U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

TO: File

FROM: Center for Drug Evaluation and Research

DATE: July 29, 2020

SUBJECT: Clinical need for trichloroacetic acid (TCA) in compounding under section 503B of the FD&C Act

This memorandum reflects the discussions of the 503B Working Group, comprised of representatives from the following: CDER Office of New Drugs, Office of Pharmaceutical Quality, Office of Regulatory Policy, Office of Compliance, and Office of Regulatory Affairs.

The Food and Drug Administration (FDA or Agency) is developing a list of bulk drug substances that can be used in compounding under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b). Section 503B of the FD&C Act describes the conditions that must be satisfied for drug products compounded by an outsourcing facility to be exempt from requirements concerning FDA approval prior to marketing (section 505 (21 U.S.C. 355)); labeling of drugs with adequate directions for use (section 502(f)(1) (21 U.S.C. 352(f)(1))); and drug supply chain security requirements (section 582 (21 U.S.C. 360eee-1)).[1]

To qualify for the exemptions available in section 503B of the FD&C Act, a drug product must be compounded in an outsourcing facility that does not compound using bulk drug substances unless: (1) the bulk drug substance appears on a list established by the Secretary of Health and Human Services identifying bulk drug substances for which there is a clinical need (the 503B Bulks List), or (2) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FD&C Act (21 U.S.C. 356e) at the time of compounding, distribution, and dispensing.

This memorandum evaluates trichloroacetic acid (TCA) for the 503B Bulks List as a chemical skin peeling agent for the treatment of acne and melasma under the "clinical need" standard in section 503B of the Act.[2]

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[1] In general, drug products compounded under the conditions in section 503B must meet current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)). Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound. Outsourcing facilities may or may not obtain prescriptions for identified individual patients and can, therefore, distribute compounded drugs to healthcare practitioners for "office stock," to hold in their offices in advance of patient need.

[2] The proposed use as a "chemical peel" refers to a procedure rather than a recognized medical condition. However, we have considered information about use of TCA as a chemical peel where relevant, including in discussion of

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We evaluated TCA for potential inclusion on the 503B Bulks List under the clinical need standard in section 503B, consistent with the interpretation and policies described in FDA's March 2019 guidance, "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (the Clinical Need Guidance). Because TCA is not a component of an FDA-approved drug, we did not ask the questions in the Part 1 analysis described in the Clinical Need Guidance. Consistent with the Part 2 analysis in the Clinical Need Guidance, we have considered data and information regarding the physical and chemical characterization of TCA, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding.[3] **For the reasons stated below, we conclude that the Agency should propose adding the bulk drug substance TCA to the 503B Bulks List with a limitation for topical use only.**

I. Background

A. Nominated Product

Sincerus Florida, LLC (Sincerus) nominated TCA for topical use as a chemical skin peeling agent for the treatment of acne and melasma (Docket No. FDA-2018-D-1067, document no. FDA-2018-D-1067-0005). (See Appendix A – Sincerus Nomination.)

B. Other Materials Reviewed

In addition to Sincerus's nomination for the 503B Bulks List, the Agency considered data and information from its earlier evaluation regarding the use of TCA for the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (21 U.S.C. 353a) (the 503A Bulks List) (the 503A Evaluation). TCA was nominated for use in compounding drug products under section 503A for topical use in the treatment of warts and as a chemical skin peeling agent.[4] FDA reviewed TCA in a September 29, 2016 memorandum to the Pharmacy Compounding Advisory Committee (PCAC). (See Appendix B – September 29, 2016 Memorandum.) At its meeting on November 3, 2016, the PCAC voted to include TCA for topical use on the 503A Bulks List.[5] FDA also consulted with the United States Pharmacopoeia Convention (USP) as part of the Agency's consideration of TCA for inclusion on the 503A

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reported adverse reactions from use of TCA in conditions potentially related to chemical peels (discussed in section II.B.2.a) and efficacy information from references about chemical peels in the nomination in section II.C.1.

[3] In particular, OPQ has reviewed the data and information regarding the physical and chemical characterization of TCA, OND has reviewed safety issues raised by use of this substance in compounding and available evidence of effectiveness or lack of effectiveness, and Compliance has reviewed information about the historical and current use in compounding.

[4] In the 503A Evaluation, the proposed use as a chemical peel referred to a procedure rather than a recognized medical condition. FDA considered information about use of TCA as a chemical peel where relevant, including in discussion of reported adverse reactions from use of TCA in conditions potentially related to chemical peels and efficacy information from references about chemical peels in the nomination for the 503A Bulks List.

[5] Materials from the PCAC's 2016 meetings are available on FDA's website at https://www.fda.gov/advisory-committees/pharmacy-compounding-advisory-committee/2016-meeting-materials-pharmacy-compounding-advisory-committee.

Bulks List. FDA has proposed to add this substance to the 503A Bulks List with a limitation for topical use only (84 FR 46688).[6]

FDA also considered the report provided by the University of Maryland Center of Excellence in Regulatory Science and Innovation (CERSI), (see Appendix C – CERSI Report on TCA) and conducted a search for relevant scientific literature and safety information, as described below in footnote 9, focusing on materials published or submitted to FDA since the 503A Evaluation.

II. Evaluation

A. Physical and Chemical Characterization

We agree with the conclusion in the September 29, 2016 memorandum to the PCAC that TCA, a small organic molecule, is well-characterized physically and chemically and is likely to be stable when refrigerated.[7] In addition, the preparation of this compound has been well developed. Likely impurities include monochloroacetic acid, dichloroacetic acid, residual starting materials such as acetic acid, and degradation products such as chloroform.

B. Safety Issues Raised by Use of the Substance in Compounding

We agree with the conclusions in the September 29, 2016 memorandum to the PCAC which reviewed nonclinical data and human safety data.

The September 29, 2016 memorandum did not identify any repeat dose dermal toxicity studies or dermal carcinogenicity studies conducted with TCA. Although the toxicity of TCA after topical administration has not been fully evaluated in nonclinical studies, the available animal data indicate that topical use of TCA does not raise serious safety issues for humans.[8]

> With regard to human safety data, there have been no clinical trials specifically designed to address the safety of TCA but safety assessments were among the study procedures in several clinical trials.[9] Reports of adverse reactions have included burning, pain,

[6] The Agency has not finalized the rulemaking at this time, but we have reviewed the comments submitted to the docket on the proposed rule.

[7] See Appendix B – September 29, 2016 Memorandum, at Section II.A.

[8] See Appendix B – September 29, 2016 Memorandum, at Section II.B.1.

[9] See Appendix B – September 29, 2016 Memorandum, at Section II.B.2.

In March and April 2020, a search of the FAERS, CAERS, EMBASE, PubMed, TOXNET, and Google/Google Scholar databases was conducted, focusing on materials published or submitted to FDA since the 503A Evaluation. Our determination regarding TCA's safety and efficacy profile is unchanged. The March 2020 FAERS search identified only two new reports both of which related to topical skin reactions and neither of which suggest new safety concerns for TCA. The March 2020 CAERS search identified two reports, both of which predated the 503A Evaluation. Moreover, while both CAERS reports involved severe burn, the concentration of TCA was not disclosed and the reported reactions are consistent with anticipated adverse effects -- especially with use of high concentrations of TCA. The other sources identified 25 new articles (see Section IV. - Bibliography) that relate to the use of compounded TCA for melasma and acne, including acne scars. While the 503A Evaluation for TCA related to use for warts and as a chemical skin peeling agent, it addressed TCA use for the treatment of melasma and

erythema, hyperpigmentation and hypopigmentation. Other adverse reactions reported were ulcerations, scarring, pustules, punctate keratitis and conjunctival infection.

Although adverse events were reported more frequently with higher concentrations, we recognize that current use of TCA includes strengths between 1% to 100% depending on the clinical presentation and the technique for peeling. The PCAC considered this range as standard of care at its meeting in November 2016, and the adverse reactions were readily manageable, especially since procedures using TCA have been routinely in an office setting. Therefore, we do not recommend an upper limit for TCA strength in compounding.

C. Available Evidence of Effectiveness or Lack of Effectiveness

Although TCA was not nominated for the 503A Bulks List specifically as a treatment for scarring or melasma, the September 29, 2016 memorandum considered several studies as potentially relevant for consideration of TCA as a chemical skin peeling agent.[10]

Leheta et al., (2011) compared percutaneous collagen induction and TCA chemical reconstruction of skin scars (CROSS) method for the treatment of atrophic acne scars and found that acne scarring improved in all subjects but improvement was not statistically significant between the groups. Lee et al. (2002), and Nofal et al. (2014) found improvement in atrophic acne scars from baseline after TCA peel but, similar to the Leheta study, the comparators were not FDA-approved therapies.

Kumari and Thappa (2010) compared the response of melasma in 40 Indian women with a minimum melasma area and severity index (MASI) of 10 to glycolic acid versus TCA for chemical peeling. The study found a reduction in MASI after 12 weeks in both groups but no significant difference between the groups. Hong et al. (2012), and Soliman et al. (2007) also evaluated the use of TCA peel in melasma. Both studies showed improvement of melasma from baseline after TCA peel but, similar to the Kumari study, the comparators are not FDA-approved therapies.

D. Historical and Current Use in Compounding

Historically, TCA has been used as a chemical peel for over 40 years and has been used in compounding for at least 20 years.[11] TCA and TCA solution are listed in the European Pharmacopeia (8th Edition, 2016, 8.8) and the British Pharmacopoeia (BP 2016).

Information obtained by CERSI from its review of articles, other materials, and interviews supports our assessment of the historical use and suggests a similar profile for the current use of

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acne. The findings in these new articles, albeit potentially promising in expanding the use of TCA in chemical peels, do not alter conclusions reached previously on the use of TCA in compounding for the treatment of melasma and acne.

[10] See Appendix B – September 29, 2016 Memorandum, at Section II.C, and footnote 7 above.

[11] See Appendix B – September 29, 2016 Memorandum, at Section II.D.

TCA. This information describes the use of TCA as therapy for acne scarring, among other uses, and reports TCA being held as "office stock" in advance of patient need.

III. Recommendation

TCA was nominated as a bulk drug substance for the 503B Bulks List to compound drug products for topical use at concentrations ranging from 6 percent to 20 percent as a chemical skin peeling agent for the treatment of acne and melasma.[12] The nominated bulk drug substance is not a component of an FDA-approved drug product. We evaluated TCA for potential inclusion on the 503B Bulks List under the clinical need standard in section 503B, considering data and information regarding the physical and chemical characterization of TCA, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding.

TCA is well characterized in its physical and chemical properties. Nonclinical evidence suggests that topical use of TCA does not raise serious safety issues for humans. Although there have been no clinical trials specifically designed to address the safety of TCA, safety assessments were among the study procedures in several clinical trials and reports of adverse reactions have included burning, pain, erythema, hyperpigmentation and hypopigmentation. More serious adverse reactions reported were ulcerations, scarring, and pustules. Adverse events were reported more frequently with higher concentrations. Several studies indicate that TCA may be effective as a chemical peel for the treatment of acne (Leheta et al., (2011)) and melasma (Kumari and Thappa (2010)), but there is a lack of evidence comparing TCA to FDA-approved drug products for those uses. TCA has been used, in the United States and worldwide, for dermatologic conditions for over 40 years and for at least 20 years in pharmacy compounding.

On balance, the physical and chemical characterization, safety, effectiveness, and historical and current use of TCA weigh in favor of including this substance on the 503B Bulks List. Accordingly, we propose adding TCA to the 503B Bulks List for topical dermal use only. Nominators did not submit, and we have not identified, significant evidence to support use in other routes of administration.

[12] See Docket No. FDA-2018-D-1067, document no. FDA-2018-D-1067-0005.

IV. Bibliography

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APPENDIX SECTION A

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April 13, 2018

FILED ELECTRONICALLY
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, Maryland 20852

Re: Docket No. FDA-2015-N-3469 for Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket - Allantoin

Dear Sir or Madam:

Sincerus Florida, LLC, located in Pompano Beach, Florida submits the attached nomination in accordance with the Notice published in the Federal Register for Docket No. FDA-2015-N-3469 Bulk Drug Substance's That Can Be Used To Compound Drug Products in Accordance With Section 503B of the Federal, Food, Drug and Cosmetic Act; Establishment of a Public Docket. For reasons set forth in the attached Excel Spreadsheet that complies with the data requirements established by the FDA, Sincerus submits the drug substance Allantoin for inclusion on the list of bulk drug substances that may be used in compounding by an outsourcing facility pursuant to Section 503B(a)(2)(A)(i) of the Federal Food, Drug, and Cosmetic Act.

