DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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FEB 4 2013

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Re: Docket No. FDA-2009-P-0216

Dear Ms. Rattray,

This letter is a response to a citizen petition submitted by Ortho-Biotech Products, L.P. (Ortho-Biotech) that was received by the Food and Drug Administration (FDA or the Agency) on March 8, 2009, and assigned docket number FDA-2009-P-0216 (the Petition). In your petition, you request that FDA adopt certain requirements relating to the demonstration of sameness and bioequivalence required for the approval of any abbreviated new drug application (ANDA) or 505(b)(2) new drug application (NDA) for any product relying on Doxil (doxorubicin hydrochloride (HCl) liposome injection) as its listed drug.[1] These requirements include: (1) pharmacokinetic properties equivalent to those exhibited by Doxil; (2) the same physicochemical properties as Doxil as specifically enumerated in the Petition; and (3) comparable effectiveness and safety to Doxil as demonstrated in clinical and other studies recommended in the petition.[2] Specifically, you request that FDA require clinical studies to demonstrate that ovarian cancer patients treated with the generic product experience a clinical benefit similar to that resulting from treatment with Doxil, and that the level of cardiotoxicity of the generic product be no greater than that of Doxil.[3]

We have carefully considered your petition. For the reasons described below, your petition is granted in part and denied in part. We grant your request that applicants seeking approval of generic liposomal doxorubicin injection products demonstrate equivalence to Doxil in pharmacokinetic properties and sameness in key physicochemical properties. We deny your request that such products demonstrate comparable effectiveness and safety in clinical trials.

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[1] Petition at 1. For convenience, this response will refer to a liposomal doxorubicin product referencing Doxil as a "generic liposomal doxorubicin product" regardless of whether approval is being sought under an ANDA or a 505(b)(2) NDA.

[2] Id.

[3] Id. at 28-29.

I. BACKGROUND

A. Doxil

Doxil (NDA 050718), initially approved by FDA on November 17, 1995, is a pegylated liposome formulation of doxorubicin HCl encapsulated in liposomes for intravenous administration and approved for the treatment of AIDS-related Kaposi's sarcoma (KS), ovarian cancer (OC), and multiple myeloma. The active ingredient, doxorubicin HCl, is a cytotoxic anthracycline topoisomerase inhibitor, and was first approved in a non-liposome formulation (Adriamycin, NDA 050467) on August 7, 1974. Your petition states that the liposomes employed in Doxil are microscopic (80 to 100 nanometer (nm)) vesicles with a lipid bilayer the surfaces of which have a coating of methoxypolyethylene glycol (MPEG), and an aqueous core with entrapped doxorubicin HCl.[4] The lipid bilayer is composed of fully hydrogenated soy phosphatidylcholine (HSPC), cholesterol, and lipids (1,2-distearoyl-sn-glycero3-phosphoethanolamine sodium salt (DSPE)) a small percentage of which have been modified to allow for covalent binding to MPEG at a specific molar ratio.[5] The pegylation of Doxil helps the liposomes avoid detection by the body's reticuloendothelial system,[6] and reduces liposome adhesion to cells and blood vessel walls, resulting in longer circulation times in the bloodstream. The longer circulation times allow greater uptake of the liposomes by tumor tissue and subsequent release of the encapsulated doxorubicin in the tumor tissue.[7] This is important because in vivo, Doxil liposomes accumulate in tumor sites due to the enhanced permeability and retention (EPR) effect.[8] The mechanism for the EPR effect is that leaky microvasculatures and impaired lymphatics at tumor sites allow long circulating liposomes in the Doxil liposomes size range (100 nm) to extravasate into and accumulate within tumors.[9]

B. Statutory and Regulatory Requirements

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) established two abbreviated pathways for drug product approval: the pathway described in section 505(j) of the Federal Food, Drug and Cosmetic Act (FD&C Act) (U.S.C. 355(j)) and the pathway described in section 505(b)(2) of the FD&C Act.[10] Section 505(j) describes the ANDA approval process. To

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[4] Id. at 4-5, 22.

[5] Id. at 4, 21.

[6] Also often referred to in the scientific literature as the "mononuclear phagocyte system" (MPS).

[7] Petition at 5.

[8] Id. at 5-6.

[9] Id. at 22.

[10] Section 505(b)(2) of the FD&C Act was also enacted as part of the Hatch-Waxman Amendments. A 505(b)(2) application is an NDA that relies for approval, at least in part, on data and information that are

obtain approval of an ANDA, an applicant does not need to provide independent evidence of safety and effectiveness but, instead, relies on the finding of safety and effectiveness for a drug that has been previously approved. An ANDA must identify a listed drug on which it seeks to rely and, with limited exceptions, an ANDA must have the same active ingredient, strength, dosage form, route of administration, conditions of use, and labeling as the listed drug it references (sections 505(j)(2)(A) and (j)(4) of the FD&C Act). An ANDA applicant must establish that its drug is bioequivalent to the listed drug it references.

