substances 3,4-DAP and 4-AP are currently being used in compounding to treat patient populations estimated at 1,000 and 10,000 patients, respectively; hydrazine sulfate is currently being used to treat between 5,000 and 10,000 patients annually; and the annual production of mild silver protein is approximately 9 kilograms. FDA does not have a firm estimate of the number of patients being treated with mild silver protein, but estimates it to be several thousand.

Similarly, FDA does not have usage or sales data for the six other deferred drug substances, but estimates that their usage is also relatively low. The agency invites comments and data on any projected loss of sales or other compliance costs directly attributable to this proposal.

If a rule is expected to have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize these impacts. Section 503A of the act specifically directs FDA to develop a list of bulk drug substances that may be used in pharmacy compounding. The agency received nominations from the public for 41 bulk drugs to be included on this list. All the nominations are either proposed for inclusion on the list or are still under review. The agency therefore certifies that this proposal will not have a significant economic impact on a substantial number of small entities. The agency invites public comment and data on these issues, specifically the number and size of the bulk drug manufacturers and compounding pharmacies that sell any of the deferred substances, or drug products containing them, and any sales data on these compounded drug products.

The Unfunded Mandates Reform Act requires (in section 202) that agencies prepare an assessment of anticipated costs and benefits before proposing any expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any 1 year. The publication of FDA's list of bulk drug substances for use in pharmacy compounding is not expected to result in any expenditure of funds by State, local and tribal governments or the private sector. Because the proposed rule is not expected to result in any mandated expenditures, FDA is not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VII. Request for Comments

Interested persons may, on or before March 23, 1999, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that

individuals may submit one copy. Comments are to be identified with docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 216 be added as follows:

1. Part 216 is added to read as follows:

PART 216—PHARMACY COMPOUNDING

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

Sec.

216.23 Bulk drug substances for use in pharmacy compounding.

216.24 [Reserved]

Authority: 21 U.S.C. 351, 352, 353a, 355, 371.

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

§ 216.23 Bulk drug substances for use in pharmacy compounding.

(a) The following bulk drug substances, which are neither the subject of a current United States Pharmacopeia or National Formulary monograph nor components of the Food and Drug Administration approved drugs, may be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.

- Bismuth citrate.
- Caffeine citrate.
- Cantharidin (for topical use in the professional office setting only).
- Choline bitartrate.
- Diloxanide furoate.
- Dimercapto-1-propanesulfonic acid.
- Ferric subsulfate (for topical use only).
- Ferric sulfate hydrate (for topical use only).
- Glutamine.
- Guaiacol.
- Iodoform (for topical and intradental use only).
- Metronidazole benzoate.
- Myrrh gum tincture (for topical use only).
- Phenindamine tartrate.
- Phenyltoloxamine dihydrogen citrate.
- Piracetam.
- Sodium butyrate (for rectal enema use only).

Taurine.
Thymol iodide (for topical use only).
Tinidazole.

(b) FDA balances the following criteria in evaluating substances considered for inclusion on the list set forth in paragraph (a) of this section: The chemical characterization of the substance; the safety of the substance; the historical use of the substance in pharmacy compounding; and the available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists.

(c) Based on evidence currently available there are inadequate data to establish substantial evidence or general recognition of the safety or effectiveness of any of the drug substances set forth in paragraph (a) of this section, for any indication.

§ 216.24 [Reserved]

Dated: December 29, 1998.

William K. Hubbard,
Associate Commissioner for Policy
Coordination.

[FR Doc. 99-277 Filed 1-6-99; 8:45 am]

BILLING CODE 4160-01-F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 52 and 81

[FL-75-1-9806b; FRL 6196]

Designation of Areas for Air Quality Planning Purposes Florida: Redesignation of the Duval County Sulfur Dioxide Unclassifiable Area to Attainment

AGENCY: Environmental Protection
Agency (EPA).

ACTION: Proposed rule.

SUMMARY: On January 28, 1997, the Florida Department of Environmental Protection (DEP) submitted a request for redesignation to attainment for sulfur dioxide (SO₂) in Duval County, Florida. The redesignation request included five years of quality assured monitoring data which showed no exceedances of the National Ambient Air Quality Standards (NAAQS) for SO₂. Duval County was originally designated as an unclassifiable area in 1978 due to lack of adequate monitoring data. Sufficient data have now been collected to make affirmative declaration of attainment status. The EPA is redesignating Duval County from unclassifiable to attainment for SO₂ and approving three permits that provide SO₂ emission reductions.

In the Final Rules Section of this **Federal Register**, EPA is approving the

Florida State Plan submittal as a direct final rule without prior proposal because the Agency views this as a noncontroversial submittal and anticipates that it will not receive any significant, material, and adverse comments. A detailed rationale for the approval is set forth in the direct final rule and incorporated herein. If no significant, material, and adverse comments are received in response, to this rule, no further activity is contemplated in relation to this proposed rule. If EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. EPA will not institute a second comment period on this action.

DATES: Comments must be received in writing by February 8, 1999.

ADDRESSES: All comments should be addressed to Scott Martin at the EPA Regional Office listed below. Copies of the documents relevant to this proposed rule are available for public inspection during normal business hours at the following locations. The interested persons wanting to examine these documents should make an appointment with the appropriate office at least 24 hours before the day of the visit.

Environmental Protection Agency,
Region 4, Air Planning Branch, 61
Forsyth Street, SW, Atlanta, Georgia
30303-3104.

Florida Department of Environmental
Protection, Twin Towers Office
Building, 2600 Blair Stone Road,
Tallahassee, Florida 32399-2400.

FOR FURTHER INFORMATION CONTACT:
Scott Martin at (404) 562-9036.

SUPPLEMENTARY INFORMATION: See the information provided in the Direct Final action which is located in the Rules Section of this **Federal Register**.

Dated: November 10, 1998.

A. Stanley Meiburg,
Acting Regional Administrator, Region 4.
[FR Doc. 99-230 Filed 1-6-99; 8:45 am]

BILLING CODE 6560-50-M

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 90

[WT Docket No. 96-86; DA 98-2588]

The Development of Operational, Technical and Spectrum Requirements for Meeting Federal, State and Local Public Safety Agency Communication Requirements Through the Year 2010, Establishment of Rules and Requirements for Priority Access Service

AGENCY: Federal Communications
Commission.

ACTION: Proposed rule; extension of time
for comments.

SUMMARY: This document extends the time to file comments concerning the Commission's *Third Notice of Proposed Rule Making* ("Third Notice") adopted on August 6, 1998. Comments on the *Third Notice* were due on or before January 4, 1999, and Reply Comments were due on or before February 1, 1999. Because of the many petitions for reconsideration and clarification filed in response to the *First Report and Order* ("First Report") in this proceeding and the close proximity of the deadlines for responding to these petitions and the *Third Notice*, the Commission extended the time to file comments.

DATES: Comments are due on or before January 19, 1999, and reply comments are due on or before February 18, 1999.

ADDRESSES: Federal Communications
Commission, Office of the Secretary,
Publications Branch, Room TW-B204,
The Portals II, 445 12th St., SW,
Washington, D.C. 20554.

FOR FURTHER INFORMATION CONTACT:
Peter Daronco or Michael Pollak, at the
Public Safety & Private Wireless
Division, (202) 418-0680.

SUPPLEMENTARY INFORMATION: This is a summary of the Commission's *Order* in WT Docket No. 96-86, adopted on December 23, 1998, and released on December 24, 1998, (DA 98-2588). The full text of the *Order* is available for inspection and copying during normal business hours in the FCC Reference Center, Room 239, 1919 M St., NW, Washington, DC 20554. The complete text of this decision may also be purchased from the Commission's duplicating contractor, International Transcription Services, 1231 20th Street, NW, Washington, DC 20036, 202-857-3800. Alternative formats (computer diskette, large print, audio cassette and Braille) are available to persons with disabilities by contacting

Reference 5

accordance with all applicable conditions that are necessary to prevent the drug or category of drugs from presenting such demonstrable difficulties (see section 503B(a)(6)(A) and (a)(6)(B) of the FD&C Act). Section 503B(c)(2) of the FD&C Act requires that before issuing regulations to implement section 503B(a)(6) of the FD&C Act, an advisory committee on compounding be convened and consulted.

FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded and still qualify for any of the exemptions set forth in sections 503A and 503B because they present demonstrable difficulties for compounding.

II. Request for Nominations

To identify candidates for the difficult-to-compound list, FDA is seeking public input in the form of specific drug products or categories of drug products that are difficult to compound. Interested groups and individuals may nominate drug products or categories of drug products that are difficult to compound for inclusion on the list. After evaluating the nominations and, as required by Congress, consulting with the Pharmacy Compounding Advisory Committee (see sections 503A(d)(1) and 503B(c)(2) of the FD&C Act), FDA will issue the list as a regulation under notice-and-comment rulemaking procedures.

Nominations should include the following for each drug product or drug product category nominated, and any other relevant additional information available:

- Name of drug product or drug product category;
- Reason why the drug product or drug product category should be included on the list, taking into account the risks and benefits to patients.

Reasons may include but are not limited to:

- The potential effect of compounding on the potency, purity, and quality of a drug product, which could affect the safety and effectiveness of the drug product. Factors that may be relevant to this determination include:

1. Drug Delivery System

- Is a sophisticated drug delivery system required to ensure dosing accuracy and/or reproducibility?
- Is the safety or efficacy of the product a concern if there is product-to-product variability?

2. Drug Formulation and Consistency

- Is a sophisticated formulation of the drug product required to ensure dosing accuracy and/or reproducibility?
- Because of the sophisticated formulation, is product-to-product uniformity of the drug product often difficult to achieve?
- Is the safety or efficacy of the product a concern if there is product-to-product variability?

3. Bioavailability

- Is it difficult to achieve and maintain a uniformly bioavailable dosage form?
- Is the safety or effectiveness of the product a concern if the bioavailability varies?

4. Complexity of Compounding

- Is the compounding of the drug product complex?
- Are there multiple, complicated, or interrelated steps?
- Is there a significant potential for error in one or more of the steps that could affect drug safety or effectiveness?

5. Facilities and Equipment

- Are sophisticated facilities and/or equipment required to ensure proper compounding of the drug product?
- Is there a significant potential for error in the use of the facilities or equipment that could affect drug safety or effectiveness?

6. Training

- Is specialized, highly technical training essential to ensure proper compounding of the drug product?

7. Testing and Quality Assurance

- Is sophisticated, difficult-to-perform testing of the compounded drug product required to ensure potency, purity, performance characteristics, or other important characteristics prior to dispensing?
- Is there a significant potential for harm if the product is compounded without proper quality assurance procedures and end-product testing?
 - Adverse effects that could result when the drug product or drug product category is not made according to appropriate conditions.

FDA cannot guarantee that all drug products or drug product categories nominated during the nomination period will be considered for inclusion on the next published difficult to compound list. Nominations received during the comment period that are supported by the most complete and relevant information will likely be evaluated first. Nominations that are not evaluated during this first phase will

receive consideration for list amendments, because the development of this list will be an ongoing process. Individuals and organizations also will be able to petition FDA to make additional list amendments after the list is published.

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set comments. Identify comments with the docket number found in the brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Dated: November 27, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-28980 Filed 12-2-13; 11:15 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Chapter I

[Docket No. FDA-2013-N-1525]

List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Withdrawal of proposed rule; request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is withdrawing the proposed rule to list bulk drug substances used in pharmacy compounding and preparing to develop a list of bulk drug substances (bulk drugs) that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. To identify candidates for this bulk drugs list, interested groups and individuals may nominate specific bulk drug substances, and FDA is describing the information that should be provided to the Agency in support of each nomination.

DATES: FDA is withdrawing the proposed rule published January 7, 1999 (64 FR 996), as of December 4, 2013.

Submit written or electronic nominations for the bulk drug substances list by March 4, 2014.

ADDRESSES: You may submit nominations, identified by Docket No. FDA-2013-N-1525, by any of the following methods.

Electronic Submissions

Submit electronic nominations in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting “comments.”

Written Submissions

Submit written nominations in the following ways:

- *Mail/Hand delivery/Courier (for paper submissions):* Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and docket number FDA-2013-N-1525 for this request for nominations. All nominations received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting nominations, see the “Request for Nominations” heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or nominations received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Marissa Chaet Brykman, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, suite 5100, Silver Spring, MD 20993-0002, 301-796-3110.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a) describes the conditions under which a human drug product compounded for an identified individual patient based on a prescription is entitled to an exemption from three sections of the FD&C Act: (1) section 501(a)(2)(B) (21 U.S.C.

351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) for drugs); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (21 U.S.C. 355) (concerning the approval of human drug products under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).

One of the conditions for such an exemption is that a drug product may be compounded if the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that: “(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding; (II) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or (III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d) [of Section 503A]” (section 503A(b)(1)(A)(i) of the FD&C Act).

Section 503A refers to the definition of “bulk drug substance” in FDA regulations at 21 CFR 207.3(a)(4): “any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.” See section 503A(b)(1)(A) of the FD&C Act.

Section 503A(d)(1) of the FD&C Act requires that, before issuing regulations to implement section 503A(b)(1)(A)(i)(III) of the FD&C Act, an advisory committee on compounding be convened and consulted “unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health” (section 503A(d)(1) of the FD&C Act).

As described in more detail below, in 1998, FDA began to develop a list of bulk drug substances that may be used in compounding, but before a final rule was published, the constitutionality of section 503A was challenged in court because it included restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug and the solicitation of prescriptions for compounded drugs. These provisions were held unconstitutional by the U.S.

Supreme Court in 2002.¹ After the court decision, FDA suspended its efforts to develop the list of bulk drug substances that could be used in compounding.

The Drug Quality and Security Act (DQSA) removes from section 503A of the FD&C Act the provisions that had been held unconstitutional by the U.S. Supreme Court in 2002.² By removing these provisions, the new law removes uncertainty regarding the validity of section 503A, clarifying that it applies nationwide. Therefore, FDA is reinitiating its efforts to develop a list of bulk drug substances that may be used in compounding under section 503A.

II. Previous Efforts To Develop the List of Bulk Drug Substances Under Section 503A of the FD&C Act

In the **Federal Register** of April 7, 1998 (63 FR 17011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the list of bulk drug substances that may be used in compounding under section 503A. In total, FDA received nominations for 41 different drug substances. After evaluating the nominated drugs and consulting with the Pharmacy Compounding Advisory Committee as required by section 503A, FDA published a proposed rule proposing to list 20 drugs on the section 503A bulk drugs list in January 1999 (64 FR 996, January 7, 1999). The proposed rule also discussed 10 nominated drug substances that were still under consideration for the bulk drugs list. The Pharmacy Compounding Advisory Committee reconvened in May 1999 to discuss drugs included in the proposed rule, in addition to other bulk drug substances (see 64 FR 19791 (April 22, 1999)). However, as explained previously (see the “Background” section), after the 2002 U.S. Supreme Court decision, the Agency suspended its efforts to develop the bulk drugs list under section 503A.

FDA intends to reconsider the bulk drug substances that were proposed for inclusion on the list and that neither have an applicable USP or NF monograph nor are components of an FDA-approved drug due to the time

¹ See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).

² The DQSA also adds a new section 503B to the FD&C Act (21 U.S.C. 353b) that creates a new category of “outsourcing facilities.” For additional information concerning bulk drug substances that may be used to compound drug products in accordance with section 503B, see the notice, “Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance with Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations” published in this issue of the **Federal Register**.

lapse since the last proposal. Therefore, the Agency withdraws the proposed rule, "List of Bulk Drug Substances That May Be Used in Pharmacy Compounding," published in the **Federal Register** of January 7, 1999 (64 FR 996).

III. Request for Nominations

To identify candidates for this list, FDA is seeking public input in the form of specific bulk drug nominations. All interested groups and individuals may nominate specific bulk drug substances for inclusion on the list. After evaluating the nominations and, as required by section 503A, consulting with the USP and the Pharmacy Compounding Advisory Committee, FDA will issue the list as a regulation under notice-and-comment rulemaking procedures.

Nominations should include the following information about the bulk drug substance being nominated and the product(s) that will be compounded using such substance, and any other relevant information available. If the information requested is unknown or unavailable, that fact should be noted accordingly.

Bulk Drug Substance

- Ingredient name;
- Chemical name;
- Common name(s);
- Chemical grade or description of the strength, quality, and purity of the ingredient;
- Information about how the ingredient is supplied (e.g., powder, liquid);
- Information about recognition of the substance in foreign pharmacopeias and the status of its registration(s) in other countries, including whether information has been submitted to USP for consideration of monograph development; and
- A bibliography of available safety and efficacy data,³ including any relevant peer-reviewed medical literature.

Compounded Product

- Information about the dosage form(s) into which the drug substance will be compounded (including formulations);
- Information about the strength(s) of the compounded product(s);
- Information about the anticipated route(s) of administration of the compounded product(s);

- Information about the past and proposed use(s) of the compounded product(s), including the rationale for its use or why the compounded product(s), as opposed to an FDA-approved product, is necessary; and
- Available stability data for the compounded product(s).

FDA cannot guarantee that all drugs nominated during the nomination period will be considered for inclusion on the next published bulk drugs list. Nominations received during the nomination period that are supported by the most complete and relevant information will likely be evaluated first. Nominations that are not evaluated during this first phase will receive consideration for list amendments, as the development of this list will be an ongoing process. Individuals and organizations also will be able to petition FDA to make additional list amendments after the list is published.

Interested persons may submit either electronic nominations to <http://www.regulations.gov> or written nominations to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of nominations. Identify nominations with the docket number found in the brackets in the heading of this document. Received nominations may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Dated: November 27, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-28979 Filed 12-2-13; 11:15 am]

BILLING CODE 4160-01-P

OVERSEAS PRIVATE INVESTMENT CORPORATION

22 CFR Part 706

[No. FOIA-2013]

RIN 3420-ZA00

Freedom of Information

AGENCY: Overseas Private Investment Corporation.

ACTION: Notice of Proposed Rulemaking.

SUMMARY: This rule proposes revisions to the Overseas Private Investment Corporation's ("OPIC") Freedom of Information Act (FOIA) regulations by making substantive and administrative changes. These revisions are intended to supersede OPIC's current FOIA regulations, located at this Part. The

proposed rule incorporates the FOIA revisions contained in the Openness Promotes Effectiveness in our National Government Act of 2007 ("OPEN Government Act"), makes administrative changes to reflect OPIC's cost, and organizes the regulations to more closely match those of other agencies for ease of reference. The proposed rule also reflects the disclosure principles established by President Barack Obama and Attorney General Eric Holder in their FOIA Policy Memoranda issued on January 12, 2009 and March 19, 2009, respectively.

DATES: Written comments must be postmarked and electronic comments must be submitted on or before January 3, 2014.

ADDRESSES: You may submit comments, identified by Docket Number FOIA-2013, by one of the following methods:

- *Email:* foia@opic.gov. Include docket number FOIA-2013 in the subject line of the message.
- *Mail:* Nichole Cadiente, Administrative Counsel, Overseas Private Investment Corporation, 1100 New York Avenue NW., Washington, DC 20527. Include docket number FOIA-2013 on both the envelope and the letter.

FOR FURTHER INFORMATION CONTACT: Nichole Cadiente, Administrative Counsel, (202) 336-8400, or foia@opic.gov.

SUPPLEMENTARY INFORMATION: The revision of Part 706 incorporates changes to the language and structure of the regulations and adds new provisions to implement the OPEN Government Act. OPIC is already complying with these changes and this proposed revision serves as OPIC's formal codification of the applicable law and its practice.

The most significant change in this proposed rule revision is the treatment of business submitters. This section will define confidential commercial information more concisely and provide a default expiration date for confidentiality labels. This will enable OPIC to more efficiently process requests for commercial information, which compose the majority of OPIC's FOIA requests. Among other substantive changes: the search date is now the responsive record cutoff date, the information OPIC posts online has been clarified, there is more detail on how to request records about an individual, and illustrative examples have been added.

In general, comments received, including attachments and other supporting materials, are part of the

³ FDA recognizes that the available safety and efficacy data supporting consideration of a bulk drug substance for inclusion on the list may not be of the same type, amount, or quality as is required to support an NDA.

Reference 6

Cantharidin Revisited

A Blistering Defense of an Ancient Medicine

Lisa Moed, BA; Tor A. Shwayder, MD; Mary Wu Chang, MD

Cantharidin, a vesicant produced by beetles in the order Coleoptera, has a long history in both folk and traditional medicine. In dermatology, topical cantharidin has long been used to treat warts and molluscum. In 1962, cantharidin lost Food and Drug Administration (FDA) approval owing to the failure of its manufacturers to submit data attesting to cantharidin's efficacy. However, it is expected that the FDA will soon include cantharidin on its "Bulk Substances List," which would permit physicians or pharmacists to compound cantharidin to be used in the office for individual patients. A comprehensive discussion of the origins, folk uses, current FDA status, current dermatologic uses, and effects of cantharidin poisoning has been compiled herein. No cases of systemic intoxication or scarring have been reported with the proper use of cantharidin by a physician. Cantharidin is a safe and valuable medication and should be readded to the dermatologic therapeutic armamentarium.

Arch Dermatol. 2001;137:1357-1360

Historically, cantharidin has been used as an aphrodisiac, an abortifacient, and a veterinary medicine diuretic. In dermatology, topical cantharidin has been used as a vesicant for the treatment of warts and molluscum since the 1950s. Despite its removal from the market in 1962, some dermatologists continue to use cantharidin in the United States in either proprietary or nonproprietary formulations, as there is currently no other topical medication that has an equivalent therapeutic effect. However, the availability of cantharidin is limited, and physicians or hospitals may forgo its use because FDA approval is lacking. In this review, the folk and current dermatologic uses of cantharidin, the legal issues involved in the use of cantharidin, and cantharidin poisoning will be discussed.

BLISTER BEETLES AND SPANISH FLY

Cantharidin is a vesicant produced by beetles belonging to the order of Coleoptera and the family of Meloidae.¹ There are currently more than 1500 species of cantharidin-producing beetles.² Commonly known as *blister beetles* or *Spanish fly*, they are variable in color, measure up to 2.5 cm in length,³ and do not bite or sting.¹ *Epicauta vittata* and *Epicauta pennsylvanica* can be found in alfalfa fields, along fence rails, or in flower beds in the South and southwestern parts of the United States.³ Cantharidin is found in all body fluids of blister beetles.⁴ The male beetle synthesizes cantharidin for use as a defense mechanism, and the female acquires cantharidin as a copulatory gift from her mate.⁵ Blister beetle dermatosis is a seasonal vesiculobullous skin disorder that occurs several hours after contact with the beetle.⁴ If contact with a beetle is noted, blowing off the beetle, rather than brushing it off, will minimize cantharidin exposure.³

From the Ronald O. Perelman Department of Dermatology (Ms Moed and Dr Chang) and the Department of Pediatrics (Dr Chang), New York University School of Medicine, New York City, and the Department of Dermatology, Henry Ford Hospital, Detroit, Mich (Dr Shwayder). Ms Moed was a medical student at New York University School of Medicine during this study.

