The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Pharmacy Compounding Advisory Committee (advisory committee). We are bringing certain compounding issues to this advisory committee to obtain the committee’s advice. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The FDA does not intend to issue a final determination on the issues at hand until input from the advisory committee process has been considered, all reviews have been finalized, consultation with the United States Pharmacopeia has occurred, and public comment has been considered through notice and comment rulemaking. The final determination may be affected by issues not discussed at the advisory committee meeting.
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   A. Bulk Drug Substances That Can Be Used by Compounders under Section 503A  
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II. Substances Nominated for Inclusion on the Section 503A Bulk Drug Substances List  
    (in order of discussion at the meeting) ...................................................................................... 5  

III. Draft Points to Consider ............................................................................................................. 7
I. Introduction

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the following three sections of the FD&C Act: section 505 (concerning the approval of drugs under new drug applications or abbreviated new drug applications); section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and section 501(a)(2)(B) (concerning current good manufacturing practice requirements).

On November 27, 2013, President Obama signed the Drug Quality and Security Act, legislation that contains important provisions relating to the oversight of compounding of human drugs. Title I of this law, the Compounding Quality Act, created a new section 503B of the FD&C Act under which a compounder can elect to register as an outsourcing facility. Registered outsourcing facilities can compound drugs without receiving patient specific prescriptions or orders. If the conditions under section 503B of the FD&C Act are satisfied, drugs compounded by or under the direct supervision of a licensed pharmacist in a registered outsourcing facility may qualify for exemptions from the new drug approval requirements (section 505 of the FD&C Act), the requirement to label products with adequate directions for use (section 502(f)(1) of the FD&C Act) and the Drug Supply Chain Security Act (section 582 of the FD&C Act). Outsourcing facilities remain subject to current good manufacturing practice (CGMP) requirements.

A. Bulk Drug Substances That Can Be Used by Compounders under Section 503A

One of the conditions that must be met for a drug product that is compounded using bulk drug substances to qualify for the exemptions in Section 503A of the Act is that a licensed pharmacist or licensed physician compunds the drug product using bulk drug substances that:

(1) Comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding;
(2) If such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or
(3) If such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appears on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A.

(See section 503A(b)(1)(A)(i) of the FD&C Act).
FDA is considering those substances nominated for inclusion on the list of bulk drug substances that can be used to compound drug products under section 503A of the FD&C Act. As discussed at the February 2015 PCAC meeting, in the July 2014 Federal Register notice (79 FR 37747) (July 2, 2014) soliciting nominations for the section 503A bulk drug substances list, FDA proposed the following criteria to evaluate the nominated substances:

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

The agency is considering each criterion in the context of the others and balancing them, on a substance-by-substance basis, in deciding whether a particular substance is appropriate for inclusion on the list.

**B. Expanded Access to Investigational New Drugs**

Expanded access, sometimes referred to as “compassionate use,” is the use of an investigational drug outside of a clinical trial, including for emergency use, for the purpose of treating a patient or patients with serious or life-threatening disease(s) or condition(s) who have no acceptable medical options. The use of an investigational drug under expanded access is subject to all applicable requirements regarding informed consent and institutional review board (IRB) review.

At previous meetings, there have been discussions about the use of an IND as an option for patients who seek to use drugs that are nominated for, but not placed on, the 503A and 503B bulks lists. At this meeting, the Agency plans to describe additional details about the expanded access program. Further information on the use of INDs is available on the Agency’s website at:

[http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm](http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm)
II. Substances Nominated for Inclusion on the Section 503A Bulk Drug Substances List (in order of discussion at the meeting)

A. Chrysin (Tab 1)

1. Nominations (Tab 1a)
   (a) Fagron
   (b) International Academy of Compounding Pharmacists
   (c) National Community Pharmacists Association

2. FDA Review (Tab 1b)

B. Cesium Chloride (Tab 2)

1. Nominations (Tab 2a)
   (a) American Association of Naturopathic Physicians
   (b) Alliance for Natural Health USA
   (c) Integrative Medical Consortium
   (d) McGuff Compounding Pharmacy Services, Inc.

2. FDA Review (Tab 2b)

C. Sodium Dichloroacetate (Tab 3)

1. Nominations (Tab 3a)
   (a) McGuff Compounding Pharmacy Services, Inc.
   (b) Alliance for Natural Health USA
   (c) Integrative Medical Consortium
   (d) American Association of Naturopathic Physicians

2. FDA Review (Tab 3b)

D. Pyruvic Acid (Tab 4)

1. Nominations (Tab 4a)
   (a) Fagron

2. FDA Review (Tab 4b)
E. Tea Tree Oil (Tab 5)

1. Nominations (Tab 5a)
   (a) National Community Pharmacists Association
   (b) International Academy of Compounding Pharmacists

2. FDA Review (Tab 5b)

F. 2,3-Dimercapto-1-propanesulfonic acid (DMPS) (Tab 6)

1. Nominations (Tab 6a)
   (a) Alliance for Natural Health USA
   (b) American Association of Naturopathic Physicians
   (c) Integrative Medical Consortium
   (d) McGuff Compounding Pharmacy Services, Inc.
   (e) International Academy of Compounding Pharmacists

2. FDA Review (Tab 6b)
III. Draft Points to Consider

A. June 23, 2016, a.m. session

Draft points to consider for the PCAC Regarding Whether to Include Certain Bulk Drug Substances on the 503A Bulk List

1. FDA is proposing that chrysin NOT be placed on the list of bulk drug substances that can be used in pharmacy compounding in accordance with section 503A of the FD&C Act (“the 503A bulk list”). Should chrysin be placed on the list?

2. FDA is proposing that cesium chloride NOT be placed on the 503A bulk list. Should cesium chloride be placed on the list?

3. FDA is proposing that sodium dichloroacetate NOT be placed on the 503A bulk list. Should sodium dichloroacetate be placed on the list?

B. June 23, 2016, p.m. session

Draft points to consider for the PCAC Regarding Whether to Include Certain Bulk Drug Substances on the 503A Bulk List

1. FDA is proposing that pyruvic acid for topical use be INCLUDED on the 503A bulk list. Should pyruvic acid for topical use be placed on the list?

2. FDA is proposing that tea tree oil NOT be placed on the 503A bulk list. Should tea tree oil be placed on the list?

3. FDA is proposing that 2, 3-dimercapto-1-propanesulfonic acid (DMPS) NOT be placed on the 503A bulk list. Should DMPS be placed on the list?
Tab 1

Chrysin
Tab 1a

Chrysin Nominations
Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

"List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act"

Dear Sir or Madam,

Fagron appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

We hereby nominate the bulk drug substances in the attached spreadsheets for FDA’s consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

None of these items appear on an FDA-published list of drugs that present demonstrable difficulties for compounding. In addition, none are a component of a drug product that has been withdrawn or removed from the market because the drug or components of the drug have been found to be unsafe or not effective.

We include references in support of this nomination for your consideration.

Thank you for your consideration. If Fagron can answer any questions, please contact me (j.letwat@fagron.com; 847-207-6100).

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs
Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlsx file)

7-Keto Dehydroepiandrosterone
Acetyl-D-Glucosamine
Aloe Vera 200:1 Freeze Dried
Astragalus Extract 10:1
Beta Glucan (1,3/1,4 –D)
Boswellia Serrata Extract
Bromelain
Cantharidin
Cetyl Myristoleate Oil
Cetyl Myristoleate 20% Powder
Chrysin
Cittruline
Dehydroepiandrosterone
Deoxy-D-Glucose (2)
Diindolylmethane
Domperidone
EGCg
Ferric Subsulfate
Glycolic Acid
Glycosaminoglycans
Hydroxocobalamin Hydrochloride
Kojic Acid
Methylcobalamin
Nicotinamide Adenine Dinucleotide
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)
Ornithine Hydrochloride
Phosphatidyl Serine
Pregnenolone
Pyridoxal 5-Phosphate Monohydrate
Pyruvic Acid
Quercetin
Quinacrine Hydrochloride
Ribose (D)
Silver Protein Mild
Squaric Acid Di-N-Butyl Ester
Thymol Iodide
Tranilast
Trichloroacetic Acid
Ubiquinol 30% Powder
### What is the name of the nominated ingredient?

**Chyrsin**

### Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?


### Is the ingredient listed in any of the three sections of the Orange Book?

The nominated substance was searched for in all three sections of the Orange Book located at [http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm](http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm). The nominated substance does not appear in any section searches of the Orange Book.

### Were any monographs for the ingredient found in the USP or NF monographs?

The nominated substance was searched for at [http://www.uspnf.com](http://www.uspnf.com). The nominated substance is not the subject of a USP or NF monograph.

### What is the chemical name of the substance?

5,7-Dihydroxy-2-phenyl-4H-chromen-4-one

### What is the common name of the substance?

Chrysin, Galangin flavanone

### Does the substance have a UNII Code?

N/A

### What is the chemical grade of the substance?

no grade
| What is the strength, quality, stability, and purity of the ingredient? | Appearance: Light yellow fine powder  
Identification: Positive  
Particle Size: ≥ 80% through 80 mesh  
Melting Point: 284.0°C - 290.0°C  
Assay: ≥ 99.0%  
Loss on Drying: ≤ 1.0%  
Ash: ≤ 0.2%  
Heavy Metals: ≤ 10 ppm  
Lead: ≤ 2 ppm  
Arsenic: ≤ 2 ppm  
Total Plate Count: ≤ 1000 cfu/g  
Yeast and Molds: ≤ 100 cfu/g  
E. Coli: Negative  
Salmonella: Negative |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>How is the ingredient supplied?</td>
</tr>
<tr>
<td>Is the substance recognized in foreign pharmacopeias or registered in other countries?</td>
</tr>
<tr>
<td>Has information been submitted about the substance to the USP for consideration of monograph development?</td>
</tr>
<tr>
<td>What dosage form(s) will be compounded using the bulk drug substance?</td>
</tr>
<tr>
<td>What strength(s) will be compounded from the nominated substance?</td>
</tr>
<tr>
<td>What are the anticipated route(s) of administration of the compounded drug product(s)?</td>
</tr>
<tr>
<td>Has the bulk drug substance been used previously to compound drug product(s)?</td>
</tr>
<tr>
<td>What is the proposed use for the drug product(s) to be compounded with the nominated substance?</td>
</tr>
<tr>
<td>What is the reason for use of a compounded drug product rather than an FDA-approved product?</td>
</tr>
<tr>
<td>Is there any other relevant information?</td>
</tr>
</tbody>
</table>
September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA’s request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.
Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

**ISSUE: The Issuance of This Proposed Rule is Premature**

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created a series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency’s activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee prior to the implementation and issuance of regulations including the creation of the bulk ingredient list.

(2) Advisory committee on compounding.—Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee’s review of any submitted drug, regardless of FDA’s statement in the published revised call for nominations that:

General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

David G. Miller, R.Ph.
Executive Vice President & CEO
General Background on Bulk Drug Substance

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Chrysin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical/Common Name</td>
<td>5,7-Dihydroxyflavone</td>
</tr>
<tr>
<td>Identifying Codes</td>
<td>480-40-0</td>
</tr>
<tr>
<td>Chemical Grade</td>
<td>Provided by FDA Registered Supplier/COA</td>
</tr>
<tr>
<td>Description of Strength, Quality, Stability, and Purity</td>
<td>Provided by FDA Registered Supplier/COA</td>
</tr>
<tr>
<td>How Supplied</td>
<td>Varies based upon compounding requirement</td>
</tr>
<tr>
<td>Recognition in Formularies</td>
<td>Not Listed in USP/NF</td>
</tr>
</tbody>
</table>

Information on Compounded Bulk Drug Preparation

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Varies based upon compounding requirement/prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>Varies based upon compounding requirement/prescription</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Varies based upon compounding requirement/prescription</td>
</tr>
<tr>
<td>Bibliography (where available)</td>
<td></td>
</tr>
</tbody>
</table>

Past and Proposed Use

The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA’s request for this information is an insurmountable hurdle that has not been requested by the PCAC.
March 4, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No.: FDA-2013-N-1525: List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Withdrawal of Proposed Rule; request for nominations

Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation’s retail prescription drugs, and, according to a NCPA member survey, almost 86% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet of 2,403 bulk drug substances submitted by the International Academy of Compounding Pharmacists (IACP) as our formal submission of bulk drug substances that are currently used by compounding pharmacies and do not have a specific USP monograph nor are components of FDA approved prescription drug products.