1. The Agency's Flexibility in Establishing Bioequivalence Requirements

The FD&C Act, applicable regulations, and case law give FDA and ANDA applicants considerable flexibility in determining how the requirement for establishing bioequivalence can be met. Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the RLD if the following conditions exist:

> . . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . . .[11]

FDA's regulations reflect the flexibility that FDA has in choosing the appropriate methods to establish bioequivalence for particular drug products. In 21 CFR 320.1(e), FDA defines bioequivalence (in part) as:

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not owned by the applicant and to which the applicant does not have a right of reference. The requirements for applications approved using the section 505(b)(2) pathway differ from the requirements for ANDA approval under section 505(j) of the FD&C Act.[10] A 505(b)(2) application, like any drug approved in an NDA, must contain information adequate to show that the drug is safe and effective. The Agency may approve 505(b)(2) applications that rely on published literature or on the Agency's finding of safety and effectiveness for another listed drug product, provided that such reliance is scientifically justified and the 505(b)(2) applicant complies with the applicable statutory requirements regarding patent certification. A 505(b)(2) applicant must also submit data necessary to support the safety and effectiveness of any aspects of the proposed drug product that represent modifications to or changes from the listed drug on which it relied. See FDA draft guidance for industry *Applications Covered by Section 505(b)(2)* (64 FR 68697, December 8, 1999), available on the internet at http://www.fda.gov/Drugs under Guidances. This draft guidance, when finalized, will represent FDA's current thinking on this topic. See also October 14, 2003, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Katherine Sanzo, et al., Docket Nos. 2001P-0323, 2002P-0447, and 2003P-0408.

We note that your petition relates only to the standards that you believe FDA should apply when a evaluating a new drug application for a liposomal doxorubicin product that is considered to be therapeutically equivalent to Doxil. Although bioequivalence to the listed drug is not a required element for approval of a 505(b)(2) application, to the extent that approval of a 505(b)(2) application for a liposomal doxorubicin product that is therapeutically equivalent to Doxil requires consideration of whether the product is bioequivalent to Doxil, similar principles would apply with respect to a showing of bioequivalence regardless of whether an applicant submits an ANDA or 505(b)(2) application.

[11] *See also* 21 CFR 320.1(e) and 320.23(b).

> . . . the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Although an ANDA applicant is required to submit "[e]vidence demonstrating that the drug product that is the subject of the [ANDA] is bioequivalent to the reference listed drug[,]"[12] the regulations explicitly permit submission of "information to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence. . . "[13]

The regulations also make it clear that although in vivo studies may be the preferred approach to demonstrate bioequivalence in many cases, they are not the only permissible one. On the contrary, under the regulations, "bioequivalence may be demonstrated by several in vivo and in vitro methods."[14] The regulations provide the following:

> FDA may require in vivo or in vitro testing, or both, to . . . establish the bioequivalence of specific drug products . . . The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of . . . establishing bioequivalence, as appropriate, for the product being tested.[15]

FDA's regulations at 21 CFR 320.24 describe these methods in descending order of accuracy, sensitivity, and reproducibility as follows: (1) in vivo pharmacokinetic studies, (2) in vivo pharmacodynamic effect studies, (3) comparative clinical endpoint studies, and (4) in vitro studies. In addition, consistent with section 505(j)(8)(C) of the FD&C Act, § 320.24(b)(6) of the regulations states that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."

If FDA determines that in vivo data is the appropriate means of demonstrating bioequivalence for a product or product class, 21 CFR 320.21(f) provides that applicants may apply for a waiver of such a requirement consistent with § 320.22.[16] That regulation in turn directs that, subject to the exceptions described below, FDA "shall" waive that in

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[12] 21 CFR 320.21(b)(1).

[13] 21 CFR 320.21(b)(2).

[14] 21 CFR 320.24(a).

[15] Id.