HISTORICAL AND FOLK USES OF CANTHARIDIN

Mylabris, the dried body of the Chinese blister beetle, has been used medicinally for more than 2000 years in China and is still used as a folk medicine today in Asia.⁶ Today in North America, cantharidin continues to be made from blister beetle extracts by a process that is a well-kept trade secret. In Asia, topical cantharidin was used historically for furuncles and piles, ulcers, venomous worms, and tuberculous scrofuloderma.^{6,7} It was used orally for abdominal masses⁸ and rabies, as well as an abortifacient⁹ and anticancer agent.⁶ In Europe, it appeared in *Materia Medica*, a medical monograph written by Pedanios Dioscorides in 50 to 100 AD.⁶ Hippocrates prescribed cantharidin as a treatment for dropsy.⁹ In South Africa, the Tswanas grind cantharidin-producing beetles into a powder and use it in a medicine called *seletsa* as an aphrodisiac, as an abortifacient, and for "purifying the blood." *Seletsa* fatalities are relatively common.¹

Cantharidin has a long, infamous reputation for being an aphrodisiac and is known as Spanish fly in the vernacular. This reputation is based on the observation of pelvic congestion in women and priapism in men after cantharidin ingestion.¹ In 1772, the Marquis de Sade is said to have poisoned prostitutes with candies containing Spanish fly to increase sexual pleasure.¹⁰

Although cantharidin is not a true aphrodisiac, poisonings after surreptitious placement still occur.^{11,12} In England, a man gave coconut ice laced with cantharidin to 2 women, hoping to facilitate a sexual interaction. Both women died of the poisoning.¹³ In 1996, 4 young adults presented to the emergency department at Temple University, Philadelphia, Pa, after ingesting a liquid consisting of water and powdered drink mix (Kool-Aid) contaminated with cantharidin, self-administered as a trial run, intended ultimately for one of their girlfriends. All 4 survived.¹¹ One fatality resulted after a man tried to use cantharidin as fishing bait:

A keen fisherman obtained some pure cantharidin from an illicit source with the object of attracting fish. . . . He mixed the substance with water in a bottle, and, having no stopper for this, he used his thumb to occlude the opening. . . . Immediately following this, the patient handled his fishing-hooks, and in the process accidentally pricked the thumb . . . this caused him to suck the thumb. In this way, it appears, the cantharidin was transferred to the patient's mouth.¹⁴

Cantharidin may be easily (and illegally) purchased from health food stores or erotic Web sites as Spanish fly. But caveat emptor—there has been at least 1 report of poisoning due to strychnine contamination in Spanish fly aphrodisiac pills.¹⁵

CANTHARIDIN AND THE FDA

Cantharidin in a collodion vehicle has been used by dermatologists as a treatment for molluscum contagiosum and warts since the 1950s.^{16,17} It satisfied all the safety requirements of the Food, Drug, and Cosmetic Act of 1938. However, in 1962, the FDA initiated an amendment to the Food, Drug, and Cosmetic Act, called the Drug Efficacy Study Implementation, which required manu-

facturers to submit efficacy data for their products.¹⁸ No efficacy data were submitted to the FDA, and cantharidin was removed from the market in 1962.¹⁹ However, the status of cantharidin may be changing in the near future. In 1997, President Clinton signed into law an amendment to the Food, Drug, and Cosmetic Act, adding section 503A, which provides that certain drug products may be compounded by a physician or a pharmacist on a customized basis for individual patients.²⁰ Among other criteria, section 503A would permit the compounding of drug products that appear on a "Bulk Substances List," which is to be issued and maintained by the FDA. Although the list has not been finalized, cantharidin was 1 of 30 substances nominated for inclusion on the list. The FDA is on the verge of including cantharidin on its final "Bulk Substances List," along with other substances that are familiar to dermatologists, such as ferric subsulfate, iodoform, and thymol iodide. Diphenylcyclopropanone, squaric acid dibutyl ester, and others are still under consideration. In 1998, the FDA established an interim policy stating that, in general, it would not take regulatory action against drug products compounded with one of the substances nominated for inclusion on the list, as long as there did not appear to be a significant safety risk. Thus, a physician or pharmacist may administer drug products compounded with cantharidin, unless the FDA issues a notice that cantharidin appears to present a significant safety risk.²¹ Because of cantharidin's toxicity, the FDA has proposed that cantharidin should be limited to "topical use in the professional office setting only."

Proprietary formulations of cantharidin are not uncommonly used in the United States, because it is often impracticable for a physician or pharmacist to compound the drug on each occasion that it is needed in the office. Also, proprietary formulations may offer a greater degree of consistency of product or predictability of performance than a drug that is compounded. We are not aware of any enforcement actions by the FDA against the use of such proprietary formulations.

MECHANISM OF ACTION

Cantharidin is absorbed by the lipid layers of epidermal cell membranes. Application of cantharidin to the epidermis results in the activation or release of neutral serine proteases that cause degeneration of the desmosomal plaque, leading to detachment of tonofilaments from desmosomes. This process leads to acantholysis and intraepidermal blistering, and nonspecific lysis of skin.²² Lesions heal without scarring, as acantholysis is intraepidermal.

DERMATOLOGICAL USES OF CANTHARIDIN

Cantharidin in a flexible collodion medium has long been considered a viable option for the treatment of warts and molluscum.^{16,17,23-26} Proprietary formulations consisting of 0.7% cantharidin in a film-forming vehicle containing acetone, ether, and alcohol can be purchased from several companies (eg, Dormer Laboratories, Rexdale, Ontario; Omniderm, Hudson, Quebec; PharmaScience, Montreal, Quebec; College Pharmacy, Colorado Springs, Colo;

Belle Haven Pharmacy, Alexandria, Va; and Dermatologic Lab and Supply, Council Bluffs, Iowa). Alternatively, compounding 0.7% or 0.9% cantharidin solution with equal parts of acetone and flexible collodion may be done.^{16,24} Camphor or pine oil is often added to proprietary formulations to lend a medicinal aroma.

Topical cantharidin treatment causes formation of blisters within 24 to 48 hours. Healing is complete 4 to 7 days after application. The degree of blistering is controlled by instructing the patient to wash the treated site with soap and water after a specified length of time, usually in the range of 2 to 6 hours. Blistering may be intensified by lengthening the contact time or by occlusion with nonporous tape to increase percutaneous absorption. Fair-skinned individuals tend to blister more easily, and contact time should be adjusted accordingly.²⁷ We treat molluscum initially with a 2-hour contact time, without occlusion. Retreatment may be done as early as 1 week. Warts are treated more intensively. Warts are pared, followed by cantharidin application to the wart and a 1-mm rim of normal skin, and occluded with nonporous tape. Cantharidin is washed off in 4 hours. If necessary, paring and retreatment are done in 1 to 2 weeks, with contact time increased if needed. In our experience, pain and excessive blistering are exceedingly rare when these guidelines are followed.

Cantharidin should be applied only in the office by a physician²⁶ or under the direct supervision of a physician. Although 1 report advocates home use of cantharidin for warts, we believe that home use should be strictly avoided,²⁸ because severe blistering can result from improper use,²⁴ and because ingestion, especially by children, can be fatal. Treatment of mucous membranes is contraindicated owing to increased propensity for blistering.¹⁷ Also, placement of cantharidin near the eyes and eyelids should be avoided to prevent scleral erosion.²⁹

When cantharidin is used appropriately, complications are exceedingly rare. Mild to moderate pain, temporary erythema, a transient burning sensation, and pruritis may occur.³⁰ There is no scarring with proper use.^{16,24} Adverse effects include a ring of small satellite warts surrounding the original wart. Ring warts occurred in 1 of 100 patients in one study²⁸ and in 3 of 61 patients in another.¹⁷ The same or different therapy, such as cryosurgery, can be used to remove the larger warts.¹⁷ Ring warts can arise after any type of destructive therapy for warts, and this complication deserves mention in the informed consent process. Postinflammatory hypopigmentation or hyperpigmentation can take weeks to months to resolve. Informed consent should also include mention of this temporary but potentially distressing effect.^{16,31}

The treatment of plantar warts may have a higher rate of significant complications. Two patients with plantar warts were treated with cantharidin and 40% salicylic acid plaster, under occlusion for 24 hours. Lymphangitis developed 30 hours later.³² An adult whose plantar warts were treated with 0.7% cantharidin solution developed lymphangitis and refractory lymphedema.³³ Cellulitis developed in 4 patients whose plantar warts were initially treated with a mixture of 1% cantharidin, salicylic acid, and podophyllin that was left on for 24 hours, and then the warts were debrided with silver nitrate.²⁶

In a retrospective study of 300 children with molluscum contagiosum treated with cantharidin, 90% of the patients experienced resolution of symptoms and an additional 8% noted some improvement.³⁰ The authors used 52.5 mg of cantharidin crystals mixed in 7.5-mL flexible collodion. Treated areas were rinsed 4 to 6 hours after application. No cases of systemic toxic reactions were noted.³⁰ In 1971, 1 manufacturer of 0.7% cantharidin wart-remover solution reported 1 500 000 mL of product sold over the prior 10-year period, with no reports of systemic intoxication.³⁴

CANTHARIDIN POISONING

Poisoning usually results after aphrodisiac ingestion.¹¹ Beetle ingestion by children has also caused poisoning.^{35,36} The clinical signs of cantharidin poisoning are nonspecific. Gas chromatography/mass spectrometry can be used to confirm cantharidin poisoning.^{37,38} The fatal dose of cantharidin is estimated to range from 10 to 65 mg,³⁹ with the median lethal dose being approximately 1 mg/kg⁴⁰; however, individuals have survived after consuming oral doses as high as 175 mg.¹² Fatalities usually result from renal failure, and severe morbidity can result from injury to the gastrointestinal tract.¹¹

With cantharidin ingestion, a burning sensation of the lips, mouth, and pharynx occurs within minutes.^{12,39} Blisters form shortly thereafter, leading to dysphagia, abdominal cramping, hematemesis, and vomiting. Total loss of normal mucosa of the gastrointestinal tract may occur.^{12,13,41} Damage is dose dependent and is directly related to the amount of fatty food within the gastrointestinal tract at the time of ingestion, as fats and lipids promote absorption.³⁵ Lumbar pain, dysuria, proteinuria, hematuria, and renal failure can result.^{9,11,12,41,42} Coagulopathy,¹¹ seizures, and a Guillain-Barré-like flaccid paralysis have been reported.^{43,44}

To the best of our knowledge, there have been no reports of cantharidin intoxication caused by the reasonable application of cantharidin solution by a physician. One unusual report from South Africa describes a case in which topical cantharidin was applied to an area of abdominal skin approximately 18 × 8 cm as a treatment for pleurisy (cantharidin was thought to act medicinally as a counterirritant).⁴⁵ Dysuria and hematuria occurred, but the patient recovered fully within 1 week.

TREATMENT OF CANTHARIDIN POISONING

The treatment of cantharidin intoxication is largely supportive. There is no known antidote.³⁵ For topical exposures, the affected area should be cleaned with acetone, ether, fatty soap, or alcohol, which helps to dissolve and dilute the cantharidin. The skin should then be cleaned thoroughly with soap and water. A topical steroid may be applied to intact skin if it is symptomatic.³

For oral ingestions, several support measures may be taken. If possible, the patient should swallow generous quantities of water but should avoid fatty foods (such as milk) because they increase cantharidin absorption.³⁵ Vomiting should not be induced, as oropharyngeal and esophageal damage is increased with reexposure. Gas-

tric lavage is recommended in patients who present early and do not have severe esophageal involvement. Activated charcoal may also be administered, although there is no evidence that cantharidin binds to this material.¹¹ Hospitalization may be necessary for supportive care and pain management.¹¹

INVESTIGATIVE USES OF CANTHARIDIN

Cantharidin has been demonstrated to act as a vasoconstrictor and positive inotrope in guinea pig⁴⁶ and human cardiac⁴⁷ tissue in vitro. These effects are mediated in part by cantharidin's action as a protein phosphatase inhibitor.^{48,49} Although cantharidin is too toxic to administer systemically, it is possible that safer derivatives will be developed in the future, offering new therapeutic options for the treatment of human cardiac failure.

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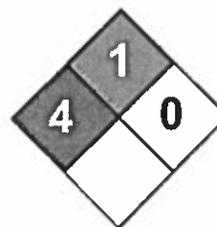
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Reference 7



Health	4
Fire	1
Reactivity	0
Personal Protection	E

Material Safety Data Sheet Cantharidin MSDS

Section 1: Chemical Product and Company Identification

Product Name: Cantharidin

Catalog Codes: SLC3634

CAS#: 56-25-7

RTECS: RN8575000

TSCA: TSCA 8(b) inventory: Cantharidin

CI#: Not available.

Synonym: Hexahydro-3a,7a-dimethyl-4,7-epoxyisobenzofuran-1,3-dione

Chemical Name: Not available.

Chemical Formula: C₁₀H₁₂O₄

Contact Information:

Sciencelab.com, Inc.

14025 Smith Rd.

Houston, Texas 77396

US Sales: 1-800-901-7247

International Sales: 1-281-441-4400

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call:
1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Cantharidin	56-25-7	100

Toxicological Data on Ingredients: Cantharidin: ORAL (LD50): Acute: 1 mg/kg [Mouse]. 1.71 mg/kg [Mammal].

Section 3: Hazards Identification

Potential Acute Health Effects:

Extremely hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation. Very hazardous in case of skin contact (permeator). Hazardous in case of skin contact (corrosive). Severe over-exposure can result in death. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Potential Chronic Health Effects:

CARCINOGENIC EFFECTS: Not available. **MUTAGENIC EFFECTS:** Not available. **TERATOGENIC EFFECTS:** Not available. **DEVELOPMENTAL TOXICITY:** Not available. Repeated exposure to an highly toxic material may produce general deterioration of health by an accumulation in one or many human organs.

Section 4: First Aid Measures

Eye Contact: Check for and remove any contact lenses. Do not use an eye ointment. Seek medical attention.

Skin Contact:

If the chemical got onto the clothed portion of the body, remove the contaminated clothes as quickly as possible, protecting your own hands and body. Place the victim under a deluge shower. If the chemical got on the victim's exposed skin, such as the hands : Gently and thoroughly wash the contaminated skin with running water and non-abrasive soap. Be particularly careful to clean folds, crevices, creases and groin. If irritation persists, seek medical attention. Wash contaminated clothing before reusing.

Serious Skin Contact:

Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek immediate medical attention.

Inhalation: Allow the victim to rest in a well ventilated area. Seek immediate medical attention.

Serious Inhalation:

Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. If breathing is difficult, administer oxygen. If the victim is not breathing, perform mouth-to-mouth resuscitation. Seek medical attention.

Ingestion:

Do not induce vomiting. Examine the lips and mouth to ascertain whether the tissues are damaged, a possible indication that the toxic material was ingested; the absence of such signs, however, is not conclusive. Loosen tight clothing such as a collar, tie, belt or waistband. If the victim is not breathing, perform mouth-to-mouth resuscitation. Seek immediate medical attention.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: May be combustible at high temperature.

Auto-Ignition Temperature: Not available.

Flash Points: Not available.

Flammable Limits: Not available.

Products of Combustion: These products are carbon oxides (CO, CO2).

Fire Hazards in Presence of Various Substances: Not available.

Explosion Hazards in Presence of Various Substances:

Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions:

SMALL FIRE: Use DRY chemical powder. LARGE FIRE: Use water spray, fog or foam. Do not use water jet.

Special Remarks on Fire Hazards: Not available.

Special Remarks on Explosion Hazards: Not available.

Section 6: Accidental Release Measures

Small Spill: Use appropriate tools to put the spilled solid in a convenient waste disposal container.

Large Spill: Use a shovel to put the material into a convenient waste disposal container.

Section 7: Handling and Storage

Precautions:

Keep locked up Keep container dry. Keep away from heat. Keep away from sources of ignition. Empty containers pose a fire risk, evaporate the residue under a fume hood. Ground all equipment containing material. Do not ingest. Do not breathe dust. Never add water to this product In case of insufficient ventilation, wear suitable respiratory equipment If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes

Storage:

Keep container dry. Keep in a cool place. Ground all equipment containing material. Keep container tightly closed. Keep in a cool, well-ventilated place. Highly toxic or infectious materials should be stored in a separate locked safety storage cabinet or room.

Section 8: Exposure Controls/Personal Protection

Engineering Controls:

Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection:

Splash goggles. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:

Splash goggles. Full suit. Dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits: Not available.

Section 9: Physical and Chemical Properties

Physical state and appearance: Solid.

Odor: Not available.

Taste: Not available.

Molecular Weight: 196.21 g/mole

Color: Not available.

pH (1% soln/water): Not applicable.

Boiling Point: Decomposes.

Melting Point: 218°C (424.4°F)

Critical Temperature: Not available.

Specific Gravity: Not available.

Vapor Pressure: Not applicable.

Vapor Density: Not available.

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water, acetone.

Solubility:

Partially soluble in acetone. Very slightly soluble in hot water, diethyl ether. Insoluble in cold water.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Not available.

Incompatibility with various substances: Not available.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity: Not available.

Special Remarks on Corrosivity: Not available.

Polymerization: No.

Section 11: Toxicological Information

Routes of Entry: Dermal contact. Eye contact. Inhalation. Ingestion.

Toxicity to Animals: Acute oral toxicity (LD50): 1 mg/kg [Mouse].

Chronic Effects on Humans: Not available.

Other Toxic Effects on Humans:

Extremely hazardous in case of skin contact (irritant), of ingestion, of inhalation. Very hazardous in case of skin contact (permeator). Hazardous in case of skin contact (corrosive).

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans: Not available.

Special Remarks on other Toxic Effects on Humans: Not available.

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:

Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The products of degradation are more toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:

Section 14: Transport Information

DOT Classification: CLASS 6.1: Poisonous material.

Identification: : Toxic solid, organic, n.o.s. (Cantharidin) : UN2811 PG: I

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations:

Pennsylvania RTK: Cantharidin Florida: Cantharidin Massachusetts RTK: Cantharidin New Jersey: Cantharidin TSCA 8(b) inventory: Cantharidin SARA 302/304/311/312 extremely hazardous substances: Cantharidin CERCLA: Hazardous substances.: Cantharidin

Other Regulations: OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200).

Other Classifications:

WHMIS (Canada):

CLASS D-1A: Material causing immediate and serious toxic effects (VERY TOXIC). CLASS D-2B: Material causing other toxic effects (TOXIC).

DSCL (EEC):

R38- Irritating to skin. R41- Risk of serious damage to eyes.

HMIS (U.S.A.):

Health Hazard: 4

Fire Hazard: 1

Reactivity: 0

Personal Protection: E

National Fire Protection Association (U.S.A.):

Health: 4

Flammability: 1

Reactivity: 0

Specific hazard:

Protective Equipment:

Gloves. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Wear appropriate respirator when ventilation is inadequate. Splash goggles.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

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Last Updated: 05/21/2013 12:00 PM

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Reference 8

CANTHARONE® AND CANTHARONE® PLUS

HIGH POTENCY WART REMOVERS FOR DOCTOR'S USE
THE ORIGINAL AND MOST EFFECTIVE CANTHARIDIN TREATMENT

- Simple office procedure,
no special instruments required
- A selective procedure,
not a randomly destructive one
- Painless application
- Produces a uniform blistering action
- Leaves no permanent scars



CANTHARONE®

- COMMON WARTS
- PERIUNGAL WARTS
- MOLLUSCUM CONTAGIOSUM

● Each 7.5 mL bottle provides approximately 60 wart treatments.

CANTHARONE® PLUS

- PLANTAR WARTS
- RESISTANT & HEAVILY
KERATINIZED WARTS

EFFECTIVE WART TREATMENT

PRODUCT INFORMATION

CANTHARONE®: NOT RECOMMENDED FOR CHILDREN UNDER 3 YEARS.

Description: CANTHARONE®, cantharidin colloidion, is a topical liquid containing 0.7% cantharidin in an film-forming vehicle containing acetone, pyroxylin, castor oil, and camphor. The active ingredient, cantharidin, is a vesicant. The chemical name is Hexahydro-3a, 7a-dimethyl-4B, 7B-epoxyisobenzofuran-1, 3-dione (C₁₀ H₁₂ O₄).

Clinical Pharmacology: The vesicant action of cantharidin is the result of its primary acantholytic action. Its effectiveness against warts is presumed to result from the "exfoliation" of the tumor as a consequence of its acantholytic action. There are no reports of scarring when cantharidin is used alone as directed, presumably because the lytic action of cantharidin does not go beyond the epidermal cells. The basal layer remains intact and there is minimal effect on the corium.

Indications and Usage: CANTHARONE® is indicated for removal of common warts, molluscum contagiosum and periungual warts. It is designed for topical application by a physician. Painless application and the absence of instruments makes it especially useful for treating children. (Some pain may occur later). See Dosage and Administration, and Warnings sections, for specific directions on use contained in each package.

PRODUCT USE

BEFORE USING, PLEASE REVIEW THE WARNING AND CAUTION INFORMATION ON THE BACK PAGE TREATING MOLLUSCUM CONTAGIOSUM WITH CANTHARONE®

Important: Treat only a few lesions at the first visit until the reactivity of the patient is known. Then multiple areas can be treated in one visit.

Method:

- 1) Using a wooden applicator stick, apply a very small amount of solution to only the top of each lesion. Let dry. No dressing is needed.
- 2) Do not occlude unless lesions are large or were resistant to the first treatment, (Then occlude with non-porous tape for 4 - 6 hours.)
- 3) Suggest that patient does not bathe for 4 - 6 hours.
- 4) Prescribe medication for cases of night-time discomfort (pain, itching).
- 5) Treat once weekly for new or resistant lesions (usually 2 or 3 treatments).

NOTE: Provide patients with Cantharone patient information sheets to minimize concerns.

Treatment Progression:

No pain on application.

4 Hours: Mild discomfort may occur.

24 Hours: Blistering usually formed by this time.

4 Days: Crusted blisters fall off leaving superficial erosions. Medication may be needed to control night-time itching.

7 Days: Healed with temporary residual erythema.

If there are resistant lesions, treat as before with CANTHARONE®, but this time use non-porous tape to occlude those lesions for 4 - 6 hours. Temporary depigmentation often occurs, but no scarring.

TREATING COMMON & PERIUNGUAL WARTS WITH CANTHARONE®

No cutting or prior treatment is required. (Occasionally, nails must be trimmed to expose subungual warts to medication). Using an applicator stick, apply CANTHARONE® directly to the lesion; be sure to cover the growth completely, extending beyond about 1 mm. Allow a few minutes for a thin membrane to form and cover with a piece of non-porous adhesive tape, e.g. Blenderm® (Taping with occlusive tape is important for full activity). Instruct patient to remove tape in 24 hours and replace with a loose Band-Aid®. On next visit (1 or 2 weeks), remove necrotic tissue and re-apply CANTHARONE® to any growth remaining. A single application may suffice for normally keratinized skin.

TREATING SELECTIVE CASES OF PLANTAR WARTS WITH CANTHARONE®

CANTHARONE® may be used for the treatment of newly developed Plantar warts and on children with Plantar warts. Use the same procedure as with CANTHARONE® PLUS, Method A (see next page). Prior to treatment, thoroughly clean the surrounding skin to assure good adhesion of the occlusive tape. Proper taping with Blenderm® tape is an important part of the procedure. After 24 hours, the patient may bathe and replace the dressing as the doctor instructs. For large mosaic warts, treat a portion of the wart at a time. When destruction of the wart is complete, the healed site will appear smooth, with normal skin lines.

PRODUCT INFORMATION

CANTHARONE® PLUS: NOT RECOMMENDED FOR CHILDREN UNDER 12 YEARS.

Description: Cantharone® PLUS is a topical liquid containing 30% salicylic acid, 2% podophyllin BP, 1% cantharidin in a film-forming vehicle containing 0.5% octylphenylpolyethylene glycol, cellosolve, ethocel, collodion, castor oil and acetone. Salicylic acid is keratolytic. The chemical name is 2-hydroxy-benzoic acid. Podophyllin is a caustic. It is an extract of the rhizomes and roots of podophyllum peltatum; the major component podophyllotoxin is an anti-neoplastic and roentgenomimetic. Cantharidin is a vesicant, the chemical name is hexahydro-3a, 7a-dimethyl-4B, 7B-epoxyisobenzofuran-1, 3-dione.