If any further information is required, do not hesitate to contact me at (800) 604-5032 or via email at jliu@sincerususa.com.

Sincerely yours,

Jenny Liu, Pharm. D.
Pharmacist in Charge

Attachment 1: Nominated Drugs

1. 2-deoxy-d-glucose
2. Aluminum Chloride Hexahydrate
3. Coenzyme Q10
4. Lidocaine
5. Menthol
6. Miconazole Nitrate
7. Nystatin
8. Pramoxine Hydrochloride
9. Resorcinol
10. Tetracaine
11. Tranilast
12. Trichloroacetic Acid
13. Zinc Pyrithione

Bulk Drug Substance Nomination	
What is the name of the nominated ingredient?	Tricholoracetic Acid
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in §207.3(a)(4)?	Yes, Trichloroacetic Acid is an active ingredient as defined in 207.3(a)(4) because when added to a pharmacologic dosage form it produces a pharmacological effect. Lee, Jung Bock, et al. "Focal treatment of acne scars with trichloroacetic acid: chemical reconstruction of skin scars method." Dermatologic surgery 28.11 (2002): 1017-1021. Resnik, Sorrel S. "Chemical peeling wi h trichloroacetic acid." The Journal of dermatologic surgery and oncology 10.7 (1984): 549-550.
What is the chemical name of the substance?	2,2,2-trichloroacetic acid
What is the common name of the substance?	Trichloroacetic Acid, TCA
Does the substance have a UNII code?	5V2JDO056X
What is the chemical grade of the substance?	ACS
What is the strength, quality, stability, and purity of the ingredient?	C of A attached
How is the ingredient supplied?	Crystals
Is the substance recognized in foreign pharmacopeias or registered in other countries?	European Pharmacopeia
Has information been submitted about the substance to the USP for consideration of monograph development?	No
What medical condition(s) is the drug product compounded with the bulk drug substances intended to treat?	Acne, Melasma
Are there other drug products approved by FDA to treat the same medical condition?	There are no FDA approved chemical peel products.
If there are FDA-approved drug products that address the same medical condition, why is there a clinical need for a compounded drug product?	Chemical peels are discussed in the literature as options for treating disease such as acne or melasma, but there are not FDA approved drug products for this purpose.
Are there safety and efficacy data on compounded drugs using the nominated substance?	Pezeshkpoor F, et al. Comparative study of topical 80% trichloroacetic acid with 35% trichloroacetic acid in the treatment of the common wart. J Drugs Dermatol. 2012 Nov;11(11):e66-9. Taner ZM, et al. Therapeutic value of trichloroacetic acid in the treatment of isolated genital warts on the external female genitalia. J Reprod Med. 2007 Jun;52(6):521-5. Kumari R, Thappa DM. Comparative study of trichloroacetic acid versus glycolic acid chemical peels in the treatment of melasma. Indian J Dermatol Venereol Leprol. 2010 Jul-Aug;76(4):447. Spinowitz, AL. Stability-time profile of trichloroacetic acid at various concentrations and storage conditions. J Dermatol Surg Oncol. 1989 Sep;15(9):974-5. PMID: 2778186.
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?	There is no FDA approved drug product to compound from.
What dosage form(s) will be compounded using the bulk drug substance?	Topical solutions
What strength(s) will be compounded from the nominated substance?	6-20%
What are the anticipated route(s) of administration of the compounded drug products?	Topical
Has the bulk drug substance been used previously to compound drug product(s)?	Topical dermatological preparations as requested by prescribers.
Is there any other relevant information?	N/A

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CERTIFICATE OF ANALYSIS

PRODUCT: TRICHLOROACETIC ACID ACS REAGENT CRYSTALS
ITEM NUMBER: 50-1243
LOT NUMBER: C182786
MFG. DATE: 04/15/2017
EXPIRATION: 04/15/2019
CAS: 76-03-9
MW: 163.3900000000
FORMULA: CCl3COOH

TEST	SPECIFICATIONS	RESULTS
Assay	>=99.0 %	99.6 %
Chloride	<= 0.002 % max	0.002 % max
Clarity of solution	pass	pass
Description	pass *COLORLESS OR NEARLY COLORLESS, DELIQUESCENT PLATES, SCALES, OR CRYSTALS; SLIGHT CHARACTERISTIC ODOR; HYGROSCOPIC*	pass *Nearly Colorless Crystals*
Heavy metals	<=0.002 % max	0.002 % max
Identification	pass *TEST A 30% SOLUTION WITHIN A 24 HOUR PERIOD TO ENSURE NO APPARENT PARTICLES ARE PRESENT.*	pass
Insoluble matter	<=0.01 %	0.01 %
Iron	<= 0.001 % max	0.001 % max
Melting point	pass celsius *55-58C Or About 60C*	pass celsius *56.6 C*
Nitrate	<= 0.002 % max	0.002 % max
pH	pass *PH OF 0.1 MOLAR AQ SOLUTION 1.2*	pass *1.2*
Phosphate	<=5 ppm max *5 ppm max*	5 ppm max
Residue after ignition	<=0.03 % max	0.02 % max
Solubility	pass *SOLUBLE IN WATER WITH A CLEAR TO BROWNISH-YELLOW TINT; SOLUBLE IN ALCOHOL*	pass
Sub's darkened by H2SO4	pass	pass
Sulfate	<=0.02 % max	0.02 % max

QC APPROVED
PRINT DATE: 7/6/2017

APPENDIX SECTION B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: September 29, 2016

FROM: Ben Zhang, PhD
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Office of Pharmaceutical Quality

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Pharmacology/Toxicology Reviewer, Division of Dermatology and Dental Products

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Consumer Safety Officer, Office of Compliance, Office of Unapproved Drugs and Labeling Compliance (OUDLC)

THROUGH: Julie Beitz, MD
Director, Office of Drug Evaluation III

Kendall A. Marcus, MD
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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Trichloroacetic Acid for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

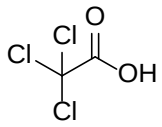
Trichloroacetic acid (TCA) has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for topical use in the treatment of common warts (verrucae vulgaris) and genital warts (condylomata accuminata), as well as for use as a chemical skin peeling agent.[1]

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 believe the evaluation criteria weigh ***in favor*** of placing trichloroacetic acid for topical use on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).[2]

II. EVALUATION CRITERIA

A. Is the substance well characterized, physically and chemically, such that it is appropriate for use in compounding?

Yes. TCA is a small organic molecule with the following molecular structure:



It is an analogue of acetic acid. This substance is currently marketed in cosmetics in various dosage forms.

Databases searched for information on TCA in regard to Section II.A of this review include PubMed, SciFinder, Analytical Profiles of Drug Substances, the European

[1] The proposed use as a *chemical peel* refers to a procedure rather than a recognized medical condition. However, we have considered information about use of TCA as a chemical peel where relevant, including in discussion of reported adverse reactions from use of TCA in conditions potentially related to chemical peels (discussed in section II.B.2.a) and efficacy information from references about chemical peels in the nomination in section II.C.1.

[2] Inclusion on the list of bulk drug substances that can be used in compounding under section 503A (503A Bulks List) should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using a substance included on the list has been proven to be safe and effective under the standards required to receive Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears on the 503A Bulks List is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act (21 U.S.C. 352(a)and (bb)).

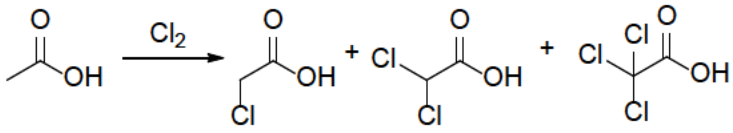
Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and United States Pharmacopeia/National Formulary (USP/NF).

1. Stability of the API and likely dosage forms

TCA decomposes when heated, especially in basic aqueous solutions (O'Neil et al., 2006; Clark 1959). Decarboxylation also occurs under basic conditions, generating carbonate and chloroform. Under refrigeration, TCA is likely to be stable as topical liquid if the pH of the solution is acidic or neutral.

2. Probable routes of API synthesis

Current synthesis of TCA is based mainly on the chlorination of acetic acid (shown below). Acetic acid is reacted with chlorine under anhydrous conditions in the presence of a catalyst. The product is usually a mixture of monochloroacetic acid, dichloroacetic acid, and trichloroacetic acid. TCA is then isolated from the mixture (Pragt et al., 2015).



3. Likely impurities

Likely impurities may include:

- Side products or byproducts from the chlorination reaction, such as monochloroacetic acid and dichloroacetic acid
- Residual starting materials, such as acetic acid
- Degradation product of TCA, such as chloroform

4. Toxicity of those likely impurities

Chloroform has high toxicity, and monochloroacetic acid and dichloroacetic acid can have toxicities depending on the exposure level. Other impurities are unlikely to be significantly toxic. Further toxicity issues are discussed in section II.B.

5. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

TCA is a colorless crystalline solid that is soluble in water. No further information on the influence of particle size and polymorphism on bioavailability has been found in the literature.

6. Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize

TCA is easily characterized with Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and mass spectrometry (MS).

Conclusions: TCA is a small organic molecule, and it is likely to be stable under refrigeration. The nominated substance is easily characterized with various analytical techniques, and the preparation of this compound has been well developed.

B. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

The following public databases were consulted in the preparation of this review: PubMed, Hazardous Substances Data Bank (HSDB), Chemical Abstracts Service (CAPLUS), and Excerpta Medica dataBASE (EMBASE).

a. Pharmacology of the drug substance and its likely impurities (see II.A.3 above)

TCA denatures and precipitates proteins.

b. Safety pharmacology

No information located.

c. Acute toxicity

The acute oral LD_{50} in rats has been reported to be 5000 mg/kg (Bailey and White 1965). TCA is assumed to be neutralized in this study. Data from an internal Hoechst study reports the acute oral LD_{50} in rats as ranging from 3310 to 6900 mg/kg and the acute oral LD_{50} in dogs as ranging from 1590 to 2000 mg/kg (not otherwise described, assumed to be neutralized TCA; reported in OECD SIDS).

Data from an internal Hoechst study reports the acute dermal LD_{50} in rats as >2000 mg/kg (not otherwise described, assumed to be neutralized TCA; reported in OECD SIDS).

Dilute solutions of TCA (<30%) will decompose to produce toxic vapors of chloroform, hydrogen chloride, carbon monoxide and carbon dioxide (Merck Index, 2013). Although the hazard is high (e.g., chloroform is a known central nervous system depressant), the risk is dependent on exposure characteristics (i.e., concentration and duration of exposure). Other potential impurities are dichloroacetic acid (DCA), monochloroacetic acid (MCA), and acetic acid. Although DCA and MCA are progressively more toxic than TCA, these unreacted impurities are unlikely to be present at levels of concern in medical grade TCA.

d. Repeat dose toxicity

No repeat dose dermal toxicity studies for TCA have been located.

Mather et al., (1990) treated male Sprague-Dawley rats (10/dose group) with neutralized TCA in drinking water (0, 50, 500, 5000 ppm; 0, 4.1, 36.5, or 355 mg/kg/day) for 90 days. TCA administration did not affect body weights at any dose. At 355 mg/kg/day, relative liver and kidney weights were significantly ($p \leq 0.05$) increased (7 and 11%, respectively) compared with controls. The liver, spleen and kidney of animals administered this dose were enlarged; however no microscopic lesions were observed at any dose. The NOAEL was determined to be 36.5 mg/kg/day based on statistically increased relative liver and kidney weights at 355 mg/kg/day.

e. Mutagenicity

TCA was non-mutagenic in many strains of *Salmonella typhimurium* (TA98, TA100, TA104, and TA1535) with or without metabolic activation (Rapson et al., 1980; Moriya et al., 1983; Nelson et al., 2001; Kargalioglu et al., 2002). However, positive mutagenicity results have been reported in TA100 and TA1535 strains of *S. typhimurium* (Giller et al., 1997; Ono et al., 1991). Mutagenicity in mouse lymphoma cells was only induced at cytotoxic concentrations (Harrington-Brock et al., 1998). Evaluation of genetic toxicity studies with TCA must consider cytotoxicity and acidification of the medium resulting in precipitation of proteins when interpreting in vitro results. TCA is commonly used as a laboratory reagent to precipitate proteins and terminate enzyme activity. Therefore, it is not surprising that the evidence for its genotoxic potential is inconclusive.