[16] 21 CFR 320.21(f) ("Information to permit FDA to waive the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence shall meet the criteria set forth in § 320.22.").

vivo requirement upon a subsequent showing that the individual applicant's product meets certain additional criteria.[17] For example, FDA's regulations provide that the Agency shall waive the requirement for submission of in vivo data for a parenteral solution intended solely for administration by injection, or for an ophthalmic or otic solution, if the ANDA applicant demonstrates that its product contains the same active and inactive ingredients in the same concentration as the reference listed drug.[18] Even in instances in which the additional criteria set forth in § 320.22(b) - (d) are met, however, FDA may require in vivo data if the Agency determines that any differences between the drug product and the RLD may affect the bioequivalence of the drug product.[19] 21 CFR 320.22 also provides that FDA "may" waive any agency-imposed in vivo bioequivalence data requirement for a particular product "for good cause ... if waiver is compatible with the protection of the public health."[20] Taken together, these provisions underscore FDA's discretion to determine the most appropriate bioequivalence methodology for each product.[21]

The Agency's authority to make bioequivalence determinations on a case-by-case basis using in vivo, in vitro, or both types of data enables FDA to effectuate several long-recognized policies that protect the public health: (1) refraining from unnecessary human research when other methods of demonstrating bioequivalence meet the statutory and regulatory standards;[22] (2) permitting the Agency to utilize the latest scientific advances in approving drug products;[23] (3) protecting the public by ensuring only safe and

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[17] 21 CFR 320.22(a).

[18] 21 CFR 320.22(b)(1). *See generally*, 21 CFR 320.22(b) - (d) (additional categories of products for which waivers of an in vivo data requirement may be sought).

[19] 21 CFR 320.22(f).

[20] 21 CFR 320.22(e).

[21] FDA also has the discretion to waive any requirement set forth in subpart C of part 314, which sets forth the approval scheme for ANDAs. *See* 21 CFR 314.99(b) ("An applicant may ask FDA to waive under this section any requirement that applies to the applicant under 314.92 through 314.99. The applicant shall comply with the requirements for a waiver under 314.90"). As FDA noted with respect to the analogous § 314.90, such waivers are intended "to give applicants the flexibility to seek alternative ways of complying with the regulatory requirements for drug approval." *New Drug and Antibiotic Regulations*, 50 Fed. Reg. 7452, 7490 (Feb. 22, 1985).

[22] 21 CFR 320.25(a) ("guiding principle" that "that no unnecessary human research should be done" expressed in regulation addressing conduct of an in vivo bioavailability study); *Abbreviated New Drug Application Regulations,* proposed rule, 54 Fed. Reg. 28872, 28883 (July 10, 1989) (in discussing § 320.22, stating "the agency does not believe that Congress intended that unnecessary human research be conducted ... if the agency concludes that bioequivalence can be demonstrated by in vitro tests").

[23] *Bioavailability and Bioequivalence Requirements: Procedures for Establishing a Bioequivalence Requirement*, 42 Fed. Reg. 1624, 1629 (Jan. 7, 1977) (in promulgating final bioequivalence regulations, FDA noted that "[a]s with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement").

effective generic drugs are approved for marketing;[24] and (4) making more safe and effective generic drugs available.[25]

Ultimately, under the statute and regulations, the choice of appropriate bioequivalence study design is based on the ability of the study to compare the drug delivered by the two products at the particular site of action of the drug, and Congress assigned this decision to FDA. Congress intended to grant FDA wide discretion to establish bioequivalence standards on a drug-by-drug basis when it enacted the Hatch-Waxman Amendments,[26] and courts that have considered FDA's bioequivalence determinations consistently have upheld FDA's scientific discretion to determine how the bioequivalence requirement should be met for a given product or class of products.[27]

2. Sameness Requirements for Parenteral Drugs

Although products for oral administration may be approved under ANDAs even though they have different excipients (inactive ingredients) than the innovator products they reference, for ANDAs for parenteral drug products, the only differences in excipients that are routinely permitted are changes in an antioxidant, a preservative, or a buffer. 21 CFR 314.94(a)(9)(iii) concerning the content and format of an ANDA states the following:

> Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant. . . . However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information

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[24] *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 650 (D.D.C. 1992) (citing as one underlying policy of the Hatch-Waxman Amendments to "ensure the safety of these drugs before they are substituted for their name-brand counterparts").

[25] Id. (purposes of Hatch Waxman Amendments are "to make more inexpensive generic drugs available" and "to ensure the safety of these drugs"); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 866-67 (D.D.C. 1994) (bioequivalence waiver provision "comports with the structure and broader policy objectives of the Hatch-Waxman Act[,]" including making safe and affordable generic drugs available).

[26] *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) ("there is no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for the purposes of ANDA approval"); *Bristol-Myers Squibb v. Shalala*, 923 F. Supp. 212, 217 (D.D.C. 1996) ("the expressed desire of Congress, through the 1984 amendments, was that FDA retain its historically wide discretion in defining showings of bioequivalence") (internal citation and quotation omitted).