In addition to the IACP spreadsheet of bulk drug substances referenced above, NCPA would also like to formally submit collectively for review and consideration of the FDA Pharmacy Compounding Advisory Committee the drugs and standards contained within the British Pharmacopeia, the European Pharmacopeia and the Japanese Pharmacopeia. NCPA respectfully requests that all drugs and standards contained within these three pharmacopeias for which no USP corresponding monograph exists be accepted and approved to be used for the preparation of compounded medications under section 503A of the Federal Food, Drug and Cosmetic Act.
NCPA is requesting the recognition of these pharmacopoeias as there are examples of situations when our members need access to these alternative compendia for monograph information. NCPA members may receive requests to compound medications that do not have a USP monograph, nor is the drug substance being used a component of an FDA approved drug product. When these situations arise, the British Pharmacopeia, the European Pharmacopeia and the Japanese Pharmacopeia are used in practice to ensure compounds are made with the highest assurance of quality.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

Steve Pfister  
Senior Vice President, Government Affairs

Attachment
<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Chrysin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Name</td>
<td>5,7-Dihydroxyflavone</td>
</tr>
<tr>
<td>Common Name</td>
<td>Chrysin</td>
</tr>
<tr>
<td>UNII Code</td>
<td>3CN01FSJ5</td>
</tr>
<tr>
<td>Description of strength, quality, stability and purity</td>
<td>From PCCA MSDS: 100% by weight and stable; avoid excess heat and oxidizing agents.</td>
</tr>
<tr>
<td>Ingredient Format(s)</td>
<td>Powder</td>
</tr>
<tr>
<td>Recognition in Pharmacopeias</td>
<td>Not USP; sold OTC in US as a dietary supplement.</td>
</tr>
<tr>
<td>Final Compounded Formulation Dosage Form(s)</td>
<td>Cream</td>
</tr>
<tr>
<td>Final Compounded Formulation Strength</td>
<td>2.5%; 5%; 10%</td>
</tr>
<tr>
<td>Final Compounded Formulation Route(s) of Administration</td>
<td>Topical</td>
</tr>
<tr>
<td>Final Compounded Formulation Clinical Rationale and History of Past Use</td>
<td>Mild Aromatase inhibitor; Chrysin is a natural aromatase inhibitor extracted from the plant Passiflora coerulea which prevents the conversion of testosterone into estrogen. This is useful in treating high estrogen levels and low testosterone. Chrysin is poorly absorbed if taken orally, even when used with penetration enhancers, so a liposomal gel base is often used which provides good transdermal absorption when applied to your skin.</td>
</tr>
</tbody>
</table>
Tab 1b

Chrysin

FDA Review
DATE: May 27, 2016

FROM: Ben Zhang, Ph.D.
ORISE Fellow, Office of New Drug Products, Office of Pharmaceutical Quality

Haw-Jyh Chiu, Ph.D.
Pharmacology/Toxicology Reviewer, Division of Hematology, Oncology, Toxicology, Office of Hematology and Oncology Products

Michael Brave, M.D.
Clinical Reviewer, Division of Oncology Products 1, Office of Hematology and Oncology Products

THROUGH: Ramesh Sood, Ph.D.
Senior Scientific Director (Acting), Office of New Drug Products, Office of Pharmaceutical Quality

Todd Palmby, Ph.D.
Supervisory Pharmacologist/Toxicologist, Division of Hematology, Oncology, Toxicology, Office of Hematology and Oncology Products

Katherine Fedenko, M.S., C.R.N.P.
Deputy Director for Safety, Division of Oncology Products 1, Office of Hematology and Oncology Products

Geoffrey Kim, M.D.
Director, Division of Oncology Products 1, Office of Hematology and Oncology Products

Christine Nguyen, M.D.
Deputy Director for Safety, Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III

Audrey Gassman, M.D.
Deputy Director, Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Chrysin for Inclusion on the 503A Bulk Drug Substances List
I. INTRODUCTION

Chrysin 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). Chrysin has been nominated for use in topical formulations “as an aromatase inhibitor which prevents the conversion of testosterone to estrogen” for the treatment of “high estrogen and low testosterone.”

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 do not recommend that chrysin be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

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

Chrysin (5,7-dihydroxyflavone) is a naturally occurring small molecule. It is one of the dihydroxyflavone derivatives, with the following molecular structure:

![Molecular structure of chrysin](image)

This substance is currently marketed as a dietary supplement in the form of capsules and tablets. It is also marketed as a topical gel.

Databases searched for information on chrysin in regard to Section A of this consultation included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and USP/NF.

1. Stability of the API and likely dosage forms

The literature was not found to contain reports of chrysin having stability problems. Under cell culture conditions, chrysin has been found to be stable in all experiments performed (Xiao et al., 2015). Chemically, most reactions of chrysin happen on the hydroxyl group at position 7 (shown in red below), which can only be activated under strong basic (alkaline, low pH) conditions. Therefore, chrysin is likely to be stable under ordinary storage conditions for topical dosage forms.
2. **Probable routes of API synthesis**

Chrysin is found in plants, such as the passion flowers *Passiflora caerulea* and *Passiflora incarnata* and *Oroxylum indicum*. It can be extracted and isolated from these plant raw materials or bee propolis.

The isolation technique usually involves extraction of flavonoids with organic solvents combined with chromatography (Gil et al., 1995; Maciejewicz 2000; Xuan et al., 2015).

3. **Likely impurities**

Likely impurities may include:

a. Residual solvents from extraction or purification processes

b. Other flavonoids, such as pinocembrin and galangin

Impurities are unlikely to be toxic. Additional toxicity issues are discussed in section B.

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

Chrysin is a yellow crystal that is practically insoluble in water, but soluble in alcohol. No further information on the influence of particle size and polymorphism on bioavailability were found in the literature.

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

Chrysin is easily characterized with proton nuclear magnetic resonance (\(^1\)H NMR) spectroscopy, carbon-13 nuclear magnetic resonance (\(^{13}\)C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), UV-Vis spectroscopy and mass spectrometry (MS).

**Conclusions:** Chrysin is a small molecule. The substance is likely to be stable under ordinary storage conditions. The nominated substance is easily characterized with various analytical techniques and the preparation of this substance has been well developed.
B. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

PubMed was the public database consulted in the preparation of this review.

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

Chrysin (5,7-dihydroxyflavone; 5,7-dihydroxy-2-phenyl-4H-chromen-4-one) is a natural flavone, which is a class of flavonoids that are naturally occurring polyphenolic phytochemicals. Chrysin is found in many plant extracts, including blue passion flower (*Passifora caerulea*), honey, and bee propolis.

Aromatase is an enzyme found in multiple tissues, such as brain, blood vessels, skin, and adipose tissue that catalyzes the aromatization of androgens into estrogens. This process is the main source of estrogens in postmenopausal women (Chumsri et al., 2011). Marketing of chrysin as a clinically effective aromatase inhibitor is based on the theory that chrysin reduces the conversion of testosterone to estrogen, resulting in increased testosterone levels, decreased estrogen levels, and related effects.

In vitro, chrysin inhibited aromatase enzyme activity in a human preadipocyte cell culture system with $I_{50}$ (inhibitor concentration that blocks 50% of Vmax) and $K_i$ values of 68 $\mu$M and 2.4 $\mu$M, respectively (Campbell and Kurzer 1993). The $K_i$ value for chrysin was the same as that of animoglutethimide ($K_i = 2.4$ $\mu$M), a synthesized aromatase inhibitor. Chrysin inhibited human placental aromatase enzyme activity with IC$_{50}$ values of 0.5 $\mu$M (Kellis and Vicker 1984) and 1.1 $\mu$g/mL (Jeong et al., 1999).

Estrogenicity and inhibition of androstenedione-induced uterine growth assays were used to assess the in vivo activity of chrysin in animals (Saarinen, 2001). When fed at doses of 50 mg/kg to immature female rats for 7 days, chrysin had no significant effect on uterine weight gain compared to controls in the estrogenicity assay. However, an aromatase inhibitor (MPV-2213ad, finrozole) was found to significantly reduce uterine weight gain. To sensitize the in vivo aromatase inhibition assay, 30 mg/kg of androstenedione was administered subcutaneously to immature female rats on the 7 days of treatment alone, with chrysin, or with the aromatase inhibitor. Animals treated with androstenedione alone, and androstenedione plus chrysin, showed an increase in uterine weight gain compared to controls. The aromatase inhibitor inhibited androstenedione-induced uterine weight increase. Investigators concluded that in both the estrogenicity and inhibition of androstenedione-induced uterine growth assays, chrysin showed no evidence of in vivo aromatase inhibiting activity.
Despite the lack of evidence that chrysin inhibits aromatase in vivo, numerous nonclinical studies claim to show benefits on the male reproductive system associated with chrysin administration. The effect of chrysin on the “virility” of male rats, concluding that following a 30-day period of oral administration, chrysin-treated rats had increased mounting behavior, sperm count, number of females impregnated and litter size, compared to an untreated control group (Dhawan et al., 2002). No assessment of systemic levels (e.g., of chrysin, testosterone, estrogen) was made. Ciftci et al., (2012) found “positive reproductive and antioxidative effects” of chrysin on rat testes after 60-day gavage treatment with chrysin in oil. Testis tissue showed a statistically significant increase compared to controls in reduced glutathione, glutathione peroxidase, tissue catalase, superoxide dismutase. Sperm concentration, sperm motility and serum testosterone levels were significantly increased in chrysin-treated rats while abnormal sperm rates were significantly decreased.

In vivo nonclinical studies also suggest that chrysin could offer therapeutic benefit in an array of diseases. Chrysin may have a role in the inhibition of carcinogenesis by modulating Phase 1 and Phase 2 metabolism enzymes, inflammation, apoptosis, cell cycle, angiogenesis, and metastasis (Kasala et al., 2015). Antioxidant, anti-inflammatory, and anti-amyloidogenic effects are proposed as the mechanism by which chrysin may be neuroprotective and useful in preventing neurologic decline in such conditions as Parkinson’s disease, epilepsy and Alzheimer’s (Nabavi et al., 2015).

No publications of nonclinical studies for topically applied chrysin were identified during our review.

b. Safety pharmacology

Based on limited data, the central nervous system is one target organ for toxicity. Oral and intraperitoneal administration of chrysin to rats resulted in a significant hyperalgesic effect in the tail-immersion test, possibly mediated by the γ-aminobutyric acid (GABA) receptor (Zhai et al., 2008). Administration of chrysin (1 mg/kg) resulted in anxiolytic effects as assessed by the elevated plus-maze test of anxiety (Wolfman et al., 1994).

Tsuji and Walle (2008) showed chrysin to be cytotoxic and to inhibit DNA synthesis in normal Rainbow trout hepatocytes. Although chrysin is believed to have antioxidant properties, this effect is thought to be due to prooxidant activity, which may be observed at higher doses and associated with the activation of chrysin by peroxidases, including the type found in human hepatic Kupffer cells.

c. Acute toxicity

No information available.
d. Repeat dose toxicity

No information available.

e. Mutagenicity

Chrysin (12.1 – 225 nmol/plate or 3 – 57 mg/plate) did not induce mutations in a bacterial mutation (Ames) assay using the Salmonella typhimurium strains TA98, TA100, and TA102 (Resende et al., 2012). However, separate investigators showed that at higher concentrations, chrysin (at 50 – 250 µg/plate) induced mutations in a bacterial mutation assay using the Salmonella TA100 strain in the absence of metabolic activation (Oliveira et al., 2012).

f. Developmental and reproductive toxicity

No information available.

g. Carcinogenicity

No information available.

h. Toxicokinetics

No information available.

Conclusions: Based on the limited available data, the central nervous system has been identified as a target organ system of toxicity. Chrysin caused hyperalgesic and anxiolytic effects in rats. Chrysin is associated with prooxidant-related cytotoxicity and DNA-damaging effects at higher exposure levels. Genetic toxicology studies showed chrysin induced mutation in the bacterial mutation (Ames) assay. The limited available toxicology data for chrysin weighs against its inclusion on the 503A list.

2. Human Safety

The following public database(s) were consulted using the search term Chrysin in the preparation of this review: PubMed, Google, proceedings of the American Society of Clinical Oncology and the American Association for Cancer Research.

The Office of Surveillance and Epidemiology (OSE) conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for chrysin through October 21, 2015.

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events for dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for adverse events associated with chrysin.
a. Reported adverse reactions

Chrysin is sold in topical formulations for male weight loss and in cosmetics. It is also widely sold and readily available in oral formulations as a dietary supplement.

We found no published reports of chrysin toxicity. The FDA Division of Pharmacovigilance II searched the FAERS database for reports of chrysin toxicity, and this search retrieved no reports. The CAERS database search retrieved 18 reports, each involving an oral formulation. Of the 18 reports, 10 described reactions that followed the ingestion of an ExtenZe™ brand name product. This line of “male enhancement” dietary supplements each contains numerous ingredients. In internet advertising, chrysin is listed as an ingredient in the ExtenZe™ maximum strength, extended release product with 22 additional ingredients including botanicals (e.g., seeds, roots, leaves, etc) and other dietary supplements, such as folic acid. The other 8 reports involved other multi-ingredient products promoted for body building and weight loss, including, GNC Total Lean™ products (3 reports), Body Fortress Test Pro-Complex™ (3 reports) various Met-Rx™ products, multiple (1 report) and GNC Appetite Control System™ (1 report). Based on these reports, it is not possible to assess the potential relationship between chrysin ingestion and reported adverse effects.

b. Clinical trials assessing safety

Tobin (2006) conducted a pilot trial in which chrysin was administered twice daily to 20 patients with previously treated advanced colorectal cancer for one week before and after treatment with single agent CPT-11. The rationale for this trial was nonclinical data suggesting that chrysin upregulates UGT1A1 in intestinal cells. No toxicity attributed to chrysin was observed. Pharmacokinetic results revealed a mass ratio of plasma SN-38G/SN-38 similar to historical controls.

c. Pharmacokinetic data

Systemic exposure to ingested chrysin in humans is low, due to poor oral bioavailability and rapid metabolism and elimination. In healthy male volunteers, after a single oral dose of 400mg, mean plasma concentration of chrysin remained <0.1mM due to presystemic intestinal and hepatic glucuronidation and sulphation and efflux of metabolites back into the intestine for hydrolysis and fecal elimination (Gambelunghe et al., 2003; Walle et al., 2001).

Although topical preparations of chrysin are marketed, we did not identify any pharmacokinetic data on topical absorption or bioavailability. An in vitro percutaneous absorption study using a pig skin model showed no detectable skin penetration by chrysin (Thitilertdecha et al., 2014).
The availability of alternative approved therapies that may be as safe or safer

d. To reiterate, chrysin has been nominated for inclusion on the section 503A list of bulk drug substances for use in topical formulations “as an aromatase inhibitor which prevents the conversion of testosterone to estrogen” for the treatment of “high estrogen and low testosterone.” These general terms lack the specificity of the indications for FDA approved drug products. This section addresses FDA approved testosterone as a hormone replacement therapy and aromatase inhibitors approved in cancer chemotherapy in women.