Action: CANTHARONE® PLUS is a mixture of three wart removers. The action of salicylic acid is thought to be due to its keratolytic activity in removing wart-virus infected epithelial cells; podophyllin has caustic properties causing destruction of tissue and cantharidin has vesicant properties which are thought to exfoliate the wart tumor. The exact pharmacological mechanism of each of these agents is not known.

Indications and Usage: CANTHARONE® PLUS is intended for removal of resistant, heavily keratinized and plantar warts. Useful where painless application is desired. See Dosage and Administration, and Warnings sections, contained in each package, for specific direction for use.

PRODUCT USE

BEFORE USING, PLEASE REVIEW THE WARNING AND CAUTION INFORMATION ON THE BACK PAGE TREATING RESISTANT, HEAVILY KERATINIZED & PLANTAR WARTS WITH CANTHARONE® PLUS

Method A: (no curettage) ; no cutting or prior treatment required. Using a wooden applicator stick, apply CANTHARONE® PLUS sparingly (one layer only) to the wart and a 1 -3 mm margin around the wart. (For large mosaic warts, treat a portion of the wart at a time.) Allow to dry for a few minutes. Cover with a piece of non-porous plastic adhesive tape, e.g. Blenderm®. Instruct patient to keep the tape on for at least four hours (up to 8 hours). Within 24 hours a blister forms which is often painful and inflamed. Have the patient return for observation in one or two weeks. During this period the patient may or may not do periodic soaks as the doctor prefers. Remove necrotic tissue and treat as before if any viable wart tissue remains. Allow tissue to re-epithelialize before re-treatment.

Method B: (with curettage): Proceed as in Method A, except have patient return in one day for curettage. (Local anesthesia may be necessary.) There are several advantages to this method: Treatment with CANTHARONE® PLUS prior to curettage enhances identification of tissue planes; increases separability of wart tissue and re-treatment is rarely necessary. Have the patient return for observation in four weeks. (The lesion normally heals completely within one to three weeks.)

Pain Management: Warn the patient that the blister may be painful. Prescribe a mild analgesic. The tape may be removed and the area soaked in cool water for 10 - 15 minutes, as needed, provided sufficient time has been allowed for the CANTHARONE® PLUS to penetrate. At the option of the doctor, the blister may be punctured using sterile technique and covered with antiseptic and a Band-Aid®. Local anesthesia may be needed during curettage (Method B).

FOR ALL TREATMENTS: SUMMARY OF USE

- 1) Both products are very potent. (CANTHARONE® PLUS is extremely so). Use each sparingly. Treatment is at one and a half to two week intervals. (Delay re-treatment if inflamed.)
- 2) Both products are to be used under occlusion with plastic (non-porous) tape, e.g. Blenderm®, occlude no longer than 8 hours with CANTHARONE® PLUS", or 24 hours with CANTHARONE®". (Note: Tape is normally not used when treating molluscum.)
- 3) Sterile puncture of the blister will help relieve discomfort and should be done at the option of the doctor.
- 4) Daily soaks following therapy are at the option of the doctor.
- 5) Antibacterial: It is recommended that a mild anti-bacterial soap be used until the tissue re-epithelializes.

PRODUCT CARE

The life of your bottle of CANTHARONE® or CANTHARONE® PLUS can often be greatly extended by taking a few precautions:

- 1) Before opening, completely remove the blue or red safety seal.
- 2) When removing the product from the bottle (with stick or broken Q-Tip® end) , try to avoid getting liquid on the top of the bottle lip. The liner of the cap seats on this top part of the bottle. THIS IS WHAT FORMS THE SEAL. (An improper seal will allow the product to dry out in the bottle.)
- 3) Replacing the cap as soon as you are finished using the product will minimize solvent evaporation.
- 4) If you notice any crust or dried material accumulating on top of the bottle lip, clean this area off with acetone and disposable wipes. (Scraping may be necessary.) WEAR DISPOSABLE GLOVES.
- 5) Finally, if either product becomes dried out or highly viscous, you may stir in some acetone. If any solids are present, stir with a metal spatula or rod. COMPLETELY REDISSOLVE ANY SOLIDS. Do not over-thin, i.e. use just enough acetone to approximate the original viscosity.

IMPORTANT INFORMATION

WARNING : CANTHARONE® and CANTHARONE® PLUS are TOXIC and are NOT TO BE DISPENSED OR PRESCRIBED for patient administration under any circumstances due to the risk of improper use and to the serious danger of FATAL poisoning if swallowed. FOR EXTERNAL USE ONLY. CANTHARONE® and CANTHARONE® PLUS are flammable. keep away from heat, sparks and flame.

Precautions: There have been no adequate and well-controlled studies on the use of cantharidin in pregnant women or nursing mothers; therefore, the use of CANTHARONE® and/or CANTHARONE® PLUS IS NOT RECOMMENDED during pregnancy or while nursing.

Contraindications: CANTHARONE® and CANTHARONE® PLUS are not recommended for use with diabetics or persons with impaired peripheral circulation. It is not recommended for use near eyes, on mucous membranes, in ano-genital, intertriginous, or axilla areas. See specific direction sheets for more details on Use, Warnings, Precautions and Adverse Reactions.

Adverse Reactions: The development of superficial annular warts in a small percentage of patients, who may become alarmed, may occur following cantharidin therapy. Warning the patient or parent of the possibility prior to treatment alleviates much of their concern. There have been several reports of chemical lymphangitis following use of CANTHARONE®, one in combination with salicylic acid plaster. Also, a case of extreme, painful blistering after treatment of multiple axillary lesions.

CAUTION: PATIENTS VARY IN THEIR SENSITIVITY TO CANTHARIDIN. A MORE INTENSE REACTION IS TO BE EXPECTED IN PATIENTS WITH FAIR SKIN AND BLUE EYES. DO NOT TREAT LARGE AREAS OR MULTIPLE LESIONS BEFORE ESTABLISHING THE SENSITIVITY OF THE PATIENT. DO NOT REAPPLY TO THE SAME LESION MORE THAN ONCE PER WEEK. DEFER SECOND TREATMENT IF INFLAMMATION IS INTENSE. SHORT TERM RESIDUAL PIGMENT CHANGES MAY OCCUR.

REFERENCES

(1) Kelly, M.G. and Hartwell, J.L., The Biological Effects And Chemical Composition of Podophyllin. A Review, j. Natl. Cancer Inst, 14, 967- 1010, Feb. 1954, (2) Epstein, W.L. and Kligman, A.M., Treatment of Warts with Cantharidin, Arch. Dermat. 77:508, May 1958, (3) Stoughton, R.B. and Bagatell, F., The Nature of Cantharidin Acantholysis, J. Invest. Dermat., 33:287, Nov. 1959. (4) Epstein, J.H. and Epstein, W.L., Cantharidin Treatment of Digital and Periungual Warts, Calif. Med., 93:11, July, 1960, (5) Funt, T.R., Cantharidin Treatment of Molluscum Contagiosum, Arch. Dermat., 83:504, March, 1961. (6) Ormond, C.S., Cantharone, A Cantharidin Tincture as a Useful Agent in Treating intractable Plantar Lesions, J. Amer. Podiat. Assn., 52:427, June, 1962. (7) Perlman, H.H., Let's Talk About Warts, Med. Times 92, 99- 112, Feb., 1964. (8) Bock, R.H., Treatment of Palpebral Warts with Cantharone, Amer. J. Ophthal., 60:529, Sept., 1965. (9) Tromovitch, T.A. and Allen, J.C., Molluscum Contagiosum, Cutis 2:21, Jan., 1966. (10) Curtis, A.C. and Thurston, C.S., What's What About Warts, Cutis 3:1297, Dec. 1967. (11) Basile, O.J., Plantar Warts - A Cantharidin-Occlusive Technique for Treatment, Cutis, 5:1134, Sept. 1969, (12) Dilairy, M., Letter to the Editor, Arch. Dermat., 111:1073, Aug., 1975. (13) Funt, T.R., Cantharidin: A Valuable Office treatment of Molluscum Contagiosum, J. Southern Med. Assoc., 72:1019, Aug. 1979, (14) Karol, M.D., Suspected Teratogenicity from Topical Application, Clin., Toxicol. 16:283-6, 1980. (15) Epstein, Ernst, Common Skin Disorders, (1988), Medical Economics Co. Inc., New Jersey.

PATIENT INFORMATION SHEETS AVAILABLE UPON REQUEST.

PRODUCT	HEALTH CANADA REGISTRATION	SIZE/PACKAGE	PRODUCT CODE
CANTHARONE® Regular	DIN 00619035	7.5 mL Bottle	9001-975
CANTHARONE® PLUS	DIN 00772011	7.5 mL Bottle	9002-975

(R) 5007

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205/5M

Reference 9

CLINICAL AND LABORATORY INVESTIGATION

Pediatric Dermatology 1–10, 2012

Cantharidin for the Treatment of Molluscum Contagiosum: A Prospective, Double-Blinded, Placebo-Controlled Trial

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Abstract: Our aim was to study the effects and safety of cantharidin in the treatment of molluscum contagiosum (MC), we conducted a prospective, double-blinded, placebo-controlled, randomized clinical trial to evaluate the safety and efficacy of topical cantharidin for treatment of pediatric MC in an academic ambulatory care center. Twenty-nine children aged 5–10 with a diagnosis of MC were enrolled to receive treatment with cantharidin or placebo. The main outcome measure was complete clearance of all molluscum lesions. In contrast to previous retrospective observational studies, the performance of cantharidin treatment over 2 months was not substantially better than the performance of placebo. The scope of follow-up was limited to five visits over 2 months of treatment. A longer follow-up period might have captured a greater effect of cantharidin. Over a 2 month period, the magnitude of the cantharidin treatment effects in the target population are, at best, not large. This study provided objective unbiased estimates of the magnitude of cantharidin treatment effects and provided important prospective safety data. Our subjects experienced minimal side effects when treated with cantharidin.

Molluscum contagiosum (MC) is a dermatologic disorder caused by the MC virus (a poxvirus). MC commonly affects children of elementary school age. The virus is spread through close skin-to-skin contact, and patients can often auto-inoculate themselves, making MC a dynamic disease within individual patients. Infection can last from several months to 4 years (1). Although self-limited, molluscum lesions can be symp-

tomatic, unsightly, and embarrassing. Parents often seek treatment to decrease symptoms and improve their appearance. There are several treatment approaches: destructive, immunologic, antiviral, and active non-intervention. Destructive measures include curettage, cryotherapy, needle pricking, and topical vesicants such as cantharidin (2,3). Other destructive approaches include retinoids, silver nitrate, potassium hydroxide,

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salicylic acid, and phenols (4–14). Immunologic therapies include imiquimod, nitric oxide, and cimetidine, although the efficacy of these therapies remains controversial. Antiviral therapies are few, but cidofovir has been used in adults with the human immunodeficiency virus with MC (15).

There is debate about the standard of care for MC. Because of its self-limiting nature, treatment options attempt to minimize scarring and other side effects while speeding recovery time. Care must be taken to find nontraumatic modalities with minimal pain. Watchful waiting or “active nonintervention” is a practice commonly employed, but parents may not be satisfied with waiting for an undetermined period of time that could last years, and there is the potential for spread to other children.

Cantharidin is a topical vesicant that has been used in the treatment of MC since at least the 1950s. It is an extraction from blister beetles, *cantharis vesicatories*, and acts as a protein phosphatase inhibitor *in vitro* (16). When applied to the skin, it produces a small intra-epidermal blister that usually heals without scarring.

Recently there have been greater restrictions in the ability of dermatologists to access preparations of cantharidin. Ambiguity regarding its Food and Drug Administration (FDA) status has made some academic institutions leery of condoning its use, although cantharidin is often cited in the dermatology and pediatric literature as a valuable treatment (3,12,16,17). Unfortunately, there have been no randomized clinical trials of cantharidin. Our study is the first prospective, placebo-controlled, randomized trial evaluating the safety and efficacy of cantharidin for pediatric MC.

MATERIALS AND METHODS

This prospective, double-blind, placebo-controlled, randomized clinical trial was designed to evaluate the safety and efficacy of cantharidin for treatment of pediatric MC. This trial was registered with <http://clinicaltrials.gov> under the identifier NCT00667225 and received approval from the Institutional Review Board of The University of North Carolina at Chapel Hill (UNC). Use of cantharidin also required an FDA Investigational New Drug application and number, which was obtained in 2007. Participating families received a \$10 gas gift card at each visit.

Study Population

Patients were recruited from local pediatrician’s offices, UNC Pediatrics Clinic, UNC Dermatology Clinic, and from mass e-mails to UNC students and staff during

December 2007–June 2009. Patients were included if they were 5–10 years old and had a clinical diagnosis of MC (confirmed by the principle investigators). There was no limit on duration of disease before enrollment. We excluded patients with immunosuppression such as HIV infection, organ transplantation, or use of immunosuppressive medications, including oral corticosteroids. Inhaled steroid use was not an exclusion criterion. Patients previously treated with cantharidin were excluded. Patients with only facial lesions were also excluded, because current convention discourages use of cantharidin on the face. Girls who had reached menarche were excluded because the effects of cantharidin use in pregnancy have never been evaluated. Please refer to Figure 5 for a flow diagram of patient enrollment and follow up.

Study Design

The study protocol specified a target sample size of 30 children with complete data for five visits spanning 8 weeks. The intended 8-week length of the study was chosen based on anecdotal experience and logistical considerations; specifically, the study was designed to be conducted within a specific 12-month period in which funding and personnel were available. Primary considerations in choosing the target sample size and the number of longitudinal evaluations (visits) included the availability of subjects, cost and time requirements, the anticipated precision of statistical estimators of interest, and reasonable conjectures about statistical power levels of a pair of hypothesis tests (interim and final) comparing rates of treatment success. The conjectures about statistical power were derived from rough estimates of efficacy based on anecdotal experience, because there were no relevant data in the literature. The primary consideration in choosing the parallel-arm experimental design, rather than a cross-over design, was immunologic; it is plausible that the irritation and blister caused by cantharidin (and not the vehicle) could attract inflammatory mediators and thereby have persistent systemic effects.

Randomization and Blinding

The eligible enrolled patients were assigned at random to cantharidin or placebo. With assistance from UNC’s Investigational Drug Service (IDS), the patients, parents, and investigators were blind to treatment assignment. The randomization schedule was computed before first recruitment using the method permuted blocks of size two. The randomization was stratified on self-reported history of atopic dermatitis (AD) because AD was considered to be a known risk factor for MC infection. Randomization was 1:1 within each of the two strata.

Investigational Drug

Cantharidin 0.7% was obtained from a local compounding pharmacy (Triangle Compounding Pharmacy, Cary, NC). It was compounded in a vehicle of acetone, hydroxypropylcellulose, and flexible collodion. Serving as a placebo, the vehicle contained the same formulation but did not include cantharidin. The vehicle was identical in texture and smell. Testing of the vehicle did not produce blisters in investigators.

Study Protocol

During visit 1, patients and their parents provided consent, and eligibility was established. Subjects and parents then provided information about demographic characteristics and potential risk factors, including history of dry skin, bathing with siblings and friends, pool use, and history of AD. The UNC IDS then assigned the next unique subject identification number and dispensed the appropriate drug. Each child was assigned his or her own bottle (cantharidin or placebo), which was returned to IDS after each visit. All of the subject's topical treatments were taken from this bottle.

During each visit, Investigator #1 recorded the number and spatial distribution of all molluscum lesions (face, trunk, back, left or right arm, left or right leg, hands, feet, buttocks, groin). This investigator examined all subjects at all visits to avoid interexaminer variation. Photographs of the lesions were taken if the patient consented to photography. Investigator #1 then left the room as Investigator #2 entered the room to apply the subject's assigned treatment (cantharidin or vehicle only). A small amount of medication was applied to the molluscum lesions using the stick end of a cotton-tipped applicator, with care not to apply to normal skin. Treatment was never applied to any lesions on the face. To allow the preparation to dry, the children were required to wait approximately 5 minutes before leaving with parents.

During visit 1, only one or two lesions were treated in order to screen for allergy or sensitivity to the preparation. In subsequent visits, up to 20 lesions were treated. Parents were instructed to wash the treated areas 4 hours after application.

Subjects and parents were asked to return for follow-up visits every 1–2 weeks for a maximum of five visits. During each visit, Investigator #2 asked whether the child had developed any blisters, pain, or inflammation. This information was kept hidden from Investigator #1, who counted lesions in subjects, so as to not bias the lesion count. All molluscum lesions were counted, including new lesions.

Statistical Analysis Strategy

Evaluation of efficacy and safety comprised a final analysis using data from all subjects and an interim analysis based on the first 10 patients completing the study. Simple tabular listings were used for analysis of safety.

Efficacy was evaluated in terms of total count of lesions observed longitudinally. The primary null hypothesis to be tested in the interim analysis ($\alpha = 0.001$) and the final analysis ($\alpha = 0.049$) was "cantharidin and placebo do not differ in regard to the incidence rate of complete clearance of MC lesions by visit 5." The two treatments were also compared in terms of the trajectory of longitudinal improvement in the lesion count. This analysis relied on statistical models supported by simple graphical figures. [The primary model was a linear mixed-effects model (20) for the response, $\log_{10}(\text{count} + 1)$. The regression equation expressed mean response as a treatment-specific linear function of time (represented by visit number 1,2,3,4,5). The model accounted for serial correlation by including a subject-specific random effect. Statistical estimates of the regression coefficients (b_1, b_2, b_3, b_4), the serial correlation coefficient (q), and the total variance (r^2) were obtained by fitting the model to the final data. Those statistical estimates were used to compute treatment specific estimates of the population mean response at each visit and the rate of improvement in mean response, along with corresponding estimates of group differences. All estimates were tabulated along with their 95% confidence intervals (CI).] In support of the primary efficacy results, auxiliary analyses were performed to evaluate the robustness of those results to reasonable perturbations of the statistical methods and assumptions. [This sensitivity analysis included numerous variations on the linear mixed-effects model in regard to the following: variance-covariance assumptions, handling of missing values, choice of temporal index (visit number or elapsed time in weeks), choice of baseline covariates and interaction terms included, and choice of dependent variable. The sensitivity analyses also included approaches focusing on the counts at visit 5; e.g., a Wilcoxon two-sample test procedure. As appropriate for count data, various log-linear models fitted via GEE methods were also examined. The only role of these auxiliary analyses was to guide our level of confidence in the primary efficacy results by verifying that the primary efficacy results were not sensitive to the choice of methods and assumptions.]

Secondary aims of the study included exploration of patient characteristics as potential predictors of baseline \log_{10} lesion count or as predictors of the magnitude of cantharidin effects (if any). These exploratory analyses

TABLE 1. Distribution of Patient Characteristics of Interest

Characteristic	Cantharidin, n = 13	Placebo, n = 16
Female, n (%)	8 (62)	10 (63)
Self-reported dry skin, n (%)	8 (67)*	6 (38)
Self-reported history of atopic dermatitis, n (%)	6 (46)	7 (44)
Reported history of inflamed lesions, n (%)	3 (25)*	3 (19)
Reported resolution of some lesions before study, n (%)	5 (42)*	7 (44)
Reported bathing with siblings, n (%)	6 (45)	6 (38)
Reported frequent swimming pool use, n (%)	10 (77)	13 (81)
Age at Visit 1, mean \pm standard deviation	6.7 (1.8)	7.3 (1.7)
Duration of molluscum contagiosum at Visit 1, mos, median (range)	6.0 (0-24)	8.5 (2-24)
Length of treatment and follow-up, weeks, median (range)	8.0 (4.6-8.3)	7.5 (5.0-11.0)

*Data were missing from one subject.

relied on linear statistical models and descriptive tabular and graphical statistical methods.

All statistical computations were performed using SAS System Software (version 9.2; SAS Institute, Inc., Cary, NC).

RESULTS

Twenty-nine children were enrolled and randomized using block randomization: 13 to cantharidin and 16 to placebo. The 13:16 allocation imbalance (6:7 in the AD stratum, 7:9 in the non-AD stratum) was due to drop-out. Two of the patients randomized were subsequently excluded when it was discovered that they did not meet all eligibility criteria. Because the reasons for exclusion were unrelated to treatment response, the allocation imbalance did not bias the study.

Table 1 describes the distribution of patient-specific characteristics. These distributions were generally well-balanced between the two groups, with the exception of subjective history of dry skin being more common in the cantharidin group. Figure 1 illustrates the distribution of age and self-reported duration of MC infection at visit 1, revealing some confounding of these two variables.

Median elapsed time between visits 1 and 5 (or final visit) was 8.0 weeks for cantharidin and 7.5 weeks for placebo. Most subjects (12 children in each group) were treated and followed for 7.0-9.0 weeks (Fig. 2).

All but two subjects, both girls, completed five visits. One was assigned to placebo, had no lesions at visit 3 (at 8.0 wks), and did not return for visits 4 and 5; the other subject was assigned to cantharidin and unaccountably did not return after visit 4 (at 7.7 wks).

Interim Analysis of Relative Efficacy and Safety

An interim analysis of the first 10 subjects (five per group) did not unblind the identities of the two treatment arms or patient assignments. Average age was 7.3 years,

average duration of disease at visit 1 was 8.8 months, and seven of the 10 were girls. At visit 1, the number of lesions per patient ranged from 3 to 204 (median 17.5).

Efficacy In terms of the primary endpoint, the performances of the two treatment regimens were identical, with none of the 10 children experiencing complete clearance by visit 5. By visit 5, the median lesion count for the cantharidin group was 8 (95% confidence interval [CI] = 1-106), representing an improvement of 41% (95% CI = -56 to 100), whereas the median count for the placebo group was 18 (95% CI = 5-111), representing an 8% (95% CI = -66 to 90) improvement. The difference of the two medians was 10 (95% CI = -84 to 81). The extremely wide confidence inter-

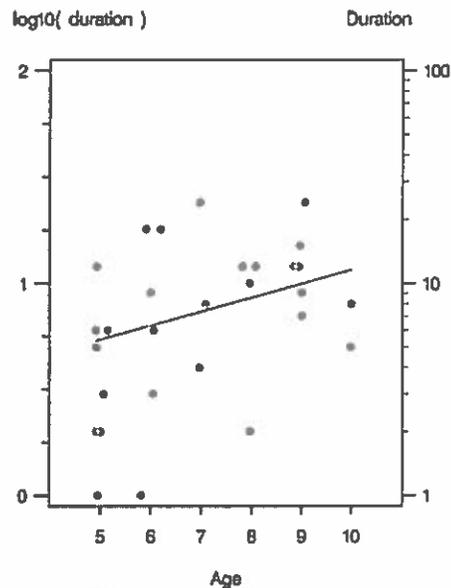


Figure 1. At visit 1, duration of molluscum contagiosum infection (weeks) was moderately confounded with age. The coefficient of correlation between age and \log_{10} (duration) was 0.42 (95% confidence interval = 0.06-0.68). Values plotted are for subjects assigned to cantharidin (solid dots) and placebo (open circles).