Although positive results were reported for unneutralized TCA during in vivo cytogenetic assays (Bhunya and Behera, 1987), later in vivo studies by Mackay et al. (1995), using neutralized TCA, reported negative results in C57BL/6 mice given two doses 24 hours apart (males:< 1080 mg/kg/dose; females:< 1300 mg/kg/dose). Previous positive reports of TCA-induced clastogenicity may be secondary to pH changes.

f. Developmental and reproductive toxicity

In an embryofetal development study conducted in rats, dams (n=20-21/dose) were administered oral TCA (0, 330, 800, 1200, 1800 mg/kg/day in distilled water, adjusted to pH 7 with NaOH) from days 6 to 15 of gestation (Smith et al., 1989). Maternal and embryonic toxicity were observed from doses of 330 mg/kg/day and above, and embryolethality from doses of 800 mg/kg/day and above. There was a dose-dependent increase in visceral anomalies, particularly in the cardiovascular system. The mean frequency of soft tissue malformations, especially in the cardiovascular system, ranged from 9% at the low dose (330 mg/kg/day) to 97% at the high dose (1800 mg/kg/day). Skeletal malformations were found only at 1200 and 1800 mg/kg/day and were mainly in the orbit. Based

on these observations, TCA was considered to be developmentally toxic in the pregnant rat at doses of 330 mg/kg/day and above.

No developmental and reproductive toxicity studies conducted in rabbits have been located.

g. Carcinogenicity

No carcinogenicity studies conducted with dermal exposure of TCA have been located.

When administered in the drinking water, TCA induced hepatocellular neoplasia in male (De Angelo et al., 2008) and female (Pereira MA, 1996) $B6C3F_1$ mice. The development of hepatocellular neoplasia in mice exposed to TCA was strongly associated with increased peroxisome proliferation (De Angelo et al., 2008). There is no evidence of carcinogenicity in male F344/N rats (50/group) exposed to TCA (0, 3.6, 32.5, or 364 mg/kg/day) in the drinking water for up to 104 weeks (De Angelo et al., 1997). Peroxisome proliferation was only minimally increased in the TCA-treated rats.

The induction of hepatic tumors by TCA appears to be a species-specific effect, mediated through nongenotoxic mechanisms (Klaunig et al., 1989). The current weight-of-evidence suggests that TCA-induced liver tumors may arise by a peroxisome proliferation-based mechanism of action (Corton 2008).

Under USEPA's Cancer Guidelines, there is suggestive evidence of carcinogenic potential for TCA based on significantly increased incidences of liver tumors in $B6C3F_1$ mice and lack of treatment-related tumors in a study of male F344/N rats (USEPA 2005). The American Conference of Industrial Hygienists considers TCA to be a confirmed carcinogen in experimental animals with unknown relevance to humans (HSDB 2012).

The International Agency for Research on Cancer (IARC) classifies the hazard of repeat dose oral exposure of TCA as possibly carcinogenic in humans (Group 2B) (IARC, 2014).[3] The possible mechanism for formation of liver tumors in mice (i.e., peroxisome proliferation) does not have clinical relevance. In addition, liver tumors noted in mice occurred after high systemic levels achieved upon oral administration of TCA in drinking water. The systemic levels of TCA achieved after topical administration of TCA under the proposed clinical conditions of use

[3] This classification is based on "sufficient evidence in experimental animals" (i.e., hepatocellular neoplasia in orally exposed mice and no evidence in similarly exposed rats) and "inadequate evidence in humans" (i.e., no data were available in humans; IARC, 2014). IARC publishes monographs containing critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures to chemicals. The monographs are limited to evaluating cancer hazard (i.e., a chemical's ability to cause cancer under specific circumstances) and do not evaluate risk (i.e., estimate of carcinogenic effects expected from human exposure to a specific chemical).

will not reach the systemic levels of TCA that caused the formation of liver tumors in mice. Therefore, the possible risk of carcinogenesis in humans exposed to TCA after topical administration is minimal based on the available animal data.

h. Toxicokinetics

No toxicokinetic studies conducted with dermal exposure of TCA have been located.

In rodents, TCA is rapidly absorbed after oral administration, but is only slowly metabolized, accumulating to a steady-state after successive exposures. Most of the absorbed dose is excreted in the urine as the parent compound. Metabolism that does occur is mainly oxidative through cytochrome P450 to dichloroacetic acid via a dichloroacetic acid radical. The results of several studies indicate that the urinary elimination or plasma clearance of TCA is slower in humans than in rodents (IARC, 2014). Also, protein binding in the plasma is greater in humans than in rodents (Lumpkin et al., 2003). The greater plasma protein binding in humans would be expected to increase the residence time for TCA in plasma and reduce the amount of TCA available in other tissues.

Conclusions: No repeat dose dermal toxicity studies or dermal carcinogenicity studies conducted with TCA have been located in the literature. Although the toxicity of TCA after topical administration has not been fully evaluated in nonclinical studies, the available animal data do not pose serious safety issues for topical use in humans.

2. Human Safety

The following database(s) were consulted in the preparation of this review: PubMed, the Cochrane Library, Federal Register, EMBASE, Web of Science, Micromedex
Key words: trichloroacetic acid, trichloroethanoic acid.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for trichloroacetic acid (TCA) use through December 14, 2015, and retrieved eleven cases.

Eight cases involved topical application of TCA:

- Six cases reported application site reactions, including pain, erythema, pruritus, inflammation, hypo- and hyperpigmentation, and second degree burns were noted with topical TCA use. The TCA concentration ranged from 20% to 35%. The four cases reporting reaction sites identified the face.

- Two cases reported concomitant use of glycolic acid, topical tretinoin, and bleach. Concomitant treatments included topical and oral agents, and hyperbaric oxygen:

- One case reported fever, urinary retention, dysuria, swelling, application site pain and ulcer associated with genital wart treatment. Signs and symptoms developed after one TCA treatment of unknown strength, followed by three alternate-day imiquimod 5% applications. The patient was hospitalized, catheterized, and treated with prednisone.

- One case reported severe glabellar injection site pain and tenderness after onabotulinumtoxinA injection, associated with a TCA 20% chemical peel. The order of administration was not specified.

Three cases involved other or unspecified routes of administration of TCA:

- One case reported elevated creatine phosphokinase, myositis, and rhabdomyolysis after use of an unspecified TCA product and an unspecified dose of simvastatin. The route and indication of TCA use were not specified. The patient improved with discontinuing both TCA and simvastatin, and hydration.

- One case reported intentional Tri-Chlor solution (TCA 80%) ingestion, along with clonazepam, amlodipine, and metoprolol in an attempted suicide. Tachycardia, lethargy, slurred speech, hyperglycemia, and hypotension were noted. The patient recovered.

- One case reported elevated concentrations of TCA, trichloroethanol, chloral hydrate, and other substances in a positive toxicology screen performed in a deceased, multiple-drug overdose patient. TCA and trichloroethanol are chloral hydrate metabolites. The substances ingested were not identified.

FDA's Center for Food Safety and Nutrition was also consulted to search their adverse event data base (CAERS) for adverse events associated with TCA and retrieved no relevant cases.

a. Reported adverse reactions

Genital Warts. Table 1 shows adverse reactions from TCA use in genital wart treatment as reported in the literature.

Table 1. Adverse Reactions from TCA Use in Genital Wart Treatment

Reference	Study Design	TCA Strength	Dosing Regimen	AR rate and type in TCA-treated subjects
Gabriel et al., 1983	TCA + 25% podophyllin vs 25% podophyllin in males	50%	1x/wk for up to 6 wks	5/31 (16%); ulceration (3), soreness (2)
Godley et al., 1987	TCA vs cryotherapy in males	unknown	1x/wk for up to 10 wks	3/57 (5%) mild discomfort, 26/57 (46%) ulceration
Abdullah et al., 1993	TCA vs cryotherapy	95%	1x/wk for up to 6 wks	9/33 (27%); ulceration (9)
Nunns et al., 1996	Case report of 2 cases	unknown	Two weekly treatments	Severe vestibulitis with erythema and tenderness up to 15 wks, and one case of posterior fourchette fissures
Schwartz et al., 1998	Retrospective record review of pregnant women: TCA used in combination with CO2 laser	85%	unknown	7/32 (22%) “extensive vulvar ablation” requiring suprapubic catheterization, 2/32 (6%) mild uterine contractions, 3/32 (9%) spontaneous rupture of membrands, 1/32 (3%) depigmentation
Sherrard et al., 2007	Randomized 5-arm study	unknown	2x/wk for up to 8 wks	0/173
Taner et al., 2007	Uncontrolled study of TCA in females	85%	1x/5days for up to 6 sessions	51/51 (100%) transient burning pain, 8/51 (16%) ulceration with permanent scarring in 3 subjects (6%)

Common Warts. Table 2 shows adverse reactions from TCA use in common wart treatment as reported in the literature.

Table 2. Adverse Reactions from TCA Use in Common Wart Treatment

Reference	Study Design	TCA Strength	Dosing Regimen	AR rate and type in TCA-treated subjects
Pezeshkpoor et al., 2012	TCA 80% vs TCA 35%	80% and 35%	1x/wk for up to 6 wks	9/31 (29%) with TCA 80%, and 5/31 (16%) with TCA 35%: burning sensations, tingling, local pain, scarring and hyperpigmentation
Silverberg et al., 2012	retrospective chart review of children comparing (a) SADBE*, (b) SADBE + TCA, (c) SADBE + TCA + cantharidin, (d) SADBE + cantharidin	50%	TCA 1-2 min immediately prior to SADBE; cantharidin 1-2 min immediately after SADBE	No adverse effects attributed to TCA
Cengiz et al., 2015	TCA 25% vs TCA 10% vs liquid nitrogen in flat warts	25% and 10%	1x/5days for up to 6 treatments	TCA 25% group (N=27): pruritus 78%, pain 26%, erythema 37%; TCA 10% group (N=28): pruritus 50%, pain 4%, erythema 7%

*SADBE = squaric acid dibutylester

b. Other conditions

- Acne and Acne Scars

Meguid et al., (2015) conducted an intrapatient comparison study of TCA 25% versus salicylic acid 30% for mild to moderate facial acne vulgaris. Twenty patients were pretreated with retinoic acid 0.1% cream. TCA and salicylic acid were then consistently applied, each to one side of the face every 2 weeks for 2 months. Prolonged erythema occurred only with the TCA side in 5 (25%) of the subjects. Hyperpigmentation was reported by 4 patients (20%) due to TCA application, which lasted 3 to 4 weeks and resolved with a "topical bleaching agent."

Lee et al. (2002) compared TCA 65% to TCA 100% using the chemical reconstruction of skin scars (CROSS) technique in treatment of acne scars. The CROSS method consists of the focal application of concentrated TCA with a sharpened wooden applicator by applying firm pressure to the depressed scar area. For 65 subjects, "mild erythema" and "transient postinflammatory hyperpigmentation" were reported; the number of patients reporting the adverse effects was not given. Four subjects developed "mild pustular eruptions" which cleared after oral antibiotic treatment.

Nofal et al., (2014) studied treatment of acne scars in 45 patients assigned to three groups: TCA 100% applied via CROSS technique; autologous platelet-rich plasma injection; combined skin needling and autologous topical platelet-

rich plasma. In the TCA group, all subjects experienced mild pain, and four patients developed hyperpigmentation.

Leheta et al., (2011) compared TCA 100% via CROSS technique to percutaneous collagen induction (PCI) to treat acne scars. The PCI procedure uses skin needling penetration of the epidermis to stimulate wound healing, collagen deposition, and tissue remodeling. All 15 TCA subjects noted burning pain, crusting, and erythema. Also, 50% of subjects completing TCA treatment developed hyperpigmentation which lasted 2 to 6 months.

- Hyperpigmented Lesions

Hong et al., (2012) conducted a split-face study comparing TCA 15% chemical peel to 1550 nm fractional photothermolysis for facial melasma. Treatments were administered during one session. Eighteen women were treated. Persistent erythema and hyperpigmentation occurred in 9 (50%) of TCA subjects and 8 (44%) of laser subjects.

Kumari et al., (2010) compared TCA (10% or 20%) with glycolic acid (GA) (20% or 35%) chemical peels to treat melasma. The 2-week, priming regimen for the TCA group was tretinoin 0.1% gel daily, and for the GA group was GA 12% cream daily. Forty subjects were treated with chemical peels, with graded concentrations and 2- or 4-minute contact times. Subjects were treated every 15 days. Of 20 subjects treated in each group, subjects treated with TCA experienced less “mild burning” compared to glycolic acid, but more “postpeel crackening.”