FDA has approved testosterone as a hormone replacement therapy in men with specific conditions associated with low or absent endogenous testosterone, also referred to as “classic hypogonadism.” These conditions are those known to cause low testosterone levels and the resultant hypogonadal clinical signs and symptoms. These conditions include testicular failure due to cryptorchidism and pituitary-hypothalamic injury from tumors, trauma, or radiation. The safety and efficacy of approved medications has not been established in men for the treatment of low testosterone due to aging, or other conditions not recognized as “classic hypogonadism.” Testosterone therapy is not approved for use in women except for a limited number of formulations indicated for treatment of female metastatic breast cancer. Use of high doses of testosterone has been associated with serious and life-threatening adverse effects. Due to known abuse potential of anabolic steroids, all FDA-approved testosterone replacement therapies are Schedule III drugs, subject to the requirements under the Controlled Substance Act. FDA-approved testosterone replacement therapies include various formulations and routes of administration:

- Skin patch (transdermal)
- Topical gels applied or pumped on to the skin or axilla
- Nasal spray to the inside of the nose
- Tablet that is applied inside the mouth (buccal)
- Injectable formulations for intramuscular injection and pellets for implantation in soft tissue
- Oral tablets and capsules (methyltestosterone).

The following three aromatase inhibitors are currently FDA approved in cancer chemotherapy in women, primarily for hormone receptor-positive tumors, to lower tumor exposure to estrogen. These drugs have not been found to have comparable effects in the treatment of male breast cancer (Fentiman, 2016).
These drugs are not indicated to treat “high estrogen.” None of these drugs is available as a topical formulation.

- **Anastrazole** was initially approved in 1995. Anastrazole is formulated as an oral tablet and is indicated for:

  o Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer
  o First-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer
  o Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy

- **Letrozole** was initially approved in 1999. Letrozole is formulated as an oral tablet and is indicated for:

  o Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer
  o Extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy
  o First- and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer

- **Exemestane** was initially approved in 1999. Exemestane is formulated as an oral tablet and is indicated for:

  o Adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy
  o Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.

**Conclusions:** Systemic exposure to ingested chrysin in humans is low, due to poor oral bioavailability and rapid metabolism and elimination. No pharmacokinetic information regarding topical bioavailability was found. We found insufficient information about systemic exposure or topical exposure to chrysin from which to draw a conclusion regarding its safety. There are many FDA-approved testosterone replacement products and aromatase inhibitors used in cancer chemotherapy in women that have been established to be safe when used as directed.
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

At high concentrations, chrysin inhibits aromatase in vitro (see Section II.B.). Chrysin is sold as a bodybuilding supplement and topical product, and it is claimed that it raises testosterone levels or stimulates testosterone production. However, Gambelunghe et al., (2003) showed there was no change in urinary testosterone compared to baseline levels after 21 days of treatment with chrysin-containing propolis or honey in healthy human male volunteers. There are no trials of chrysin reported on the ClinicalTrials.gov website.

There is no clinical evidence that chrysin acts in vivo as an aromatase inhibitor or as a treatment for cancer.

2. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Testosterone deficiency can produce serious, but not life-threatening, conditions. Cancer, the condition for which aromatase inhibitors are used, is a life-threatening disease. Topical and oral chrysin formulations have not been shown to be safe or effective in the treatment of testosterone deficiency or cancer.

3. Whether there are any alternative approved therapies that may be as effective or more effective.

There are no approved products for “low testosterone” or “high estrogen.” See response to Question II.B.2.d. above.

Conclusions: No data are available to support the efficacy of topical chrysin for the treatment of testosterone deficiency. As discussed above, it is poorly bioavailable when taken orally, and there are no data that support topical bioavailability. Multiple testosterone replacement products are FDA approved to treat primary or secondary hypogonadism from well-recognized conditions. There are no data available to suggest that chrysin is effective as an aromatase inhibitor in vivo. There are several FDA-approved therapies that have been determined to be effective for use as an aromatase inhibitor in the treatment of breast cancer, which is a life-threatening condition.

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

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

Insufficient information is available to determine how long chrysin has been used in pharmacy compounding. Results from a Google search using the term chrysin compounding pharmacy indicate that it is currently being compounded in both oral and topical forms.
2. The medical condition(s) it has been used to treat

Based on information posted on several compounding pharmacy websites, oral chrysin is most commonly promoted for aromatase inhibition, as a “natural alternative to toxic cancer treatments,” bodybuilding, and “men’s health.” Topical compounded treatments appear to be mainly promoted for bodybuilding or “testosterone replacement.” Topical formulations combining testosterone and chrysin are listed on various compounding pharmacy sites.

3. How widespread its use has been

Insufficient data are available from which to draw conclusions about the extent of use of chrysin in compounded drug products.

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


Conclusions: Information is insufficient to determine the historical use of chrysin in pharmacy compounding. Based on a Google search, several pharmacies appear to be compounding the topical product for bodybuilding or “testosterone replacement.” There is no evidence of official recognition of chrysin by other countries.

III. RECOMMENDATION

Chrysin has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act. The substance was nominated for use as “an aromatase inhibitor.” We recommend that chrysin not be included on the list based on consideration of the following criteria: (1) physicochemical characterization; (2) safety; (3) effectiveness; and (4) historical use of the substance in compounding.

With regard to physicochemical characterization, chrysin is a small molecule that can be characterized easily using various analytical techniques. It is likely to be stable under ordinary storage conditions.

With regard to safety, limited nonclinical studies show chrysin to have potential for neurotoxicity and mutagenicity. Clinical safety information is scant, and is mostly derived from the use of orally ingested chrysin as a nutritional supplement. There is insufficient information to assess the safety of chrysin in this setting. No information was found to assess the safety of topically applied chrysin.
We found no clinical studies that demonstrate the efficacy of topical or oral chrysin as an aromatase inhibitor, for treatment of “low testosterone” or “high estrogen,” or for the treatment of cancer. There are many approved testosterone replacement formulations and there are several FDA-approved aromatase inhibitors for the treatment of breast cancer in postmenopausal women.

There is insufficient information to evaluate the historical use of chrysin in pharmacy compounding. Chrysin appears to be compounded currently and is promoted for use in aromatase inhibition, primarily with regard to bodybuilding and “men’s health” indications.

Based on a balancing of the four evaluation criteria, we find that chrysin is not a suitable substance for the bulk drug substance list under 503A of the FD&C Act. Therefore, we recommend it not be included on this list.
BIBLIOGRAPHY


Tab 2

Cesium Chloride
Tab 2a

Cesium Chloride
Nominations
September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

“To Whom It May Concern:

The American Association of Naturopathic Physicians (AANP) appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

This is a significant issue for our members and their patients. AANP strongly supports efforts to ensure that the drug products dispensed to patients are safe and effective.

Background: AANP Submissions to Date

On January 30, 2014, we submitted comments to Docket FDA-2013-D-1444, “Draft Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Withdrawal of Guidelines” relating to congressional intent in crafting HR 3204. These comments highlighted the fact that, for compounding pharmacies subject to Section 503A, Congress intended that States continue to have the authority to regulate the availability of safely compounded medications obtained by physicians for their patients. As we further noted, compounded medications that are formulated to meet unique patient needs, and that can be administered immediately in the office, help patients receive the products their physicians recommend and reduce the medical and financial burden on both the patient and
doctor that restrictions on office use would impose. Such medications, we emphasized, provide a unique benefit to patients and have an excellent track record of safety when properly produced and stored.

AANP also (on March 4, 2014) nominated 71 bulk drug substances. We identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring. We estimated, at that time, that at least 6 hours per ingredient would be needed to do so—time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP sought a 90-day extension to more completely respond to the Agency’s request.

In this renomination, we have narrowed our focus to 42 bulk drug substances that are most important for the patients treated by naturopathic doctors. Twenty-one of these bulk drug substances are formally nominated in the attachments as well as noted by name in this letter. Given the limitations imposed by the fact that our physician members spend the majority of their day providing patient care, however, AANP again found that the span of time the Agency provided for renominations was insufficient to prepare the documentation needed for the remaining 21 bulk drug substances.

We now request that FDA extend the deadline for which comments are due by 120 days, so that we may provide this further documentation. We have determined that as much as 40 hours per ingredient will be needed to do so—time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP respectfully seeks an additional 120-day period for the purpose of gathering this essential information.

Naturopathic Medicine and Naturopathic Physicians

A word of background on our profession is in order. AANP is a national professional association representing 4,500 licensed naturopathic physicians in the United States. Our members are physicians trained as experts in natural medicine. They are trained to find the underlying cause of a patient’s condition rather than focusing solely on symptomatic treatment. Naturopathic doctors (NDs) perform physical examinations, take comprehensive health histories, treat illnesses, and order lab tests, imaging procedures, and other diagnostic tests. NDs work collaboratively with all branches of medicine, referring patients to other practitioners for diagnosis or treatment when appropriate.

NDs attend 4-year, graduate level programs at institutions recognized through the US Department of Education. There are currently 7 such schools in North America. Naturopathic medical schools provide equivalent foundational coursework as MD and DO schools. Such coursework includes cardiology, neurology, radiology, obstetrics, gynecology, immunology, dermatology, and pediatrics. In addition, ND programs provide extensive education unique to the naturopathic approach, emphasizing disease prevention and whole person wellness. This includes the prescription of clinical doses of vitamins and herbs and safe administration via oral, topical, intramuscular (IM) and intravenous (IV) routes.
Degrees are awarded after extensive classroom study and clinical training. In order to be licensed to practice, an ND must also pass an extensive postdoctoral exam and fulfill annual continuing education requirements. Currently, 20 states and territories license NDs to practice.

Naturopathic physicians provide treatments that are effective and safe. Since they are extensively trained in pharmacology, NDs are able to integrate naturopathic treatments with prescription medications, often working with conventional medical doctors and osteopathic doctors, as well as compounding pharmacists, to ensure safe and comprehensive care.

**Characteristics of Patients Seen by Naturopathic Physicians**

Individuals who seek out NDs typically do so because they suffer from one or more chronic conditions that they have not been able to alleviate in repeated visits to conventional medical doctors or physician specialists. Such chronic conditions include severe allergies, asthma, chronic fatigue, chronic pain, digestive disorders (such as irritable bowel syndrome), insomnia, migraine, rashes, and other autoimmune disorders. Approximately three-quarters of the patients treated by NDs have more than one of these chronic conditions. Due to the fact that their immune systems are often depleted, these individuals are highly sensitive to standard medications. They are also more susceptible to the numerous side effects brought about by mass-produced drugs.

Such patients have, in effect, fallen through the cracks of the medical system. This is why they seek out naturopathic medicine. Safely compounded medications – including nutritional, herbal, and homeopathic remedies – prove efficacious to meet their needs every day in doctors’ offices across the country. Such medications are generally recognized as safe (GRAS), having been used safely for decades in many cases. As patients’ immune function improves, and as they work with their ND to improve their nutrition, get better sleep, increase their exercise and decrease their stress, their health and their resilience improves. This is the ‘multi-systems’ approach of naturopathic medicine – of which compounded drugs are an essential component.

**Bulk Drug Substances Nominated at this Time**

Notwithstanding the concerns expressed and issues highlighted in the foregoing, AANP nominates the following 21 bulk drug substances for FDA’s consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A. Thorough information on these substances is presented in the spreadsheets attached with our comments. The documentation is as complete and responsive to the Agency’s criteria as we can offer at this time.

The bulk drug substances nominated are:

Acetyl L Carnitine
Alanyl L Glutamine
Alpha Lipoic Acid
Artemisia/Artemisinin
Boswellia
Calcium LS Methyltetrahydrofolate
Cesium Chloride
Choline Chloride
Curcumin
DHEA
Dichloroacetic Acid
DMPS
DMSA
Germanium Sesquioxide
Glutathione
Glycyrrhizin
Methylcobalamin
MSM
Quercitin
Rubidium Chloride
Vanadium

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating the patients of naturopathic doctors. AANP wishes to specify these 21 ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination. The additional bulk drug substances include:

7 Keto Dehydroepiandrosterone
Asparagine
Calendula
Cantharidin
Choline Bitartrate
Chromium Glycinate
Chromium Picolinate
Chrysin
Co-enzyme Q10
Echinacea
Ferric Subsulfate
Iron Carbonyl
Iscador
Pantothenic Acid
Phenindamine Tartrate
Piracetam
Pterostilbene
AANP Objects to Unreasonable Burden

AANP believes it necessary and proper to lodge an objection to FDA’s approach, i.e., the voluminous data being required in order for bulk drug substances to be considered by the Agency for approval. FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of the persons most knowledgeable about and experienced in the application of compounded medications are either small business owners or busy clinicians, and given the extent and detail of information on potentially hundreds of ingredients as sought by FDA, this burden is unreasonable. The approach has no basis in the purpose and language of the Drug Quality and Security Act (“Act”) – particularly for drugs that have been safely used for years, not only with the Agency’s implicit acceptance, but without any indication of an unacceptable number of adverse patient reactions.

The volume of data being required in this rulemaking is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, the Agency contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with the resources to seek regulatory approvals. The FDA’s analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The burden on respondents to this current rulemaking is further aggravated by the FDA’s complete absence of consideration of the harm that will be caused if needed drugs are removed from the market. The “Type 2” errors caused by removing important agents from clinical use could far exceed the “Type 1” errors of adverse reactions, particularly given the strong track record of safely compounded medications. The infectious contamination that gave rise to the Act has little to do with the process set out by FDA for determining which ingredients may be compounded. Yet the Agency has offered little consideration of the respective risks and benefits of its approach. Based on the fact that compounding pharmacies and physicians are carrying the full burden of proof, as well as how much time it is likely to take for the process of documentation and evaluation to conclude, the Agency itself may well find that it has caused more harm to patients’ clinical outcomes than provided a bona fide contribution to patient safety.
Conclusion

AANP appreciates the Agency’s consideration of the arguments and objection presented herein, the request for an extension of time to gather the documentation that FDA is seeking, and the nominations made and referenced at this time.