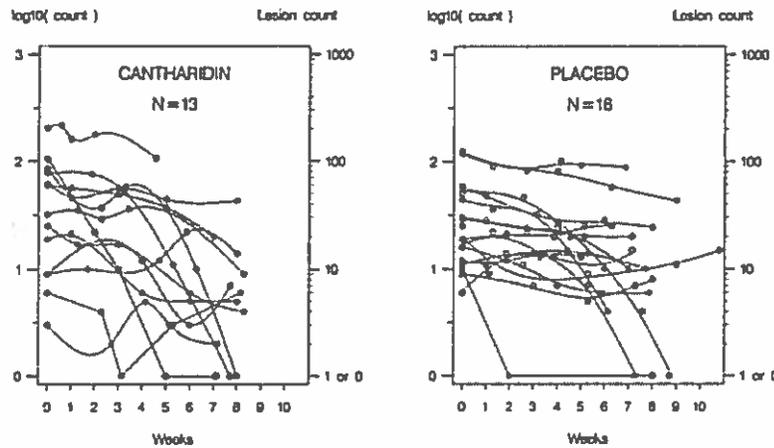


Figure 2. The individual-specific lesion counts in log₁₀ scale for each treatment group. As a visual aid, each nonparametric smooth curve describes the trajectory for an individual child. The temporal index is weeks. Only three subjects experienced complete clearance (squared symbol plotted at "1 or 0"). Two other subjects (placebo) have one lesion at visit 5. Another subject (cantharidin, age 5) had only one lesion at visit 3 but six lesions at visit 5.

vals around the 41 and 8% indicate that the numerical difference between 41 and 8% is not meaningful.

Safety The first 10 subjects experienced no adverse events associated with treatments.

Final Analysis of Relative Efficacy and Safety

Efficacy The longitudinal counts per child (Fig. 2) decreased for 85% of those given cantharidin and 75% of those given placebo. Few experienced complete clearance of lesions by visit 5: 15% (2/13) (95% CI = 0–35) for cantharidin, 6% (1/16) (95% CI = 0–18) for placebo. The difference between the two rates of complete clearance was 9% (95% CI = –16 to 36) two-sided p = .99. The one-sided 95% upper confidence limit was

30%. The two groups were similar in the number of subjects who had no or one lesion on their final visit: 23% (3/13) (95% CI = 5–54) for cantharidin, 19% (3/16) (95% CI = 4–46) for placebo, and difference 4% (95% CI = –23 to 34). The longitudinal trajectory of MC toward eventual clearance is shown in Fig. 3 and Table 2 in terms of mean response on the log₁₀ count scale and in terms of median count. The entries in Table 2 were obtained by fitting a linear mixed-effects model for log₁₀ count. This model provided estimates and inferences about the visit-to-visit rate of change: for cantharidin, the rate of –0.17 logs per visit corresponds to a median count decrease of approximately 32% per visit, whereas for placebo, the rate estimate of –0.10 corresponds to median decrease of approximately 21% per visit. The difference between the two rates was –0.07 (95% CI = –0.19

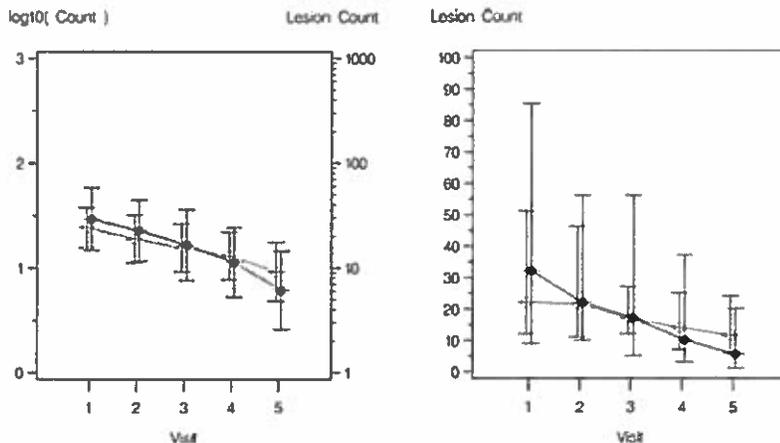


Figure 3. For cantharidin (•) and placebo (⊕), visit-specific sample means (left) and sample medians (right) are shown with their corresponding 95% confidence intervals.

TABLE 2. Response According to Treatment and Visit

Visit	Treatment		Difference
	Cantharadin	Placebo	
Log ₁₀ (count), mean (95% CI)			
1	1.5 (1.2–1.8)	1.4 (1.1–1.6)	0.1 (–0.2 –0.5)
2	1.3 (1.1–1.6)	1.3 (1.0–1.5)	0.0 (–0.3 –0.4)
3	1.2 (0.9–1.5)	1.2 (0.9–1.5)	0.0 (–0.4 –0.4)
4	1.0 (0.6–1.4)	1.1 (0.8–1.4)	–0.1 (–0.6 –0.4)
5	0.8 (0.4–1.3)	1.0 (0.6–1.4)	–0.2 (–0.7 –0.4)
Slope	–0.17 (–0.25 to –0.08)	–0.10 (–0.18 to –0.02)	–0.07* (–0.19 –0.05)
Lesion count, median (95% CI)			
1	32 (17–61)	24 (14–43)	10.0 (–12 –47)
2	22 (12–42)	19 (11–35)	3.0 (–12 –24)
3	15 (7–30)	15 (8–29)	1.0 (–11 –29)
4	10 (4–23)	12 (6–26)	–2.5 (–11 –12)
5	7 (3–18)	10 (4–23)	–4.0 (–13 –5)

Table characterizes the longitudinal trajectory of molluscum contagiosum toward eventual clearance. From visit to visit, the estimates of mean response decreased by 0.17 log units for cantharadin and by 0.10 log units for placebo (slope). Similarly, from visit to visit, the median estimates decreased approximately 32% for cantharadin and 21% for placebo. The estimates of means and medians were obtained by fitting a linear mixed-effects model for log₁₀ (count). The estimates of the differences between medians were computed using the nonparametric method of Hodges and Lehmann (21).

CI, confidence interval.

*p = .24 for a two-sided test of the null hypothesis that “difference in slopes is zero.”

TABLE 3. Subjects with Self-Reported Blisters

For each visit and across visits 2–5, the entry shown is the percentage of children who reported blisters. Almost all subjects treated with cantharadin reported blistering

Treatment		During study				During study
		Visit 2	Visit 3	Visit 4	Visit 5	
%						
Cantharadin (n = 13)	31	77	54	46	92*	92*
Placebo (n = 16)	25	31	20	25	50*	50*

*For the test of “the proportion of children experiencing blisters is the same for cantharadin and placebo” using the Fisher exact procedure, p = .02.

to 0.05; p = .24). If the intended primary null hypothesis had been “cantharadin and placebo are not different with respect to rate of change in mean response,” the test of that hypothesis would not be statistically significant.

Auxiliary analyses demonstrated that these efficacy results were not sensitive to the choice of statistical methods and assumptions used.

Safety Twenty-three percent (3/13) of cantharadin-treated children and 6% (1/16) of placebo-treated children reported pain (difference 17%, 95% CI = –10 to 44), and 92% (12/13) of cantharadin-treated children (Table 3) (95% CI = 67%, 99%) and 50% (8/16) (95% CI = 28–72) of placebo-treated children reported blistering (difference 42% [95% CI = 9–65; p = 0.02]). Six patients, all in the cantharadin group, reported hypo- or hyperpigmentation after treatment.

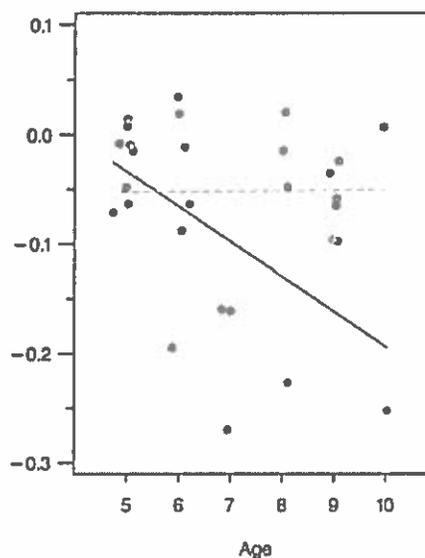
Change in Log₁₀(Count) per Week

Figure 4. Rate of change in log₁₀ (count) per week was computed for each child using linear regression. Rate = 0 indicates that the count did not change, whereas Rate = –0.5 indicates a rapid decrease in lesion count. For cantharadin (solid dots), the coefficient of correlation between age and rate of change (per week) was –0.57 (95% CI = –0.85 to 0.03). For placebo, r = 0.01 (95% CI = –0.49 to 0.50).

Exploratory Analyses Patient characteristics recorded at baseline are listed in Table 1. It is plausible that some of these nine variables might be predictive of baseline lesion count, but such predictive value was not detected.

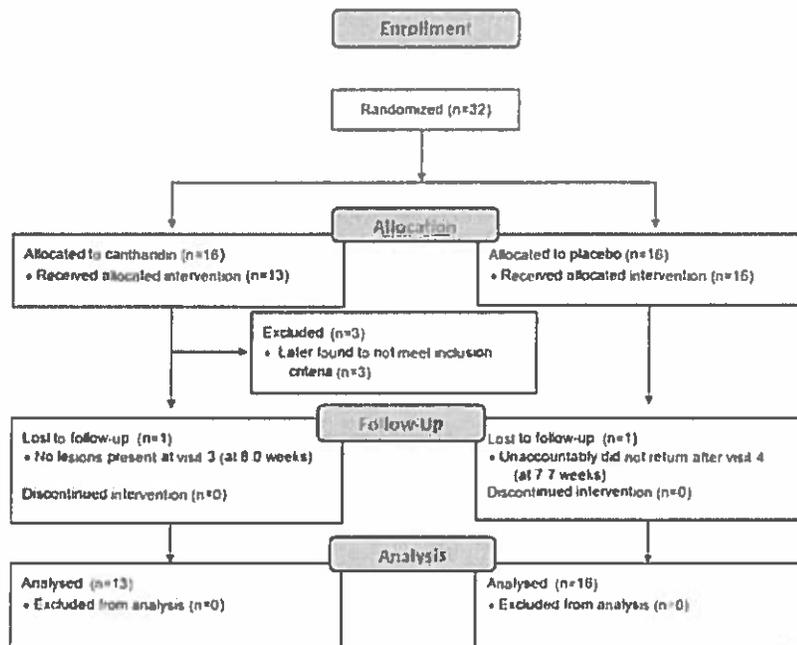


Figure 5. Flow diagram of participant progress throughout the trial.

It is also plausible that some of the nine variables might be predictive of the rate of clearance of lesions. In exploratory analyses, such predictive value was detected only for age. Figure 4 illustrates the apparent relationship between age and rate of change in the \log_{10} count per week. This result suggests that cantharidin may have efficacy that depends on the age of the child (efficacy increasing with age or with increasing age and duration, which are partially confounded together) (Fig. 1).

DISCUSSION

Previous literature has noted the commonplace use of cantharidin in pediatric dermatology practice (18). Parents (19) and practitioners (3) have reported satisfaction with results achieved with cantharidin. In a previous retrospective review of a similar patient population, the average time to molluscum clearance was 2.3 months using monthly follow-up visits (19). Our 2-month study aimed to quantify the difference between the efficacy of cantharidin and that of vehicle. To our knowledge, there have been no other vehicle-controlled randomized trials evaluating cantharidin's efficacy.

In this randomized, 2-month, placebo-controlled clinical trial, the performance of cantharidin was observed to be similar to that of placebo. In terms of the temporal rate of improvement in median lesion count, the estimated rate for cantharidin was 32% fewer lesions

per visit, whereas the estimated rate for placebo was 21% fewer lesions per visit. The primary hypothesis test of efficacy was inconclusive (not statistically significant.) This test procedure does not, and cannot, establish that cantharidin has zero efficacy. Although the hypothesis test was inconclusive, the point estimates and CIs provide information about the plausible range of the magnitude of efficacy. In terms of complete clearance of lesions by visit 5, the observed treatment success rate was 15% (2/13) for cantharidin patients and 6% (1/16) for placebo, yielding an observed difference of 9 percentage points (95% CI = -16 to 36 percentage points). The CI suggests that it is plausible that the true magnitude of difference is in the range of -16% to 36%. It also suggests that it is unlikely that the true difference is as large as anecdotal and retrospective reports have suggested.

Cathcart et al (19) noted that 54% (29/54) of cantharidin-treated patients reported subjective complete clearance when treated for approximately 2 months. Silverberg et al (3) reported that parents of 95% of cantharidin-treated patients stated that they would proceed with cantharidin treatment again. A possible explanation for the contrast between our study and these retrospective studies is the preciseness and strictness of our definition of clearance. Additionally, parents may look back favorably on their treatment with cantharidin even without complete resolution of all lesions. If this is the case, then there may be some recall bias and overestimation of clearance. There may also be some pressure

to please investigators in a telephone survey and potential for inflation of satisfaction.

In secondary analyses, we explored self-reported patient characteristics as potential risk factors for poor outcomes and as predictors of lesion count at baseline. The exploratory results suggested a new hypothesis: the biological effects and relative efficacy of cantharidin may depend on the age of the child, specifically, increasing efficacy with increasing age.

Self-reported patient characteristics of interest included previously inflamed lesions. Molluscum lesions that exhibit irritation or inflammation are classically thought to be nearing spontaneous resolution. It has been hypothesized that a "switch" occurs when the immune system starts to recognize an individual focus of molluscum virus, gathers inflammatory cells and mediators in the area, and soon thereafter clears the virus, with subsequent disappearance of the lesion. We did not detect any association between lesion clearance and prior history of irritated, inflamed, or previously resolved lesions.

For the immunologic reasons cited above, we did not choose to use a cross-over study design. The irritation and blister caused by cantharidin (and not with the vehicle) could theoretically attract inflammatory mediators and possibly speed the resolution of untreated or vehicle-treated lesions according to the hypothesis outlined above.

Blistering was self-reported and not observed by the physician, because it typically occurred at home after the patient encounter. As expected, 92% of cantharidin-treated subjects reported blistering. The substantial number of placebo-treated subjects that reported blistering (50%) was surprising, but the investigators did not confirm this blistering—it is our sense that patients may have interpreted the collodion membrane from the vehicle as a blister. There may be some recall bias in patients' self-reporting as well. Finally, the sometimes surprisingly strong placebo effect should not be discounted. None of the ingredients in the vehicle preparation are known to have blister-inducing properties.

No patients dropped out because of side effects. The most common side effects were local irritation and blistering with cantharidin. Six cantharidin and no vehicle patients reported pigmentary change. We suspect this is due to postinflammatory pigment alteration that is comparable with other destructive techniques, but subjects were not followed for longer than 8 weeks to assess duration of the pigmentary change.

Six percent of placebo-treated patients and 23% (3/13) of cantharidin-treated subjects reported pain; for example, one experienced pain when scrubbing off the medication. The 23% rate is much lower than would be seen with other destructive techniques, and the discom-

fort is delayed until after the patient leaves the office. This allows for nontraumatic treatment of molluscum and preservation of the relationship and trust between the dermatologist and child. Our results demonstrate that, when used correctly, cantharidin can be used with minimal side effects.

This study characterized longitudinal improvement in total lesion counts during 8 weeks of treatment. Anecdotal experience and previously published retrospective reviews indicated that roughly half of cantharidin-treated subjects would experience complete clearance of lesions. This study was not designed to address the longitudinal course of MC beyond the first 8 weeks of treatment, which could potentially capture a greater efficacy of cantharidin—further studies would be needed to investigate this theory.

The target sample size, 30, was chosen based on considerations of the availability of subjects, cost and time requirements, the anticipated precision of statistical estimators of interest, and reasonable conjectures about statistical power levels of a pair of hypothesis tests (interim and final) comparing rates of treatment success. The conjectures about statistical power were derived from rough estimates of efficacy based only on anecdotal experience, because there were no relevant data in the literature.

Enrollment of 30 subjects was surprisingly difficult. Families were reluctant to enroll their children in a study that had a 50% risk of being assigned to placebo when they could decline participation and receive verified cantharidin in the regular clinic.

An important aspect of our study design was the stratification of patients with atopic dermatitis. Future studies involving patients with MC should control for atopic status because other studies have demonstrated that they tend to have a longer, more-severe course.

It is possible that the two treatment groups were not balanced with respect to other important factors in spite of randomization. For example, we do not know how many subjects in each group were patients on the verge of spontaneous remission; consequently, it might be conjectured that there were more "spontaneous resolvers" in the placebo arm of the study, but clearance was infrequent in both arms; neither arm of the study experienced the higher rates of complete clearance that had been expected based on anecdotal experience and previous retrospective observational reports.

Subjects assigned to placebo had had their MC lesions for 8.5 months, on average, whereas the average duration for cantharidin-treated subjects was only 6 months. The longer the lesions are present, the better the chance for spontaneous remission, although clearance was infrequent even in the placebo arm. Furthermore, the primary efficacy results were invariant to

whether duration of MC was taken into account as a covariate.

The interim analysis demonstrated, as did the final analysis, that the "complete clearance" endpoint is a poor summary variable in this context, characterization of the longitudinal trajectory of lesion counts is more informative, and the counts follow distributions that are approximately log-normal. In contrast to the "complete clearance" endpoint, endpoints defined in terms of interval-scale measures of the decrease in lesion count offer more-powerful tests of efficacy hypotheses.

This study serves as a platform for future studies investigating tools for the treatment of MC. It has provided objective unbiased estimates of the magnitude of cantharidin treatment effects and of variance and correlation, contributed important prospective safety data, and generated a new hypothesis about age-dependent efficacy. If the relative efficacy of cantharidin is smaller than placebo, a larger sample size may be warranted in future studies.

The value of our study is that it can help future studies better assess the efficacy of cantharidin in MC. In addition, the clinician is informed that almost weekly application of cantharidin to molluscum lesions over a span of 8 weeks does not have statistically greater benefit than placebo. Our institution has patients willing to come on a weekly basis to clear the virus from their homes; we can confidently inform them that weekly visits are not necessary. Based on our anecdotal experience, we still believe that cantharidin is useful and safe in the treatment of childhood MC and are in favor of further studies with a larger sample size and longer duration.

The magnitude of the cantharidin treatment effect in the target population was, at best, not large during the 2 month study period; the temporal rate of clearance of lesions and the incidence of complete clearance of all lesions were not dramatically different from those achieved with placebo. In addition, cantharidin can be used with minimal side effects and is safe in children when used properly.

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Reference 10

INFECTIOUS DISEASE

Cantharidin treatment for recalcitrant facial flat warts: A preliminary study

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Abstract

Background: Topical cantharidin has been reported to be effective and safe in the treatment of cutaneous warts but it has not previously been used for the treatment of facial flat warts. **Objective:** To evaluate the efficacy and safety of topical cantharidin in the treatment of recalcitrant facial flat warts. **Methods:** A total of 15 consecutive patients with recalcitrant facial flat warts were enrolled in this study. Patients having warts near the eye region were excluded from the study. Cantharidin 0.7% solution was applied to treat a maximum of five lesions per session. Repeat therapy was performed at 3-week intervals. Assessment for response and the occurrence of side effects was performed after every session until clinical cure or up to a maximum of 16 weeks. **Results:** Of the study population, patients had 8.2 ± 4.37 lesions before the treatment. The average duration of lesions was 12.6 ± 6.75 months. All the patients were clinically cured within 16 weeks and the number of required sessions for complete clearance was 2.6 ± 1.18 . Cantharidin therapy was well tolerated, with mild adverse events related to skin. **Conclusion:** Cantharidin is safe and effective when applied to flat warts without occlusion for 4–6 hours every 3 weeks till clear.

Key words: Cantharidin, flat warts, topical therapy

Introduction

Warts are extremely common viral infections of the skin. The human papilloma virus (HPV) is responsible for warts and actually represents a large group of closely related viruses with over 100 types. HPVs can infect any site with stratified squamous epithelium and many of them roughly correspond to different clinical phenotypes (1). Flat warts on the face are a frustration for both patients and clinicians; they can affect a patient's quality of life by causing embarrassment, fear of negative appraisal by others and frustration from their persistence and recurrence. One study showed that nearly 70% of a healthy control group had detectable HPV on the forehead without any clinical evidence of warts at all (2). In the same study, almost half of these individuals had persistent infection after 6 years, providing insight as to why warts can be so difficult to eradicate. There is currently no cure for HPV infection (3). Therefore, current therapy

aims at eliminating signs and symptoms. No single treatment is fully effective in all patients.

Cantharidin, a vesicant produced by beetles in the order Coleoptera, has a long history in both folk and traditional medicine. In dermatology, topical cantharidin has long been used as a vesicant for the treatment of warts and molluscum since the 1950s (4). Because the blistering is so focused and within the epidermis, scarring is generally not seen from this treatment, even in more exuberant reactions (5). There is no pain from application of cantharidin, though blister formation can be painful (6). Cure rates have been reported to be as high as 80% for common, plantar and periungual warts (6). Based on this background, we reasoned that topical cantharidin could also be an effective and safe therapy for recalcitrant facial flat warts. Although topical cantharidin has been reported to be effective in the treatment of cutaneous warts, to our knowledge it has not previously been used for the treatment of facial flat warts.

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Patients and methods

A total of 15 consecutive patients with recalcitrant facial flat warts, seen in our dermatology department, were recruited over a 5-month period. Diagnosis was made on clinical appearance in most of the patients. Biopsies were made in a few problematic patients.

Exclusion criteria included pregnancy or lactation, immunosuppression, use of medication or having some procedures for warts within 1 month of enrollment, known sensitivity to any component of the study solution, dermatologic conditions such as infection at the site of application, eczema, and psoriasis. Patients having warts near the eye region, unrealistic expectations or fear regarding the potential of treatment and patients believed to be unable to tolerate and comply with treatment recommendations were excluded from the study. All patients or parents gave written informed consent before being included in the study.

A proprietary formulation containing cantharidin 0.7% solution in an adherent film-forming vehicle containing acetone was applied according to the standard approach in our division: sparing application with the blunt wooden end of a cotton-tipped applicator to each lesion, avoiding contact with surrounding normal-appearing skin, and with treatment of a maximum of five lesions per session. Patients were observed until the liquid film dried and lesions were not covered with occlusive tapes. Patients or parents were instructed to rinse the treated areas after 4–6 hours or sooner if burning or discomfort was felt, or if vesiculation was observed.

Patient or parent education handouts on procedure were provided and details on after treatment expectations and recurrences which might be seen were discussed at the time of initial treatment. Participants were warned that blister formation might be painful and should this occur they were instructed to take appropriate analgesics. The patient or parents were told to call the investigator about any unexpected consequences such as burning or discomfort in the eye, fever, diarrhea, or vomiting.

All participants were followed up by telephone and a further appointment after 24 and 48 hours and 1 week after each session. At the conclusion of each session, patients or parents were asked whether they would proceed again with cantharidin therapy if it was necessary. Repeat therapy was performed at 3-week intervals. Assessment for response and the occurrence of side effects was performed after every session until clinical cure or up to a maximum of 16 weeks.

Patients were assessed by the same dermatologist who had recorded patients' previous therapies and response ratings to them according to patients' or

parents' point of view, baseline severity of lesions before cantharidin application according to the number of lesions, previous treatments, number of required sessions for complete clearance, adverse effects due to cantharidin treatment, patient or parent satisfaction, and recurrence rate after 6 months.

Results

A total of 15 patients were enrolled in the study and all of them completed the course of treatment. Of the study population, three were male and 12 were female and the average age was 18.26 ± 9.37 . Six of them were pediatrics (one male and five females), with an average age of 8.83 ± 2.92 years; nine were adults (two males and seven females), with an average age of 24.5 ± 6.1 years. The demographic and clinical data of patients are summarized in Table I.

Before treatment, five patients had less than six lesions, four patients had 6–10 lesions and six patients had more than 11 with a maximum of 15 lesions. The average duration of lesions was 12.6 ± 6.75 months. All the patients had different previous treatments which are given in Table I. The response ratings to previous treatments were as follows: three (20%) = worse; three (20%) = none; seven (46.66%) = partial; two (13.33%) = complete; and three (20%) = scar formation. Two patients who had a complete response to previous treatments had recurred within 6 months. After the first session of cantharidin treatment none of the patients became worse; all lesions disappeared completely in four patients (26.6%); seven patients had partial response (46.66%); four patients had complete response (26.6%) limited to the area cantharidin was applied (they had more than 10 lesions, while we applied a maximum of five lesions per session). All the patients had clinical cure within 16 weeks and the number of required sessions for complete clearance was 2.6 ± 1.18 .