Soliman et al., (2007) compared TCA 20% chemical peel alone (15 women) to TCA 20% with ascorbic acid 5% chemical peel (15 women) to treat melasma. All patients were primed for two weeks with tretinoin 0.05% gel daily and hydroquinone 4% cream daily. Also, the TCA/ascorbic acid group applied ascorbic acid compounded in cold cream daily. TCA chemical peels were performed weekly until clear or up to six treatments. Erythema was reported in 30% of TCA alone patients and 20% of TCA/ascorbic acid patients. “Discomfort” was reported in 25% of patients in both groups. Acne was noted in one patient in the TCA/ascorbic acid group.

Fung et al., (2002) reported one case of TCA 35% facial peel to treat dyschromia and for rejuvenation causing corneal punctate keratitis and conjunctival infection.

Raziee et al. (2008) compared TCA 33% solution with cryotherapy within subject to treat solar lentigines. TCA and liquid nitrogen were applied to the dorsal hands of 25 women. Postinflammatory hyperpigmentation was reported in 11 (44%) of TCA applications compared to 10 (40%) of cryotherapy treatments.

- Actinic Keratosis

Lawrence et al., (1995) conducted a split-face study comparing Jessner's solution followed by TCA 35% chemical peel to fluorouracil 5% cream application to treat actinic keratoses. Fourteen of 15 subjects reported erythema for the side treated by Jessner's/TCA chemical peel, which persisted for 3 months in one subject.

- Xanthelasma

Haque et al., (2006) compared TCA 100%, 70% and 50% strengths for treatment of eyelid xanthelasma. Fifty-one subjects were treated every 2 weeks until lesions cleared. Follow up visits were scheduled once a month. With TCA application, there was white discoloration immediately with "peri-lesional erythema" that subsided in a few hours, followed by a "dark, brownish-black crust". Follow up visits reported 11 patients with hypopigmentation (four treated with TCA 100%, three treated with TCA 70% and four patients treated with TCA 50%). Five patients developed hyperpigmentation (three patients treated with TCA 100% and two patients treated with TCA 70%). One patient developed "mild scarring", not defined, after TCA 100% treatment.

Nahas et al., (2009) studied TCA 70% for eyelid xanthelasma in 24 subjects. Adverse events noted were "scar practically invisible" in 11 patients (45.8%), "presence of mild dyschromia" (hypopigmentation and hyperpigmentation) reported in 8 patients (33.4%), and "marked dyschromia or alteration of relief" in 5 patients (20.8%).

Güngör et al., (2014) conducted an intrapatient comparison study of TCA 70% with erbium: YAG laser treatment in 21 patients with eyelid xanthelasma. Treatments were 4 weeks apart, if needed. Follow up evaluation occurred 4 weeks after the first treatment by two independent dermatologists. Improvement and adverse effects were assessed by scoring system. Over 50% of patients treated with TCA and laser noted "mild dispigmentation," and over 30% reported "marked dispigmentation"; there was no statistically significant difference between the treatments.

c. Clinical trials assessing safety

There have been no clinical trials specifically designed to address the safety of TCA. Safety assessments were among the study procedures in several clinical trials. The safety profile of TCA in these trials was consistent with that provided in the reports cited above. See Section II.B.2.a.

d. Pharmacokinetic data

There are no reports of human pharmacokinetic (PK) studies following topical application of TCA.

e. The availability of alternative approved therapies that may be as safe or safer.

FDA approved therapies for warts include the following.

Prescription:

- Imiquimod 5% cream and 3.75% cream for genital warts
- Podofilox 0.5% gel and solution for external genital warts
- Sinecatechins 15% ointment for external genital warts
- Interferon alfa-2b intralesional injection for genital warts

There are no approved prescription therapies for warts outside of the genital area.

Non-prescription:

- Salicylic acid 5 % to 40% topically for common and plantar warts is subject to the final monograph Miscellaneous External Drug Products For Over-The-Counter Human Use - Wart Remover Drug Products (21 CFR 358 subpart B).
- Cryosurgical system/kit (dimethyl ether and propane) to freeze common and plantar warts, indicated for ages 4 years and up

Other widely used therapies for warts include procedural therapies, such as cryotherapy; laser therapy; electrosurgery; surgical excision; and duct tape occlusion.

Conclusions:

1. Clinical data from the use of TCA in the treatment of genital and common warts show that adverse reactions secondary to TCA (concentration 10% to 100%) application included burning, pain, erythema, hyperpigmentation and hypopigmentation. More serious adverse reactions reported were ulcerations, scarring, pustules, punctate keratitis and conjunctival infection. Adverse events were reported more frequently with higher concentrations.

2. Ulcerations were reported in most studies with wart treatment in the genital area. For localized wart involvement, scars or hypopigmentation were the most frequent sequelae. With more extensive genital wart treatment, requirement for suprapubic catheterization has been reported (catheterization reported in FAERS and in literature). Also, urinary retention was reported.

3. Other FDA approved therapies are available to treat genital warts and common warts. We have not been able to locate clinical trials directly comparing TCA and FDA-approved treatments for warts.

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

External genital warts

Abdullah et al., (1993) compared topical TCA 95% (N=33) to liquid nitrogen (N=53) cryotherapy in the treatment of external genital warts with once weekly application for up to 6 treatments. In the TCA group, lesions were cleared in 64% of subjects, compared to 70% of subjects in the liquid nitrogen group.

Gabriel et al., (1983) compared TCA 50%, in combination with podophyllin 25%, to podophyllin 25% alone to treat genital warts with once weekly treatment for 6 weeks and follow-up for at least 3 months after initial treatment. For subjects treated with TCA/podophyllin, 20 (69%) of 29 subjects were cleared of lesions at week 6, and 9 (31%) subjects were cleared of lesions at 3 months. In the podophyllin alone group, 21 (60%) of 35 subjects were cleared of lesions at 6 weeks, and 10 (29%) subjects were cleared of lesions at 3 months.

Godley et al., (1987) compared treatment of genital warts in men with TCA (of unknown concentration) (N=57) to liquid nitrogen cryotherapy (N=49), with TCA applied weekly for up to 10 treatments. At week 10, 46 (81%) subjects in the TCA group, and 43 (88%) subjects in the cryotherapy group had complete clearance of lesions. Of patients cleared of lesions who returned for follow up 2 months after the last treatment, lesions recurred in 14 (36%) of 39 subjects in the TCA group, and in 15 (40%) of 38 subjects in the cryotherapy group.

Sherrard et al., (2007) compared treatment with TCA (of unknown concentration) followed by podophyllin 25% (N=85), TCA alone (N=88), podophyllin 25% alone (N=79), cryotherapy alone (N=81), and cryotherapy followed by podophyllin 25% (N=76), with once a week treatment for up to 8 weeks. The efficacy endpoint was complete clearance of all lesions. The results are as follows:

- Complete clearance of lesions was reported in 49 (56%) subjects treated with TCA alone and in 63 (74%) subjects treated with TCA/podophyllin combination therapy. In the cryotherapy alone treatment group, complete clearance was reported in 61 (75%) subjects compared to 59 (78%) subjects in cryotherapy/podophyllin treatment group. In the podophyllin alone treatment group, complete clearance was reported in 46 (58%) subjects.

- Persistent lesions were reported for 10 (13%) subjects treated with podophyllin alone, 9 (10%) subjects treated with TCA alone, 5 (6%) subjects treated with cryotherapy alone, 2 (2%) subjects treated with TCA/podophyllin and none (0%) of the subjects treated with the cryotherapy/ podophyllin combination.

Taner et al., (2007) conducted an open label trial with TCA 85% application to genital warts in 51 female subjects. TCA was applied every 5 days until all lesions cleared, or

up to 6 treatments. Subjects were followed-up in 2-month intervals for 6 months. Follow-up was extended for an additional 6 months for a subset of these subjects.

- Complete clearance of all lesions was reported in all subjects by the end of the fifth cycle. At the end of first 6-month follow-up, no recurrence was reported.

- At the end of the second 6-month follow-up period, 9 subjects (18%) had recurrent lesions. Of these subjects, 3 subjects reported lesions in areas treated with TCA, and 6 subjects had developed new lesions.

Common Warts

Pezeshkpoor et al., (2012) compared TCA 80% with TCA 35% to treat common warts. Fifty-five subjects were included in the final analysis after treatment with TCA once a week for up to 6 weeks, and followed up weekly up to the end of week 7 (N=30 for TCA 80% and N=25 for TCA 35%). All subjects were evaluated for recurrence after 12 weeks. A "good" response was defined as fewer than or equal to 3 warts remaining. In the TCA 80% group, 14 subjects (47%) had a good response, while 3 subjects (12%) in the TCA 35% group had a good response. However, since the number of subjects completely cleared of wart lesions was not reported, this study is essentially uninformative.

Cengiz et al., (2015) conducted an open, comparative clinical trial for flat warts (verruca plana) in three arms: TCA 10% (N=28); TCA 25% (N=27); cryotherapy (N=25), with weekly treatment for up to 8 weeks, and evaluation every 2 weeks. There was no follow up beyond treatment week 8. In the TCA 10% group, 24 subjects (85.7%) cleared of warts completely by 8 weeks, while for those treated with TCA 25%, 25 (92.6%) subjects' wart lesions cleared, and with cryotherapy, 23 (92%) subjects' wart lesions cleared.

In 2008, Patidar reported one case of 2 periungual warts on the hands treated by electrodessication and curettage, followed by TCA 30% application. There was no recurrence after one year.

Chemical Skin Peeling

One of the nominations included two references for TCA potentially related to its use as a chemical peel: Leheta et al. (2011) on atrophic acne scars and Kumari and Thappa (2010) on melasma. Note that TCA was not nominated as a treatment for scarring or melasma, and we consider these studies to the extent they are relevant for consideration of the chemical peel nomination.

- Atrophic acne scars

Leheta et al., (2011) compared percutaneous collagen induction (PCI) and 100% TCA chemical reconstruction of skin scars (CROSS) method for the treatment of atrophic acne scars. The CROSS method is a focal application of TCA 100% to atrophic acne scars. The study included 30 subjects randomly divided (1:1) into two groups: group 1

underwent 4 sessions (4 weeks apart) of PCI, and group 2 similarly with 100% TCA CROSS. Acne scarring improved in all subjects. Scar severity scores improved by a mean of 68.3% from baseline ($p<0.001$) in group 1 and 75.3% ($p<0.001$) in group 2, but improvement was not statistically significant between the groups ($p = 0.47$).

Besides the study described above, two other trials evaluated the use of TCA CROSS in acne scars (Lee et al. (2002), and Nofal et al. (2014)). Both studies showed improvement of the atrophic acne scars from baseline after TCA peel. Similar to the Leheta study, the comparators are not approved therapies, and no conclusions can be drawn regarding efficacy of TCA CROSS in acne scars.

- Melasma

Kumari and Thappa (2010) compared the response of melasma in 40 Indian women with a minimum melasma area and severity index (MASI) of 10 to glycolic acid (GA) versus TCA for chemical peeling. Study subjects had a pre-peel program of daily application of 12% GA cream or 0.1% tretinoin at night for 2 weeks. They were then treated with graded concentrations of 20-35% GA facial peel every 15 days in the GA group and 10-20% TCA in the TCA group. Reduction in MASI after 12 weeks was by 79% in the GA group and by 73% in the TCA group (difference not significant). Patients with epidermal-type melasma showed better response than those with mixed-type melasma ($P<0.05$). Subject evaluation was "good" or "very good" in 75% of the women of the GA group and 65% of the TCA group. No relation of treatment response to age or duration of melasma could be established.

Besides the study described above, two other trials evaluated the use of TCA peel in melasma (Hong et al., (2012), and Soliman et al. (2007)). Both studies showed improvement of melasma from baseline after TCA peel. However, similar to the Kumari study, the comparators are not approved drug therapies, and no conclusions can be drawn regarding efficacy of TCA peel in melasma.

2. Whether or not the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

No, common and genital verrucae are not serious or life-threatening diseases/conditions in healthy persons; however, there are less common circumstances in which warts may develop into extensive, recalcitrant infections, premalignancies, and carcinomas.

3. Whether or not there are any alternative approved therapies that may be as effective or more effective.

We address alternative therapies for warts here. Chemical peel involves a variety of procedures used for multiple purposes, and it is not possible to address alternatives in the current context without specific proposed uses.

There are approved drug therapies for warts that have been shown to be as effective or more effective. According to several studies (Abdullah et al., 1993; Sherrard et al.,

2007), other treatments and combinations are superior to TCA alone, although TCA may be useful as an adjunctive, destructive therapy.