We look forward to continued dialogue on these matters. As AANP can answer any questions, please contact me (jud.richland@naturopathic.org; 202-237-8150).

Sincerely,

Jud Richland, MPH
Chief Executive Officer
September 30, 2014

VIA ELECTRONIC SUBMISSION

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

Re: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations

Docket No. FDA-2013-N-1525

Dear Sir/Madam:

The Alliance for Natural Health USA ("ANH-USA") submits this comment on the Notice: “Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations” published in the Federal Register of July 2, 2014 by the Food and Drug Administration ("FDA" or the “Agency”).

ANH-USA appreciates this opportunity to comment on the list of bulk drug substances that may be used to compound drug products pursuant to Section 503A of the FD&C Act ("FDCA"), 21 U.S.C. §353a (hereinafter the “503A List”). This list of ingredients is crucial to patients who require compounded substances, in particular those substances that are available only across state lines. ANH-USA therefore write to request that the Agency:

A) Extend the deadline for nominations by at least 90 days;
B) Maintain the 1999 List; and
C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List.

“Promoting sustainable health and freedom of healthcare choice through good science and good law”
As discussed in detail below, in the interest of compiling a comprehensive 503B List, more time is needed to provide the required information. This will benefit both FDA, by reducing the subsequent number of petitions for amendments, and consumers, by allowing continued access to important substances.

Organizational Background of Commenter Alliance for Natural Health USA

ANH-USA is a membership-based organization with its membership consisting of healthcare practitioners, food and dietary supplement companies, and over 335,000 consumer advocates. ANH-USA focuses on the protection and promotion of access to healthy foods, dietary nutrition, and natural compounded medication that consumers need to maintain optimal health. Among ANH-USA’s members are medical doctors who prescribe, and patients who use, compounded medications as an integral component of individualized treatment plans.

ANH-USA’s Request and Submissions Regarding Docket No. FDA-2013-N-1525

A) Extend the deadline for nominations by at least 90 days

This revised request for nominations follows the initial notice published in the Federal Register of December 4, 2013. Like the initial notice, this revised request provides only a 90 day response period. However, FDA is requiring more information than it sought originally and yet providing the same amount of time for the submission of nominations. The September 30, 2014 deadline for such a complex and expansive request is unreasonably burdensome and woefully insufficient.

The task set forth by FDA to nominate bulk drug substances for the 503A List places an undue burden on those who are responding. The Agency requires highly technical information for each nominated ingredient, including data about the strength, quality and purity of the ingredient, its recognition in foreign pharmacopeias and registrations in other countries, history with the USP for consideration of monograph development, and a bibliography of available safety and efficacy data, including any peer-reviewed medical literature. In addition, FDA is requiring information on the rationale for the use of the bulk drug substance and why a compounded product is necessary.

For the initial request for nomination, it was estimated that compiling the necessary information for just one nominated ingredient would require five to ten hours. With the revised request requiring more information, the time to put together all of the data for a single nomination likely will be higher. Given that it is necessary to review all possible ingredients and provide the detailed support, or risk losing important therapeutic ingredients, this task requires more time than has been designated by the Agency. While ANH-USA recognizes there will be additional opportunities to comment and petition for amendments after the 503A List is published, the realities of substances not making the list initially makes this request for more time imperative. For example, if a nomination for a substance cannot be completed in full by the current September 30, 2014 deadline, doctors and patients will lose access to such clinically important substances and face the
administrative challenges in obtaining an ingredient listing once the work of the advisory committee is completed. There is no regulatory harm in providing additional time to compile a well-researched and comprehensive initial 503A List.

B) Rescind the withdrawal of the ingredient list published on January 7, 1999

In the revised request for nomination, the Agency references in a footnote its withdrawal of the proposed ingredient list that was published on January 7, 1999. ANH-USA argued against this in its March 4, 2014 comment and would like to reiterate its opposition to the withdrawal. There is no scientific or legal justification to require discarding the work that lead to the nominations and imposing the burden on interested parties to begin the process all over again.

C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List

ANH-USA submits the following ingredients for nomination for the 503B list:

1. The attached Excel spreadsheets for 21 nominated ingredients prepared by IACP in support of its petition for the nomination of these ingredients; and
2. The submissions for Copper Hydrosol and Silver Hydrosol from Natural Immunogenics Corp., with their Canadian Product Licenses as proof of safety and efficacy.

In conclusion, Alliance for Natural Health USA requests that FDA provide a more realistic time frame, adding at least 90 days to the current deadline; rescind the withdrawal of the ingredient list published on January 7, 1999; and accept the ingredient nominations for approval for use.

Sincerely,

Gretchen DuBeau, Esq.
Executive and Legal Director
Alliance for Natural Health USA

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1 As of October 1, 2014, the address for Natural Immunogenics Corp. will be 7504 Pennsylvania Ave., Sarasota, FL 34243.
September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525
Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations.

To Whom It May Concern:

The Integrative Medicine Consortium (IMC) appreciates the opportunity to address the Food and Drug Administration’s request for the submission of ingredients to be listed as allowed for compounding by compounding pharmacies pursuant to Section 503A of the Food Drug and Cosmetic Act. IMC represents the interests of over 6,000 medical and naturopathic physicians and their patients. As we noted in our submission of March 4, 2014, we know from extensive experience that the appropriate availability of compounded drugs offers significant clinical benefits for patients and raise certain objections to the manner in which the FDA is proceeding on these determinations.

First, we note that we are in support of and incorporate by reference the comments and proposed ingredients submitted by our member organization, the American Association of Naturopathic Physicians (AANP), as well as the International Association of Compounding Pharmacists (IACP), and the Alliance for Natural Health-USA (ANH-USA). We also write on behalf of the Academy of Integrative Health and Medicine (AIHM), a merger of the American Holistic Medical Association and the American Board of Integrative and Holistic Medicine.

We also write to raise objections to:

A) The ingredient submission process the FDA is following on this docket, which places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the
Comments, Integrative Medicine Consortium
Docket FDA-2013-N-1525
September 30, 2014

List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act
Page 2

process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Further, we write to ask that FDA:

D) Keep the record open for an additional 120 days for the submission of additional materials.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

F) Accept the attached nominations.

G) Accept allergenic extracts as a class without requiring individual nominations and approval.

Commenter Organizational Background: The Integrative Medicine Consortium

The Integrative Medicine Consortium (IMC) began in 2006 when a group of Integrative Medicine leaders joined together to give a common voice, physician education and support on legal and policy issues. Our comment is based on the collective experience of over 6,000 doctors from the following seven organizations:

- American Academy of Environmental Medicine (AAEM) www.aaemonline.org
- American Association of Naturopathic Physicians (AANP) www.naturopathic.org
- American College for Advancement in Medicine (ACAM) www.acam.org
- International College of Integrative Medicine (ICIM) www.icimed.com
- International Hyperbaric Medical Association (IHMA)
- www.hyperbaricmedicalassociation.org
- International Organization of Integrative Cancer Physicians (IOIP) www.ioipcenter.org

The IMC has been involved in the assessment of risk as applied to the integrative field generally, including participation in the design of malpractice policies suited to the practice of integrative care along with quality assurance efforts for the field such as initiating the move toward developing a professional board certification process. IMC and its member organizations have collectively held over a hundred conferences, attended by tens of thousands of physicians, in which clinical methods that involve the proper use of compounded drugs are a not infrequent topic and subject to Category
I CME credit. Our collective experience on these matters is thus profound, well-credentialed and well-documented.

**IMC Objections and Requests Regarding Docket FDA-2013-N-1525**

A) The ingredient submission process the FDA is following on this docket, inappropriately places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

We wish to lodge our objection to FDA’s approach to its data collection about drugs that will be placed on the list of permitted ingredients. The FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of those knowledgeable and experienced in compounded pharmaceuticals are either small businesses or busy physicians, and given the significant quality and quantity of information on potentially hundreds of ingredients requested by FDA, this burden is unreasonable. This approach has no basis in the purpose and language of the Drug Quality and Security Act ("Act"), particularly for drugs that have been in use for years, not only with FDA’s at least implicit acceptance, but without any indication of an unacceptable level of adverse reactions.

This is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with the resources to seek regulatory approvals.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

Given that the Act arose from Good Manufacturing Practice violations and not concern for any specific drug ingredient, the requirement that ingredients not the subject of a USP monograph or a component of approved drugs be withdrawn pending these proceedings has no legislative basis or rationale. The hiatus in availability and inappropriate shift of burden to the compounding industry is further aggravated by the complete absence of consideration by the FDA of the harm caused by the removal of needed drugs from practice. The “Type 2" errors caused by removing important agents from clinical use could far exceed the “Type 1" errors of adverse reactions, particularly given the
track record in this industry. This is particularly true given that the infectious contamination that
gave rise to the Act has little to do with the approval process for which ingredients may be
compounded. Yet FDA has offered little consideration of the respective risks and benefits of its
approach, and with pharmacies and physicians carrying the full burden of proof and the time
expected for the advisory process to conclude, the FDA will likely itself cause more patient harm
than provide a contribution to safety.

C) The lack of findings of the economic impact of this regulation with regard to the Executive
L. 104-4).

The FDA’s analysis of the costs of regulatory compliance did not appear to include an examination
of the impacts on the industry. The initial or continuing notice for nominations did not analyze this
under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates
Reform Act of 1995 (Pub. L. 104-4). While the FDA made this assessment for “Additions and
Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the
Market for Reasons of Safety or Effectiveness,” 79 FR 37687, in which 25 drugs were added to the
list of barred drugs, it has not done so for the much broader issue of upending the compounding
pharmaceutical industry, which bears costs both in preparation of detailed submissions on
potentially hundreds of ingredients, loss of sales of ingredients no longer approved, the economic
consequence to physicians of not being to prescribe these drugs, and the economic impacts of health
difficulties and added expense that will result from the withdrawal of drugs from clinical use. The
Agency needs to address these concerns.

D) Extend the deadline for which comments are due by 120 days.

IMC’s March 4, 2014 submission, along with AANP and ANH-USA nominated 71 bulk drug
substances. IMC identified 21 more where we did not have the capacity to research and present all
the necessary documentation within the timeframe the Agency was requiring.¹ We had determined
that at least 6 hours per ingredient would be needed to do so, time that our physician members
simply do not have in their day-to-day business of providing patient care. Thus, IMC sought a 90

¹ For example, other nominations would include 7 Keto Dehydropiandrosterone; Asparagine;
Calendula; Cantharidin; Choline Bitartrate; Chromium Glycinate; Chromium Picolinate; Chrysin;
Co-enzyme Q10; Echinacea; Ferric Subsulfate; Iron Carbonyl; Iscador; Pantothenic Acid;
Phenindamine Tartrate; Piracetam; Pterostilbene; Pyridoxal 5-Phosphate; Resveratrol; Thymol
Iodide.
day extension to more completely respond to the Agency's request.

In the renomination, we have narrowed our focus to the attached 21 bulk drug substances given restraints on available resources. These bulk drug substances are documented in the attachment. Given the limitations imposed by the fact that our physician members spent the majority of their day providing patient care, however, we have found that the span of time the Agency provided for renominations was insufficient.

We now request that FDA extend the deadline for which comments are due by at least 120 days, so that we may provide additional documentation. The FDA can certainly begin work on those nominations it has received, but nominations should remain open. We have determined that as much as 40 hours per ingredient will be needed to do, particularly given the lack of resources being offered by the Agency, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC respectfully seeks an additional 120 day period - if not greater - for the purpose of gathering this essential information. If such an extension is not granted, we will explore the prospect of submitting a Citizen's Petition along with AANP and other interested parties.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

In our submission of March 4, 2014, we raised a number of additional considerations, in particular citing a number of monographs, compendia and other authoritative sources that should be considered proper sources for authorized compounding in addition to the U.S. Pharmacopeia. We urge FDA to reach this issue as a means of allowing substances in long use on the market without undue delay or ambiguity.

F) Accept the attached nominations.

Notwithstanding the concerns expressed and issues highlighted in the foregoing, IMC nominates the bulk drug substances in the attachment for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

G) Accept allergenic extracts as a class without requiring individual nominations and acceptance.

In addition, we ask the FDA clarify its view of, and accept as appropriate for use, the category of materials that have been long used in the compounding of allergenic extracts for immunotherapy.
This should particularly be the case where such substances are compounded in manner consistent, where appropriate under its terms, with USP Monograph 797. Given both long-standing safe use, the nature of the materials and methods of clinical use,² and the safety assurances contained in this monograph, we believe that individual nominations and approval should not be imposed upon this form of treatment.

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating patients. IMC wishes to identify these additional ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination.

Sincerely,

Michael J. Cronin, N.D.
Chair, Integrative Medical Consortium

Enclosures:
Nominations

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² Such as environmental and body molds, dust mites, grasses, grass terpenes, weeds, trees, foods, as well as hormone, neurotransmitter, and chemical antigens that are used in various forms of immunotherapy and desensitization.
September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

“Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations”

To Whom It May Concern:

McGuff Compounding Pharmacy Services, Inc. (McGuff CPS) appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products.

Request for Extension
The Agency has indicated the majority of compounding pharmacies are small businesses. McGuff CPS is a small business and has found that the requirements to assemble the requested documentation have been particularly onerous. The Agency has requested information for which no one particular pharmacy, physician or physician organization can easily assemble and must be sought through coordination with the various stakeholders. To collect the information required is a time consuming process for which many practicing professionals have indicated that the time allotted for comment to the Docket has been too limited.