Eleven patients (73.3%) had adverse events; eight had post-inflammatory hyperpigmentation (53.33%), all of which resolved within 6 months; five had annular warts (33.33%), all of which were managed with an additional session; and one had scar formation (6.66%) secondary to bacterial infection. All of the annular warts recorded were the ones which were seen after the first session due to the application of cantharidin only to the wart by avoiding contact with surrounding normal-appearing skin. However, in the following sessions no further annular warts were observed by application of cantharidin to the warts, including a 1-mm rim of surrounding normal-appearing skin. According to overall sessions (data not showed), most patients (95%) experienced blistering and 25% reported erythema at treated sites, which lasted for up

Table I. Demographic and clinical data of patients.

Pt no.	Age	Sex	Skin type*	Duration and baseline severity of lesions (A = < 6 lesions; B = 6-10 lesions; C = > 10 lesions)	Previous treatments and response to them (rating according to patient) (W = worse; N = none; P = partial; C = complete; S = scar)	Clinical improvement after the first session (according to clinician) (P = partial; *P = not applied to all lesions and the ones applied cleared; C = complete)	Required sessions for complete clearance (for patients with clinical cure)	Adverse events	Patient / parent satisfaction (C = complete; P = partial; N = none)	Recurrence after 6 months
1	24	F	4	12 months, B	Cr2, T2, N	P	2	PIH	P	-
2	35	F	4	16 months, B	Cr3, T3, P	P	3	AW, PIH	P	-
3	33	F	4	24 months, A	Cr3, L, P	C	1	PIH	C	-
4	20	F	2	8 months, A	Cr1, T1, N	P	2	-	C	-
5	19	F	4	6 months, C	Cau, W, S	*P	4	AW, PIH	P	+
6	23	F	3	12 months, A	Cr2, T5, P	C	1	-	C	-
7	20	F	3	24 months, A	OR, C	C	1	-	C	+
8	19	M	4	8 months, C	OR, P	*P	4	PIH	P	-
9	28	M	3	6 months, C	Cr1, T4, W	P	3	AW	P	-
10	8	F	3	7 months, B	T3, N	P	3	AW	C	-
11	6	F	5	12 months, C	T1, W	*P	4	PIH	C	+
12	7	F	4	8 months, C	T5, P	*P	3	S, PIH	N	-
13	12	M	3	16 months, B	Cr3, T3, P, S	P	4	AW	C	-
14	13	F	4	24 months, A	Cr2, T5, C, S	C	1	PIH	C	+
15	7	F	2	6 months, C	T3, P	P	3	-	C	-

*Fitzpatrick skin type. AW = annular wart; Cau = cauterization; Cr = cryotherapy with sessions 1-3; L = pulsed dye laser therapy; OR = oral retinoid treatment; PIH = post-inflammatory hyperpigmentation; Pt = patients; S = scar; T = topical therapy with T1 = retinoic acid gel; T2 = salicylic acid; T3 = imiquimod; T4 = 5-fluorouracil; T5 = combined therapy with more than one topical agent.

to 2 weeks. Other reported symptoms included mild to moderate pain (20%) and a transient burning sensation (40%); both of which started within 12 hours and cleared within 24 hours after therapy. Recurrence after 6 months was recorded in four patients.

Patient/parent satisfaction due to cantharidin treatment was as follows: nine complete, five partial, one none. All the patients who had post-inflammatory hyperpigmentation had a Fitzpatrick skin type ≥ 4 . Seven patients who had a Fitzpatrick skin type ≤ 3 were completely satisfied and none of them had post-inflammatory hyperpigmentation. Complete satisfaction was seen in five out of six patients in the pediatric population, while it was four out of nine in the adult population. Of the parents interviewed, all of them stated they would proceed again with cantharidin therapy if necessary. They ascribed this decision to the lack of pain and emotional trauma during the procedure. Patients who stated partial satisfaction ascribed their dissatisfaction to the blistering and post-inflammatory hyperpigmentation, though most of them stated they would proceed again with cantharidin therapy if necessary because the treatment was relatively painless.

Discussion

Warts are estimated to occur in up to 10% of young children and young adults (7). The range of greatest incidence is between 12 and 16 years of age. Warts occur with greater frequency in females than in males. Warts typically continue to increase in size and distribution, and are socially unacceptable when located on visible areas (7). No single therapy has been proven effective at achieving complete remission in every patient (8). Different types of warts may need different site-dependant treatments and treatments may need to be combined (8). Recalcitrant warts that have been present for over 6 months are more resistant to treatment than warts present for less than 6 months (6). The ultimate wart treatment would resolve all or a great percentage of warts, be painless, lead to resolution of distant untreated warts, respond with one or a few treatments, create no scarring, offer HPV immunity for a lifetime, and be available to all patients (9). An armamentarium of wart treatments exists, including over-the-counter treatments and therapies provided by primary care and dermatology offices (6). In 1995, the American Academy of Dermatology developed criteria for the indications for wart treatment (9) including: the patient's desire for therapy, symptoms of pain, bleeding, itching or burning, disabling or disfiguring lesions, large numbers or large sizes of lesions, the patient's desire to prevent the spread of warts to unblemished skin of self or others, and an

immunocompromised condition. For common warts, if receiving no treatment is acceptable to the patient, this is a viable option. However, warts are less likely to resolve spontaneously and are more resistant to treatment in adults and in those with persistent warts (6).

Treatment options for flat warts include salicylic acid, imiquimod, cryotherapy, retinoids, intralesional immunotherapy and pulsed dye laser (7). Salicylic acid is one of the first-line therapies for flat warts, though it requires time to achieve a response, and causes occasional contact dermatitis and systemic toxicity in children if large areas of treatment are used (6,7). Imiquimod is an additional first-line therapy for flat warts but it requires time to achieve a response. In an open label uncontrolled study using imiquimod cream to treat common warts, an adverse local inflammatory reaction was reported in 31% patients. Other side effects were erosions, pruritus, bacterial infection, fever and scarring (10). Second-line therapy for flat warts includes cryotherapy, but this is a painful procedure that can produce hyperpigmentation and scarring (7). The pain and emotional trauma associated with cryotherapy make it undesirable for use, especially in the pediatric population. Another second-line therapy is retinoids, which cause local irritation with topical administration. Topical retinoids are rated by the Food and Drug Administration (FDA) as pregnancy category C. Oral administration of retinoids causes systemic side effects (6,7). Intralesional immunotherapy and pulsed dye laser therapy are third-line therapies. Influenza-like illness is a disadvantage of intralesional immunotherapy. Intraoperative pain, scarring, and dyspigmentation limit the utility of CO₂ laser therapy (6,7). Pulsed dye laser therapy produces less pain and scarring than with CO₂ laser treatment, though there are reports that some patients have severe intraoperative pain (11,12).

Cantharidin is a potent vesicant produced by blister beetles belonging to the order Coleoptera and the family Meloidae. There are currently more than 1500 species of cantharidin-producing beetles, commonly known as blister beetles or Spanish fly (4). In dermatology, cantharidin has long been used to remove benign epithelial growths, such as warts or molluscum contagiosum. The application is painless, though mild to moderate pain, temporary erythema, burning and pruritus may occur subsequently. The active ingredient is a blister beetle-derived protein phosphatase inhibitor (13). Application of cantharidin to the epidermis results in the application or release of neutral serine proteases that cause degeneration of the desmosomal plaque, leading to detachment of tonofilaments from desmosomes. This process leads to acantholysis and intraepidermal blistering, and non-specific lysis of skin. Lesions heal without scarring, as acantholysis is intraepidermal (4).

In experienced hands, cantharidin preparations have been reported to be safe and effective (4,5,14). The largest study of cantharidin use is reported in 300 children for the treatment of molluscum (5). In this report, no major side effects such as scarring, infection or toxicity were seen. Cantharidin poisoning usually results after ingestion (4). A fatal dose of cantharidin is estimated to range from 10 mg to 65 mg (15), with the median lethal dose being approximately 1 mg/kg (4). One report describes a 4-year-old boy who suffered toxic shock syndrome caused by *Staphylococcus aureus* following application of cantharidin to about 20 molluscum contagiosum lesions on his chest. A key feature, likely to have precipitated this reaction, was the application of occlusive surgical tape over the lesions, permitting more extensive damage to the skin than expected (16). In this report, authors suggested limited areas should be treated at one time, and application of paper tape over the treated areas should be left on for a few hours. Another report describes a case in which topical cantharidin was applied to an area of abdominal skin (approximately 18 × 8 cm) as a treatment for pleurisy. Dysuria and hematuria occurred, but the patient recovered fully within 1 week (4). To the best of our knowledge, there have been no more reports of cantharidin intoxication. Moreover, there have been no reports caused by the reasonable application of cantharidin solution by a physician.

Our patients found facial flat warts distressing and demanded treatment. Although spontaneous regression of warts had been considered, the patients in our series had tried multiple treatments without success with an average duration of lesions of 12.6 ± 6.75 months. Considering the ethical problems, we only used cantharidin in treating resistant and multiple facial warts as a last resort after the failure of other treatments. This definite selection decreased our patient population and was a study limitation. In our study population, treatment with topical cantharidin resulted in complete clearing of the lesions in all patients in 2.6 ± 1.18 sessions. The small number of lesions seen in our patients may be a factor in complete clearance. Application of cantharidin to only a small number of lesions seems to be very effective, even to the recalcitrant warts which are known to be more resistant to treatment (6). As it is painless at the time of application, children and even adults were at once relieved. Scarring is not common following the induction of cantharidin blisters, though one of our patients had one mild scarring after her last session due to secondary bacterial infection. One of our main observations was that patients who had lighter skin (Fitzpatrick skin type ≤ 3) had no post-inflammatory hyperpigmentation after cantharidin treatment.

On the other hand, all of the patients who had darker skin (Fitzpatrick skin type ≥ 4) did have post-inflammatory hyperpigmentation after cantharidin treatment.

At the beginning of our study, our first technique was regarding application of cantharidin only to the lesions by avoiding contact with surrounding normal-appearing skin. That was because the largest study of cantharidin use had a similar technique to treating molluscum, which became a standard approach in our division (5). However, the annular warts which were observed after the first session were more than we expected. Therefore, we changed our technique to application of cantharidin to the lesion and a 1-mm rim of surrounding normal-appearing skin. In the following sessions no further annular warts were observed. The reported phenomenon of peripheral wart spread around the margins of the traumatized wart represents either a seeding by HPV viruses or a failure to treat subclinical marginal infected tissues (6), and it seems that applying cantharidin to the wart and a 1-mm rim of surrounding normal-appearing skin prevents the occurrence of annular warts.

For children, it is desirous to have an effective and painless treatment that shows rapid results. Our pediatric patient population tolerated the therapy very well. However, we paid more attention than a typical patient would receive in a typical clinical setting by having multiple contacts just because it was an important part of our methodology. Parent satisfaction was superior to that of adult patients because of the lack of emotional trauma during the application. Besides, it was discovered that the lack of pain at the time of application was not only preferred by the pediatric population but also by the adults, though some experienced pain commonly after 12 hours.

Conclusion

Cantharidin is a safe and effective therapy for facial flat warts in children and adults if used to treat limited areas at a time without occlusion and by avoiding contact near the eyes and eyelids to prevent scleral erosion.

Acknowledgement

All the patients/parents completed the study, complied with treatment recommendations and gave informed consent. The authors wish to thank them.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Reference 11

Cantharidin Treatment of Digital and Periungual Warts

JOHN H. EPSTEIN, M.D., and WILLIAM L. EPSTEIN, M.D., San Francisco

CANTHARIDIN, a potent blistering agent extracted from blister beetles, has been advocated for the local therapy of warts.¹ This study was designed to evaluate use of this form of therapy in a dermatologic practice. Preliminary data having suggested cantharidin would be most successful in the treatment of warts on the digits and those under or around the nails, the investigation was concentrated on such lesions.

Forty patients with 76 digital, periungual subungual warts were treated as previously suggested¹ by applying a small amount of 0.7 per cent cantharidin solution in equal parts acetone and flexible collodion* to the surface of the wart. When the solvent evaporated, the area was occluded with a small piece of plastic band-aid tape cut to just cover the wart. Finally, a loose protective bandage was put over the whole area. The patients were seen at weekly intervals and the lesions were debrided and re-treated if necessary. After the last treatment they were asked to return in a month. Further follow-up depended upon the patient. Each was instructed that recurrences may occur with any method of treatment and that what they had received was just another kind of therapy for warts.

Aside from effectiveness, the main points of evaluation were the ease of application and acceptance by the patient.

RESULTS

Complete disappearance of visible warts for three to four weeks is deemed a satisfactory clinical response. The results in this study were:

Type of Wart	No. of Warts	No. Clinically Cleared for 3 to 4 Weeks
Digital	61	57
Periungual and subungual	15	12

A single treatment cleared 32 of the 61 digital warts and 4 of the 12 periungual and subungual warts. The others generally required one or two additional treatments. In a few cases, prolonged therapy seemed indicated. Usually in these cases the warts were periungual, and they slowly but steadily

disappeared. In one instance, nine treatments with cantharidin caused a long term cure.

A "long term cure" was defined as clinical clearing lasting 4 to 6 months. In this category the results were:

The incidence of recurrence appeared somewhat lower than that following most conventional means of therapy, except possibly curettage and desiccation.

Finally, 17 patients who obtained a long term cure were specifically questioned 12 to 18 months later. In this group, there was recurrence of only one of 29 digital warts and no recurrence of nine periungual warts.

disappeared. In one instance, nine treatments with cantharidin caused a long term cure.

A "long term cure" was defined as clinical clearing lasting 4 to 6 months. In this category the results were:

Type of Wart	No. of Warts	No. with Long Term Cure
Digital	45	32
Periungual and subungual	12	9

The incidence of recurrence appeared somewhat lower than that following most conventional means of therapy, except possibly curettage and desiccation.

Finally, 17 patients who obtained a long term cure were specifically questioned 12 to 18 months later. In this group, there was recurrence of only one of 29 digital warts and no recurrence of nine periungual warts.

DISCUSSION

Cantharidin proved a successful treatment for the types of warts selected. We also obtained good results in plantar warts (9 of 17 clearing) but the procedure was so frequently associated with a dis-

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Submitted February 9, 1960.

*Cantharone®, Ingram Pharmaceutical Co., San Francisco.

trussing pain deep in the foot that we stopped using it. Nine plain warts situated on the arms and trunk were not affected by cantharidin treatment; and because of previous advice¹ no mosaic or acuminate warts were treated.

Certain advantages of cantharidin can be cited. It is easily and rapidly applied. No pretreatment is required. The solution effectively spreads under nails and into crevices of the nail fold and proper bandaging on the digits is facilitated. Treatment is well received by the patient. As it is painless at the time of application, children and squeamish adults are at once relieved and rapport is established. Scarring is not a sequela to cantharidin blisters, which are caused by rupture of the intercellular bridges between epidermal cells.³

The main disadvantage is pain and tenderness in the treated area coming on after about 24 hours and lasting usually two to four days. This discomfort occurs with all forms of destructive therapy. Although the pain does not occur immediately, it may last longer than after liquid nitrogen application or electrodesiccation. About half of the patients noted some distress. Six felt it was severe, but it was relieved by opening the blister and compressing the area. We learned how to avoid this complication. In the first place, some patients are very sensitive to the action of cantharidin. Within a few hours of application they feel a tingling or burning at the treated site. Normally a large blister will form which can be very annoying, but if the outer protective bandage is removed shortly after symptoms begin, the blister is much smaller, and the pain less. The other cause of painful lesions is use of too much cantharidin. Large amounts of this potent blistering agent are not needed for large succulent warts. A thin film spread over the wart and properly occluded to aid penetration will suffice.

The necessity of retaining the original bandage in place for a few days may present a problem. Patients whose hands are frequently in water find it a hardship. Treating one hand at a time may help.

Another untoward reaction is the recurrence of wart in the bulla margin, forming a doughnut-shaped tumor,^{1,2} which may be quite alarming in appearance. This occurred in two cases, involving two of three treated sites, in the present series. We have adopted curettage and desiccation as routine for the treatment of this unique complication, although it may be controlled by further use of cantharidin.

"Cures" for warts are legion. Psychotherapy works in some cases, and may add to the effectiveness of all therapies. But it is also true that destructive treatment is the most rapid and successful. Liquid nitrogen and curettage and desiccation have become standard methods. Cantharidin is less painful than either of these. It is at least as effective as liquid nitrogen and, generally, is more available. Furthermore, there is no danger of scarring. Perhaps curettage and desiccation is more effective, but it is poorly received by many patients, and it is unselectively destructive. The lytic action of cantharidin does not go beyond the epidermal cells, the site of the wart virus infection. If cantharidin treatment fails, it has done nothing that would prevent the use of other means of therapy.

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Tab 85

FDA Review of Cantharidin



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: February 4, 2015

FROM: Patricia Brown
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Doanh Tran
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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Cantharidin for Inclusion on the 503A Bulk Drug Substances
List

I. Introduction

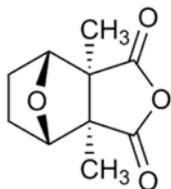
Cantharidin has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Indications identified in the nominations include the treatment of molluscum contagiosum and warts. FDA reviewed this substance in 1998. Cantharidin was included on a proposed list of bulk drug substances published in January 1999. The background materials from the prior review are attached. This substance is now being reevaluated.

We have reviewed the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. Based on those factors, for the reasons

discussed below, we recommend that cantharidin be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?



1. *Stability of the API and likely dosage forms*

Cantharidin is stable in the solid state under ambient conditions and in solution at neutral pH.

2. *Probable routes of API synthesis*

Although it has been prepared by Diels-Alder-based synthetic routes (Dauben et al., 1980, Grieco et al., 1990), it seems probable that commercially available API is obtained from dried insects by solvent extraction and purification.

3. *Likely impurities*

The likely impurities are residual solvent, other extractable organic compounds from the insects, and possibly pesticide residue.

The comment to the docket from Hyman, Phelps & McNamara, P.C. Docket of September 30, 2014, stated that “Visual and melt point analysis are not comprehensive enough for the chemical characterization.”

FDA response: Crystallization of cantharidin to a constant melting point can give highly pure material. Its high melting point of 212° C is expected to be significantly depressed by impurities. Because it is a white crystalline material, visual inspection may detect colored impurities. Furthermore, its small size containing only 10 carbons and its high melting point suggest that it should be easy to purify, and analytical procedures for its assay (Ray et al., 1979) and adulterants (Bogusz et al., 2006) have been published.

Consequently, if the product comes from solid cantharidin, it should be quite pure. However, if it is a crude or partially purified extract, its purity could be highly variable, and the impurities are likely to be insect extracts, solvents, or residual pesticide.

4. *Toxicity of those likely impurities*

The impurities cannot be specifically defined, so their toxicity is unknown. However, the toxicity of organic impurities from the insects is likely not significant in comparison to the toxicity of cantharidin.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

Diluted solutions of cantharidin are used as a topical medication to remove warts. Cantharidin is soluble in organic solvents such as ethanol and DMSO. Because it is used as a solution, the particle size and polymorphism are irrelevant.

6. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

Cantharidin, a well-known, well characterized, small molecular weight API is a high-melting crystalline solid.

Conclusions: From a chemistry viewpoint, cantharidin seems acceptable for inclusion on the 503A list, because it is a relatively simple, well-characterized API, likely to be stable in the solution formulations into which it is likely to be compounded, and unlikely to contain significant amounts of toxic impurities.

B. Are there concerns about the safety of the substance for use in compounding?

1. *Nonclinical Assessment*

a. Pharmacology of the drug substance

Cantharidin is a vesicant produced by many species of blister beetle. It is absorbed by the lipid membranes of epidermal cells, resulting in the activation or release of serine proteases. This causes the disintegration of desmosomal plaques and detachment of tonofilaments. This process leads to acantholysis and intra-epidermal blistering. Since the lesions are intradermal, they heal without scarring.

b. Safety pharmacology

A single-dose IV injection of cantharidin ranging from 0.6 to 1.9 mg/kg to conscious albino rabbits induced fatal cardiac arrhythmias and myocardial damage. High doses were usually fatal within 3 hrs. The most common arrhythmias associated with the high doses of cantharidin were frequent ventricular ectopic beats, ventricular tachycardia, ventricular fibrillation, or asystole.

c. Acute toxicity

Cantharidin is extremely toxic whether exposed via skin or eye contact, ingestion, or inhalation. The LD₅₀ is 1 mg/kg (IP) in mouse. Horses are highly sensitive to cantharidin; the minimum lethal oral dose in horses appears to be lower than 1 mg/kg. When taken orally in toxic doses, it produces severe irritation of the gastrointestinal tract and urinary tract, inducing albuminuria, nephritis, myocardial dysfunction, and shock. It also has a stimulant action and causes quickened respiration and excitement, followed by coma and collapse. Rats treated with 10 mg cantharidin via IP injection showed extensive damage to epithelium of all organs noted. Exams of hepatocytes at 5-15 min after injection revealed injury to cell membrane, endoplasmic reticulum, and mitochondria.

d. Repeat dose toxicity

No information available.

e. Mutagenicity

No information available.

f. Developmental and reproductive toxicity

No information available.

g. Carcinogenicity

In several dermal mouse carcinogenicity studies, cantharidin produced an increased incidence of skin papillomas and a low incidence of skin carcinomas. The WHO International Agency for Research on Cancer classification of carcinogenicity for cantharidin is Group 3: not classifiable as to its carcinogenicity to humans, based on (1) evidence in humans: no adequate data and (2) evidence in animals: limited evidence.

h. Toxicokinetics

No information available.

Conclusions: Cantharidin is extremely toxic and induces severe acute toxicity in animals with very low LD₅₀ values. Due to its mechanism of action its toxicity involves many organs, including skin, eye, GI tract, urinary tract, respiratory tract, heart, kidney, and liver. It is listed as a Category 4 in the Hazardous Material Identification System (life-threatening, major or permanent damage may result from single or repeated overexposures). Cantharidin's toxicity profile weighs against its inclusion on the 503A list. However, please refer to the human safety discussion (Section II B 2) and final recommendations (Section III).

2. *Human Safety*

a. Adverse reactions the substance has caused

Application site:

After treatment of warts: Mild to moderate pain, pruritus, transient burning sensation, and/or transient erythema, annular warts (Epstein & Kligman 1958)

Systemic:

After treatment of warts on lower leg and foot: Allergic reactions, consisting of inflammation, tenderness, edema, and ulceration with secondary lymphatic responses such as lymphangitis and lymphedema (Stazzone et al. 1998)

After treatment of molluscum contagiosum* on chest of 4-year-old boy: Toxic shock syndrome caused by *Staphylococcus aureus* within 24 hours of treatment (Langley et al. 2003)

(Molluscum contagiosum is a poxvirus that causes a chronic localized infection, consisting of flesh-colored, dome-shaped papules on the skin of an affected individual. Molluscum contagiosum is a common disease of childhood.)

After ingestion (e.g. “Spanish Fly”): Neurological effects—generalized seizures, ataxia, and increased deep tendon reflexes

Cardiovascular effects: Sinus tachycardia (the most common cardiac effect in poisoning), hypotension (with ingestion of large amounts of cantharidin), pericardial and subendocardial hemorrhages (seen at autopsy), dose-related myofibril degeneration and mitochondrial swelling (observed in controlled studies). ECG abnormalities: ST segment elevation in inferior limb leads and anterior precordial leads, as well as transient T wave inversions. Ventricular ectopy, asystole, ventricular tachycardia and fibrillation have been noted.