[27] *Schering Corp.*, *supra* note 26 at 397-400; *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 19 (D.D.C. 2009) (the "high degree of deference" given to FDA's scientific determinations "has been applied to the FDA's determinations regarding which methodologies it determines are needed to test the bioequivalency of a given generic."); *Fisons Corp*, *supra* note 25 at 866-67 ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion."); *Sullivan*, *supra* note 24 at 651 (deference afforded Agency's determination so long as it is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion").

> demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

21 CFR 314.127(a)(8)(ii)(B), the corresponding provision that addresses the refusal to approve an ANDA, provides the following:

> FDA will consider an active ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the [ANDA] unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

Thus, parenteral drug products that differ from the listed drug in inactive ingredients other than differences in preservatives, buffers, or antioxidants are not approvable in an ANDA but may, instead, be the subject of a 505(b)(2) application.

C. Draft Guidance on Demonstration of Bioequivalence for Doxorubicin Hydrochloride Liposome Products.

In February 2010 the Agency published a draft guidance for industry *Doxorubicin Hydrochloride (Liposomal Injection)* (herein referred to as the Doxorubicin Draft BE Guidance) as part of its ongoing endeavors to provide bioequivalence recommendations for specific products through guidance.[28] This draft guidance recommends that, as a scientific matter, human pharmacokinetic studies and in vitro dissolution studies, as well as a showing of sameness of certain physicochemical characteristics, be used to demonstrate bioequivalence for an injectable pegylated doxorubicin hydrochloride liposome product.[29] With respect to physicochemical sameness, the Doxorubicin Draft BE Guidance recommends that the proposed drug product show sameness to Doxil with respect to the following characteristics: (1) liposome composition; (2) state of encapsulated drug; (3) internal environment of liposome (volume, pH, sulfate and ammonium ion concentration); (4) liposome morphology and lamellarity (number of lamellae); (5) liposome size distribution; (6) electrical surface potential or charge; (7) in vitro leakage rates under multiple conditions; (8) grafted PEG at the liposome surface;

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[28] See Bioequivalence Recommendations for Specific Products in draft guidance for industry *Doxorubicin Hydrochloride (Liposomal Injection)*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf, (doxorubicin draft bioequivalence (BE) guidance) (Docket No. FDA-2007-D-0369); see also *Draft and Revised Draft Guidances for Industry Describing Product-Specific Bioequivalence Recommendations; Availability*, 77 Fed. Reg. 3777 (Jan. 25, 2012), a Federal Register notice announcing draft product-specific recommendations, either new or revised, that were posted on FDA's web site in the period from December 1, 2009, through June 30, 2011.

[29] See Doxorubicin Draft BE Guidance, generally.

and (9) lipid bilayer phase transitions.[30] With respect to in vivo pharmacokinetic studies, the Doxorubicin Draft BE Guidance recommends that in vivo bioequivalence (90% confidence interval (CI)) be based on the pharmacokinetic measures area under the curve (AUC) and peak concentration (C_{max}) for both free doxorubicin and liposome encapsulated doxorubicin measured in ovarian cancer patients[31] who were given a single dose of 50 milligram/meter^2 (mg/m)^2.[32] The measurement of both free and liposomal doxorubicin is recommended to demonstrate that the generic doxorubicin and Doxil have the same in vivo stability.

Because liposome size distribution is crucial to tissue distribution of liposomal doxorubicin hydrochloride, the Doxorubicin Draft BE Guidance specifically recommends that population bioequivalence be demonstrated with respect to the mean particle size and by a measure of the width of distribution using either a polydispersity index or a Span $(D_{90}-D_{10})/D_{50}$.[33] The guidance recommends that in vitro liposome characterization should be conducted on at least three batches of the ANDA and RLD products, and that at least one of the ANDA batches should be produced by the commercial scale process and used in the in vivo bioequivalence study."[34]

An objective of the Doxorubicin Draft BE Guidance is to ensure that, like other parenteral drug products, any generic doxorubicin HCl liposome injection be qualitatively and quantitatively the same as Doxil (except for permissible differences in buffers, preservatives and antioxidants), as required by FDA's regulations.[35] The guidance states, and the Agency expects, that any such differences must be identified and characterized, and, as required by FDA's regulation at 21 CFR 314.94(a)(9)(iii), the generic applicant must demonstrate that the differences do not affect the safety and efficacy profile of the drug product.[36]

Finally, the Doxorubicin Draft BE Guidance recommends that the active liposome loading process of doxorubicin hydrochloride be conducted under an ammonium sulfate gradient in order to have the same drug composition as Doxil and meet other

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[30] Doxorubicin Draft BE Guidance at 3-4.

[31] The Doxorubicin Draft BE Guidance specifically recommends that these patients be those whose disease has progressed or recurred after platinum-based chemotherapy.