This is an issue of great importance which will limit the number of available compounded drugs products available to physicians and, therefore, will limit the number of individualized treatments to patients. McGuff CPS and physician stakeholders have not had the time to collect, review, and collate all documentation necessary to submit the intended list of compounded drugs required to assure all patient therapies are represented in our submission. McGuff CPS respectfully seeks an additional 120 day period for the purpose of coordinating the various stakeholders and gathering the essential information necessary to provide the Agency with the most comprehensive information.
The Agency has not announced the process of follow on communication or failure e.g. what happens if a nominated substance needs more detailed information of a particular nature? Will the whole effort be rejected or will a “deficiency letter” be issued to the person or organization that submitted the nomination? The Agency issues “deficiency letters” for NDA and ANDA submissions and this appears to be appropriate for compounded drug nominations. McGuff CPS respectfully requests the FDA issue “deficiency letters” to the person or organization that submitted the nomination so that further documentation may be provided.

Nominations

To comply with the current time limits established by the Docket, attached are the nominations prepared to date for bulk drug substances that may be used in pharmacy compounding under Section 503A.

Sincerely,

[Signature]

Ronald M. McGuff
President/CEO
McGuff Compounding Pharmacy Services, Inc.
<table>
<thead>
<tr>
<th>Column A—What information is requested?</th>
<th>Column B—Put data specific to the nominated substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the name of the nominated ingredient?</td>
<td>Cesium chloride</td>
</tr>
<tr>
<td>Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?</td>
<td>Yes. Please access this article: 3. Sartori HE. Cesium therapy in cancer patients. Pharmacol Biochem Behav 1984;21:11-3.</td>
</tr>
<tr>
<td>Is the ingredient listed in any of the three sections of the Orange Book?</td>
<td>No</td>
</tr>
<tr>
<td>Were any monographs for the ingredient found in the USP or NF monographs?</td>
<td>No</td>
</tr>
<tr>
<td>What is the chemical name of the substance?</td>
<td>Cesium chloride</td>
</tr>
<tr>
<td>What is the common name of the substance?</td>
<td>Cesium</td>
</tr>
<tr>
<td>Does the substance have a UNII Code?</td>
<td>GNR9HML8BA</td>
</tr>
<tr>
<td>What is the chemical grade of the substance?</td>
<td>Cesium chloride, BioTech grade</td>
</tr>
<tr>
<td>What is the strength, quality, stability, and purity of the ingredient?</td>
<td>A valid Certificate of Analysis accompanies each lot of raw material received.</td>
</tr>
<tr>
<td>How is the ingredient supplied?</td>
<td>Colorless solid. (Deliquescent crystals solid.)</td>
</tr>
<tr>
<td>Is the substance recognized in foreign pharmacopeias or registered in other countries?</td>
<td>WHMIS (Canada) Not controlled under WHMIS (Canada). DSCL (EEC) R36/38- Irritating to eyes and skin.</td>
</tr>
<tr>
<td>Has information been submitted about the substance to the USP for consideration of monograph development?</td>
<td>Information not known</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>What dosage form(s) will be compounded using the bulk drug substance?</td>
<td>The proposed product will be compounded as a sterile injectable, 30 mL multiple dose vial, and an example formulation is below. Each mL contains: 500 mg Cesium 1 % Benzyl Alcohol q.s. Water for Injection, Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH. Or The proposed product will be compounded as a sterile injectable, 30 mL preservative free vial, and an example formulation is below. Each mL contains: 500 mg Cesium q.s. Water for Injection, Sodium hydroxide and/or Hydrochloric acid may be added to adjust pH.</td>
</tr>
<tr>
<td>What strength(s) will be compounded from the nominated substance?</td>
<td>Up to 500 mg/mL</td>
</tr>
<tr>
<td>What are the anticipated route(s) of administration of the compounded drug product(s)?</td>
<td>Slow intravenous</td>
</tr>
<tr>
<td>Are there safety and efficacy data on compounded drugs using the nominated substance?</td>
<td>There are anecdotes on the internet of occasional isolated incidents in patients who allegedly had a problem after cesium chloride. However, none of those are peer-reviewed articles that also show that patient’s entire treatment regimen. We do not know if those patients had a toxic chemotherapy regimen also. We do not know if the cesium chloride was administered by knowledgeable, experienced medical personnel. Cesium chloride 500 mg/ml has been helpful and useful in combination with other natural substances in treating individuals with numerous types of cancers, by a presumed alkalinizing effect. Cancer has been found to thrive in a low-pH environment, and to be hindered in a high pH environment. It has been known for decades that a thriving cancer cell produces an acidic micro-environment, and a weak cancer cell does not. (Jahde and Rajewsky, &quot;Tumor-selective modification of cellular microenvironment in vivo: effect of glucose infusion on the pH in normal and malignant rat tissues.&quot; Cancer Research. 1982 Apr 42(4): 1505-12). This is known to be due to cancer’s product, lactic acid. However, it is also known that acidic fluid holds less oxygen than alkaline fluid. Thus the acidic, deoxygenated water in the cancer microenvironment is conducive to anaerobic metabolism, which is the default metabolism of cancer cells. Thus an alkaline agent that can be delivered to that intracellular and extracellular microenvironment indirectly has a selectively suppressive effect on cancer cells. AK Brewer found that cesium was taken up efficiently by cancer cells, in the presence of other nutrients. This was sufficient to raise the cell to the pH range of 8, where cell mitosis was inhibited and the cancer cell died. Tests on mice fed cesium found that tumor masses shrank within 2 weeks. Also the mice showed none of the morbid effects of cancer. (Brewer AK, “The high pH therapy for cancer tests on mice and humans,” Pharmacol Biochem Behav 21: Suppl. 1, 1-5. 1984. Cesium chloride has a history of use among various professions in integrative medicine in the U.S., and many hundreds of patients have been helped by cesium chloride in their fight against cancer. SEE APPENDIX 1: 1. Environmental Protection Agency. Cesium. 2002. Available at: <a href="http://www.epa.gov/radiation/radionuclides/cesium.htm">www.epa.gov/radiation/radionuclides/cesium.htm</a> 2. Pinsky C, Bose R. Pharmacological and toxicological investigations of cesium. Pharmacol Biochem Behav 1984;21:17-23. 3. Sartori HE. Cesium therapy in cancer patients. Pharmacol Biochem Behav 1984;21:11-3. 4. Sartori HE. Nutrients and cancer: an introduction to cesium therapy. Pharmacol Biochem Behav 1984;21:3-10.</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Has the bulk drug substance been used previously to compound drug product(s)?</td>
<td>Yes. Please see Dosage section above.</td>
</tr>
<tr>
<td>What is the proposed use for the drug product(s) to be compounded with the nominated substance?</td>
<td>Please see Safety and Efficacy section above.</td>
</tr>
<tr>
<td>What is the reason for use of a compounded drug product rather than an FDA-approved product?</td>
<td>No existing drug matches the advantages of cesium chloride against cancer: the evident ability to enter the cancer cell together with the pH rise, as well as the high remission rate and lack of observed side effects at therapeutic dose. Generally safe and non-toxic substances such as cesium chloride are a viable alternative.</td>
</tr>
<tr>
<td>Is there any other relevant information?</td>
<td>No approved drug product exists that addresses the condition adequately. No existing drug matches the unique therapeutic effect of cesium chloride against cancer. Patients who are refractory to, or at high risk of life-threatening side effects from, conventional cytotoxic chemotherapy need an alternative. Generally safe and non-toxic substances such as cesium chloride are a viable alternative. Cesium chloride has a history of use among various professions in alternative medicine in the U.S., and many hundreds of patients have been helped by cesium chloride in their fight against cancer. There is a need to compound cesium chloride, in order to serve the patient population for whom chemotherapy is no longer effective, as well as those cancer patients who have determined that chemotherapy is not in their best interest. As an estimate of such patient population, we expect the number of cancer patients choosing cesium chloride as part of their cancer care to rise over time. No approved drug product exists that addresses the condition of cancer adequately. Conventional cytotoxic chemotherapy drugs are generally very poorly tolerated, having life-threatening side effects, and a high mortality rate. With a realistic assessment of their odds, there are patients who choose to avoid chemotherapy, and have opted instead for alternatives, including cesium chloride. It is estimated that over half of all cancer patients use complementary and alternative medicine. (Horneber M, Bueschel G, Dennert G, et al. “How many cancer patients use complementary and alternative medicine: a systematic review and meta-analysis”. Integr Cancer Ther 11 (3): 187-203, 2012.)</td>
</tr>
</tbody>
</table>
As cancer incidence continues to rise, the numbers of those seeking effective integrative treatments is also expected to rise. The clinics using integrative, complementary and alternative medicine are small and few and not expected to be able to meet demand. The American Cancer Society reports that in 2014 there will be over 1.6 million new cases of cancer diagnosed and over 500,000 cancer deaths in the U.S. http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/. Neither allopathic medical establishments nor alternative medical establishments have the resources in place to meet this overwhelming demand. Because cancer is such a difficult spectrum of diseases to fight, and because an appropriate treatment for one patient with one kind of cancer may not be at all well-indicated for a different patient with a different kind of cancer, or a different pattern of metastasis, it is certainly to the benefit of the American public and very fortunate for American cancer patients that a broad array of treatment options are available to them.
Appendix 1: References Cited in the 503A Nomination for Cesium Chloride


Tab 2b

Cesium Chloride

FDA Review
DATE: May 31, 2016
FROM: Ben Zhang, Ph.D.
ORISE Fellow, Office of New Drug Products,
Office of Pharmaceutical Quality

Haw-Jyh Chiu, Ph.D.
Pharmacology/Toxicology Reviewer, Division of Hematology, Oncology,
Toxicology, Office of Hematology and Oncology Products

Michael Brave, M.D.
Clinical Reviewer, Division of Oncology Products 1, Office of
Hematology and Oncology Products

THROUGH: Todd Palmby, Ph.D.
Supervisory Pharmacologist/Toxicologist, Division of Hematology,
Oncology, Toxicology, Office of Hematology and Oncology Products

Kathy Fedenko
Clinical Team Leader, Division of Oncology Products 1, Office of
Hematology and Oncology Products

Geoffrey Kim, M.D.
Director, Division of Oncology Products 1, Office of Hematology and
Oncology Products

Ramesh Sood, Ph.D.
Senior Scientific Director (Acting), Office of New Drug Products, Office
of Pharmaceutical Quality

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Cesium Chloride for Inclusion on the 503A Bulk Drug
Substances List

I. INTRODUCTION

Cesium chloride has been nominated for inclusion on the list of bulk drug substances that
can be used in compounding under section 503A of the Federal Food, Drug, and
Cosmetic Act (FD&C Act) for use in combination with other natural substances in
treating individuals with numerous types of cancers, by a presumed alkalinizing effect.

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 do not recommend that cesium chloride be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

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

Cesium chloride is an inorganic chloride salt with the formula CsCl.

Databases searched for information on cesium chloride in regard to Section II.A of this consultation included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and USP/NF.

Cesium chloride can be easily characterized with atomic absorption/emission spectroscopy, and mass spectrometry (MS).

This active pharmaceutical ingredient (API) is sold in a variety of forms as a dietary supplement, e.g., in aqueous solution (1.5 gm per 15 ml), as powder containing capsules (500 mg) and as loose salt crystal material. It is also sold in mixtures with other dietary supplement ingredients. The nomination identifies that it is currently available as an injectable solution, but this could not be verified.

1. Stability of the API and likely dosage forms

Cesium chloride is stable in aqueous solutions. Its solid form is also chemically stable, but due to its high solubility in water, the solid is very hygroscopic and gradually disintegrates at ambient conditions. The nominated dosage form is injectable solution. Cesium chloride is very stable under ordinary storage conditions in the proposed injection formulations.

2. Probable routes of API synthesis

Currently, cesium chloride is mainly obtained from liquid extraction of concentrated brine (usually obtained from seawater), and several extraction systems have been established (Wu et al., 2014; Gao et al., 2014; Bakke et al., 2008). Other isolation methods involve the selective adsorption of cesium ions onto the adsorbent material followed by desorption (Onodera et al., 2003; Tanihara et al., 2000; Zhang et al., 2013).

3. Likely impurities

Likely impurities may include:
a. Residual reagents and solvents from extraction or purification processes, such as nitrobenzene, benzene and 4-Tert-butyl-2-(α-methylbenzyl) phenol (t-BAMBP);

b. Other salts in the brine, such as NaCl, KCl, RuCl and MgCl₂.

Depending on the specific manufacturing processes, some residual reagents may have higher toxicity, such as benzene. Other impurities are unlikely to be significantly toxic. Further toxicity issues are discussed in section B.

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

Cesium chloride is a colorless crystal that is highly soluble in water. No further information on the influence of particle size and polymorphism on bioavailability was found in the literature.

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

Cesium chloride can be easily characterized with atomic absorption/emission spectroscopy, and mass spectrometry (MS).

**Conclusions:** Cesium chloride is an inorganic substance. The compound is likely to be stable as a solid under ordinary storage conditions when kept away from moisture. The nominated substance is easily characterized, and the synthesis of this compound has been well developed.

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

1. **Nonclinical Assessment**

PubMed, a public database, was consulted in the preparation of this review.