For a list of approved therapies for the treatment of external genital warts and common warts, see section II.B.2.d.

Conclusions:

1. We did not identify adequate and well-controlled clinical trials evaluating TCA efficacy in the treatment of genital or common warts. The available information suggests that TCA may be efficacious in the treatment of these conditions; however, the limited data are from small, open-label, active controlled trials, or a case report.

2. Some of the trials presented above evaluated efficacy of TCA in combination with other wart treatments (e.g., cryotherapy, podophyllin). One report suggested an increase in TCA efficacy when used in combination with podophyllin (Sherrard et al., 2007). Some reports (Cenzig et al., 2015, Pezeshkpoor et al., 2012) suggested an increase in efficacy of TCA therapy for common or flat warts at higher concentrations. However, even with higher TCA concentrations, current data do not suggest an advantage in efficacy of TCA alone over available approved or over-the-counter treatments for warts.

D. Has the substance been used historically as a drug in compounding?

Databases searched for information on TCA in regard to Section D of this consultation included PubMed, Natural Medicines Database, clinicaltrials.gov, Google, European Pharmacopoeia, British Pharmacopoeia and Japanese Pharmacopoeia.

1. Length of time the substance has been used in pharmacy compounding

TCA has been used for treating warts and as a chemical peel for over 40 years (Heaumebh, 1964, Resnick et. al., 1973). From the literature, it appears that TCA has been used in pharmacy compounding for at least 20 years. (Bridenstine 1996, Bridenstine et. al., 1994).

2. The medical condition(s) it has been used to treat

TCA has been used to treat dermatologic conditions including warts, actinic keratoses, melasma, solar lentigines, acne, acne scarring, and xanthelasma. However, it is not clear to what extent TCA has been used in the treatment of these conditions either in marketed product formulations or via pharmacy compounding.

3. How widespread its use has been

TCA has been used to treat warts in the United States and internationally. Insufficient data are available from which to draw conclusions about the extent of use of TCA in compounded drug products.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

TCA and TCA solution are listed in the European Pharmacopeia (8th Edition, 2016, 8.8) and the British Pharmacopoeia (BP 2016). Per the British Pharmacopoeia, TCA solution is a cutaneous solution used in the treatment of warts, although it is not currently licensed in the United Kingdom. TCA is not listed in the Japanese Pharmacopoeia (17th Edition).

Conclusions: TCA has been used to treat warts for over 40 years and there is evidence of its use in pharmacy compounding for at least 20 years. TCA and TCA solution have official recognition in other countries.

III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate TCA for the 503A Bulks List. In the Agency's view, after considering the information currently available, a balance of the criteria weighs ***in favor*** of TCA for topical use being placed on the list based on the following:

1. TCA is well characterized in its physical and chemical properties.

2. The safety profile shows that TCA commonly causes erythema, crusting, hyperpigmentation and hypopigmentation, burning, and pain at the application site. More adverse effects have been reported upon use of TCA at higher concentrations, as well as in the facial and genital areas. At higher concentrations, the potential for ulceration and subsequent absorption through open wounds increases. Ulcerations have been reported in most studies of TCA in the treatment of genital warts.

3. Although we did not identify adequate and well-controlled trials evaluating TCA efficacy in the treatment of warts, available information from small open label trials suggests that TCA may have some efficacy in their treatment. Studies suggest that TCA is more efficacious when used at higher concentrations or in conjunction with an additional wart treatment and, thus, may have a place in treating refractory warts or patients intolerant of other therapies. However, with higher concentrations, the potential for ulceration and subsequent absorption through open wounds increases.

4. TCA has been used for dermatologic conditions for over 40 years and for at least 20 years in pharmacy compounding. Its use is worldwide.

Based on the information the agency has considered, a balancing of the four evaluation criteria weighs in favor of TCA for topical use being added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act.

Because of the potential for complications when used at high concentrations, the standard of care is in-office application by a licensed health care professional.

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ACRONYM LIST

CEBS	Chemical Effects in Biological Systems
CROSS	Chemical reconstruction of skin scars
NIEHS	National Institute of Environmental Health Sciences
NOAEL	No-Observed-Adverse-Effect Level
PCI	Percutaneous collagen induction

APPENDIX SECTION C

Summary Report

Trichloroacetic Acid

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 2U01FD005946

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
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January 2020

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REVIEW OF NOMINATION

Trichloroacetic acid (TCA; UNII code: 5V2JDO056X) was nominated for inclusion on the 503B Bulks List by Sincerus for use as a chemical peel to treat acne and melasma as a 6-20% topical solution.

The reason provided for nomination to the 503B Bulks List is that chemical peels are discussed in the literature as treatment options for acne and melasma but there are no FDA-approved drug products for this purpose. Compounding from bulk is necessary, as there is no FDA-approved product to use as the source of TCA.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of TCA products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, route of administration (ROA), and approval status) provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the European Medicines Agency (EMA) and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched as some medicines are authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for TCA; name variations of TCA were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing TCA. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

Two databases (PubMed and Embase) were searched including any date through January 22, 2019. The search included a combination of ("trichloroacetic acid"[TIAB] OR "acide trichloracetique"[TIAB]) AND (treatment[TIAB] OR therapy[TIAB] OR therapeutic*[TIAB] OR clinical[TIAB] OR acne[TIAB] OR melasma[TIAB] OR topical[TIAB] OR skin[TIAB] OR derm*[TIAB]) AND humans[MeSH Terms] AND English[lang] NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of TCA or the implementation of TCA in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

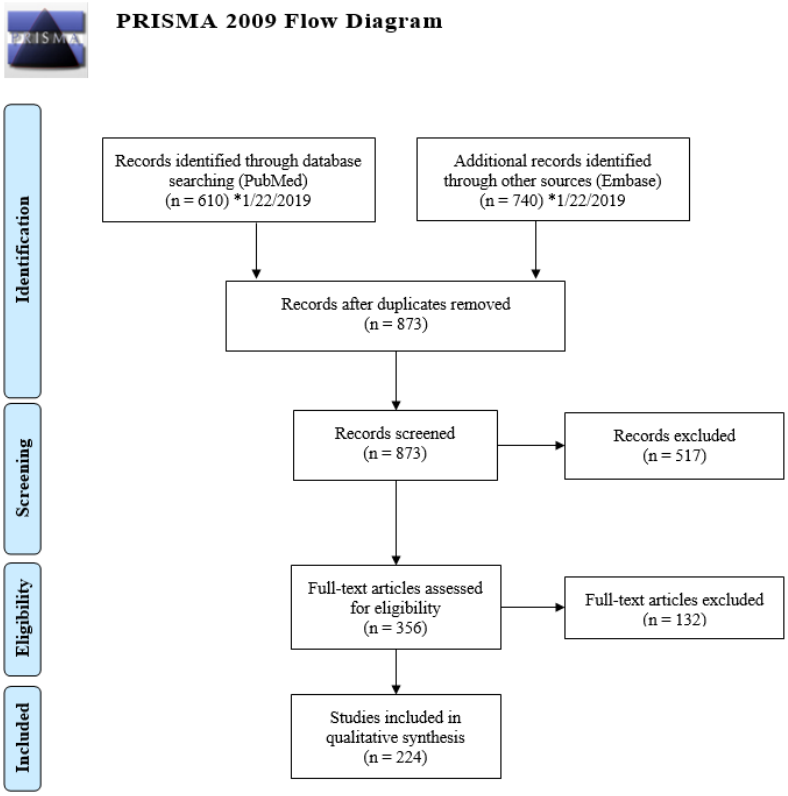
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for TCA use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of TCA compared to alternative therapies.

Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses:* The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indications from the nomination and the results of the literature review, two (2) medical specialties that would potentially use TCA were identified: dermatology and otolaryngology. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. One (1) expert was contacted for interviews, of which one (1) accepted and zero (0) declined interviews. Interviews were recorded and transcribed via ©Rev.com. QSR International's Nvivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

General professional medical associations and specialty associations for dermatology and otolaryngology, identified from the nominations, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to seven (7) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

Specialty	Association
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Failed to respond
	American Academy of Otolaryngic Allergy (AAOA)	Declined, did not think otolaryngologists are the target market for the survey
	American Rhinologic Society (ARS)	Declined, do not send out surveys unless they are requested by a member, unable to identify a member to request survey distribution

CURRENT AND HISTORIC USE

Summary of background information

- TCA is not a component of an FDA-approved product, is not available as an OTC product, nor has a United States Pharmacopeia (USP) monograph.
- TCA is not available in any of the select non-US countries and regions searched.

Table 3. Currently approved products – US

No approved products in the US

Table 4. Currently approved products – select non-US countries and regions

No approved products in selected non-US countries and regions

Summary of literature review

TCA has been used since 1945 as a chemical peel and in the treatment of acne scars and was first tried in 1993 in pyriform sinus fistula.[1,2] Chemical peels that were less deep than phenol peels became feasible in the 1980s as many modalities of TCA peel techniques were introduced.[3,4]

Most of the studies identified were from the US (70), followed by Egypt (27), Korea (19), and Iran (18). In the US, the most prevalent indication for TCA was in aging skin (24). Three (3) studies discussed use in acne scars and no studies were identified that used TCA in melasma. Of the studies that identified a ROA, all but three (3) applied TCA topically and of these studies all but one (1) used TCA as a solution. Seven (7) of the US studies identified the use of TCA as a compounded product with concentrations ranging from 15-95%. Of the non-US studies, the most frequent indication was for melasma (16) followed by acne scars (14).

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1,3–96]	95
Experimental[97–209]	113
Observational[2,210–224]	16

Table 6. Number of studies by country

Country	Number of Studies
Argentina[16,61,136]	3
Austria[37,141]	2
Belgium[166]	1
Brazil[5,20,21,23,24,29,73,94,119,151,186]	11
Canada[30]	1
Colombia[218]	1
Egypt[98,101,112,120,122,125–128,133,144,162,163,170–174,182–184,188,194,200,206–208]	27
France[175]	1
Germany[58,221]	2
Greece[55,108,156]	3
India[48,75,113,121,123,134,139,146,150,158,167,187,197]	13
Iran[40,64–66,70,99,102,135,149,178,181,189–193,199,201]	18
Iraq[1]	1
Italy[25,117,118,124,129,131]	6
Japan[88,92,142,215–217]	6
Korea[2,47,50–54,71,86,90,143,153,154,159,160,169,213,219,223]	19
Libya[84]	1
Pakistan[97,103,157,177,185]	5
Poland[164]	1

Portugal[49,59,110,196,212]	5
Romania[9–12]	4
Spain[46,81,210]	3
Sweden[85]	1
Taiwan[93,109,176,224]	4
Turkey[32,96,104,107,111,115,116,137,165,209,222]	11
UK[132,140,155,211]	4
US[3,4,6–8,13–15,17–19,22,26–28,31,33–36,38,39,41–45,56,57,60,62,63,67–69,72,74,76–80,82,83,87,89,91,95,100,105,106,114,130,138,145,147,148,152,161,168,179,180,195,198,202–205,214,220]	70
	Total US: 70 Total non-US Countries: 154

Table 7. Number of studies by combinations

No combination products were nominated

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Aging skin[3,4,6,8,14,15,17,18,26–28,33,35,36,39,43,44,57,60,62,76,91,161,203]	Apply twice weekly-every 8 weeks	10%-75%	Solution	Topical	1-8 sessions
	–	11%-16.9%	Cream		Once
Actinic keratoses[19,41,68,72,78,80,87,138,168,204]	Apply every 1-2 weeks	18%-60%	Solution	Topical	1-4 sessions
Genital warts[69,77,89,202,214]	Apply every 1-2 weeks	80%-85%	Solution	Topical	1-4 sessions
Human papillomavirus infection[31,114,147,180]	Apply every 1-2 weeks	50%-90%	Solution	Topical	1-8 sessions
Photo-damaged skin[105,106,145,198]	Apply every week	10%-40%	–	Topical	1-6 sessions
Acne scars[7,74,95]	Apply every 6 weeks-2 months	20%-95%	Solution	Topical	1-6 sessions
Anal intraepithelial neoplasia[45,100,220]	Apply every 1-2 months	80%-85%	Solution	Topical	1-4 sessions
Molluscum contagiosum[38,130,205]	Apply every 2-4 weeks	20%-100%	Solution	Topical	1-2 sessions
Hyperpigmentation[42,148]	Apply every month	35%-40%	Solution	Topical	1-3 sessions
Adnexal sudoriferous cyst[67]	0.1-0.5mL	33%	Solution	Injected into cyst	Once
Apocrine hidrocystomas[22]	1mL	20%	Solution	Injected into cyst	Once
Conjunctival cyst[79]	–	20%	Solution	Injected into cyst	Once
Eruptive syringoma[34]	–	35%	–	Topical	Once
Grover's disease[56]	1.5mL	40%	Solution	Topical	Once
Open comedones[152]	Apply twice daily	1%-15%	Solution	Topical	6 weeks
Pseudocyst of the auricle[13]	–	50%	Solution	Topical	Once

Sinus tract development within connective tissue nevus[82]	–	25%-100%	Solution	Topical	Once
Solar lentigines[179]	–	30%	Solution	Topical	Once
Striae distensae[195]	Apply every 4 weeks	15%	–	Topical	3 sessions
Verruca vulgaris[83]	–	50%	Solution	Topical	Once
Xeroderma pigmentosum[63]	–	35%-40%	–	Topical	2-3 sessions

Abbreviations: "–", not mentioned; ROA, route of administration.