[32] Doxorubicin Draft BE Guidance at 2.

[33] Id. at 1.

[34] Id. at 2.

[35] See discussion in Section I.B.2.

[36] As stated in the Doxorubicin Draft BE Guidance, currently, FDA has no recommendations for the type of studies that would be needed to demonstrate that differences in buffers, preservatives and antioxidants do not impact the safety/efficacy profile of the drug product (Id.).

bioequivalence tests.[37] The guidance recommends that the optimal values of critical process parameters be selected to meet the same liposome characteristics as those of Doxil. For instance, because lipid excipients are critical in liposome formulation, the guidance recommends that generic applicants obtain lipids from the same category of synthesis route (natural or synthetic) as found in Doxil, and that detailed information on the chemistry, manufacturing and control of the lipid components, specification on lipid excipients, and additional comparative characterization be provided.[38]

II. SPECIFIC ASSERTIONS IN THE PETITION

A. Although Pharmacokinetic Studies are Inadequate to Demonstrate the Bioequivalence of Liposomal Doxorubicin Products, a Generic Liposomal Doxorubicin Product Based on Doxil Must Have Pharmacokinetic Properties Equivalent to Doxil's.

You assert that "FDA is authorized to approve a generic version of Doxil only if the generic product is determined to be bioequivalent to Doxil."[39] You state, however, that "[t]he usual method of determining bioequivalence by pharmacokinetic profiles of two products [i.e., an in vivo measurement of the concentration of the active ingredient or active moiety in whole blood, plasma, serum, or other appropriate biological fluid measured as a function of time] is not appropriate in the case of liposomal doxorubicin products."[40] You assert that the reason for this is that unlike other parenteral drugs, Doxil is designed to preferentially release the active ingredient in tumor tissue, a process that depends on the chemical and physical breakdown of liposomes in tumor tissue leading to release of free doxorubicin.[41] You thus conclude that because Doxil is designed to preferentially release the active ingredient in tumor tissue, "there is no reason to believe that PK studies are adequate to demonstrate the bioequivalence of liposomal doxorubicin products," and that "measurement of drug levels in the blood alone would not be a sufficient method of determining whether a generic version has the same clinical effect as Doxil."[42]

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[37] Doxorubicin Draft BE Guidance at 2-3. Note that many of the critical parameters for the ammonium sulfate gradient loading process for Doxil have been disclosed in published literature.

[38] Doxorubicin Draft BE Guidance at 2, referencing Draft guidance for industry: *Liposome drug products chemistry, manufacturing, and controls; human pharmacokinetics and bioavailability; and labeling documentation*, FDA (2002) (draft liposome drug products guidance), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070570.pdf.

[39] Petition at 8.

[40] Id. at 1, 9.

[41] Id. at 9.

[42] Id.

Specifically, you assert that nonclinical studies strongly indicate that equivalent pharmacokinetics of liposomal doxorubicin products do not ensure equivalent clinical effectiveness and safety.[43] To support your assertion, you cite a study published in 2007 comparing two pegylated liposomal doxorubicin products with the same lipid composition and drug/lipid ratio but different vesicle diameters and internal ammonium sulfate composition that showed similar overall pharmacokinetic profiles in both normal and tumor-bearing mice, but different antitumor efficacy.[44] You also provide data from studies conducted by you that showed that formulation variants having pharmacokinetic profiles similar to that of Doxil showed different anti-tumor efficacy and toxicity profiles relative to Doxil.[45]

You also state that "[i]f a generic pegylated doxorubicin product does not display the same behavior in vivo as Doxil, it could result in reduced efficacy by reducing drug accumulation in tumors and increased toxicity, including cardiotoxicity, due to an increase in the systemic release of doxorubicin as compared to Doxil."[46]

You thus conclude that "although pharmacokinetic studies cannot properly serve as the basis for determining whether a generic product and Doxil are bioequivalent, pharmacokinetic studies should still be required since a generic product with a different pharmacokinetic profile is likely to have different clinical effects."[47] Specifically, you assert that it is important to have equivalent systemic levels because of the known serious side effects of doxorubicin including cardiotoxicity.[48]

B. Although a Demonstration of Physicochemical Sameness is Inadequate to Ensure Bioequivalence, as a Threshold Matter Any Generic Liposomal Doxorubicin Product Should Have the Same Physicochemical Properties as Doxil.

You state that FDA should require a showing of sameness of the physicochemical characteristics of a generic liposomal doxorubicin product to Doxil, similar to the Agency's requirement for other generic products for which bioequivalence to the reference listed drug cannot be demonstrated by ordinary methods.[49] You identify a number of identifiable physicochemical factors that you assert affect drug release and

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[43] Id.