Pulmonary effects: Rare, usually transient lung injury with poisonings. There have been reports of gross pulmonary edema, bronchial hemorrhage, and subpleural hemorrhages in fatal cantharidin poisoning cases.

Renal effects: Potentially life-threatening effects of cantharidin poisoning secondary to excretion by glomerular filtration. Symptoms include lumbar pain, polyuria, dysuria, urinary frequency, and hematuria, which may persist for up to 15 days. Death may result from acute tubular necrosis.

Lower genitourinary: Hemorrhagic bullae have been found in the bladder. Priapism in men and pelvic vascular engorgement in women have been reported.

Gastrointestinal effects (vesicant effects): Inducing of burning and blistering of the mouth, tongue, oropharynx, dysphagia, abdominal cramping, vomiting, and hematemesis.

If cantharidin passes into the lower GI tract, it can induce diarrhea, hematochezia, tenesmus, and potentially fatal GI hemorrhage. Fatty changes and parenchymatous degeneration of the liver may be seen in severe cases (Karras et al.1996).

Ingestion of whole beetles: Children, 5 years old and 2 ½ years old suffered hematuria, blood in vomit, abdominal pain; survived with supportive treatment (Mallari et al.1996). Four-year-old presented with lower abdominal pain, hematuria, proteinuria, and oliguria; survived with supportive treatment. Seven-year-old died, presumed to have ingested larger quantities of beetles (Tagwireyi et al., 2000).

b. Clinical trials assessing safety

Molluscum contagiosum:

Randomized and/or blinded trials reported for treatment of molluscum contagiosum using cantharidin include the following:

Dosal et al., (2014) describe a prospective, double-blinded, placebo-controlled trial for the treatment of molluscum contagiosum in children. A total of 29 children ages 5-10 were enrolled to receive treatment with cantharidin or placebo. Five visits occurred over a 2-month period. No patients dropped out because of side effects. The most common side effects with cantharidin were local irritation and blistering. Six subjects treated with cantharidin and no subjects treated with vehicle reported pigmentary change. Subjects were not followed for longer than 8 weeks to assess duration of the pigmentary change. A total of 6% of vehicle treated subjects and 23% (3/13) of cantharidin treated subjects reported pain. The authors state that the 23% rate is much lower than would be seen with other destructive techniques.

Hanna et al., (2006) report a prospective, randomized trial comparing the efficacy and adverse events of four recognized treatments of Molluscum contagiosum in children. A total of 124 children ages 1 to 18 years were randomized to four treatment groups; curettage, cantharidin, salicylic acid and lactic acid, and imiquimod. The rate of side effects for the groups, respectively, was; 4.7%, 18.6%, 53.5%, and 23.3%. Details regarding the side effects are not provided.

Other trials reported for treatment of molluscum contagiosum with cantharidin consist of retrospective chart reviews, outlined in the following table:

Table 1: Treatment of Molluscum Contagiosum with Cantharidin: Retrospective Chart Reviews

Reference	Year	Treatment	N	Design	Protocol	Adverse Events
Moye et al.	2014	cantharidin 0.7%	405	RC	4-hour application	Pain, blistering, and rare (pruritus, possible mild infection, significant irritation, id* reactions, bleeding)
Cathcart et al.	2009	cantharidin 0.7%	54	RC	Non-facial lesions for 2 to 4 hrs	Pain, pruritus, secondary infection, brisk immune response, temporary hypopigmentation
Silverberg et al.	2000	cantharidin 52.5mg/7.5mL colloid	300	RC	Non-facial lesions 4-6 hrs; repeat treatment	Blister, burning, pain, erythema, pruritus

RC = Retrospective chart review

* An id reaction or autoeczematization, is a generalized acute cutaneous reaction to a variety of stimuli, including infectious and inflammatory skin conditions.

Warts: There are no reports of randomized and/or blinded trials assessing treatment of warts using cantharidin. Trials reported in the literature are open label and are outlined in the following table.

Table 2: Treatment of Warts with Cantharidin: Open Label Trials

Reference	Year	Treatment	N	Design	Protocol	Adverse Events
Durmazlar et al.	2009	cantharidin 0.7% solution	15	OL	Recalcitrant facial warts: wash off 4-6 hrs, repeat every 3 weeks	Temporary post inflammatory hyperpigmentation, ring warts, scar secondary to bacterial infection, blistering, erythema
Rosenberg	1977	cantharidin 0.7%	100	OL	Verruca vulgaris: Applied daily until clinical improvement	Annular wart, well tolerated
Bock	1965	cantharidin 0.7% solution	27	OL	Palpebral warts: applied every 8-10 days for 2-3 treatments	Blistering, pain, pruritus
Epstein et al	1960	cantharidin 0.7% solution	40	OL	Digital & periungual warts: once weekly with occlusive dressing for up to 3 treatments	Pain, tenderness, blistering, annular warts
Epstein et al	1958	cantharidin 0.7% solution	61	OL	Common, plantar, periungual and subungual, mosaic and flat warts: up to 3 applications	Mild to moderate pain, pruritus, transient burning sensation, and/or transient erythema, annular warts

OL = open label

c. Pharmacokinetic data

No human pharmacokinetic information for cantharidin is reported in the literature.

- d. The availability of alternative approved therapies that may be as safe or safer

Molluscum contagiosum:

There are no approved prescription therapies for molluscum contagiosum. Over-the-counter preparations are also not available. Other treatment modalities include curettage, manual expression, liquid nitrogen, tape stripping, and laser.

Warts:

There are no approved prescription therapies for warts outside of the genital area. A variety of over-the-counter preparations are available containing salicylic acid at percentages varying from 17% to 40%.

Conclusions: It is noted that cantharidin is extremely toxic and induces severe acute toxicity in animals with very low LD₅₀ values. Because of its mechanism of action, its toxicity involves many organs, including skin, eye, GI tract, urinary tract, respiratory tract, heart, kidney, and liver.

However, clinical data accumulated since 1958 indicate that cantharidin, applied as a solution under a physician's direction and following a tested protocol, may be used on patients, including children, without causing extreme toxicity. Adverse events reported are not greater than those seen with many other destructive treatment modalities. Data on long-term safety of use and on safety of use in pregnant or lactating women are not available.

C. Are there concerns about whether a substance is effective for a particular use?

1. *Reports of trials demonstrating effectiveness of the bulk drug substance as it is used in drug products*

Molluscum contagiosum:

Dosal et al., (2014) describe a prospective, double-blinded, placebo-controlled trial for the treatment of molluscum contagiosum in children. A total of 29 children ages 5-10 were enrolled to receive treatment with cantharidin or placebo. Five visits occurred over a 2-month period. The main outcome measure was complete clearance of all molluscum lesions. The performance of cantharidin treatment over 2 months was not substantially better than placebo. The authors state that this finding was in contrast to previous retrospective studies and speculate that a longer followup period might have captured a greater effect of cantharidin.

Hanna et al., (2006) report a prospective randomized trial comparing the efficacy and adverse events of four recognized treatments of molluscum contagiosum in children. A total of 124 children ages 1 to 18 were randomized to four treatment groups; curettage, cantharidin, salicylic acid and lactic acid, and imiquimod. Efficacy was reported in terms of the number of visits to the treating dermatologist required to eliminate the mollusca. Patients needing, respectively, one, two, or three visits for treatment of their mollusca were (curettage) 80.6%, 16.1%, and 3.2%; (cantharidin) 36.7%, 43.3%, and 20.0%;

(salicylic acid and glycolic acid) 53.6%, 46.4%, and 0%; (imiquimod) 55.2%, 41.4%, and 3.4%. The authors state that based on the results of their trial, cantharidin appeared useful, although more visits were required, more than half of patients and parents were satisfied with this type of therapy. The satisfaction was higher for cantharidin than the other treatments except for curettage. Side effects (see earlier) were lower for cantharidin than for the other treatments except for curettage.

Warts

A Cochrane review (Kwok C S et al., 2012) did not identify any randomized, controlled trials that evaluated cantharidin in the treatment of cutaneous warts.

2. *Any clinical evidence of effectiveness, or lack of effectiveness, of drug products with the bulk drug substance*

Table 3: Moluscum Contagiosum: Evidence of Efficacy

Reference	Year	Treatment	N	Design	Protocol	Results
Cathcart et al.	2009	cantharidin 0.7%	54	RC	Non-facial lesions for 2 to 4 hrs	96% of patients reported some improvement
Silverberg et al.	2000	cantharidin 52.5mg/7.5mL colloid	300	RC	Non-facial lesions 4-6 hrs; repeat treatment	90% of patients cleared and 8% improved – average number of treatment visits 2.1

RC = retrospective chart review

Table 4: Warts: Evidence of Efficacy

Reference	Year	Treatment	N	Design	Protocol	Results
Durmazlar et al.	2009	cantharidin 0.7% solution	15	OL	Recalcitrant facial warts:wash off 4-6 hrs, repeat every 3 weeks	Clinical cure within 16 weeks for all patients, number of required sessions for complete clearance 2.6 ± 1.18
Rosenberg	1977	cantharidin 0.7%	100	OL	Verruca vulgaris: Applied daily until clinical improvement	Resolution of 112 of 178 (63%) subungual or paronychial warts, and 103 of 158 (65%) common warts on hands and fingers
Bock	1965	cantharidin 0.7% solution	27	OL	Palpebral warts: applied every 8-10 days for 2-3 treatments	13 of 27 cases (48%) cured with 1 application, 9 (33%) needed repeated applications, 5 (19%) did not respond
Epstein et al.	1960	cantharidin 0.7% solution	40	OL	Digital & periungual warts: once weekly with occlusive dressing for up to 3 treatments	Efficacy measure = complete clearance of visible warts for 3 to 4 weeks All warts cleared for 3 to 4 weeks; 61 digital, 15 periungual and subungual
Epstein et al	1958	cantharidin 0.7% solution	61	OL	Common, plantar, periungual and subungual, mosaic and flat warts: up to 3 applications	Tentative cure defined as clearing lasting for at least 3 to 6 weeks All types of warts 99 (88%) showed tentative cure and 14 (12%) non responsive

OL = open label

In the book, *Comprehensive Dermatologic Drug Therapy*, Sheth and Landis (2013) report cure rates as high as 80% for common, plantar, and periungual warts.

3. *Any anecdotal reports of effectiveness, or lack of effectiveness, of drug products with the bulk drug substance*

Anecdotal reports of effectiveness for cantharidin have been reported for acquired perforating dermatosis, post herpetic neuralgia, and in cancer chemotherapy (Torbeck et al., 2014, Kadioglu et al., 2014).

4. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

Cantharidin has been used principally to treat molluscum contagiosum and warts.

5. *Whether there are any alternative approved therapies that may be as effective or more effective*

Molluscum contagiosum:

There are no approved prescription therapies for molluscum contagiosum. Over-the-counter preparations are also not available. Other destructive treatment modalities include curettage, manual expression, liquid nitrogen, tape stripping, and laser. Other topical treatments include retinoid creams, imiquimod cream, salicylic acid, trichloroacetic acid, cidofovir (1%, 3%), and silver nitrate.

Warts:

There are no approved prescription therapies for warts outside of the genital area. A variety of over-the-counter preparations are available containing salicylic acid at percentages varying from 17% to 40%. Other treatment modalities include liquid nitrogen, salicylic acid, duct tape, intralesional bleomycin, topical 5-fluorouracil, laser therapy, and curettage.

Conclusions: A double-blinded, placebo-controlled trial, having a main outcome measure as complete clearance of all molluscum lesions, found the performance of cantharidin treatment over 2 months was not substantially better than placebo. However, the authors speculated that perhaps the performance of cantharidin was understated because of the relatively short follow-up period. A second, prospective, randomized trial found evidence of some efficacy (treating molluscum contagiosum) for cantharidin coupled with high patient/parent satisfaction. A number of other studies (retrospective chart review for molluscum treatment (2) and open label (5) for wart treatment) found varying degrees of efficacy.

D. Has the substance been used historically in compounding?

1. *Length of time the substance has been used in pharmacy compounding*

Cantharidin in a collodion vehicle has been used by dermatologists since the 1950s.

2. *The medical condition(s) it has been used to treat;*

Cantharidin has been used principally to treat molluscum contagiosum and warts.

3. *How widespread its use has been*

Coloe and Morrell (2009) performed a study to determine the breadth of use of cantharidin among pediatric dermatologists (Society of Pediatric Dermatology). They found that cantharidin is a common modality in treatment of molluscum contagiosum among pediatric dermatologists. Among surveys returned (95/300), 92% of respondents reported satisfaction with cantharidin's efficacy (but 79% reported side effects, with discomfort/pain and blistering the most common).

In a review of childhood molluscum contagiosum, Brown et al., (2006) state that "Skillfully employed, cantharidin may be a treatment of choice in young children." Also, regarding molluscum contagiosum, in a well-known dermatology textbook, *Fitzpatrick's Dermatology in General Medicine*, it is stated that patients generally find cantharidin treatment the most efficient and least painful.

Regarding warts, cantharidin is included in a list of topical therapies for warts in the textbook, *Fitzpatrick's Dermatology in General Medicine*.

From the literature it is difficult to say how many patients have been using cantharidin on a yearly basis.

In a review of treatment of HIV-related skin disease (Osborne et al., 2003), cantharidin is mentioned as an option, among multiple others, for treatment of molluscum contagiosum.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

Cantharidin is marketed in Turkey, Canada, and China.

Conclusions: Cantharidin has been considered a viable option for the treatment of warts and molluscum since the 1950s. Use appears to be widespread, particularly for molluscum contagiosum. Cantharidin is marketed in Turkey, Canada, and China.

RECOMMENDATION

We have reviewed the physiochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. Cantharidin is well characterized chemically and has been used in compounding since the 1950s. Regarding safety, cantharidin is extremely toxic and induces severe acute toxicity in animals with very low LD₅₀ values. Cases of severe toxicity in humans and even death have been reported after oral ingestion.

However, abundant clinical information indicates that, with careful use under physician direction, toxicities are seen that are no worse than and sometimes less severe than those seen with other destructive modalities in the treatment of molluscum contagiosum and warts. Cantharidin is considered by some to be a treatment of choice for molluscum contagiosum in young children. For warts it is a useful alternative to methods such as liquid nitrogen, salicylic acid, laser therapy, and imiquimod. Standard of care is in-office application by a licensed health care professional.

Therefore, we recommend that cantharidin be included on the bulks drug list for topical use.

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A. INGREDIENT NAME:

CANTHARIDIN

B. Chemical Name:

2,3 Dimethyl-7-Oxabicyclo [2.2.1.1 Heptane-2,3 Dicarboxylic Anhydride

C. Common Name:

Canthacur, Cantharone, Verr-Canth. Canthacur-PS; Cantharone Plus, Verrusol

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Result: The IR Spectrum exhibits the at $\text{WN} > 1800$, which is typical of Anhydrides and it conforms with the data reported in literature [Stork, G. van Tamelen, E. et. al, J Am Chem Soc. 75, 388 (1953)]

E. Information about how the ingredient is supplied:

Colorless glistening or orthorhombic plates, scales

F. Information about recognition of the substance in foreign pharmacopeias:

Span.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Rosenberg, E. W., Amonette, R. A., and Gardner, J. H. Cantharidin treatment of warts at home (letter). *Arch Dermatol*, 1977; 113(8):1134.

Harwell, W. B., Buchanan, Jr., R. N., and Hamilton, J. R. Foot Care. *J. Tennessee Med Assoc.*, 1978;71:830.

Rosenberg, E. W., Amonette, R. A., and Gardner, J. H. Foot Care. *Arch. Dematol.*; 1977;113:1134.

1998-3454B1-02-18-BDL05

H. Information about dosage forms used:

Liquid

Apply directly to the lesion and cover the growth completely.

I. Information about strength:

0.7%

J. Information about route of administration:

Topically

K. Stability data:

Melts at about 216-218°. Sublimes at about 110° with some fumes.

Stable

L. Formulations:

M. Miscellaneous Information:

No. Records Request
* 1 14 cantharidin

Record 1 of 3 - IPA 1970-3/98

TI: Warts and their remedies

AU: Lau-J; Grant-D

SO: On-Contin-Pract (OCP-On-Continuing-Practice); 1986; 13(Oct); 29-34

PY: 1986

AB: A review of the different categories of standard wart treatment is presented. Nonprescription therapy including salicylic acid, and collodions and an evaluation of some wart remedies are discussed. Schedule drugs such as cantharidin, podophyllum resin (podophyllin) are described. It was concluded that the pharmacist has a valuable role to play by offering information and advice on the proper use of the many nonprescription medications available to treat warts.

AN: 24-07153

Record 2 of 3 - IPA 1970-3/98

TI: Psoriasis: a defect in the regulation of epidermal proteases, as shown by serial biopsies after cantharidin application

AU: Dubertret-L; Bertaux-B; Fosse-M; Touraine-R

SO: Br-J-Dermatol (British-Journal-of-Dermatology); 1984; 110(Apr); 405-410

PY: 1984

AB: The effect of cantharidin (I) solutions on normal and psoriatic skin was studied in order to elucidate the possible role of epidermal serine proteases in the genesis of psoriatic lesions. In the skin of normal subjects, I induced epidermal damage was followed by the transient appearance of proteolytic activity in the upper epidermis accompanied by temporary hyperacanthosis and perivascular inflammatory cells in the superficial dermis. In the uninvolved skin of 5 psoriasis patients this proteolysis persisted longer, for more than 7 days. Thereafter, in 3 of the patients, the proteolysis abated, and this was followed by the disappearance of the hyperacanthosis and the dermal infiltrate; in the other 2 psoriatics the proteolysis and hyperacanthosis increased. It was suggested that the abnormal persistence of proteolytic activity in the upper epidermis after I application distinguishes the normal from the psoriatic skin injury response and might initiate the psoriatic lesion.

AN: 22-03599

Record 3

TI: Warts and what to do about them

AU: Rasmussen-JE

SO: Drug-Therapy (Drug-Therapy); 1981; 11(Nov); 65-67, 71-72, 74

PY: 1981

AB: Factors influencing the therapy of warts are discussed, and recommendations on the use of cryotherapy with liquid nitrogen, caustics or irritants, cantharidin, and other drugs, are given. The treatment is based on the number, size, location of the warts, as well as the patient's lifestyle and physical condition.

AN: 20-02288

CANTHARIDIN

Human Toxicities:

As little as 10 milligrams has been reported to cause death but the usual “minimum lethal dose” quoted is between 32 and 65 milligrams.

Exposure to 175 milligrams caused second and third degree burns of the mouth, seizures, kidney damage and hypotension, but the patient survived.

Ingestion of 105 to 140 milligrams produced ulceration and inflammation of the oral mucosa; the patient developed hematuria and T wave abnormalities, but recovered (adult ingested 1.5 to 2 ml of wart remover containing 0.7% cantharidin). Arrhythmias have been reported to occur.

It is extremely toxic (1 mg/kg) orally and by inhalation and is corrosive to eyes, skin and mucous membranes.

Systemic toxicity can develop after dermal (topical) or oral exposure.

Could be a potential carcinogen (limited evidence) from dermal mouse carcinogenicity studies (squamous cell carcinomas, papillomas). Internal tumors (lymphomas, reticulum cell tumors) may be of significance.

Cantharidin is irritating to the mouth and throat, and can cause keratitis, iritis and edema of the eyelids. Hypotension, tachycardia, arrhythmias, ataxia, syncope and delirium have been noted.

Cantharidin (cont.)

Symptoms of acute poisoning from ingestion include burning of the mouth, nausea, dysphagia, hematemesis, hematuria, dysuria, erosion and hemorrhage of the upper GI tract, renal dysfunction and failure due to acute tubular necrosis and destruction of the glomeruli. Less common effects are cardiac abnormalities, priapism and seizures.

Low grade disseminated intravascular coagulation has been reported in patients with acute cantharidin poisoning.

Fatty changes, parenchymatous degeneration, and a severe effect on hepatic organ structure may be seen.

TOPICAL application of cantharidin produced acute lymphangitis and persistent lymphedema in one case. Although edema and subpleural hemorrhages may be seen, the lungs are usually not seriously damaged. Respiration is greatly stimulated, then greatly depressed.

Mild to severe skin reactions may occur. Acantholysis has been reported as in pemphigus (skin blistering diseases).

It has been recommended that “owing to the high toxicity of Cantharidin, it is recommended that preparations containing it should not be used medicinally.”

Public Safety: Toxic and/or corrosive. Upon decomposition emits corrosive, toxic and irritating fumes. In contact with metals, it may evolve hydrogen gas.

Cantharidin (cont.)

Uses:

Cantharidin has been used:

-as a homicidal agent in South Africa.

Herbalist uses: for treatment of dropsy, pleurisy, pericarditis, kidney infections, kidney stones, stranguria (painful micturation), certain venereal diseases and amenorrhea, and as a putative aphrodisiac.

Modern uses: a counter irritant and vesicant in a 0.7% concentration in collodion (Verr-Canth, Pallsades Co.; Cantharone).

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Tab 86

Piracetam Nominations

Submitted electronically via www.regulations.gov

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No.: FDA-2013-N-1525: *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations*

Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

A handwritten signature in black ink, appearing to read "Steve Pfister", with a long horizontal flourish extending to the right.

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Nomination from National Community Pharmacists Association, September 30, 2014

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format(s)	Recognition in Pharmacopeias	Final Compound Formulation Dosage Form	Final Compounded Formulation Strength	Final Compound Formulation Route(s) of Admin	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
Piracetam	2-oxo-1-pyrrolidineacetamide	Piracetam; Trade names: Breinox, Dinagen, Lucetam, Nootropil, Nootropy, Oikamid	ZH516LNZ10	From PCCA Database MSDS: Product is 98-102% by weight and stable. Protect from light and avoid strong oxidizing agents.	powder	EP	Capsule, Cream, Solution	Capsules: 100 - 800mg, Cream: 1-25%, Solution: 1-20%	Oral, topical, injectable	Federal Register 1999 Fang Y, et al. Effect of piracetam on the cognitive performance of patients undergoing coronary bypass surgery: A meta-analysis. Exp Ther Med. 2014 Feb;7(2):429-434. [http://www.ncbi.nlm.nih.gov/pubmed/24396419] Waegemans T, et al. Clinical efficacy of piracetam in cognitive impairment: a meta-analysis. Dement Geriatr Cogn Disord. 2002;13(4):217-24 [http://www.ncbi.nlm.nih.gov/pubmed/12006732]	Cognitive Impairment, Coagulation Disorders, Vertigo Piracetam, a derivative of the amino acid gamma-amino butyric acid, is well characterized chemically. Piracetam is believed by some to enhance certain cognitive skills, and has been used to treat Down's syndrome, dyslexia, and Alzheimer's disease, among other cognitive disorders. At doses reported in the literature for these indications, piracetam appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of piracetam's effectiveness for these indications is reported in the literature.



September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA's request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS

Corporate Offices: 4638 Riverstone Blvd. | Missouri City, Texas 77459 | 281.933.8400
Washington DC Offices: 1321 Duke Street, Suite 200 | Alexandria VA 22314 | 703.299.0796

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created an series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency's activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee prior to the implementation and issuance of regulations including the creation of the bulk ingredient list.

(2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

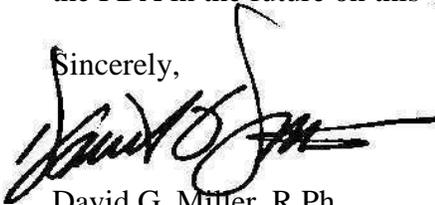
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

A handwritten signature in black ink, appearing to read "David G. Miller", with a large, stylized flourish extending upwards and to the right.