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Melasma[25,98,101,113,118,123,143,144,146,163,167,183,185,188,206,207]	Apply every week-every month	10%-35%	Solution	Topical	1-12 sessions
	Apply every 2-4 weeks	10%	Gel		3-4 sessions
Acne scars[1,97,119,127,129,154,158,171,172,174,194,197,200,223]	Apply every 5 days- every 4 months	15%-100%	Solution	Topical	1-6 sessions
Genital warts[20,29,84,102,104,132,136,155,178,187]	Apply every other day-every month	30%-100%	Solution	Topical	1-12 sessions
Xanthelasma palpebrarum[90,103,134,137,139,162,184,186,211]	Apply every week-every month	30%-100%	Solution	Topical	1-12 sessions
Cutaneous leishmaniasis lesions[66,149,189–193,199]	Apply every week-every month	50%	Solution	Topical	1-8 sessions
	Apply twice daily	5%	Cream		3 weeks
Pyriform sinus fistula[2,52,71,85,86,92,175]	Apply every week-every month	10%-50%	Solution	Topical	1-3 sessions
	Apply every 2-9 months	10%-40%	Solution	Injected into fistula	1-3 sessions
Aging skin[111,126,151,164,213,221]	Apply every 2 weeks-every month	10%-50%	Solution	Topical	1-6 sessions
Allergic rhinitis[107,142,215–217]	–	80%	Solution	Topical	Once

Molluscum contagiosum[16,49,59,94,157]	Apply every week	50%-90%	Solution	Topical	1-6 sessions
Solar lentigines[40,135,176,201,209]	Apply every month	33%-40%	Solution	Topical	1-2 sessions
Acne[73,122,170,173]	Apply every 2 weeks-every month	25%-35%	Solution	Topical	1-15 sessions
Cervical/vaginal intraepithelial neoplasia[37,131,224]	Apply every week	50%-85%	Solution	Topical	1-5 sessions
Dysfunctional uterine bleeding[133,165,222]	Up to 10mL	95%	Solution	Intrauterine instillation	Once
	Apply every week	95%	Solution	Topical	1-3 sessions
Hyperpigmentation[30,117,219]	Apply every 1-2 months	10%-65%	Solution	Topical	1-5 sessions
Ingrowing toenails[110,159,166]	–	80%-100%	Solution	Topical	Once
Actinic keratoses[124,141]	–	35%-50%	Solution	Topical	Once
Basal cell carcinoma[10,12]	Apply every 1-2 weeks	70%	Solution	Topical	1-2 sessions
Conjunctival cyst[70,81]	1-2mL	20%	Solution	Injected into cyst	Once
Diabetic foot ulcers[64,65]	Apply every week	35%-70%	Solution	Topical	1-9 sessions
Infraorbital dark circles[55,108]	Apply every 2 weeks	10%	Solution	Topical	4 sessions
	Apply every week	3.75%	Gel		4 sessions
Intracorneal cyst[54,75]	–	2.5%-10%	Solution	Ophthalmic irrigation	2 sessions
	0.5mL	20%	Solution	Injected into cyst	Once
Pyogenic granulomas[9,21]	Apply every week	70%-90%	Solution	Topical	1-2 sessions
Striae distensae[48,208]	Apply every 3 weeks	15%-35%	Solution	Topical	3-6 sessions
Verruca plana[115,150]	Apply every week	10%-30%	Solution	Topical	1-12 sessions

Vitiligo[125,182]	Apply every week	15%-25%	–	Topical	1-4 sessions
Acanthosis nigricans[112]	Apply every week	15%	–	Topical	4 sessions
Anal intraepithelial lesion[210]	Apply every 4-6 weeks	85%	Solution	Topical	2-4 sessions
Benign cervical lesions[120]	–	70%	Solution	Topical	Once
Bowenoid papulosis[23]	Apply every 3 weeks	50%	–	Topical	–
Branchial cleft fistula[51]	0.5-1mL	75%	Solution	Injected into fistula	Once
Branchial sinus of the pyriform fossa[47]	–	20%	–	Topical	1-3 sessions
Bronchopleural fistula[212]	–	50%	Solution	Injected into fistula	Once
Cheilitis[181]	–	33%	Solution	Topical	Once
Chickenpox scar[99]	Apply every 3 weeks	70%	Solution	Topical	1-6 sessions
Earlobe cleft repair[24]	–	90%	Solution	Topical	2-6 sessions
Epidermal nevus[88]	Apply every month	60%	Solution	Topical	40 sessions
Epidermodysplasia verruciformis[46]	–	35%	–	Topical	Once
Epidermoid cyst[93]	–	20%	–	Topical	Once
Facial sebaceous hyperplasia[11]	Apply every month	70%	Solution	Topical	5 sessions
Human papillomavirus oral lesions[218]	Apply every 15 days	80%	Solution	Topical	1-9 applications
Koilocytic squamous papillae[109]	–	50%	Solution	Topical	Once
Linear and whorled nevoid hypermelanosis[96]	–	35%	Solution	Topical	Once
Lupus miliaris disseminates faciei scarring[50]	Apply every 2-3 months	100%	–	Topical	10 sessions

Nasal telangiectasia[160]	–	80%	–	–	Once
Onychomycosis[169]	0.1mL every week	100%	Solution	Topical	8 sessions
Oral aphthous ulceration[177]	Apply twice daily	20%	Solution	Topical	6 days
Otitis[156]	–	5%-30%	Solution	Otic instillation	Once
Photo-aged skin[128]	Apply every 1-2 weeks	10%-30%	–	Topical	–
Pincer nails[58]	–	90%	–	Topical	Once
Plantar callus[140]	–	–	Solution	Topical	21 days
Plantar warts[116]	Apply every week	40%	Solution	Topical	4 sessions
Rhinophyma[32]	–	45%	–	Topical	–
Rosacea[5]	Apply every 1-3 weeks	10%-20%	Solution	Topical	1-4 sessions
Spongiotic gingival hyperplasia[61]	Apply every week	70%	Solution	Topical	8 sessions
Superficial nail abnormalities[121]	Apply every 1-2 weeks	15%	Solution	Topical	8 sessions
Syringoma[153]	–	50%	–	Topical	Once
Tracheocutaneous fistula[53]	–	50%	Solution	Topical	Once
Venous leg ulcer[196]	Apply every 2 days	80%	Solution	Topical	3 sessions

Abbreviations: "–", not mentioned; ROA, route of administration.

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Actinic keratoses[78,80,168]	1988, 1993, 2012	• Trichloroacetic acid crystals: 20g-60g • Distilled water: qs ad 100mL	Solution	20%-60%
Aging skin[4,28]	1998, 1999	• Trichloroacetic acid 50%: 10mL • Glycerin: 1mL • Tween 20: 1mL	Solution	40%
		• Trichloroacetic acid 30%: 10mL • Glycerin: 1mL • Tween 20: 1mL		26%
		• Trichloroacetic acid 30%: 2mL • Blue base: 2mL		15%
		• Trichloroacetic acid 30%: 4mL • Blue base: 2mL		20%
Acne scars[95]	2006	• "Made to order by a local pharmacy"	Solution	95%
Human papillomavirus infection[114]	1990	• "Prepared by pharmacy"	Solution	50%

Abbreviations: qs, quantity sufficient; ad, to make.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Acne scars[129,158,200,223]	• Trichloroacetic acid: 50mL • Distilled water: 50mL	Solution	50%
	• "Made to order by a local pharmacy"	Solution	65%-100%

Cervical/vaginal intraepithelial neoplasia[131,224]	• Trichloroacetic acid: 65g • Ethyl alcohol 70%	Solution	65%
	• Trichloroacetic acid crystals: 50g • Water: qs ad 100mL	Solution	50%
Melasma[185,206]	• "Prepared by physician"	Solution	20%
	• Trichloroacetic acid: 15g • Distilled water: 85mL	Solution	15%
Xanthelasma palprebrarum[134,139]	• Trichloroacetic acid crystals: 30g • Water: qs ad 100mL	Solution	30%
	• Trichloroacetic acid crystals: qs • Distilled water: qs ad 100mL	Solution	50%-100%
Aging skin[213]	• Trichloroacetic acid crystals: 50g • Distilled water: qs ad 100mL • Further diluted to desired concentration	Solution	10%-50%
Allergic rhinitis[107]	• "Trichloroacetic acid diluted with sterile water"	Solution	80%
Cutaneous leishmaniasis lesions[193]	• Trichloroacetic acid: 5g • Distilled water: qs to dissolve trichloroacetic acid • Eucerin: qs ad 100g	Cream	5%
Solar lentigines[176]	• Trichloroacetic acid: 35g • Water: qs ad 100mL	Solution	35%
Verruca plana	• Trichloroacetic acid crystals: 10g-25g • Distilled water: 100mL	Solution	10%-25%

Abbreviations: qs, quantity sufficient; ad, to make.

Summary of focus groups/interviews of medical experts and specialty organizations

One (1) interview was conducted.

Table 12. Overview of interviewee

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with TCA	Interview Summary Response
INT001	MD	Dermatology Dermatology/Immunology	Consultant	Yes	• Frequently used in the office • Widely used • Low risk in the sense of toxicity

Abbreviations: MD, Doctor of Medicine

- Conditions or diseases in which TCA is used
  - Caucasian women over the age of 55 develop solar lentigines (flat, brown spots on the back of the hands or on the face). TCA provides a superficial peel to treat this condition. However, more aggressive photo rejuvenation processes with Fraxel and other laser treatments have replaced use of TCA.
  - "[TCA] is still available and is still widely used…and there's a place for this one."
- Administration of TCA
  - Apply it to the skin and then use an alcohol wipe to neutralize it
  - "Seen as high as 35%, 20% is a bit on the low side. It could be that somebody's going up as high as 95%, but I'm not sure why…60% sounds like maybe on the high end."
  - Used as a simple solution. Stated a concern about people over-using the product if compounded in alternative dosage forms.
- Need for office stock
  - Frequently used in the office
  - Is a place for use in the office

Summary of survey results

Table 13. Characteristics of survey respondents (1 person responded to the survey)

Board Certification	No Response
No response	1

Table 14. Types of products used, prescribed, or recommended

Types of Products	Respondents, n (N=1[a])
Compounded	0
FDA-approved	1
Over-the-counter	1
Dietary	0
Unsure	0

[a]One responded reported using multiple types of products

Table 15. Compounded use of TCA in practice

No respondents reported using compounded TCA

Table 16. Indications for which TCA is considered standard therapy

Indication	Standard Therapy
	Non-compounded, n (N=1[a])
Acne scarring	1
Actinic keratosis	1
Cosmetic peels	1
Sebaceous hyperplasia	1

[a]One (1) respondent reported more than one indication

Table 17. Reasons for using a compounded product instead of an FDA-approved product

No respondents reported using compounded TCA

Table 18. Change in frequency of compounded TCA usage over the past 5 years

No respondents reported using compounded TCA

Table 19. Do you stock non-patient specific compounded TCA in your practice?

No respondents reported using compounded TCA

Table 20. Questions related to stocking non-patient specific compounded TCA

No respondents reported using compounded TCA

CONCLUSIONS

TCA was nominated for inclusion on the 503B Bulks List by Sincerus for use as a chemical peel to treat acne and melasma as a 6-20% topical solution.