[44] Id. at 9-10.

[45] Id. at 11-19.

[46] Id. at 9.

[47] Id. at 29.

[48] Id.

[49] Id. at 20.

delivery in the case of liposomal doxorubicin products, and state that as a threshold matter, FDA should require a generic product to be the same as Doxil in these respects.[50]

Specifically, you identify the following physicochemical characteristics for which any generic liposomal doxorubicin product to Doxil should demonstrate sameness: "(1) the composition of the lipid bilayer, (2) net charge, (3) mean particle size and particle size distribution, (4) the degree of lamellarity, (5) the percentage of drug encapsulation, (6) the drug-to-lipid ratio, (7) the concentration of ammonium sulfate within the liposomes, (8) the doxorubicin sulfate precipitate structure within the liposome, and (9) the in vitro integrity of the liposomes."[51] You state that, as reflected in FDA's draft liposome drug products guidance,[52] and your own experience, these are characteristics that potentially affect the safety and efficacy of any liposomal doxorubicin product.[53]

You state, however, that demonstrating physicochemical sameness is not adequate to ensure the bioequivalence of liposomal doxorubicin products because of the fundamental shortcoming of most currently available physicochemical tests, i.e., that they measure only the average value of the criterion involved.[54] You state that even if tests may show that mean liposome physicochemical parameters are the same, the distributions around the means may be very different.[55] Such differences in distributions, you believe, can affect the clinical performance of the product.[56] Moreover, you also assert that such tests do not provide information on individual liposome parameters within the total population of liposomes present in a particular sample.[57] To show that distributional differences matter, you claim that the pharmacokinetic profile of a liposomal doxorubicin formulation in which approximately half the liposomes were coated with 1 mole% PEG, and the other half with 9 mole% PEG for a mean PEG coverage of 5.3 mole% was different from that of Doxil, which had a mean PEG coverage of 5 mole% PEG.[58]

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[50] Id. at 1.

[51] Petition at 20.

[52] Draft liposome drug products guidance, *supra* note 38.

[53] Petition at 20.

[54] Petition at 27. You state that the exceptions are the tests for particle size distribution and degree of lamellarity which do take into account the distribution of values across the entire set of liposomes. You also state that the percentage of drug encapsulation is not an issue related to variations among liposomes.

[55] Id.

[56] Id. For instance, you state that there are currently no analytical methods that can determine pegylation coverage of a single liposome in a particular population of liposomes or vial of product.

[57] Id.

[58] Id. at 27-28.

C. Clinical Studies Should Be Required to Determine Bioequivalence.

You assert that because "the sameness of physicochemical characteristics as established by the available tests will not ensure that two liposomal doxorubicin products are bioequivalent," . . . "a generic product should demonstrate comparability to Doxil based on efficacy endpoints in a clinical trial, as was used in the approval of Doxil."[59] You state that because Doxil was initially approved for marketing based on response rate in a single-arm study of patients with refractory ovarian cancer, the generic product applicant should "be required to submit scientifically sufficient clinical study data demonstrating that ovarian cancer patients treated with the generic product will achieve a clinical benefit [based on efficacy and safety endpoints] similar to the results from treatment with Doxil."[60] You also state that "[i]n addition, the generic product should demonstrate comparability to Doxil on a key safety parameter — the risk of myocardial damage" . . . and that the generic product "should not be approved if it demonstrates cardiotoxicity greater than Doxil where "[c]ardiotoxicity was defined as a decrease of more than 20% from baseline [left ventricular ejection fraction] LVEF if LVEF remained in the normal range, or a decrease of more than 10% if the LVEF became abnormal."[61]

III. DISCUSSION

The Agency recognizes that for complex, liposomal drug products such as Doxil that are designed to selectively accumulate at tumor sites, equivalence in pharmacokinetic measurements of systemic exposure alone may not be predictive of equivalent drug concentrations in the targeted tumor tissues. Moreover, because a direct correlation between plasma and target tumor tissue concentrations has not been established, the Agency recognizes that determining the bioequivalence of liposomal products such as Doxil presents challenges. However, advances in analytical and bioanalytical technologies, an understanding of critical physicochemical and pharmacokinetic attributes, and recognition of the critical manufacturing processes for Doxil have allowed the Agency to establish a novel bioequivalence method under which bioequivalence between doxorubicin liposomal products may be established. This method, described in the Doxorubicin Draft BE Guidance, employs not only plasma pharmacokinetic data, but also a comprehensive demonstration of sameness in product composition, liposome drug loading process, and physicochemical properties described in Section I.C.[62]

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[59] Id. at 28.

[60] Id. at 28-29.