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

Cesium belongs to the group of alkaline metals, which also includes lithium, sodium, potassium, rubidium, and francium. Anti-tumor activity of cesium chloride has been observed in mice with surgically implanted murine sarcoma I or colon tumors, and in mouse xenograft model of human PC-3 tumor (Messiha et al., 1979; El-Domeiri et al., 1981; Tufte et al., 1984; Low et al., 2007).
b. Safety pharmacology

In rabbits and dogs, cesium chloride administration, either as intravenous bolus injections (1 mmol/kg) or intravenous infusion (0.018 – 0.1 mmol/kg/min), has been shown to cause ventricular tachycardia (Takahashi et al., 1998; Nayebpour et al., 1989; Senges et al., 2000). The finding in dogs was associated with early and delayed afterdepolarizations (Patterson et al., 1990). In canine cardiac Purkinje fibers, cesium chloride treatment (5 mM) resulted in prolongation of action potential duration and bradycardia-dependent early afterdepolarizations (Kinnaird et al., 1991).

c. Acute toxicity

In mice, the oral LD$_{50}$ of cesium chloride was 2300 mg/kg (Johnson, et al., 1975). The LD$_{50}$ of cesium chloride in male non-diabetic ddY mice or male streptozotocin-induced diabetic ddY mice was 11.7 mEq Cs$^+$/kg (11 mmol/kg or 1.55 g/kg) IP or 14.3 mEq Cs$^+$/kg (14.3 mmol/kg or 1.9 g/kg) IP, respectively (Fujii et al., 1987).

In mice, single-dose administration with cesium chloride caused decreased motor activity and Straub tail in a dose-dependent manner. Clinical signs included autonomic disturbance, diarrhea, and salivation (Bose et al., 1984).

d. Repeat dose toxicity

In a non-GLP study, naïve mice or nude mice bearing PC-3 or LNCaP prostate tumors were administered vehicle control or 150, 300, 600, 800, 1000, or 1200 mg/kg cesium chloride orally, once-daily for 30 days. Significant body weight loss (~10%) was noted at 1200 mg/kg or ≥1000 mg/kg when compared to control in PC3 and LNCaP tumor-bearing mice, respectively. Significant increases in water consumption were noted at ≥ 300 mg/kg in PC3 tumor-bearing mice. Increased incidence of fibrin clots in the aorta, atrium, or ventricles was noted in tumor bearing mice at ≥150 mg/kg. Histopathological finding of significant inflammation within and surrounding the bladder correlated with findings of crystals or viscous mucosal fluid in the bladder at ≥ 600 mg/kg (Low et al., 2007).

Repeat-dose administration of cesium chloride (5.0 mEq/kg/day IP for 7 days) to mice caused a phenothiazine-like effect in mice, reducing amphetamine-induced aggregation toxicity and enhancing pentobarbital-induced hypnosis (Bose et al., 1984).

e. Mutagenicity

In vivo, cesium chloride induced chromosome aberrations in bone marrow cells of female mice at ≥125 mg/kg, increased the mitotic index at 125 mg/kg, and decreased the mitotic index at 500 mg/kg (Ghosh et al., 1990; Ghosh et
al., 1991). However, a separate study showed that cesium chloride was not genotoxic in either human lymphocytes or the in vivo mouse micronucleus assay (Santos-Mello et al., 1999).

f. Developmental and reproductive toxicity

The effect of pre- and postnatal maternal ingestion of cesium chloride on neonatal growth and development was evaluated in albino mice. In this study, cesium chloride was administered in drinking water at conception and during gestation, lactation, and throughout the 21 days of breast-feeding during weaning. Maternal exposure to cesium chloride caused a sex-dependent decrease of weanling’s body weight. Decreased brain and testis weights and increased spleen weights were noted when compared to control (Messiha, 1988; Messiha, 1994). Similarly, in a separate study in mice, maternal exposure to 1mEq CsCl solution from birth and through weaning of offspring, resulted in decreased body, kidney, and brain weights in the offspring, which were breastfed until weaning (Messiha, 1998).

g. Carcinogenicity

No information available.

h. Toxicokinetics

No information available.

Conclusions: Nonclinical studies in mice, rats, and dogs identified the cardiovascular and central nervous systems as the major target organ systems of toxicity. Major toxicity findings included ventricular tachycardia, decreased motor activities, autonomic disturbances, and salivation. Genetic toxicology studies with cesium chloride have yielded equivocal results; however, some studies have shown that cesium chloride can cause chromosomal aberration in mouse bone marrow cells. Reproductive studies in mice have shown that exposure of offspring through breastfeeding by mothers administered cesium chloride in the drinking water caused decreased body and organ weights (e.g., brain, kidney, spleen, and testis) in the offspring. The toxicity profile of cesium chloride in animal studies weighs against its inclusion on the 503A list.

2. Human Safety
The following database(s) were consulted in the preparation of the clinical portions of this review: PubMed, Google, and the Proceedings of the American Society of Clinical Oncology and the American Association of Cancer Research.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for cesium chloride through October 21, 2015.

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events for dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for adverse events associated with cesium chloride.

a. Reported adverse reactions

Cesium blocks potassium rectifier channels on atrial and ventricular myocytes, resulting in prolongation of the QT interval, which can lead to arrhythmias, including torsade de pointes (Chan et al., 2009, Dalal et al., 2004, Jones et al., 2001, Himeshkumar et al., 2006, Lyon and Mayhew 2003, O'Brien et al., 2008, Pinter et al., 2002, Sessions et al., 2013, Sohn and Vassale, 1995, Wiens et al., 2009.) Because of the long half-life of cesium, it takes approximately 200 days of daily dosing to reach a steady state. It is therefore not surprising that FAERS and CAERS case reports describe arrhythmias occurring after weeks to months of therapy with cesium chloride. Several case reports describe serious toxicities resulting from cesium chloride ingested as an alternative therapy for cancer, including hypokalemia, seizures, ventricular arrhythmias, syncope, and death.

b. Clinical studies

Evidence of potential clinical benefit from oral cesium chloride in human cancer is limited to one case series published in 1984 by Sartori. That case series had major design flaws including its uncontrolled nature, retrospective design, and probable case selection bias, making its conclusions unreliable. No description of adverse events was provided in the published study report.

c. Pharmacokinetic data

Cesium, an alkali metal with chemical properties similar to lithium, potassium, and sodium, is a trace element in human metabolism. Total body cesium under normal conditions is estimated at about 1.5 mg, with the largest quantities found in soft tissues (especially skeletal muscle) at a concentration of 0.009–0.02 g/g wet weight. Plasma levels of cesium in normally range from approximately 0.00045 to 0.260 g/g wet weight.

Cesium chloride ingested by mouth is nearly 100% absorbed in the small intestine. Kinetic modeling suggests that cesium distribution is extensive, with
higher concentrations in the kidneys, skeletal muscle, liver, red blood cells, and brain. The serum half-life of cesium is approximately 70 hours in men and 96 hours in women, and elimination is 85% urinary, 13% fecal, and 2% through sweat. The renal mechanisms for excretion of cesium are thought to be similar to those of potassium.

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

Numerous anticancer agents have been granted marketing approval by FDA after demonstration of safety and efficacy.

**Conclusions:** The limited information available about the safety of cesium chloride gives rise to significant concern about its use in compounding. The evidence of cesium chloride causing hypokalemia, seizures, QT prolongation, and cardiac arrhythmias is particularly concerning. There are numerous FDA-approved agents that have demonstrated safety and efficacy for the treatment of patients with various cancers.

**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*

Cesium chloride has not been shown to be efficacious for the prevention or treatment of any form of cancer. As discussed in section 2(b) above, evidence of clinical benefit from cesium in human cancer is limited to one case series published in 1984 by Sartori. That case series had major flaws including its uncontrolled nature, retrospective design and probable case selection bias. Therefore, the results cannot be considered reliable.

2. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

Cancer is a serious and life-threatening disease.

3. *Whether there are any alternative approved therapies that may be as effective or more effective.*

Numerous anticancer agents have been granted marketing approval by FDA following demonstration of safety and efficacy in well-controlled clinical trials.

**Conclusions:** There are insufficient data to attest to the safety or efficacy of cesium chloride in the treatment of cancer. There are numerous FDA-approved products that have been demonstrated to be effective in the treatment of cancer.
D. Has the substance been used historically as a drug in compounding?

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

There are no data from which to draw conclusions. However, the studies reviewed indicate that the use of cesium chloride to treat cancer has been studied since at least the 1980s. And, currently, cesium chloride appears to be compounded by a handful of pharmacies. The specific uses of the compounded cesium chloride are unknown (see subsequent section).

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

There are reports of research, treatment, and patient self-treatment involving various cancers.

3. How widespread its use has been

Cesium therapy is widely advertised and sold, primarily through internet-based cancer treatment groups, as a treatment modality for end-stage cancers. Cesium chloride supplements are available in pill form. Proponents suggest a dosage of 1-6 g/day. It is unclear what proportion of the cesium chloride is provided by compounding pharmacies.

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

A search of the British Pharmacopoeia (2015, update 01/07/2015), the European Pharmacopoeia (8th Edition, 2016, 8.8), and the Japanese Pharmacopoeia (16th Edition) did not show cesium chloride listed as a drug substance. The Japanese pharmacopoeia listed the substance as a reagent, and there was a general listing in the European Pharmacopoeia that was not within the drug or pharmaceutical preparation categories.

Conclusions: There is insufficient information to determine the historical use of cesium chloride in pharmacy compounding. Currently, cesium chloride appears to be compounded by a handful of pharmacies. The indication(s) for which the substance is compounded are unclear. However, there appears to be an internet community promoting cesium chloride as a cancer treatment. Cesium chloride is not recognized as a drug substance or pharmaceutical preparation in foreign pharmacopoeias.

III. RECOMMENDATION

We have evaluated cesium chloride as a candidate for the list of bulk drug substances under section 503A of the FD&C Act and do not recommend it be included on the list of bulk drug substances allowed for use in compounding. Cesium chloride was nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act. The substance was nominated for use “in combination
with other natural substances in treating individuals with numerous types of cancers, by a presumed alkalinizing effect.” The following criteria were considered in the determination: (1) physicochemical characterization; (2) safety; (3) effectiveness; and (4) historical use of the substance in compounding.

Cesium chloride is an inorganic cesium salt that can be characterized using standard chemical techniques. The substance is very stable in aqueous solutions including those commonly found in injectable preparations.

There are serious safety concerns related to the use of cesium chloride indicated by the results of both non-clinical and clinical studies. Non-clinical studies show significant cardiac and central nervous system toxicity including ventricular tachycardia, decreased motor activities, and autonomic disturbances. In addition, studies in mice show reproductive effects of decreased body and organ weights in offspring. Clinically, numerous reports of serious toxicity following cesium chloride use for the treatment of cancer have been made with effects including hypokalemia seizures, ventricular arrhythmias, syncope, and death.

Cesium chloride has not been shown to be efficacious for the prevention or treatment of any form of cancer. There are numerous FDA-approved treatments for cancer with well-established safety and efficacy.

There is insufficient information to evaluate the historical use of cesium chloride in pharmacy compounding. A search of the internet indicates some compounding with cesium chloride takes place, although the extent of compounding and the indications for which compounded cesium chloride is used are unclear.

Cesium chloride is not safe for human use and there is no evidence it is effective for the treatment of any cancer. Relying on this type of treatment may have serious health consequences, including ventricular arrhythmias and cardiac arrest. In addition, use of cesium chloride may cause a patient to delay the use of treatments that have been found to be safe and effective for treating cancer. Based on a balancing of the four evaluation criteria, we find that cesium chloride is not a suitable substance for the bulk drug substance list under 503A of the FD&C Act. Therefore, we do not recommend it for this list.
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Sohn HG, Vassalle M. Cesium effects on dual pacemaker mechanisms in guinea pig sinoatrial node. J Mol Cell Cardiol 1995;27:563.


Wu et al., 2014. Method for extracting rubidium salt and cesium salt, CN103787375 A, Apr 30, 2014;

Tab 3

Sodium Dichloroacetate
Tab 3a

Sodium Dichloroacetate

Nominations
September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

“Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations”

To Whom It May Concern:

McGuff Compounding Pharmacy Services, Inc. (McGuff CPS) appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products.

Request for Extension
The Agency has indicated the majority of compounding pharmacies are small businesses. McGuff CPS is a small business and has found that the requirements to assemble the requested documentation have been particularly onerous. The Agency has requested information for which no one particular pharmacy, physician or physician organization can easily assemble and must be sought through coordination with the various stakeholders. To collect the information required is a time consuming process for which many practicing professionals have indicated that the time allotted for comment to the Docket has been too limited.

This is an issue of great importance which will limit the number of available compounded drugs products available to physicians and, therefore, will limit the number of individualized treatments to patients. McGuff CPS and physician stakeholders have not had the time to collect, review, and collate all documentation necessary to submit the intended list of compounded drugs required to assure all patient therapies are represented in our submission. McGuff CPS respectfully seeks an additional 120 day period for the purpose of coordinating the various stakeholders and gathering the essential information necessary to provide the Agency with the most comprehensive information.
The Agency has not announced the process of follow on communication or failure e.g. what happens if a nominated substance needs more detailed information of a particular nature? Will the whole effort be rejected or will a "deficiency letter" be issued to the person or organization that submitted the nomination? The Agency issues "deficiency letters" for NDA and ANDA submissions and this appears to be appropriate for compounded drug nominations. McGuff CPS respectfully requests the FDA issue "deficiency letters" to the person or organization that submitted the nomination so that further documentation may be provided.

Nominations

To comply with the current time limits established by the Docket, attached are the nominations prepared to date for bulk drug substances that may be used in pharmacy compounding under Section 503A.

Sincerely,

Ronald M. McGuff
President/CEO
McGuff Compounding Pharmacy Services, Inc.
September 30, 2014

VIA ELECTRONIC SUBMISSION

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

Re: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations

Docket No. FDA-2013-N-1525

Dear Sir/Madam:

The Alliance for Natural Health USA ("ANH-USA") submits this comment on the Notice: “Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations” published in the Federal Register of July 2, 2014 by the Food and Drug Administration ("FDA" or the “Agency”).