From the literature review, TCA has been used since 1945 as a chemical peel and in the treatment of acne scars. Chemical peels that were less deep than phenol peels became feasible in the 1980s as many modalities of TCA peel techniques were introduced. Most of the studies identified were from the US (70), followed by Egypt (27), Korea (19), and Iran (18). In the US, the most prevalent indication for TCA was in aging skin (24). Three (3) studies discussed use in acne scars and no studies were identified that used TCA in melasma. Of the studies that identified a route of administration, all but three (3) applied TCA topically and of these studies all but one (1) used TCA as a solution. Seven (7) of the US studies identified the use of TCA as a compounded product with concentrations ranging from 15-95%. Of the non-US studies, the most frequent indication was for melasma (16) followed by acne scars (14).

From the interview, TCA is commonly used as a superficial peel to treat solar lentigines, however more aggressive photo rejuvenation processes, like Fraxel and other laser treatments, have replaced TCA. A 35% solution is applied to the skin and then neutralized with alcohol. TCA is still used and would need to be stocked in a prescriber's office due to concerns of patients over-using the product.

From the survey, one (1) person responded to the survey, of which one (1) respondent reported use of TCA as an FDA-approved product and OTC product. The respondent reported that TCA is considered the standard therapy for acne scarring, actinic keratosis, cosmetic peels, and sebaceous hyperplasia. No respondents reported use of TCA as a compounded product.

APPENDICES

Appendix 1. References

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INTERVIEW_DERM_06

Interviewer 1: Get this started, and I know we sent you a pretty lengthy list and you did provide us with some additional comments so I wasn't sure if there was particular place that you wanted to start with first? Or a particular substance that you wanted to discuss.

Interviewer 1: Okay. All right. I think that was all that we had about podophyllum. So we can transition. I think trichloroacetic acid was one that you had a lot of experience with as well. So I guess we can transition to that particular substance.

DER_06: Yeah. That's a good one.

Interviewer 1: Go ahead.

DER_06: That's a good one, because it is frequently used in the office. It's used for, if you look at any woman over the age 55, who's a fair- skinned Caucasian and may have been in the sun, you'll see these flat brown spots on the back of the hands or on the face, these are solar lentigines. That's a very common use for this product. We put it on, it's a superficial peel. We used to see people get a, "Lunch time peel", where you could leave your office theoretically and in 20 minutes get this peel put on and then go back to work. It was very, very superficial. It's been I think replaced by more aggressive photo rejuvenation process with Fraxel and these other laser treatments. It's still available and still used so I'm a fan of... Yes there's a place for this one. It's fairly widely used. People who do it, know how to do it. I think that there's relatively low risk in the sense of toxicity and from a safety perspective.

This, of all the things that are on your list today, that and the caine's are the things that are actually fairly commonly used and for which there is a place in the office.

Interviewer 1: Okay.

DER_06: Whether there's a place in the office for some of these others is a different issue.

Interviewer 1: So with the trichloroacetic acid, so when we were doing some of our literature review, the nomination information says that they want to do a topical solution anywhere from 6 to 20% concentration, but in some of the literature that we found they would even go up as high as 95% on some of the concentrations. What would be the recommended range that you would use in the office for this?

DER_06: I've seen as high as 35%, 20 sounds a bit on the low side. It could be that somebody's going up as high as 95%, but I'm not sure why. The whole goal was... And I would have to look more carefully at the literature, you guys, as you've said, you've already pulled a couple hundred articles about it.

Interviewer 1: Yeah we had quite a few.

DER_06: It's probably of all the things on this list today, other than podophyllum, which has also been used since forever, although probably not much written of that. But the TCA, my guess has a big literature about it and I would see what they say. 60 sounds like maybe on the high end, but again, I'm not an aesthetic person, I did not do a lot of cosmetic procedures. I have people I could send people to, I took care of medical dermatology. I

actually look care of a lot of HIV patients with bad genital warts, so I'm sympathetic to the problem of bad warts that don't go away and that need help.

Interviewer 1: Okay. There is a place for this, would the only dosage form that you could theoretically want would be the solution so that you could apply it and then peel it off?

DER_06: Well you put it on, and then you actually would use an alcohol wipe to neutralize it.

Interviewer 1: Okay.

DER_06: That was all you had to do. It doesn't peel off per se, it's not really some sort of gel or gel forming, or adhesive layer forming product.

Interviewer 1: Okay.

DER_06: It was more just a simple solution.

Interviewer 1: Okay.

DER_06: That doesn’t obviate that somebody might choose to compound it in a cream or do something else with it. I just worry about people over-using products.

Interviewer 1: Yeah. In terms of trichloroacetic acid it seems like there is a place for that one to potentially be still needed. All right so let's move on to the next one. Interviewer 3 do you have one you want to... Or are yours all kind of...

Appendix 3. Survey instrument

Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **trichloroacetic acid**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. 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.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

End of Block: Welcome Page

Start of Block: Trichloroacetic acid

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **trichloroacetic acid**? Please check all that apply.

- ☐ Compounded drug product
- ☐ FDA-approved drug product
- ☐ Over the counter drug product
- ☐ Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)

Unsure Skip To: Q15 If What type(s) of product(s) do you use, prescribe, or recommend for trichloroacetic acid? Please c... != Compounded drug product

Skip To: Q2If What type(s) of product(s) do you use, prescribe, or recommend for trichloroacetic acid? Please c... = Compounded drug product

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Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for trichloroacetic acid? Please c... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **trichloroacetic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **trichloroacetic acid** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ▢ Single
- ▢ Combination

Skip To: Q6 If Do you use compounded trichloroacetic acid as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

If Loop current: Do you use compounded trichloroacetic acid as a single agent active ingredient, or as one active ingredient... = Combination

Q4. Please list all combination products in which you use compounded **trichloroacetic acid.**

_____

Q5. For which, if any, diseases or conditions do you consider compounded **trichloroacetic acid** standard therapy? _____

Q6. Does your specialty describe the use of compounded **trichloroacetic acid** in medical practice guidelines or other resources? _____

Q7. Over the past 5 years, has the frequency in which you have used compounded **trichloroacetic acid** changed?

- o Yes - I use it **MORE** often now (briefly describe why) _____
- o Yes - I use it **LESS** often now (briefly describe why) _____
- o No - use has remained consistent

Q8. Why do you use compounded **trichloroacetic acid** instead of any FDA-approved drug product? _____

Q9. Do you stock non-patient-specific compounded **trichloroacetic acid** in your practice location?

- o Yes
- o No

Skip To: End of Block If Do you stock non-patient-specific compounded trichloroacetic acid in your practice location? = No

Display This Question:

If Do you stock non-patient-specific compounded trichloroacetic acid in your practice location? = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **trichloroacetic acid**? Please check all that apply.

- ☐ Physician office
- ☐ Outpatient clinic
- ☐ Emergency room
- ☐ Operating room
- ☐ Inpatient ward
- ☐ Other (please describe) _____

Q11. How do you obtain your stock of non-patient-specific compounded **trichloroacetic acid**? Please check all that apply.

- ☐ Purchase from a compounding pharmacy
- ☐ Purchase from an outsourcing facility
- ☐ Compound the product yourself
- ☐ Other (please describe) _____

Q12. Why do you keep a stock of non-patient-specific compounded **trichloroacetic acid**? Please check all that apply.

- ☐ Convenience
- ☐ Emergencies
- ☐ Other (please describe) _____

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded trichloroacetic acid? Please check all that apply. = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded trichloroacetic acid? Please check all that apply. = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded trichloroacetic acid? Please check all that apply. = Other (please describe)

Q13. For which, if any, diseases or conditions do you consider **trichloroacetic acid** standard therapy?
_____

Q14. Does your specialty describe the use of **trichloroacetic acid** in medical practice guidelines or other resources? _____

End of Block: Trichloroacetic acid

Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- ▢ Doctor of Medicine (MD)
- ▢ Doctor of Osteopathic Medicine (DO)
- ▢ Doctor of Medicine in Dentistry (DMD/DDS)
- ▢ Naturopathic Doctor (ND)
- ▢ Nurse Practitioner (NP)
- ▢ Physician Assistant (PA)
- ▢ Other (please describe) _____

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- ▢ No Board certification
- ▢ Allergy and Immunology
- ▢ Anesthesiology
- ▢ Cardiovascular Disease
- ▢ Critical Care Medicine
- ▢ Dermatology
- ▢ Emergency Medicine
- ▢ Endocrinology, Diabetes and Metabolism
- ▢ Family Medicine
- ▢ Gastroenterology
- ▢ Hematology
- ▢ Infectious Disease
- ▢ Internal Medicine
- ▢ Medical Toxicology
- ▢ Naturopathic Doctor
- ▢ Naturopathic Physician
- ▢ Nephrology
- ▢ Neurology
- ▢ Obstetrics and Gynecology
- ▢ Oncology
- ▢ Ophthalmology
- ▢ Otolaryngology

- ☐ Pain Medicine
- ☐ Pediatrics
- ☐ Psychiatry
- ☐ Rheumatology
- ☐ Sleep Medicine
- ☐ Surgery (please describe) _____
- ☐ Urology
- ☐ Other (please describe) _____

End of Block: Background Information

Appendix 4. Raw survey data

See attached PDF for raw survey data.

Q144.
The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice.

There are **ten (10)** substances contained in this survey. As a medical expert, we appreciate your input regarding the use of these substances in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. 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.

If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- [x] Alpha lipoic acid (ALA)
- [x] Ascorbyl palmitate
- [x] Coenzyme Q10
- [x] Estriol
- [x] Glycolic acid
- [x] Hydroquinone
- [ ] Malic acid
- [ ] Methylcobalamin
- [x] Trichloroacetic acid
- [x] Vitamin A acetate
- [ ] None of the above

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **alpha lipoic acid (ALA)**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q3. Please list any conditions or diseases for which you use compounded **alpha lipoic acid (ALA)** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe): Atopic dermatitis	2-5%	Bid	Topical	Topical	2-4 months	Both sexes children and adults
Condition 2 (please describe): Psoriasis	2-5%	Bid	Topical	Topical	Indefinite	Children adults both sexes
Condition 3 (please describe):						
Condition 4 (please describe):						
Condition 5 (please describe):						

Q4.
Do you use compounded **alpha lipoic acid (ALA)** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [ ] Single
- [x] Combination

Q5. Please list all combination products in which you use compounded **alpha lipoic acid (ALA).**

Versabase cream, vitamin d, multiple vitamin Bs, protopic, capric triglycerides,

Q6. For which, if any, diseases or conditions do you consider compounded **alpha lipoic acid (ALA)** standard therapy?

Psoriasis atopic dermatitis

Q7. Does your specialty describe the use of compounded **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

Q8. Over the past 5 years, has the frequency in which you have used compounded **alpha lipoic acid (ALA)** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why)
- ◉ Yes - I use it **LESS** often now (briefly describe why) Better biological drugs for psoriasis so lead need for steroid soaring topicals
- ○ No - use has remained consistent

Q9. Why do you use compounded **alpha lipoic acid (ALA)** instead of any FDA-approved drug product?

Because it makes compliance better with different j gradients and the bases used allow for better penetration and one can customize for an indicidual

Q10. Do you stock non-patient-specific compounded **alpha lipoic acid (ALA)** in your practice location?

- ○ Yes
- ◉ No

Q11. In what practice location(s) do you stock non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q12. How do you obtain your stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q13. Why do you keep a stock of non-patient-specific compounded **alpha lipoic acid (ALA)**? Please check all that apply.

This question was not displayed to the respondent.

Q14. For which, if any, diseases or conditions do you consider **alpha lipoic acid (ALA)** standard therapy?

This question was not displayed to the respondent.

Q15. Does your specialty describe the use of **alpha lipoic acid (ALA)** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q388. What type(s) of product(s) do you use, prescribe, or recommend for **ascorbyl palmitate**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [x] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q389. Please list any conditions or diseases for which you use compounded **ascorbyl palmitate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q390.
Do you use compounded **ascorbyl palmitate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q391. Please list all combination products in which you use compounded **ascorbyl palmitate**.

This question was not displayed to the respondent.

Q392. For which, if any, diseases or conditions do you consider compounded **ascorbyl palmitate** standard therapy?

This question was not displayed to the respondent.

Q393. Does your specialty describe the use of compounded **ascorbyl palmitate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q394. Over the past 5 years, has the frequency in which you have used compounded **ascorbyl palmitate** changed?

This question was not displayed to the respondent.

Q395. Why do you use compounded **ascorbyl palmitate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q396. Do you stock non-patient-specific compounded **ascorbyl palmitate** in your practice location?

This question was not displayed to the respondent.

Q397. In what practice location(s) do you stock non-patient-specific compounded **ascorbyl palmitate**? Please check all that apply.

This question was not displayed to the respondent.