[61] Id. at 29.

[62] Although the Agency generally grants a bioequivalence waiver for parenteral drug products if the ANDA applicant demonstrates that its product contains the same active and inactive ingredients in the same concentration as the reference drug, the Agency recognizes that such a waiver would not be appropriate for generic versions of Doxil given the complexity of the drug.

Specifically, the Agency currently believes that although blood/plasma pharmacokinetic studies alone, or characterization of physicochemical properties alone, are not adequate to demonstrate bioequivalence between a generic doxorubicin liposomal product and Doxil, these methodologies (in combination with use of the same liposome drug loading process) together provide a scientifically sound and reliable demonstration of bioequivalence. Such a characterization of doxorubicin HCl liposome injection products ensures qualitative similarity between generic and reference listed products (Q1), quantitative similarity of composition (Q2), and structural similarity (Q3 —the physical attributes and higher order arrangement of the product).

The Agency remains confident that the scientific principles upon which this method is based are sound, and believes that the application of these principles, as described in the draft doxorubicin BE guidance, is consistent with your request that a generic doxorubicin product referencing Doxil have equivalent pharmacokinetic properties, and the same physicochemical properties as those of Doxil.[63] The Agency, however, disagrees with your assertions that a showing of equivalence of pharmacokinetic properties together with a showing of sameness for certain physicochemical factors has serious shortcomings that necessitate the need for clinical studies.

With respect to pharmacokinetic studies, you state in the Petition that "there is no reason to believe that pharmacokinetic studies are adequate to demonstrate the bioequivalence of liposomal doxorubicin products."[64] You state this in part because Doxil is designed to preferentially release doxorubicin HCl at tumor sites, a process that is dependent on the chemical and physical breakdown of liposomes in tumor tissue leading to the release of free doxorubicin within the tissue.[65] You thus state that measurement of drug levels in the blood alone would not be an adequate method to determine bioequivalence. However, with advances in bioanalytical technologies, both free and encapsulated doxorubicin can now be accurately measured, and in its Doxorubicin Draft BE Guidance, the Agency recommends that a generic applicant demonstrate equivalence of both.[66]

The Agency also believes that in addition to blood/plasma concentrations, drug loading mechanism, particle size distributions, liposome composition and many other physicochemical properties profoundly affect the stability of the drug product and the

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[63] It is important to note that, as the Doxorubicin Draft BE Guidance makes clear, recommendations set forth in guidances are not mandatory, and FDA is unwilling to make them an absolute requirement for all pending and future applications for liposomal doxorubicin products. As with Agency guidance in general, these recommendations describe the Agency's current thinking and should be viewed as recommendations unless specific regulatory or statutory requirements are cited. The Agency is not bound by recommendations made in a draft or final guidance and, as noted above, the laws and regulations governing ANDAs and BE permit flexibility in the submission and review of BE data. As such, the Agency will not foreclose the possibility that an applicant could satisfactorily demonstrate BE to Doxil using other methods.

[64] Petition at 9.

[65] Id.

[66] Doxorubicin Draft BE Guidance at 1.

availability of doxorubicin at the target sites. For instance, to achieve therapeutically effective drug concentrations at the targeted tissue sites, it is critical to achieve high drug loading into the liposomes and to ensure that doxorubicin will not leak out of the liposomes during circulation. This attribute is controlled by the drug loading mechanism, the state of encapsulated doxorubicin, and the properties of the lipid bilayer.

Specifically, the manufacturing of Doxil involves: (1) a highly efficient ammonium sulfate gradient loading process in which the ammonium sulfate is encapsulated at an internal concentration of 250 millimolar when the liposome is created; and (2) exposure of the liposome to doxorubicin, which diffuses into the liposome and precipitates to form a gel-like amorphous solid. The gel state increases the stability of the doxorubicin, effectively trapping the doxorubicin in the liposomal interior such that the percentage of encapsulated drug reaches at least 90% of the total drug. The intra-liposomal environment is maintained by the careful selection of the buffer/salt system which may contain histidine, hydrochloric acid and/or sodium hydroxide, and sucrose. Other critical parameters during the loading process include the internal ammonium sulfate concentration,[67] buffer contents and buffer pH. These parameters affect the in vitro and in vivo stability of Doxil (i.e. leakage of doxorubicin from the liposomes). Lipid bilayer properties, such as lipid contents, also have been identified as critical factors that influence the in vitro and in vivo stability of encapsulation and the efflux rate of encapsulated material.