ANH-USA appreciates this opportunity to comment on the list of bulk drug substances that may be used to compound drug products pursuant to Section 503A of the FD&C Act ("FDCA"), 21 U.S.C. §353a (hereinafter the “503A List”). This list of ingredients is crucial to patients who require compounded substances, in particular those substances that are available only across state lines. ANH-USA therefore write to request that the Agency:

A) Extend the deadline for nominations by at least 90 days;
B) Maintain the 1999 List; and
C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List.

“Promoting sustainable health and freedom of healthcare choice through good science and good law”
As discussed in detail below, in the interest of compiling a comprehensive 503B List, more time is needed to provide the required information. This will benefit both FDA, by reducing the subsequent number of petitions for amendments, and consumers, by allowing continued access to important substances.

Organizational Background of Commenter Alliance for Natural Health USA

ANH-USA is a membership-based organization with its membership consisting of healthcare practitioners, food and dietary supplement companies, and over 335,000 consumer advocates. ANH-USA focuses on the protection and promotion of access to healthy foods, dietary nutrition, and natural compounded medication that consumers need to maintain optimal health. Among ANH-USA’s members are medical doctors who prescribe, and patients who use, compounded medications as an integral component of individualized treatment plans.

ANH-USA’s Request and Submissions Regarding Docket No. FDA-2013-N-1525

A) Extend the deadline for nominations by at least 90 days

This revised request for nominations follows the initial notice published in the Federal Register of December 4, 2013. Like the initial notice, this revised request provides only a 90 day response period. However, FDA is requiring more information than it sought originally and yet providing the same amount of time for the submission of nominations. The September 30, 2014 deadline for such a complex and expansive request is unreasonably burdensome and woefully insufficient.

The task set forth by FDA to nominate bulk drug substances for the 503A List places an undue burden on those who are responding. The Agency requires highly technical information for each nominated ingredient, including data about the strength, quality and purity of the ingredient, its recognition in foreign pharmacopeias and registrations in other countries, history with the USP for consideration of monograph development, and a bibliography of available safety and efficacy data, including any peer-reviewed medical literature. In addition, FDA is requiring information on the rationale for the use of the bulk drug substance and why a compounded product is necessary.

For the initial request for nomination, it was estimated that compiling the necessary information for just one nominated ingredient would require five to ten hours. With the revised request requiring more information, the time to put together all of the data for a single nomination likely will be higher. Given that it is necessary to review all possible ingredients and provide the detailed support, or risk losing important therapeutic ingredients, this task requires more time than has been designated by the Agency. While ANH-USA recognizes there will be additional opportunities to comment and petition for amendments after the 503A List is published, the realities of substances not making the list initially makes this request for more time imperative. For example, if a nomination for a substance cannot be completed in full by the current September 30, 2014 deadline, doctors and patients will lose access to such clinically important substances and face the
administrative challenges in obtaining an ingredient listing once the work of the advisory committee is completed. There is no regulatory harm in providing additional time to compile a well-researched and comprehensive initial 503A List.

B) Rescind the withdrawal of the ingredient list published on January 7, 1999

In the revised request for nomination, the Agency references in a footnote its withdrawal of the proposed ingredient list that was published on January 7, 1999. ANH-USA argued against this in its March 4, 2014 comment and would like to reiterate its opposition to the withdrawal. There is no scientific or legal justification to require discarding the work that lead to the nominations and imposing the burden on interested parties to begin the process all over again.

C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List

ANH-USA submits the following ingredients for nomination for the 503B list:

1. The attached Excel spreadsheets for 21 nominated ingredients prepared by IACP in support of its petition for the nomination of these ingredients; and
2. The submissions for Copper Hydrosol and Silver Hydrosol from Natural Immunogenics Corp., with their Canadian Product Licenses as proof of safety and efficacy.

In conclusion, Alliance for Natural Health USA requests that FDA provide a more realistic time frame, adding at least 90 days to the current deadline; rescind the withdrawal of the ingredient list published on January 7, 1999; and accept the ingredient nominations for approval for use.

Sincerely,

Gretchen DuBeau, Esq.
Executive and Legal Director
Alliance for Natural Health USA

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1 As of October 1, 2014, the address for Natural Immunogenics Corp. will be 7504 Pennsylvania Ave., Sarasota, FL 34243.
To Whom It May Concern:

The Integrative Medicine Consortium (IMC) appreciates the opportunity to address the Food and Drug Administration’s request for the submission of ingredients to be listed as allowed for compounding by compounding pharmacies pursuant to Section 503A of the Food, Drug, and Cosmetic Act. IMC represents the interests of over 6,000 medical and naturopathic physicians and their patients. As we noted in our submission of March 4, 2014, we know from extensive experience that the appropriate availability of compounded drugs offers significant clinical benefits for patients and raise certain objections to the manner in which the FDA is proceeding on these determinations.

First, we note that we are in support of and incorporate by reference the comments and proposed ingredients submitted by our member organization, the American Association of Naturopathic Physicians (AANP), as well as the International Association of Compounding Pharmacists (IACP), and the Alliance for Natural Health-USA (ANH-USA). We also write on behalf of the Academy of Integrative Health and Medicine (AIHM), a merger of the American Holistic Medical Association and the American Board of Integrative and Holistic Medicine.

We also write to raise objections to:

A) The ingredient submission process the FDA is following on this docket, which places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the
Comments, Integrative Medicine Consortium
Docket FDA-2013-N-1525
September 30, 2014
List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act
Page 2

process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Further, we write to ask that FDA:

D) Keep the record open for an additional 120 days for the submission of additional materials.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

F) Accept the attached nominations.

G) Accept allergenic extracts as a class without requiring individual nominations and approval.

Commenter Organizational Background: The Integrative Medicine Consortium

The Integrative Medicine Consortium (IMC) began in 2006 when a group of Integrative Medicine leaders joined together to give a common voice, physician education and support on legal and policy issues. Our comment is based on the collective experience of over 6,000 doctors from the following seven organizations:

- American Academy of Environmental Medicine (AAEM) www.aaemonline.org
- American Association of Naturopathic Physicians (AANP) www.naturopathic.org
- American College for Advancement in Medicine (ACAM) www.acam.org
- International College of Integrative Medicine (ICIM) www.icimed.com
- International Hyperbaric Medical Association (IHMA) www.hyperbaricmedicalassociation.org
- International Organization of Integrative Cancer Physicians (IOIP) www.ioipcenter.org

The IMC has been involved in the assessment of risk as applied to the integrative field generally, including participation in the design of malpractice policies suited to the practice of integrative care along with quality assurance efforts for the field such as initiating the move toward developing a professional board certification process. IMC and its member organizations have collectively held over a hundred conferences, attended by tens of thousands of physicians, in which clinical methods that involve the proper use of compounded drugs are a not infrequent topic and subject to Category
I CME credit. Our collective experience on these matters is thus profound, well-credentialed and well-documented.

**IMC Objections and Requests Regarding Docket FDA-2013-N-1525**

A) The ingredient submission process the FDA is following on this docket, inappropriately places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

We wish to lodge our objection to FDA’s approach to its data collection about drugs that will be placed on the list of permitted ingredients. The FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of those knowledgeable and experienced in compounded pharmaceuticals are either small businesses or busy physicians, and given the significant quality and quantity of information on potentially hundreds of ingredients requested by FDA, this burden is unreasonable. This approach has no basis in the purpose and language of the Drug Quality and Security Act (“Act”), particularly for drugs that have been in use for years, not only with FDA’s at least implicit acceptance, but without any indication of an unacceptable level of adverse reactions. This is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with the resources to seek regulatory approvals.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

Given that the Act arose from Good Manufacturing Practice violations and not concern for any specific drug ingredient, the requirement that ingredients not the subject of a USP monograph or a component of approved drugs be withdrawn pending these proceedings has no legislative basis or rationale. The hiatus in availability and inappropriate shift of burden to the compounding industry is further aggravated by the complete absence of consideration by the FDA of the harm caused by the removal of needed drugs from practice. The “Type 2” errors caused by removing important agents from clinical use could far exceed the “Type 1” errors of adverse reactions, particularly given the
track record in this industry. This is particularly true given that the infectious contamination that gave rise to the Act has little to do with the approval process for which ingredients may be compounded. Yet FDA has offered little consideration of the respective risks and benefits of its approach, and with pharmacies and physicians carrying the full burden of proof and the time expected for the advisory process to conclude, the FDA will likely itself cause more patient harm than provide a contribution to safety.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The FDA’s analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). While the FDA made this assessment for “Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness,” 79 FR 37687, in which 25 drugs were added to the list of barred drugs, it has not done so for the much broader issue of upending the compounding pharmaceutical industry, which bears costs both in preparation of detailed submissions on potentially hundreds of ingredients, loss of sales of ingredients no longer approved, the economic consequence to physicians of not being to prescribe these drugs, and the economic impacts of health difficulties and added expense that will result from the withdrawal of drugs from clinical use. The Agency needs to address these concerns.

D) Extend the deadline for which comments are due by 120 days.

IMC’s March 4, 2014 submission, along with AANP and ANH-USA nominated 71 bulk drug substances. IMC identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring.1 We had determined that at least 6 hours per ingredient would be needed to do so, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC sought a 90

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1 For example, other nominations would include 7 Keto Dehydroepiandrosterone; Asparagine; Calendula; Cantharidin; Choline Bitartrate; Chromium Glycinate; Chromium Picolinate; Chrysin; Co-enzyme Q10; Echinacea; Ferric Subsulfate; Iron Carbonyl; Iscador; Pantothenic Acid; Phenindamine Tartrate; Piracetam; Pterostilbene; Pyridoxal 5-Phosphate; Resveratrol; Thymol Iodide.
day extension to more completely respond to the Agency's request.

In the renomination, we have narrowed our focus to the attached 21 bulk drug substances given restraints on available resources. These bulk drug substances are documented in the attachment. Given the limitations imposed by the fact that our physician members spent the majority of their day providing patient care, however, we have found that the span of time the Agency provided for renominations was insufficient.

We now request that FDA extend the deadline for which comments are due by at least 120 days, so that we may provide additional documentation. The FDA can certainly begin work on those nominations it has received, but nominations should remain open. We have determined that as much as 40 hours per ingredient will be needed to do, particularly given the lack of resources being offered by the Agency, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC respectfully seeks an additional 120 day period - if not greater - for the purpose of gathering this essential information. If such an extension is not granted, we will explore the prospect of submitting a Citizen's Petition along with AANP and other interested parties.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

In our submission of March 4, 2014, we raised a number of additional considerations, in particular citing a number of monographs, compendia and other authoritative sources that should be considered proper sources for authorized compounding in addition to the U.S. Pharmacopeia. We urge FDA to reach this issue as a means of allowing substances in long use on the market without undue delay or ambiguity.

F) Accept the attached nominations.

Notwithstanding the concerns expressed and issues highlighted in the foregoing, IMC nominates the bulk drug substances in the attachment for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

G) Accept allergenic extracts as a class without requiring individual nominations and acceptance.

In addition, we ask the FDA clarify its view of, and accept as appropriate for use, the category of materials that have been long used in the compounding of allergenic extracts for immunotherapy.
This should particularly be the case where such substances are compounded in manner consistent, where appropriate under its terms, with USP Monograph 797. Given both long-standing safe use, the nature of the materials and methods of clinical use, and the safety assurances contained in this monograph, we believe that individual nominations and approval should not be imposed upon this form of treatment.

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating patients. IMC wishes to identify these additional ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination.

Sincerely,

Michael J. Cronin, N.D.
Chair, Integrative Medical Consortium

Enclosures:
Nominations

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2 Such as environmental and body molds, dust mites, grasses, grass terpenes, weeds, trees, foods, as well as hormone, neurotransmitter, and chemical antigens that are used in various forms of immunotherapy and desensitization.
September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD  20852

Re:  Docket FDA-2013-N-1525

“To Whom It May Concern:

The American Association of Naturopathic Physicians (AANP) appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

This is a significant issue for our members and their patients. AANP strongly supports efforts to ensure that the drug products dispensed to patients are safe and effective.

**Background: AANP Submissions to Date**

On January 30, 2014, we submitted comments to Docket FDA-2013-D-1444, “Draft Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Withdrawal of Guidances” relating to congressional intent in crafting HR 3204. These comments highlighted the fact that, for compounding pharmacies subject to Section 503A, Congress intended that States continue to have the authority to regulate the availability of safely compounded medications obtained by physicians for their patients. As we further noted, compounded medications that are formulated to meet unique patient needs, and that can be administered immediately in the office, help patients receive the products their physicians recommend and reduce the medical and financial burden on both the patient and
doctor that restrictions on office use would impose. Such medications, we emphasized, provide a unique benefit to patients and have an excellent track record of safety when properly produced and stored.

AANP also (on March 4, 2014) nominated 71 bulk drug substances. We identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring. We estimated, at that time, that at least 6 hours per ingredient would be needed to do so—time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP sought a 90-day extension to more completely respond to the Agency’s request.

In this renomination, we have narrowed our focus to 42 bulk drug substances that are most important for the patients treated by naturopathic doctors. Twenty-one of these bulk drug substances are formally nominated in the attachments as well as noted by name in this letter. Given the limitations imposed by the fact that our physician members spend the majority of their day providing patient care, however, AANP again found that the span of time the Agency provided for renominations was insufficient to prepare the documentation needed for the remaining 21 bulk drug substances.

We now request that FDA extend the deadline for which comments are due by 120 days, so that we may provide this further documentation. We have determined that as much as 40 hours per ingredient will be needed to do so—time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP respectfully seeks an additional 120-day period for the purpose of gathering this essential information.