David G. Miller, R.Ph.
Executive Vice President & CEO



Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Piracetam
Chemical/Common Name	Pyrrolidone Acetamide; 2-(2-Oxopyrrolidin-1-yl)acetamide
Identifying Codes	7491-74-9
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	EP

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	

Past and Proposed Use The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.



September 30, 2014

Submitted electronically via www.regulations.gov

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

PCCA respectfully submits the following list of nineteen chemicals to be considered for the List of Bulk Drug Substances that may be used in Pharmacy Compounding in accordance with Section 503A.

PCCA provides its more than 3,600 independent community compounding pharmacy members across the United States with drug compounding ingredients, equipment, extensive education, and consulting expertise and assistance.

Regarding the specific nominations, we would like to reference the attached spreadsheet and point out a couple of facts regarding our research. To the best of our knowledge, all items submitted:

- Do not appear in any of the three sections of the Orange Book.
- Do not currently have a USP or NF monograph.
- Meet the criteria of a “bulk drug substance” as defined in § 207.3(a)(4).

In regards to the request for chemical grade information, we would like to point out that many of the items submitted do not currently have a chemical grade. PCCA believes that pharmacists should use the highest grade chemical available on the market for all aspects of pharmaceutical compounding and we continue to actively source graded chemicals from FDA-registered manufacturers. However, in the current marketplace, some graded chemicals cannot be obtained for various reasons. PCCA actively tests all products received to ensure they meet our required standards to ensure our members receive the highest quality chemicals possible.

We would like to echo the concerns, voiced by NCPA and others in our industry, the strong recommendation to formalize the process by which the list is updated and communicated to the pharmacy industry. We also recommend an annual process to ensure understanding and adherence to the list. All submissions and updates to the list should be reviewed by the Pharmacy Compounding Advisory Committee (PCAC) and no changes to the list should occur with input and review by the PCAC.

PCCA USA: 9901 S. Wilcrest Drive Houston, Texas 77099 | 800.331.2498 (f) 800.874.5760 | www.pccarx.com

PCCA Canada: 744 Third Street London, ON Canada N5V 5J2 | 800.668.9453 (f) 800.799.4537 | www.pccarx.ca

PCCA Australia: Unit 1, 73 Beauchamp Road Matraville NSW 2036 Australia | 02.9316.1500 (f) 02.9316.7422 | www.pccarx.com.au



We are also dismayed in the fact that no appointments have been made to the PCAC despite the call for nominations closing in March 2014. Without these appointments, FDA is unable to consult the Committee regarding this list, as outlined in the Act. PCCA, along with industry partners, strongly recommends that the FDA consult with the PCAC related to every single submission the Agency received in relation to FDA-2013-N-1525.

We appreciate this opportunity to submit this list for consideration and we look forward to continuing to work with the FDA in the future on this and other important issues as they relate to the practice of pharmacy compounding.

Sincerely,

A handwritten signature in black ink, appearing to read 'A. Lopez', with a stylized flourish at the end.

Aaron Lopez
Senior Director of Public Affairs
PCCA

A handwritten signature in black ink, appearing to read 'John Voliva', with a stylized flourish at the end.

John Voliva, R.Ph.
Director of Legislative Relations
PCCA

<i>PCCA Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations</i>	
Ingredient Name	Piracetam
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	2-(2-Oxopyrrolidin-1-yl)acetamide
Common Name(s)	Piracetam
UNII Code	ZH516LNZ10
Chemical Grade	EP
Strength, Quality, Stability, and Purity	Assay, Description, Solubility; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmacopeias or registered in other countries	EP; Available in many countries
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Capsules, Cream, Solution
Compounded Strengths	Capsules: 100 – 800 mg; Cream: 1 - 25%; Solution: 1 - 20%
Anticipated Routes of Administration	Oral, Topical, Injectable
Safety & Efficacy Data	Fang Y, et al. Effect of piracetam on the cognitive performance of patients undergoing coronary bypass surgery: A meta-analysis. Exp Ther Med. 2014 Feb;7(2):429-434. [http://www.ncbi.nlm.nih.gov/pubmed/24396419]

	<p>Waegemans T, et al. Clinical efficacy of piracetam in cognitive impairment: a meta-analysis. Dement Geriatr Cogn Disord. 2002;13(4):217-24 [http://www.ncbi.nlm.nih.gov/pubmed/12006732]</p>
	<p>Bartus RT, et al. Profound effects of combining choline and piracetam on memory enhancement and cholinergic function in aged rats. Neurobiol Aging. 1981 Summer;2(2):105-11. [http://www.ncbi.nlm.nih.gov/pubmed/7301036]</p>
	<p>Fesenko UA. Piracetam improves children's memory after general anaesthesia. Anesteziol Intens Ter. 2009 Jan-Mar;41(1):16-21. [http://www.ncbi.nlm.nih.gov/pubmed/19517672]</p>
	<p>Moriau M, et al. Platelet anti-aggregant and rheological properties of piracetam. A pharmacodynamic study in normal subjects. Arzneimittelforschung. 1993 Feb;43(2):110-8. [http://www.ncbi.nlm.nih.gov/pubmed/8457235]</p>
	<p>Ozdemir H, et al. Comparison of the effectiveness of intravenous piracetam and intravenous dimenhydrinate in the treatment of acute peripheral vertigo in the emergency department. Singapore Med J. 2013 Nov;54(11):649-52. [http://www.ncbi.nlm.nih.gov/pubmed/24276103]</p>

Nomination from PCCA, September 30, 2014

Used Previously to compound drug products	Cognitive Impairment, Coagulation Disorders, Vertigo
Proposed use	Cognitive Impairment, Coagulation Disorders, Vertigo
Reason for use over and FDA-approved product	Treatment failures and/or patient unable to take FDA approved product
Other relevant information - Stability information	Unless other studies performed / found: Capsule: USP <795> recommendation of BUD for nonaqueous formulations – “no later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier. Topical: USP <795> recommendation of BUD for water containing topical formulations – “no later than 30 days." Injection: USP <797> recommendations for high risk level compounded sterile products

Tab 87

FDA Review of Piracetam



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: January 30, 2015

FROM: Norman Schmuff
Associate Director for Science and Communication (CMC Reviewer),
Office of Process and Facilities

David Hawver
Pharmacologist (Pharmacology Reviewer), Division of Neurology
Products

Kenneth Bergmann
Medical Officer, Division of Neurology Products

THROUGH: Lois Freed
Supervisory Pharmacologist, Division of Neurology Products

Gerald D. Podskalny
Clinical Team Leader, Division of Neurology Products

Eric Bastings
Deputy Director, Division of Neurology Products

Billy Dunn
Director, Division of Neurology Products

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Piracetam for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

Piracetam has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Indications identified in the nominations include the treatment of cognitive impairment, coagulation disorders and their sequelae, and vertigo. FDA reviewed this substance in 1998, and it was included on a proposed list of bulk drug substances published in January 1999. The background materials from the prior review are attached.

Upon further review of the substance's physicochemical characteristics, safety, effectiveness, and historical use in compounding, we recommend that piracetam *not* be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?

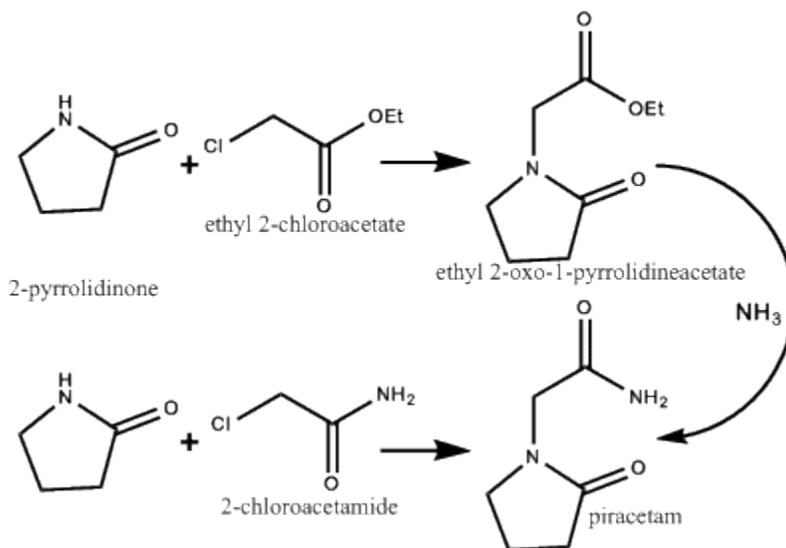
1. Stability of the API and likely dosage forms

The API and all dosage forms are expected to have good stability (Sahu, Kapendra, et al., 2012).

2. Probable routes of API synthesis

Based on a search of Chemical Abstract's SciFinder, there appear to be many possible routes of synthesis.

A 1969 patent, US 3,459,738, details the route from 2-oxo-1-pyrrolidineacetate, which itself was probably synthesized from ethyl 2-chloroacetate as shown at the top of the scheme below. However, based on commercial raw material availability and cost, the most likely route is that shown here from 2-pyrrolidinone and 2-chloroacetamide:

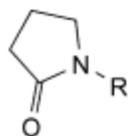


3. Likely impurities

The likely impurities for the routes above are unreacted starting material(s) and piracetam's only observed degradation product,¹ which is formed only under extreme conditions.

The API monograph in the *European Pharmacopoeia 8th Edition* lists controls for the four impurities shown here.

¹ Identified by retention time only in Malykh, 2010 and likely to be 2-oxopyrrolidin-1-yl)acetic acid.



- A. R = H: pyrrolidin-2-one (2-pyrrolidone),
- B. R = CH₂-CO-O-CH₃: methyl (2-oxopyrrolidin-1-yl)acetate,
- C. R = CH₂-CO-O-C₂H₅: ethyl (2-oxopyrrolidin-1-yl)acetate,
- D. R = CH₂-CO₂H: (2-oxopyrrolidin-1-yl)acetic acid.

4. *Toxicity of those likely impurities*

Note that 2-chloroacetamide contains a “structural alert” for genotoxicity (Blagg, 2006). Its toxicity is assessed below. Assuming that the API is recrystallized, it is likely to contain less than a few tenths of a percent of 2-chloroacetamide.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

Although two polymorphs are known to exist in commercial products (Titova, et al., 2008), there is little difference in their solubility (Maher, et al., 2012), and, consequently, polymorph control is unlikely to be important for consistent product performance.

Conclusions: Piracetam is a small, well-characterized material, suitable for compounding from the perspective of its physical and chemical characteristics.

B. Are there concerns about the safety of the substance for use in compounding?

1. *Nonclinical Assessment*

In addition to the specific references cited below, PubMed and ToxNet databases were consulted in the preparation of this review.

a. Pharmacology of the drug substance

The mechanisms of action of piracetam relevant to the treatment of cognitive impairment and other indications for which it has been used clinically are unknown. Piracetam exerts several cellular effects of unknown relationship to its purported clinical uses, including modulation of cellular and mitochondrial membrane permeability and alteration of signal trafficking (Malykh, 2010).

b. Safety pharmacology

Electrocardiographic parameters were not affected in dogs administered up to 1000 mg/kg/day piracetam intravenously for one month (Giurgea, 1977).

c. Acute toxicity

Acute oral studies conducted with piracetam in mouse, rat, and dog have been reported. LD₅₀ values of 26 g/kg, >10 g/kg, and >10 g/kg, respectively, have been reported (UK EMC label for Nootropil (the trade name for piracetam in the United Kingdom); Giurgea, 1977).

d. Repeat dose toxicity

According to the labeling for Nootropil, chronic oral toxicity studies of piracetam were conducted in rat (up to 2 g/kg/day for 6 months) and dog (up to 10 g/kg/day for 12 months). No target organs were identified. Mean piracetam plasma C_{max} levels at the highest doses tested were approximately 8-fold (rat) and 50-fold (dog) greater than those observed in humans at the maximum recommended human dose (MRHD) of 24 g/day (in 2 or 3 divided doses); mean plasma AUC levels in rats and dogs “were a multiple of the human AUC level” at the MRHD. In a 112-week oral (gavage) study of piracetam, an increased incidence of progressive glomerulonephrosis was observed in male rats at 2.4 g/kg/day; similar changes were not seen in females.

e. Mutagenicity

Piracetam was not mutagenic or clastogenic; the specific genotoxicity assays conducted were not described (Nootropil label).

f. Developmental and reproductive toxicity

Oral piracetam did not cause teratogenicity in mouse or rat at up to 4.8 g/kg/day, or in rabbit at up to 2.7 g/kg/day, and no adverse effects were observed on fertility, perinatal, or postnatal parameters in rats given oral piracetam at up to 2.7 g/kg/day (Nootropil label; Giurgea M., 1977).

g. Carcinogenicity

The UK labeling for Nootropil indicates that piracetam does not pose a carcinogenic risk to humans. However, it is not clear if this conclusion was based on the negative genotoxicity findings, or on negative findings in carcinogenicity studies in animals. No carcinogenicity studies with piracetam were described in the labeling or identified in published literature.

h. Toxicokinetics

In vivo studies have not identified any metabolites of piracetam in humans (Nootropil label; Shorvon, 2001).

i. Other issues

As stated in the prior section of this review, the piracetam drug substance may contain an impurity, 2-chloroacetamide, which has a structural alert for genotoxicity. However, the weight of evidence available in the published literature suggests that 2-chloroacetamide is neither mutagenic nor clastogenic (*Toxikologische Bewertung*, 2000; Christian, 1991; Plewa, et al., 2008).

Conclusions: The available nonclinical data on piracetam have not identified any safety concerns. The lack of toxicity, mutagenicity, and clastogenicity supports the inclusion of piracetam on the 503A list.

2. *Human Safety*

a. Background

Piracetam has been used to treat a variety of neurological conditions and complaints, some of which are indications for which FDA-approved products are available. Piracetam originated in the UCB Pharma laboratories in 1964. It has marketing authorization in the UK for the adjunctive treatment of cortical myoclonus. Piracetam, as a member of the pyrrolidones chemical family, is closely related to levetiracetam, which has been approved for use in epilepsy in the United States. The drug substance is widely available in Europe, South America, and Asia from diverse manufacturers via different commercial mechanisms.

In the United Kingdom, piracetam (Nootropil) is only available by prescription. The product information from the Nootropil label and patient information leaflet in the United Kingdom (Nootropil, in 33% solution, 800, and 1200 mg tablets) recommends titration to a maximum of 24 grams by mouth daily in divided doses for cortical myoclonus from any etiology. The initial dose is 7.2 grams followed by titration every 3 to 4 days depending on the effect on the patient's myoclonus. The following safety concerns are found in the label:

- Dosing requires adjustment for poor kidney function.
- Sudden discontinuation has caused generalized seizures or exacerbation of myoclonus.
- Patients who require salt restriction in their diet should be aware of the salt content of the pills (24 g contains 46 mg of sodium chloride).
- This drug crosses the placenta and is excreted in human milk. Its effect upon the fetus and neonate is unknown.
- Somnolence, nervousness, and depression have been described with doses from 1.6 and 15 grams daily. The effect of piracetam on ability to drive is unknown.
- Piracetam reduces platelet function, interferes with clotting factors (Fibrinogen and Factor VIII), and prolongs bleeding time starting at doses above 8 to 9.6 grams/day.

b. Reported adverse reactions

The Nootropil label summarizes safety information from 3000 people with varying exposures to piracetam for diverse conditions:

Common (affect between 1 in 10 and 1 in 100 people)

- Nervousness.
- Weight gain.
- Increased body movements (hyperkinesia).

Uncommon (affect between 1 in 100 and 1 in 1000 people)

- Sleepiness.
- Depression.
- Feeling weak.

FDA's orphan designation of piracetam in 1987 for the treatment of myoclonus (held by UCB Pharma) was withdrawn.

This review considers informative citations from the scientific literature published since FDA's last review of piracetam for the purpose of compounding in 1998. There are 1,155 English language scientific citations involving people (as opposed to nonclinical studies) found with piracetam as the search term in PubMed from 2000 until now.

Piracetam has been subject to four independent systematic evidence-based reviews by the Cochrane Collaboration (see below). These reviews are focused on clinical efficacy and comment on safety when there is sufficient information present. Because clinical trials published in medical journals generally do not include detailed safety information and often de-emphasize adverse events, these reports carry little information on risks related to piracetam, which is often broadly characterized as "well tolerated."

- Flicker L, Grimley E J. 2004. Piracetam for dementia or cognitive impairment. The Cochrane Database for Systematic Reviews 1: 1–42, updated 2012 DOI: 10.1002/14651858.CD001011. (24 studies, 11959 participants)
- Ricci S, Celani M G, Cantisani T A, and Righetti E. 2012. Piracetam for acute ischaemic stroke. Cochrane Database of Systematic Reviews, Issue 9. Art. No.: CD000419. DOI: 10.1002/14651858.CD000419.pub3. (3 trials, 1002 patients)
- Al Hajeri A, Fedorowicz Z, Omran A, and Tadmouri G O. 2007. Piracetam for reducing the incidence of painful sickle cell disease crises. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD006111. DOI: 10.1002/14651858.CD006111.pub2. (3 trials, 169 participants)
- Hofmeyr G J and Kulier R. 2012. Piracetam for fetal distress in labour. Cochrane Database of Systematic Reviews, Issue 6. Art. No.: CD001064. DOI: 10.1002/14651858.CD001064.pub2. (1 study, 96 women)

One of the few trials to present a table of adverse events studied piracetam versus aspirin for the prevention of secondary stroke in 506 patients over a mean of 17 months. This was a secondary endpoint of the study and thus the reason information was provided in such detail. In general, piracetam had fewer adverse events than aspirin, had more patients able to complete the study in the piracetam arm (52 vs. 46%) and was considered overall to be better tolerated. There were more deaths in the piracetam arm, both due to vascular causes (15.2 vs. 11.7%) and all-cause mortality (2.7 vs. 0.3%). No clear etiological relationship to drug could be proven (Grottemeyer, et al., 2000).

There are no reports suggesting rare or idiosyncratic adverse reactions to piracetam.

c. Clinical trials assessing safety

Study in Mild Cognitive Impairment (MCI)

UCB Pharma conducted a 52-week, placebo controlled clinical trial of two doses of Piracetam compared to placebo in 675 patients (ITT population) (UCB Pharma SA, 2007). The study started in 2000 and finished in 2004, and the study synopsis of the completed study results was reported by UCB. These results were published and made available via hyperlink found on clinicaltrials.gov:

http://www.ucb.com/up/ucb_com_patients/documents/N01001_CSS_20070907.pdf

The study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of 9600 and 4800 mg/day piracetam (oral 800 mg tablets, b.i.d.) taken for 12 months by subjects suffering from mild cognitive impairment (MCI) (UCB Pharma SA, 2007). This study enrolled men and women age 50-89 years (mean approximately 68 years) with MCI, defined by a Clinical Dementia Rating Scale score equal to 0.5 and declining cognitive function of at least 3 months duration interfering with complex activities of daily living. Key exclusion criteria included history of dementia, psychiatric or neurological disorders, mental retardation, learning disabilities and stroke, the use of concomitant anticoagulant medications, bleeding disorders, insulin-dependent diabetes.

The study results failed to show a significant difference on the primary endpoint, the Cognitive Battery Composite Score (CBCS). The results of the 4800 mg dose versus placebo showed there was a difference of -0.291 [95% CI: -0.787, 0.206] (p-value of 0.251), and the results for the 9600 mg dose showed a difference of -0.298 [95% CI: -0.790, 0.193] at month 12 (p-value 0.234) for the ITT population.

This large, multicenter, well-designed and adequately controlled clinical trial would be suitable for submission to a regulatory body for review. The negative result provides strong evidence that Piracetam is ineffective for the treatment of MCI.

The following table shows adverse reactions from the study.

Table: Adverse Reactions (UCB Pharma)

Treatment-Emergent AEs:	PBO (N=225)	PIR 4800 mg/day (N=226)	PIR 9600 mg/day (N=224)
Subjects with at least 1 TEAE, n (%):	171 (76.0)	163 (72.1)	153 (68.3)
<i>MedDRA Primary System Organ Class with an incidence of ≥ 10%</i>	<i>n (%) [n considered drug-related by the Investigator]</i>		
Gastrointestinal disorders	55 (24.4) [22]	50 (22.1) [22]	47 (21.0) [25]
General disorders and administration site conditions	25 (11.1) [8]	20 (8.8) [6]	19 (8.5) [4]
Infections and infestations	74 (32.9) [2]	65 (28.8) [0]	66 (29.5) [0]
Injury, poisoning and procedural complications	16 (7.1) [0]	19 (8.4) [0]	23 (10.3) [0]
Musculoskeletal and connective tissue disorders	39 (17.3) [2]	42 (18.6) [1]	32 (14.3) [1]
Nervous system disorders	47 (20.9) [15]	52 (23.0) [15]	37 (16.5) [11]
Psychiatric disorders	43 (19.1) [14]	25 (11.1) [11]	34 (15.2) [9]
Death, other SAEs:	PBO (N=225)	PIR 4800 mg/day (N=226)	PIR 9600 mg/day (N=224)
Death, n (%):	1 (0.4)	3 (1.3)	0
Subjects with SAEs, n (%):	21 (9.3)	22 (9.7)	16 (7.1)
<i>MedDRA Primary System Organ Class with an incidence of ≥ 1%</i>	<i>n (%) [n considered drug-related by the Investigator]</i>		
Cardiac disorders	5 (2.2) [0]	6 (2.7) [0]	3 (1.3) [1]
Gastrointestinal disorders	0	3 (1.3) [0]	2 (0.9) [0]
General disorders and administration site	3 (1.3) [0]	0	1 (0.4) [0]

UCB Pharma SA. (2007). A multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of 9600 and 4800 mg/day piracetam (oral 800 mg tablets, b.i.d.) taken for 12 months by subjects suffering from mild cognitive impairment (MCI) Brussels: UCB, Inc. Clinical Study Summary Accessible by URL: http://www.ucb.com/up/ucb_com_patients/documents/NO1001_CSS_20070907.pdf

d. Pharmacokinetic data

From the U.K. Product Label (revised: February 2013)

Piracetam is rapidly and almost completely absorbed. Peak plasma levels are reached within 1.5 hours after administration. The extent of oral bioavailability, assessed from the area under curve (AUC), is close to 100% for capsules, tablets, and solution. Peak levels and AUC are proportional to the dose given. The volume of distribution of piracetam is 0.7 L/kg, and the plasma half-life is 5.0 hours, in young adult men. Piracetam crosses the blood-brain and the placental barrier and diffuses across membranes used in renal dialysis. Up to now, no metabolite of piracetam has been found. Piracetam is excreted almost completely in urine and the fraction of the dose excreted in urine is independent of the dose given. Excretion half-life values are consistent with those calculated from plasma/blood data. Clearance of the compound is dependent on the renal creatinine clearance and would be expected to diminish with renal insufficiency.

e. The availability of alternative approved therapies that may be as safe or safer

Aricept (donepezil), Exelon (rivastigmine), Namenda (memantine), and Razadyne (galantamine) are FDA approved for the treatment of dementia caused by Alzheimer's disease. Exelon (rivastigmine) is also approved for treatment of dementia caused by Parkinson's disease.

Keppra (levetiracetam) tablets and oral solution is an FDA approved anticonvulsant that is a member of the same family of compounds as piracetam (pyrrolidones). Although it is approved for the treatment of myoclonic epilepsy, there are several publications describing successful treatment of myoclonus caused by other conditions (e.g., post-hypoxic, neurodegenerative disorders) with levetiracetam.