Q398. How do you obtain your stock of non-patient-specific compounded **ascorbyl palmitate**? Please check all that apply.

This question was not displayed to the respondent.

Q399. Why do you keep a stock of non-patient-specific compounded **ascorbyl palmitate**? Please check all that apply.

This question was not displayed to the respondent.

Q400. For which, if any, diseases or conditions do you consider **ascorbyl palmitate** standard therapy?

Sun damage

Q401. Does your specialty describe the use of **ascorbyl palmitate** in medical practice guidelines or other resources?

Yes

Q402. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- [ ] Compounded drug product
- [ ] FDA-approved drug product
- [x] Over the counter drug product
- [x] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q403. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q404.
Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q405. Please list all combination products in which you use compounded **coenzyme Q10.**

This question was not displayed to the respondent.

Q406. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

This question was not displayed to the respondent.

Q407. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q408. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

This question was not displayed to the respondent.

Q409. Why do you use compounded **coenzyme Q10** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q410. Do you stock non-patient-specific compounded **coenzyme Q10** in your practice location?

This question was not displayed to the respondent.

Q411. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q412. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q413. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

This question was not displayed to the respondent.

Q414. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

Fibromyalgia and when patient is on statin and other medicarions

Q415. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

Yes

Q416. What type(s) of product(s) do you use, prescribe, or recommend for **estriol**? Please check all that apply.

- [x] Compounded drug product
- [ ] FDA-approved drug product
- [ ] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q417. Please list any conditions or diseases for which you use compounded **estriol** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe): Lichen sclerosus et atrophicus	1-2 mg	Bid	Mg	Topical	Indefinitely	Peri to post menopausal women
Condition 2 (please describe): Atrophic vaginitis	5 mg	Biweekly	Mg	Intravaginal suppository	Indefinitely	Peri to post menopausal women
Condition 3 (please describe): Erosive desquamative vaginitis	1-2 mg	Bi weekly	Mg	Intravaginal suppositories	3-6months	Older adult women
Condition 4 (please describe):						
Condition 5 (please describe):						

Q418.
Do you use compounded **estriol** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- [x] Single
- [x] Combination

Q419. Please list all combination products in which you use compounded **estriol.**

Mucolox amd sometimes testosterone

Q420. For which, if any, diseases or conditions do you consider compounded **estriol** standard therapy?

Atrophic vaginitis and lichen sclerosis et ateophicus

Q421. Does your specialty describe the use of compounded **estriol** in medical practice guidelines or other resources?

Yea

Q422. Over the past 5 years, has the frequency in which you have used compounded **estriol** changed?

- (●) Yes - I use it **MORE** often now (briefly describe why) [More comfortable with experience of ise]
- ( ) Yes - I use it **LESS** often now (briefly describe why) [ ]
- ( ) No - use has remained consistent

Q423. Why do you use compounded **estriol** instead of any FDA-approved drug product?

It is less inflammatory and also a less potent estrogen

Q424. Do you stock non-patient-specific compounded **estriol** in your practice location?

- ( ) Yes
- (●) No

Q425. In what practice location(s) do you stock non-patient-specific compounded **estriol**? Please check all that apply.

This question was not displayed to the respondent.

Q426. How do you obtain your stock of non-patient-specific compounded **estriol**? Please check all that apply.

This question was not displayed to the respondent.

Q427. Why do you keep a stock of non-patient-specific compounded **estriol**? Please check all that apply.

This question was not displayed to the respondent.

Q428. For which, if any, diseases or conditions do you consider **estriol** standard therapy?

This question was not displayed to the respondent.

Q429. Does your specialty describe the use of **estriol** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q430. What type(s) of product(s) do you use, prescribe, or recommend for **glycolic acid**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [x] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q431. Please list any conditions or diseases for which you use compounded **glycolic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q432.
Do you use compounded **glycolic acid** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q433. Please list all combination products in which you use compounded **glycolic acid.**

This question was not displayed to the respondent.

Q434. For which, if any, diseases or conditions do you consider compounded **glycolic acid** standard therapy?

This question was not displayed to the respondent.

Q435. Does your specialty describe the use of compounded **glycolic acid** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q436. Over the past 5 years, has the frequency in which you have used compounded **glycolic acid** changed?

This question was not displayed to the respondent.

Q437. Why do you use compounded **glycolic acid** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q438. Do you stock non-patient-specific compounded **glycolic acid** in your practice location?

This question was not displayed to the respondent.

Q439. In what practice location(s) do you stock non-patient-specific compounded **glycolic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q440. How do you obtain your stock of non-patient-specific compounded **glycolic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q441. Why do you keep a stock of non-patient-specific compounded **glycolic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q442. For which, if any, diseases or conditions do you consider **glycolic acid** standard therapy?

Acne anti-aging sun damage

Q443. Does your specialty describe the use of **glycolic acid** in medical practice guidelines or other resources?

Yes

Q444. What type(s) of product(s) do you use, prescribe, or recommend for **hydroquinone**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [x] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q445. Please list any conditions or diseases for which you use compounded **hydroquinone** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q446.
Do you use compounded **hydroquinone** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q447. In which combination(s) do you use compounded **hydroquinone**? Please check all that apply.

This question was not displayed to the respondent.

Q448. For which, if any, diseases or conditions do you consider compounded **hydroquinone** standard therapy?

This question was not displayed to the respondent.

Q449. Does your specialty describe the use of compounded **hydroquinone** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q450. Over the past 5 years, has the frequency in which you have used compounded **hydroquinone** changed?

This question was not displayed to the respondent.

Q451. Why do you use compounded **hydroquinone** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q452. Do you stock non-patient-specific compounded **hydroquinone** in your practice location?

This question was not displayed to the respondent.

Q453. In what practice location(s) do you stock non-patient-specific compounded **hydroquinone**? Please check all that apply.

This question was not displayed to the respondent.

Q454. How do you obtain your stock of non-patient-specific compounded **hydroquinone**? Please check all that apply.

This question was not displayed to the respondent.

Q455. Why do you keep a stock of non-patient-specific compounded **hydroquinone**? Please check all that apply.

This question was not displayed to the respondent.

Q456. For which, if any, diseases or conditions do you consider **hydroquinone** standard therapy?

Melisma and pre and post laser therapy

Q457. Does your specialty describe the use of **hydroquinone** in medical practice guidelines or other resources?

Yes

Q458. What type(s) of product(s) do you use, prescribe, or recommend for **malic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q459. Please list any conditions or diseases for which you use compounded **malic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q460.
Do you use compounded **malic acid** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q461. Please list all combination products in which you use compounded **malic acid.**

This question was not displayed to the respondent.

Q462. For which, if any, diseases or conditions do you consider compounded **malic acid** standard therapy?

This question was not displayed to the respondent.

Q463. Does your specialty describe the use of compounded **malic acid** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q464. Over the past 5 years, has the frequency in which you have used compounded **malic acid** changed?

This question was not displayed to the respondent.

Q465. Why do you use compounded **malic acid** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q466. Do you stock non-patient-specific compounded **malic acid** in your practice location?

This question was not displayed to the respondent.

Q467. In what practice location(s) do you stock non-patient-specific compounded **malic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q468. How do you obtain your stock of non-patient-specific compounded **malic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q469. Why do you keep a stock of non-patient-specific compounded **malic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q470. For which, if any, diseases or conditions do you consider **malic acid** standard therapy?

This question was not displayed to the respondent.

Q471. Does your specialty describe the use of **malic acid** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q472. What type(s) of product(s) do you use, prescribe, or recommend for **methylcobalamin**? Please check all that apply.

This question was not displayed to the respondent.

Q473. Please list any conditions or diseases for which you use compounded **methylcobalamin** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q474.

Do you use compounded **methylcobalamin** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q475. In which combination(s) do you use compounded **methylcobalamin**? Please check all that apply.

This question was not displayed to the respondent.

Q476. For which, if any, diseases or conditions do you consider compounded **methylcobalamin** standard therapy?

This question was not displayed to the respondent.

Q477. Does your specialty describe the use of compounded **methylcobalamin** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q478. Over the past 5 years, has the frequency in which you have used compounded **methylcobalamin** changed?

This question was not displayed to the respondent.

Q479. Why do you use compounded **methylcobalamin** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q480. Do you stock non-patient-specific compounded **methylcobalamin** in your practice location?

This question was not displayed to the respondent.

Q481. In what practice location(s) do you stock non-patient-specific compounded **methylcobalamin**? Please check all that apply.

This question was not displayed to the respondent.

Q482. How do you obtain your stock of non-patient-specific compounded **methylcobalamin**? Please check all that apply.

This question was not displayed to the respondent.

Q483. Why do you keep a stock of non-patient-specific compounded **methylcobalamin**? Please check all that apply.

This question was not displayed to the respondent.

Q484. For which, if any, diseases or conditions do you consider **methylcobalamin** standard therapy?

This question was not displayed to the respondent.

Q485. Does your specialty describe the use of **methylcobalamin** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q486. What type(s) of product(s) do you use, prescribe, or recommend for **trichloroacetic acid**? Please check all that apply.

- [ ] Compounded drug product
- [x] FDA-approved drug product
- [x] Over the counter drug product
- [ ] Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- [ ] Unsure

Q487. Please list any conditions or diseases for which you use compounded **trichloroacetic acid** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q488.
Do you use compounded **trichloroacetic acid** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q489. Please list all combination products in which you use compounded **trichloroacetic acid.**

This question was not displayed to the respondent.

Q490. For which, if any, diseases or conditions do you consider compounded **trichloroacetic acid** standard therapy?

This question was not displayed to the respondent.

Q491. Does your specialty describe the use of compounded **trichloroacetic acid** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q492. Over the past 5 years, has the frequency in which you have used compounded **trichloroacetic acid** changed?

This question was not displayed to the respondent.

Q493. Why do you use compounded **trichloroacetic acid** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q494. Do you stock non-patient-specific compounded **trichloroacetic acid** in your practice location?

This question was not displayed to the respondent.

Q495. In what practice location(s) do you stock non-patient-specific compounded **trichloroacetic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q496. How do you obtain your stock of non-patient-specific compounded **trichloroacetic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q497. Why do you keep a stock of non-patient-specific compounded **trichloroacetic acid**? Please check all that apply.

This question was not displayed to the respondent.

Q498. For which, if any, diseases or conditions do you consider **trichloroacetic acid** standard therapy?

Cosmetic peels, actinic keratosis, sebaceous hyperplasia, acne scarring

Q499. Does your specialty describe the use of **trichloroacetic acid** in medical practice guidelines or other resources?

Yes

Q500. What type(s) of product(s) do you use, prescribe, or recommend for **vitamin A acetate**? Please check all that apply.

This question was not displayed to the respondent.

Q501. Please list any conditions or diseases for which you use compounded **vitamin A acetate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

This question was not displayed to the respondent.

Q502.
Do you use compounded **vitamin A acetate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

This question was not displayed to the respondent.

Q503. Please list all combination products in which you use compounded **vitamin A acetate.**

This question was not displayed to the respondent.

Q504. For which, if any, diseases or conditions do you consider compounded **vitamin A acetate** standard therapy?

This question was not displayed to the respondent.

Q505. Does your specialty describe the use of compounded **vitamin A acetate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q506. Over the past 5 years, has the frequency in which you have used compounded **vitamin A acetate** changed?

This question was not displayed to the respondent.

Q507. Why do you use compounded **vitamin A acetate** instead of any FDA-approved drug product?

This question was not displayed to the respondent.

Q508. Do you stock non-patient-specific compounded **vitamin A acetate** in your practice location?

This question was not displayed to the respondent.

Q509. In what practice location(s) do you stock non-patient-specific compounded **vitamin A acetate**? Please check all that apply.

This question was not displayed to the respondent.

Q510. How do you obtain your stock of non-patient-specific compounded **vitamin A acetate**? Please check all that apply.

This question was not displayed to the respondent.

Q511. Why do you keep a stock of non-patient-specific compounded **vitamin A acetate**? Please check all that apply.

This question was not displayed to the respondent.

Q512. For which, if any, diseases or conditions do you consider **vitamin A acetate** standard therapy?

This question was not displayed to the respondent.

Q513. Does your specialty describe the use of **vitamin A acetate** in medical practice guidelines or other resources?

This question was not displayed to the respondent.

Q16. What is your terminal clinical degree? Please check all that apply.

This question was not displayed to the respondent.

Q17. Which of the following Board certification(s) do you hold? Please check all that apply.

This question was not displayed to the respondent.

Q145. How has access to compounded medications affected patient care?

This question was not displayed to the respondent.