Once equivalent liposome distribution in tumor tissues is reached, equivalent in vivo pharmacokinetics and in vitro liposome characteristics are expected to result in equivalent drug delivery into tumors. For example, the characterization of liposome surface chemistry is a means of assessing the equivalence of liposome-cell interactions involved in liposome fusion or uptake by tumors. Equivalence in liposome internal environment, size distribution, state of encapsulated doxorubicin, and drug leakage ensures equivalent drug leakage around tumor tissues or inside tumor cell endosomes or lysosomes. Plasma pharmacokinetics of free drug reflects the amount of drug released from the liposomes. Moreover, it should be noted that the examples you cite in the Petition[68] further support the Agency's opinion that in determining bioequivalence, it is important to ensure sameness in certain critical characteristics (e.g., vesicle diameters and internal ammonium sulfate concentrations) of doxorubicin hydrochloride liposome injection products.

The Agency also disagrees with your assertion that equivalence in distributional properties of all the identified physicochemical properties is necessary to determine bioequivalence. The Agency believes that the average values of such physicochemical properties in liposomes are sufficient to represent test samples. For all physicochemical characterization tests, FDA recommends that applicants obtain data from at least three

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[67] Collapse or partial collapse of the ammonium sulfate gradient or an increase in phospholipase activity can lead to hydrolyzing of the liposome phospholipids, thereby destabilizing the liposome membrane.

[68] Petition at 9, 25.

batches. Repeated measures of the mean value provide estimates of the product variability and monitor batch-to-batch consistency. As for liposome particle size, the Agency requests an in vitro bioequivalence study on at least three lots of both test and reference products to demonstrate bioequivalence in liposome size distribution as determined by 95% upper confidence interval on D_{50} and $(D_{90}-D_{10})/D_{50}$ or polydispersity index using the population bioequivalence approach. The Agency also requests information regarding the distribution of the molecular species of lipid excipients. Moreover, changes in some physicochemical properties are often reflected in the altered plasma pharmacokinetics of free and liposome encapsulated doxorubicin. For example, distributional differences in the coverage of surface grafted PEG are readily reflected in altered plasma pharmacokinetic profiles.[69] However, if a physicochemical property (e.g., liposome particle size distribution) is known to affect tissue distribution and drug release at different sites of action but may not impact systemic pharmacokinetics, the Agency intends to request a demonstration of equivalence in distributional properties.

Finally, the Agency denies your request that clinical trials with an efficacy endpoint be required to demonstrate bioequivalence. The Agency does not believe that a bioequivalence study with a clinical endpoint is necessary from either a legal or scientific perspective. As a preliminary matter, your request reflects a misunderstanding of the approval process for generic drugs established under the Hatch-Waxman Amendments. To be approved, an ANDA is not required to demonstrate through clinical endpoint trials that its product is safe and effective for its labeled conditions of use. Rather, it can rely on the finding of safety and effectiveness of the RLD as long as the product meets other requirements of the statute, including a demonstration that the proposed generic product is bioequivalent to the RLD. The purpose of bioequivalence testing is not to measure safety or efficacy directly. Accordingly, in order to be approved, an ANDA applicant does not have to demonstrate that its product "will achieve a clinical benefit [based on efficacy and safety endpoints] similar to the results from treatment with Doxil" as you suggest.[70]

Although you state that FDA's regulations in 21 CFR 320.24(b)(4) identify drugs that deliver their active moieties locally as a type of product for which clinical trials can be an appropriate method of establishing bioequivalence,[71] the Agency remains unconvinced that the clinical endpoints employed in the clinical trials for the approval of Doxil are sensitive enough to capture differences between doxorubicin liposomal products. FDA's regulations warn that bioequivalence studies with clinical endpoints tend to be "the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence,"[72] and FDA believes that this

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[69] Id. at 27.

[70] Id. at 29.

[71] Id. at 28.

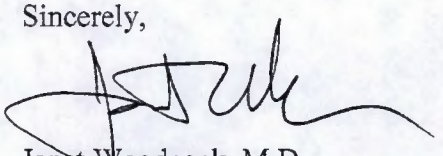
[72] "This approach [comparative clinical endpoint trials] is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence" (21 CFR 320.24(b)(4)).

observation holds true with respect to Doxil as well. Specifically, FDA believes that clinical endpoints employed in the clinical trials for the approval of Doxil would be far less sensitive to potential formulation changes than pharmacokinetic studies. Furthermore, the Agency believes that demonstrations of equivalent in vivo pharmacokinetics and sameness in the specified physicochemical properties described in the Doxorubicin Draft BE Guidance are adequate to demonstrate bioequivalence by showing the same in vivo drug release, systemic exposure, tissue distribution, and cellular uptake of the active pharmaceutical ingredient.

IV. CONCLUSION

For the reasons stated above, your petition is granted in part and denied in part.

Sincerely,



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