Conclusions: Piracetam is not recommended for patients with severe renal impairment or in those taking concomitant anticoagulants, other medications that prolong bleeding or in individuals with medical conditions that cause prolonged bleeding. Women who are pregnant, planning to become pregnant and women who are breast-feeding should not take piracetam. Because of the salt content of the pills, patients who require salt restriction in their diet should beware (24 g contains 46 mg of sodium chloride). Doses below 8 kg/day appear to be unlikely to cause serious adverse reaction or drug interaction.

C. Are there concerns about whether a substance is effective for a particular use?

1. Reports of trials demonstrating effectiveness of the bulk drug substance as it is used in drug products

Piracetam has been judged to be safe and effective in the United Kingdom for cortical myoclonus based on the results of a single center, retrospective review of 40 patients treated with piracetam (Obeso, et al., 1988) for myoclonus. Several case reports and smaller case series describe the use of piracetam to successfully treat several different forms of cortical myoclonus.

a. Any clinical evidence of effectiveness, or lack of effectiveness, of drug products with the bulk drug substance

Piracetam has been studied for a number of different uses, described below. Most of these studies, however, were either poorly designed or did not clearly demonstrate piracetam to be effective for the conditions at issue.

Cognitive Disorders

Dementia

A Cochrane review addressed the effectiveness of piracetam in dementia or other cognitive impairment, its most common usage (Flicker, et al., 2004). It evaluated the clinical efficacy of piracetam for features of dementia (classified into the major subtypes: vascular, Alzheimer's disease or mixed vascular and Alzheimer's disease, or unclassified dementia) or cognitive impairment not fulfilling diagnostic criteria for dementia. It looked at 24 studies with a total of 11,959 patients with varying doses, lengths of exposure, and outcome measures. Because of the variability in the design of these studies, pooling of data was only possible in 4 studies using the Clinical Global Impression of Change (CGI). In these four studies, the entry criteria and target population were different: organic brain syndrome, psycho-organic syndrome and cerebrovascular insufficiency. Data were only available for a completer population and

the studies were subject to a large numbers of dropouts, leaving a positive result in question due to completer bias. Design varied with regard to diagnostic criteria, dosing, length of exposure, and a wide range of outcome measures, often not validated and/or without clear metric properties.

With the limited interpretable data available, no significant differences were found between treatment and placebo groups for cognition (immediate memory, visuospatial, Mini Mental Status Examination, delayed memory or speech), for dependency, or for depression.

Alzheimer's Disease

Only one placebo controlled, blinded trial of piracetam by itself in patients with well-defined Alzheimer's disease (AD) has been carried out (Croisile, et al., 1993). For 1 year, participants with probable AD received either placebo or 8 grams/d of piracetam. At baseline and every 3 months thereafter, the patients underwent a battery of 14 neuropsychological tests. At completion, 14 patients were on piracetam, and 16 were on placebo. The two treatment arms did not differ in performance at the end of the trial, even without a correction for multiplicity of testing. The authors reported the results of several post-hoc analyses of the data without adjustment for multiple comparisons. Although these results were interpreted as showing that piracetam patients deteriorated less quickly than the placebo group, the methods of analysis lacked sufficient rigor to serve as a basis for valid conclusions.

Mild Cognitive Impairment (MCI)

MCI is a prodromal state of cognitive impairment prior to fulfilling diagnostic criteria for Alzheimer's disease. UCB, as reported by Jelic, et al., (2006), conducted a randomized, double blind, placebo controlled, multicenter trial in MCI using two doses of piracetam 4.8 and 9.6 grams daily in divided doses for 52 weeks. A total of 776 patients were enrolled, divided equally among three arms. Approximately 75% completed the trial and all but one participant was evaluable to some extent. The primary outcome was a composite score from a battery of neuropsychological tests for memory and cognition. The end result was no change in the primary or secondary outcome measures. Adverse events occurred in the same proportion in each group.

Stroke

Piracetam has been studied in various populations prone to stroke:

Coronary artery bypass

Piracetam has been investigated to measure its potential to reduce heart surgery related cognitive impairment, presumably due to perisurgical microemboli and related ischemic events. A meta-analysis (Fang, et al., 2014) found 184 patients in three randomized, double blind trials suitable for analysis. Two different dose regimens were used: a single, 12 gram dose prior to surgery (piracetam n =92, placebo n= 92) and 12 grams daily for 6 weeks (piracetam n=50, placebo n=48). The meta-analysis looked at the measurement of cognition by neuropsychological testing 3 days after surgery. The authors concluded that there were statistically significant improvements from baseline measurements in recall tasks, but not attention. However, this analysis failed to address

the multiplicity of testing, the effect of learning by repeated testing, or the durability of the treatment effect. (Salma, et al., 2006, a trial providing treatment for 6 weeks, had a non-significant result at that time point). No evidence was offered in any trial to suggest that the change from baseline (numerically small overall) was clinically meaningful.

Cardiopulmonary bypass

Patients undergoing heart surgery (n=88) with cardiopulmonary bypass were randomized to 12 g of piracetam or placebo at the start of surgery (Holinski, et al., 2011). Neuropsychological tests including the Alzheimer's Disease Assessment Scale were performed at baseline and 3 days after surgery. Both groups showed equivalent decline after bypass in their neuropsychological functioning with no benefit from piracetam.

Treatment of acute ischemic stroke

A Cochrane review (Ricci, et al., 2012) investigated the utility of piracetam in ameliorating acute stroke. Three of 19 studies fulfilled evaluable criteria. Outcome consisted of all-cause death, stroke related death, and stroke severity. The trials involved 1,002 patients, with one trial contributing 93% of the data. The conclusion of the meta-analysis was that "Piracetam was associated with a statistically non-significant increase in death at one month (approximately 31% increase, 95% CI 81% increase to 5% reduction). This trend was no longer apparent in the large trial after correction for imbalance in stroke severity. Limited data showed no difference between the treatment and control groups for functional outcome, dependence or proportion of patients dead or dependent." Adverse events were not otherwise reported.

Secondary stroke prevention:

Patients who had had a previous stroke (n=563) were randomized to double blind piracetam 1200 mg versus aspirin 200 mg (Grotemeyer, et al., 2000). After 2 years' follow-up, neither group showed significant benefit although there were fewer secondary events in the aspirin group (11.7 vs. 15.2%). Because drug safety was a secondary outcome measure in this trial, it is one of the few trials to present a table of adverse events. In general, piracetam had fewer adverse events than aspirin, had more patients able to complete the study in the piracetam arm (52 vs. 46%), and was considered over all to be better tolerated. There were more deaths in the piracetam arm, both due to vascular causes (15.2 vs. 11.7%) and all-cause mortality (2.7 vs. 0.3%). No clear etiological relationship to drug could be proven.

Vertigo

In a double blind study of 143 geriatric patients with chronic vertigo, piracetam 2.4 g per day was compared with placebo (Rosenhall, et al., 1996). Following 8 weeks of treatment, the number of episodes of vertigo had decreased by approximately 9 with piracetam compared with an increase of approximately 3 with placebo ($p < 0.05$). There was no difference between the treatments in attack severity. The data were "not evaluable" for 54 out of 143 patients because of adverse events or protocol violations. The authors analyzed multiple endpoints without an adjustment for multiple comparisons. These factors severely limit the ability to base conclusions on the data.

In another trial, 200 consecutive patients with acute vertigo were infused with piracetam 1000 mg versus dimenhydrinate 50 mg (Ozdemir, et al, 2013). The authors' conclusion was that they were both equally effective in treating acute vertigo as measured by a patient reported visual analog scale. However, this paper is flawed in its analysis, using both multiple comparisons and an inappropriate statistical design for comparing the two drugs. By the second evaluation performed after infusion, there were no differences in outcome when compared to the pre-infusion vertigo scores.

Dyslexia and language disorders

Aphasia after stroke

A Cochrane review (Greener, et al., 2001) analyzed the effectiveness of piracetam in improving acquired language dysfunction following acute stroke. Five trials with a total of 661 participants and sharing evaluable outcome measures for aphasia following stroke were evaluated. Piracetam appeared to have a slight benefit, though this vanished when proper statistical methods were applied (corrections for multiplicity of testing).

Dyslexia

Dyslexia as a learning disability has no effective pharmacological treatment. Piracetam has been studied in this population. In one study, 225 children with dyslexia, between 7 and 12 years of age, received piracetam 3.3 g/day or placebo for 36 weeks (Wilsher, et al., 1987). At the end of treatment, piracetam improved reading, compared with placebo as measured by standard reading and comprehension tests. However, the improvement of dyslexia with piracetam was modest in effect size and of unknown clinical significance. The potential effect of remedial language intervention was not considered.

Painful Crises in Sickle Cell Anemia

In looking at 169 patients in three randomized controlled trials, a Cochrane review (Al Hajeri, et al., 2007) judged piracetam to be of unproven use in reducing the number or severity of sickle cell associated crises. The review also points out that it is telling that this treatment has not been adopted as an alternative treatment for a population that has little effective therapy for the prevention of painful crises.

Breath-Holding Spells

Botrous and Sawires (2012) reported piracetam was effective for the treatment of breath holding spells in 2 placebo controlled trials. The first study was a double blind, placebo controlled trial of 40 patients (n=20 piracetam and n= 20 placebo) ages 6 months to 5 years. The dose of piracetam administered in the first study was 50 mg/kg daily, divided into 2 doses for 4 months. A second study (Donma, 1998) was conducted in 76 patients (n=39 piracetam and n=37 placebo) with breath holding spells, ages 6 to 36 months. Patients were treated with piracetam received 40 mg/kg divided twice daily for 2 months. Safety information was very limited as “the side effect of most concern for patients taking piracetam was sleeping disorder.” The recommended treatment for routine breath holding spells is reassurance without pharmacological treatment (Goldson & Reynolds, 2014).

In 2001, Lobaugh, et al., reported the results of a double blind, placebo controlled, crossover study that assessed the ability of piracetam to enhance cognitive function in children with Down's syndrome. The patients were age 6.9 to 12.9 years, and they were treated with 80-100 mg/kg of piracetam, divided into 3 daily doses. Piracetam was not found to improve cognitive function, and aggressive or violent behavior was observed in 4 children during treatment with piracetam.

- b. Any anecdotal reports of effectiveness, or lack of effectiveness, of drug products with the bulk drug substance

In the many studies that have been performed with piracetam, there are both negative and positive results for the conditions investigated. As indicated above, when closely inspected, the trials with positive outcomes have generally suffered from significant methodologically flaws.

- c. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

As judged by literature citations on the topic, the most likely compounded use for this drug is for cognitive enhancement. Although not immediately life-threatening, cognitive impairment is disabling and is a common cause of death in America. Alzheimer's disease is now the 6th leading cause of death in the United States overall, replacing diabetes, and it is the 5th leading cause of death in individuals age 65 and older. The CDC reported 84,974 individuals in the United States died due to Alzheimer's disease in 2011. (Centers for Disease Control and Prevention (CDC), 2014)

- d. Whether there are any alternative approved therapies that may be as effective or more effective

Aricept (donepezil), Exelon (rivastigmine), Namenda (memantine), and Razadyne (galantamine) are FDA-approved for the treatment of dementia caused by Alzheimer's disease. Exelon (rivastigmine) is also approved for treatment of dementia caused by Parkinson's disease.

Keppra (levetiracetam) tablets and oral solution is an FDA-approved anticonvulsant that is a member of the same family of compounds as piracetam (pyrrolidones). Although it is approved for the treatment of myoclonic epilepsy, there are several publications describing successful treatment of myoclonus caused by other conditions (e.g., post-hypoxic, neurodegenerative disorders) with levetiracetam.

Conclusions: Many studies have found that piracetam improves cognitive impairment due to a variety of different causes. However, these studies were poorly designed and applied flawed analyses. UCB, the Sponsor of Nootropil, conducted a larger (n=675), well-designed and controlled study that included a prespecified analysis plan. The results of that study show that piracetam was ineffective for the treatment of mild cognitive impairment. Studies of piracetam for many other uses report conflicting or negative results. For the most part, these studies were

also poorly designed or executed, and they used highly flawed statistical methods to analyze the results. Thus, there is no clear evidence that piracetam is effective to treat any condition. There is, however, high-quality clinical trial data that conclude that piracetam is ineffective for treating mild cognitive impairment. Mild cognitive impairment causes significant disability and is associated with Alzheimer's disease, an increasingly frequent cause of death in the United States.

D. Has the substance been used historically in compounding?

1. Length of time the substance has been used in pharmacy compounding

Piracetam was first available in France in 1971. Its earliest use in the United States appears to be in 1981 (Friedman E, 1981), reported in the *New England Journal of Medicine*. The earliest human use appears in published reports from Europe starting in 1972. In several cases, FDA has taken enforcement action where piracetam was sold as a nutritional supplement without meeting the standards, or where the sale was linked to medical claims.

2. The medical condition(s) it has been used to treat

Piracetam has historically been used to treat alcoholism and cognitive impairment due to multiple etiologies such as Down's syndrome, Alzheimer's disease (including mild cognitive impairment), and cardiopulmonary bypass. It has also been used to treat patients with sickle cell anemia with crisis, myoclonus, dyslexia, acute stroke, secondary stroke prevention, vertigo, and breath-holding spells (pediatric use).

3. How widespread its use has been

Piracetam (alone or in combination with at least one other drug) is listed under 249 proprietary product names, and it is sold in at least 38 countries (Truven Health Analytics Inc., 2014). In some cases, piracetam is the sole active ingredient or it is combined with other ingredients. In some instances, there are more than 20 products containing piracetam sold in the same country.

4. Recognition of the substance in other countries or foreign pharmacopeias

Piracetam is available in many countries in Europe, Asia, South America, and in Australia, with or without a prescription (Truven Health Analytics Inc., 2014).

Conclusions: Piracetam has been available for approximately 40 years and was recommended for inclusion on the 1999 503A List of Bulk Drug Substances That May Be Used To Compound Drug Products. As discussed above, FDA has taken enforcement action when piracetam has been sold as a nutritional supplement.

RECOMMENDATION

We recommend that piracetam *not* be included on the list of bulk drug substances allowed for use in compounding. Our recommendation is based on the absence of a clear benefit associated with piracetam, the seriousness of the conditions for which piracetam is used, and the availability of safe and effective medications for many of these uses that have undergone greater scientific scrutiny.

Piracetam is well-characterized chemically and is unlikely to cause serious adverse reactions in adults, at moderate doses. It also has been used historically for approximately 40 years. However, of the numerous studies of piracetam that have been conducted, all but a few were designed poorly or used inappropriate statistical methods to support conclusions that piracetam is effective as a treatment for the studied condition. The publications that suggest piracetam is effective for treating cognitive impairment, acute vertigo, or stroke are inconsistent, and there are also publications that conclude that piracetam is ineffective for treating these same conditions.

The single, well-designed and executed study conducted by the commercial sponsor of piracetam, UCB Pharma, showed that it is ineffective for the treatment of cognitive impairment (UCB Pharma SA, 2007). Since 1999, several medications have been approved for the treatment of mild, moderate, and severe dementia caused by Alzheimer's disease, which is a serious condition. Levetiracetam is chemically related to piracetam, and it is safe and effective for treatment of myoclonic epilepsy in the United States. There are anecdotal reports that describe successful treatment of other forms of myoclonus with levetiracetam. We are not aware of studies that have compared the effects (safety or efficacy) of piracetam to these FDA-approved drugs. However, our assessment of effectiveness included the results of several systematic reviews and a few adequately designed, multicenter clinical studies that failed to demonstrate a benefit associated with the use of piracetam, even at high doses.

There is little long-term safety information to support the use of piracetam in the pediatric population. Studies of piracetam report inconsistent benefit or no benefit associated with piracetam to treat cognitive impairment in children. Although piracetam may be effective in the short-term for reducing the frequency of breath holding spells in children, in most cases, breath-holding spells do not require treatment.

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A. INGREDIENT NAME:

PIRACETAM

B. Chemical Name:

1-Acetamido-2-Pyrrolidinone, Euvicor, Gabacet, Genogris, 2-Ketopyrrolidine-1-Ylacetamide, Nootron, Nootropil, Nootropyl, Normabrain, 2-Oxo-Pyrrolidine-Acetamide, 2-Oxo-Pyrrolidin-1-Ylacetamide, Piracetam, Pirazetam, Pirroxil, Pyracetam, Pyramem, 2-Pyrrolidininnoneacetamide, 2-Pyrrolidoneacetamide, UCB 6215

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.27%

E. Information about how the ingredient is supplied:

White or almost white crystal powder

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Mondadori, C. Nootropics: Preclinical Results in the Light of Clinical Effects; Comparison with Tacrine. *Critical Reviews™ in Neurobiology*, 1996; 10: 357-370.

Tallal, U., Chase, C., and Russell, G. Calculation of the Efficacy of Piracetam in Treating Information Processing, Reading, and Writing Disorders in Dyslexic Children. *International Journal of Psychophysiology*, 1986; 4: 41-52.

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Mondadori, C., Petschke, F., and Häusler, A. The Effects of Nootropics on Memory: new Aspects for Basic Research. *Pharmacopsychiatry*. 1989; 22: 102-106.

YaI, V., Derzhiruk, L. P., and Mogilevskii, A. Piracetam-induced changes in the functional activity of neurons as a possible mechanism for the effects of nootropic agents. *Neurosci Behav. Physiol.*, 1996; 26(6): 507-515.

Pepeu, G. and Spignoli, G. Nootropic drugs and brain cholinergic mechanisms. *Prog. Neuropsychopharmacol Biol. Psychiatry*. 1989; 13Suppl: S77-78.

Pilch, H. and Muller, W. E. Piracetam elevates muscarinic cholinergic receptor density in the frontal cortex of aged but not of young mice. *Psychopharmacology*. 1988; 94(1): 74-78.

De Deyn, P. P., Reuck, J. D., and Deberdt, W. Treatment of acute ischemic stroke with Piracetam. Members of the Piracetam in Acute Stroke Study (PASS) Group. *Stroke*. 1997; 28(12): 2347-2352.

Di Ianni, M., Wilsher, C. R., and Blank, M. S. The effects of Piracetam in children with dyslexia. *J. Clin Psychopharmacol*. 1985; 5(5): 272-278.

Wilsher, C. R., Bennett, D., and Chase, C. H. Piracetam and dyslexia: effects on reading tests. *J. Clin Psychopharmacol*. 1987; 7(4): 230-237.

Reisberg, B., Ferris, S. H., and Gershon, S. An overview of pharmacologic treatment of cognitive decline in the aged. *Am J. Psychiatry*. 1981; 138(5): 593-600.

Bartus, R. T., Dean, R. L., and Sherman, K. A. Profound effects of combining choline and Piracetam on memory enhancement and cholinergic function in aged rats. *Neurobiol Aging*. 1981; 2(2): 105-111.

Buresova, O. and Bures, J. Piracetam-induced facilitation of interhemispheric transfer of visual information in rats. *Psychopharmacologia*. 1976; 46(1): 93-102.

Dimond, S. J., Scammell, R. E., and Pryce, I. G. Some effects of Piracetam (UCB 6215, Nootropyl) on chronic schizophrenia. *Psychopharmacology*. 1979; 64(3): 341-348.

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Mindus, P., Cronholm, B., and Levander, S. E. Does Piracetam counteract the ECT-induced memory dysfunctions in depressed patients? *Acta Psychiatr. Scand*. 1975; 52(5): 319-326.

Mondadoori, C., Classen, W., and Borkowski, J. Effects of oxiracetam on learning memory in animals: comparison with piracetam. *Clin Neuropharmacol*. 1986; 9 Suppl 3 S27-38.

Song, C., Earley, B., and Leonard, B. E. Effect of chronic treatment with piracetam and tacrine on some changes caused by thymectomy in the rat brain. *Pharmacol Biochem. Behav.* 1997; 56(4): 697-704.

H. Information about dosage forms used:

Patients received either 3.3 g of Piracetam daily or matching placebo syrup. Each dose of test medication was 5 ml. administered before breakfast and again before the evening meal. A 5 ml dose of active medication contained 1.65 g of Piracetam. No dosage adjustments were allowed. The patient's parents were contacted to review dosage instructions and to determine whether any adverse effects had been observed.

I. Information about strength:

1.65 g -3.3 g

J. Information about route of administration:

Orally

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

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TITLE: Treatment of acute ischemic stroke with piracetam. Members of the Piracetam in Acute Stroke Study (PASS) Group.

AUTHOR: De Deyn PP; Reuck JD; Deberdt W; Vlietinck R; Orgogozo JM

AUTHOR AFFILIATION: Department of Neurology, Middelheim Hospital, Antwerp, Belgium.

SOURCE: Stroke 1997 Dec;28(12):2347-52

NLM CIT. ID: 98074088

ABSTRACT:

BACKGROUND AND PURPOSE: Piracetam, a nootropic agent with neuroprotective properties, has been reported in pilot studies to increase compromised regional cerebral blood flow in patients with acute stroke and, given soon after onset, to improve clinical outcome. We performed a multicenter, randomized, double-blind trial to test whether piracetam conferred benefit when given within 12 hours of the onset of acute ischemic stroke to a large group of patients. **METHODS:** Patients received placebo or 12 g piracetam as an initial intravenous bolus, 12 g daily for 4 weeks and 4.8 g daily for 8 weeks. The primary end point was neurologic outcome after 4 weeks as assessed by the Orgogozo scale. Functional status at 12 weeks as measured by the Barthel Index was the major secondary outcome. CT scan was performed within 24 hours of the onset of stroke but not necessarily before treatment. Analyses based on the intention to treat were performed in all randomized patients (n = 927) and in an "early treatment" population specified in the protocol as treatment within 6 hours of the onset of stroke but subsequently redefined as less than 7 hours after onset (n = 452). **RESULTS:** In the total population, outcome was similar with both treatments (the mean Orgogozo scale after 4 weeks: piracetam 57.7, placebo 57.6; the mean Barthel Index after 12 weeks: piracetam 55.8, placebo 53.1). Mortality at 12 weeks was 23.9% (111/464) in the piracetam group and 19.2% (89/463) in the placebo group (relative risk 1.24, 95% confidence interval, 0.97 to 1.59; P = .15). Deaths were fewer in the piracetam group in those patients in the intention-to-treat population admitted with primary hemorrhagic stroke. Post hoc analyses in the early treatment subgroup showed differences favoring piracetam relative to placebo in mean Orgogozo scale scores after 4 weeks (piracetam 60.4, placebo 54.9; P = .07) and Barthel Index scores at 12 weeks (piracetam 58.6, placebo 49.4; P = .02). Additional analyses within this subgroup, confined to 360 patients with moderate and severe stroke (initial Orgogozo scale score < 55), showed significant improvement on piracetam in both outcomes (P < .02). **CONCLUSIONS:** Piracetam did not influence outcome when given within 12 hours of the onset of acute ischemic stroke. Post hoc analyses suggest that piracetam may confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate and severe degree. A randomized, placebo-controlled, multicenter study, the Piracetam Acute Stroke Study II (PASS II) will soon begin.

**MAIN MESH
SUBJECTS:**

Cerebral Ischemia/*DRUG THERAPY/MORTALITY
Cerebrovascular Disorders/*DRUG THERAPY/MORTALITY
Neuroprotective Agents/ADVERSE EFFECTS/*THERAPEUTIC USE
Nootropic Agents/ADVERSE EFFECTS/*THERAPEUTIC USE
Piracetam/ADVERSE EFFECTS/*THERAPEUTIC USE

PIRACETAM

Non-toxic in rodents having an oral LD50 > 10g/kg.

While the toxic properties of piracetam have not been thoroughly investigated it may produce insomnia, psychomotor agitation, nausea, G.I. distress and headache and may enhance the effects of amphetamines, psychotropics and hydergine.

It has been given to children with dyslexia and in people with Alzheimer's disease to increase learning and memory. It may increase muscarinic cholinergic receptors in the brain?

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