**Naturopathic Medicine and Naturopathic Physicians**

A word of background on our profession is in order. AANP is a national professional association representing 4,500 licensed naturopathic physicians in the United States. Our members are physicians trained as experts in natural medicine. They are trained to find the underlying cause of a patient’s condition rather than focusing solely on symptomatic treatment. Naturopathic doctors (NDs) perform physical examinations, take comprehensive health histories, treat illnesses, and order lab tests, imaging procedures, and other diagnostic tests. NDs work collaboratively with all branches of medicine, referring patients to other practitioners for diagnosis or treatment when appropriate.

NDs attend 4-year, graduate level programs at institutions recognized through the US Department of Education. There are currently 7 such schools in North America. Naturopathic medical schools provide equivalent foundational coursework as MD and DO schools. Such coursework includes cardiology, neurology, radiology, obstetrics, gynecology, immunology, dermatology, and pediatrics. In addition, ND programs provide extensive education unique to the naturopathic approach, emphasizing disease prevention and whole person wellness. This includes the prescription of clinical doses of vitamins and herbs and safe administration via oral, topical, intramuscular (IM) and intravenous (IV) routes.
Degrees are awarded after extensive classroom study and clinical training. In order to be licensed to practice, an ND must also pass an extensive postdoctoral exam and fulfill annual continuing education requirements. Currently, 20 states and territories license NDs to practice.

Naturopathic physicians provide treatments that are effective and safe. Since they are extensively trained in pharmacology, NDs are able to integrate naturopathic treatments with prescription medications, often working with conventional medical doctors and osteopathic doctors, as well as compounding pharmacists, to ensure safe and comprehensive care.

**Characteristics of Patients Seen by Naturopathic Physicians**

Individuals who seek out NDs typically do so because they suffer from one or more chronic conditions that they have not been able to alleviate in repeated visits to conventional medical doctors or physician specialists. Such chronic conditions include severe allergies, asthma, chronic fatigue, chronic pain, digestive disorders (such as irritable bowel syndrome), insomnia, migraine, rashes, and other autoimmune disorders. Approximately three-quarters of the patients treated by NDs have more than one of these chronic conditions. Due to the fact that their immune systems are often depleted, these individuals are highly sensitive to standard medications. They are also more susceptible to the numerous side effects brought about by mass-produced drugs.

Such patients have, in effect, fallen through the cracks of the medical system. This is why they seek out naturopathic medicine. Safely compounded medications – including nutritional, herbal, and homeopathic remedies – prove efficacious to meet their needs every day in doctors’ offices across the country. Such medications are generally recognized as safe (GRAS), having been used safely for decades in many cases. As patients’ immune function improves, and as they work with their ND to improve their nutrition, get better sleep, increase their exercise and decrease their stress, their health and their resilience improves. This is the ‘multi-systems’ approach of naturopathic medicine – of which compounded drugs are an essential component.

**Bulk Drug Substances Nominated at this Time**

Notwithstanding the concerns expressed and issues highlighted in the foregoing, AANP nominates the following 21 bulk drug substances for FDA’s consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A. Thorough information on these substances is presented in the spreadsheets attached with our comments. The documentation is as complete and responsive to the Agency’s criteria as we can offer at this time.

The bulk drug substances nominated are:

Acetyl L Carnitine
Alanyl L Glutamine
Alpha Lipoic Acid
Artemisia/Artemisinin
Boswellia
Calcium L5 Methyltetrahydrofolate
Cesium Chloride
Choline Chloride
Curcumin
DHEA
Dicholoroacetic Acid
DMPS
DMSA
Germanium Sesquioxide
Glutathione
Glycyrrhizin
Methylcobalamin
MSM
Quercitin
Rubidium Chloride
Vanadium

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating the patients of naturopathic doctors. AANP wishes to specify these 21 ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination. The additional bulk drug substances include:

7 Keto Dehydroepiandrosterone
Asparagine
Calendula
Cantharidin
Choline Bitartrate
Chromium Glycinate
Chromium Picolinate
Chrysin
Co-enzyme Q10
Echinacea
Ferric Subsulfate
Iron Carbonyl
Iscador
Pantothenic Acid
Phenindamine Tartrate
Piracetam
Pterostilbene
Pyridoxal 5-Phosphate
Resveratrol
Salicinium
Thymol Iodide

AANP Objects to Unreasonable Burden

AANP believes it necessary and proper to lodge an objection to FDA’s approach, i.e., the voluminous data being required in order for bulk drug substances to be considered by the Agency for approval. FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of the persons most knowledgeable about and experienced in the application of compounded medications are either small business owners or busy clinicians, and given the extent and detail of information on potentially hundreds of ingredients as sought by FDA, this burden is unreasonable. The approach has no basis in the purpose and language of the Drug Quality and Security Act (“Act”) – particularly for drugs that have been safely used for years, not only with the Agency’s implicit acceptance, but without any indication of an unacceptable number of adverse patient reactions.

The volume of data being required in this rulemaking is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, the Agency contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with the resources to seek regulatory approvals. The FDA’s analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The burden on respondents to this current rulemaking is further aggravated by the FDA’s complete absence of consideration of the harm that will be caused if needed drugs are removed from the market. The “Type 2” errors caused by removing important agents from clinical use could far exceed the “Type 1” errors of adverse reactions, particularly given the strong track record of safely compounded medications. The infectious contamination that gave rise to the Act has little to do with the process set out by FDA for determining which ingredients may be compounded. Yet the Agency has offered little consideration of the respective risks and benefits of its approach. Based on the fact that compounding pharmacies and physicians are carrying the full burden of proof, as well as how much time it is likely to take for the process of documentation and evaluation to conclude, the Agency itself may well find that it has caused more harm to patients’ clinical outcomes than provided a bona fide contribution to patient safety.
Conclusion

AANP appreciates the Agency’s consideration of the arguments and objection presented herein, the request for an extension of time to gather the documentation that FDA is seeking, and the nominations made and referenced at this time.

We look forward to continued dialogue on these matters. As AANP can answer any questions, please contact me (jud.richland@naturopathic.org; 202-237-8150).

Sincerely,

Jud Richland, MPH
Chief Executive Officer
**Nomination Submitted by:** McGuff Compounding Pharmacy Services, Inc., Alliance for Natural Health USA, Integrative Medical Consortium, American Association of Naturopathic Physicians

<table>
<thead>
<tr>
<th>Column A—What information is requested?</th>
<th>Column B—Put data specific to the nominated substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the name of the nominated ingredient?</td>
<td>Dichloroacetate (DCA)</td>
</tr>
<tr>
<td>Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?</td>
<td>There is ample information in Pubmed regarding therapeutic uses of DCA. Please access this link <a href="http://www.ncbi.nlm.nih.gov/pmc/?term=dichloroacetate">http://www.ncbi.nlm.nih.gov/pmc/?term=dichloroacetate</a></td>
</tr>
<tr>
<td>Is the ingredient listed in any of the three sections of the Orange Book?</td>
<td>No</td>
</tr>
<tr>
<td>Were any monographs for the ingredient found in the USP or NF monographs?</td>
<td>No USP monographs available</td>
</tr>
<tr>
<td>What is the chemical name of the substance?</td>
<td>Dichloroacetic acid sodium salt (aka dichloroacetate sodium)</td>
</tr>
<tr>
<td>What is the common name of the substance?</td>
<td>Dichloroacetate (DCA)</td>
</tr>
<tr>
<td>Does the substance have a UNII Code?</td>
<td>42932X67B5</td>
</tr>
<tr>
<td>What is the chemical grade of the substance?</td>
<td>Reagent grade</td>
</tr>
<tr>
<td>What is the strength, quality, stability, and purity of the ingredient?</td>
<td>A valid Certificate of analysis accompanies each lot of raw material received.</td>
</tr>
<tr>
<td>How is the ingredient supplied?</td>
<td>Dichloroacetic acid sodium salt is a powder, hygroscopic.</td>
</tr>
</tbody>
</table>
| Is the substance recognized in foreign pharmacopeias or registered in other countries? | TSCA Chemical Inventory (EPA)  
This product is NOT on the EPA Toxic Substances Control Act (TSCA) inventory. The following notices are required by 40 CFR 720.36 (C) for those products not on the inventory list:  
(i) These products are supplied solely for use in research and development by or under the supervision of a technically qualified individual as defined in 40 CFR 720.0 et seq.  
(ii) The health risks of these products have not been fully determined. Any information that is or becomes available will be supplied on an MSDS sheet.  
WHMIS Classification (Canada) WHMIS CLASS D-2B: Material causing other toxic effects (TOXIC).  
EINECS Number (EEC) 218-461-3  
EEC Risk Statements R23/24/25- Toxic by inhalation, in contact with skin and if swallowed.  
R36/37/38- Irritating to eyes, respiratory system and skin. |
| Has information been submitted about the substance to the USP for consideration of monograph development? | Information unknown |
| What dosage form(s) will be compounded using the bulk drug substance? | Oral capsule |
| What strength(s) will be compounded from the nominated substance? | Oral capsule strengths can range from 5 mg to 500 mg per capsule.  
Injection: up to 500 mg/mL. |
| What are the anticipated route(s) of administration of the compounded drug product(s)? | Oral, injection |
Are there safety and efficacy data on compounded drugs using the nominated substance?

1. FOXO1-mediated Upregulation of Pyruvate Dehydrogenase Kinase-4 (PDK4) Decreases Glucose Oxidation and Impairs Right Ventricular Function in Pulmonary Hypertension: Therapeutic Benefits of Dichloroacetate
   Lin Piao, Vaninder K. Sidhu, Yong-Hu Fang, John J. Ryan, Kishan S. Parikh, Zhigang Hong, Peter T. Toth, Erik Morrow, Shelby Kutty, Gary D. Lopashuk, Stephen L. Archer
   J Mol Med (Berl) Author manuscript; available in PMC 2013 March 12.
   PMCID: PMC3584201
   ArticlePubReaderPDF–3.5MSupplementary MaterialSelect item 3140604

2. Role of SLC5A8, a plasma membrane transporter and a tumor suppressor, in the antitumor activity of dichloroacetate
   Ellappan Babu, Sabarish Ramachandran, Veena CoothanKandaswamy, Selvakumar Elangovan, Purtutt D. Prasad, Vadivel Ganapathy, Muthusamy Thangaraju
   Oncogene. Author manuscript; available in PMC 2012 March 22.
   Published in final edited form as: Oncogene. 2011 September 22; 30(38): 4026–4037. Published online 2011 April 18. doi: 10.1038/onc.2011.113
   PMCID: PMC3140604
   ArticlePubReaderPDF–1.9MSelect item 3140604

3. The inhibition of pyruvate dehydrogenase kinase improves impaired cardiac function and electrical remodeling in two models of right ventricular hypertrophy: resuscitating the hibernating right ventricle
   Lin Piao, Yong-Hu Fang, Virgilio J. J. Cadete, Christian Wietholt, Dalia Urbioniene, Peter T. Toth, Glenn Marsboom, Hannah J. Zhang, Idith Haber, Jalees Rehman, Gary D. Lopashuk, Stephen L. Archer
   J Mol Med (Berl) Author manuscript; available in PMC 2011 August 12.
   PMCID: PMC3155251
   ArticlePubReaderPDF–4.7MSupplementary MaterialSelect item 3668464

4. Dichloroacetate inhibits aerobic glycolysis in multiple myeloma cells and increases sensitivity to bortezomib
   Br J Cancer. 2013 April 30; 108(8): 1624–1633. Published online 2013 March 26. doi: 10.1038/bjc.2013.120
   PMCID: PMC3668464
   ArticlePubReaderPDF–1.1MSupplementary MaterialSelect item 2787291

5. Dichloroacetate alleviates development of collagen II-induced arthritis in female DBA/1 mice
   Li Bian, Elisabet Josefsson, Ing-Marie Jonsson, Margareta Verdenneh, Claes Ohlsson, Maria Bokarewa, Andrej Tarkowski, Mattias Magnusson
   Osteoarthritis Cartilage. 2009 11(5) R132  Published online 2009 S 29 29 10 1186/2799

Has the bulk drug substance been used previously to compound drug product(s)? Yes

What is the proposed use for the drug product(s) to be compounded with the nominated substance? Ajunct Cancer treatment

What is the reason for use of a compounded drug product rather than an FDA-approved product? There are patients that choose or may benefit from DCA treatment when the conventional chemotherapeutic agents fail or are not appropriate.

Is there any other relevant information? DCA is a relatively simple molecule which has been used in the past as treatment for lactic acidosis. It inhibits lactate formation and releases pyruvate dehydrogenase kinase from negative regulation, thus promoting pyruvate entry into the TCA cycle. This increases oxygen consumption and ROS formation while glycolysis and lactate formation are repressed. Non-cancerous human cells prefer this aerobic pathway for energy formation via ETC use. Cancerous cells undergo the Warburg Effect where they convert most glucose to lactate regardless of oxygen availability. Forcing a cancerous cell into TCA / ETC use thereby increases ROS formation and oxygen consumption.

DCA is a relatively small molecule, which has been used as treatment for lactic acidosis. It inhibits lactate formation and releases pyruvate dehydrogenase kinase from negative regulation, thus promoting pyruvate entry into the TCA cycle. This increases oxygen consumption and reactive oxygen species (ROS) formation while glycolysis and lactate formation are repressed. Non-cancerous human cells prefer this aerobic pathway for energy formation via the electron transport chain (ETC) use. Cancerous cells experience the Warburg Effect where most glucose is converted to lactate regardless of oxygen availability. Forcing a cancerous cell into TCA / ETC use thereby increases ROS formation and oxygen consumption.

*See Appendix 1: Complete List of Sources Cited in the Nomination*
Appendix 1

Sources Cited in the 503A Nominations for Dichloroacetate

1. FOXO1-mediated Upregulation of Pyruvate Dehydrogenase Kinase-4 (PDK4) Decreases Glucose Oxidation and Impairs Right Ventricular Function in Pulmonary Hypertension: Therapeutic Benefits of Dichloroacetate.

   Published in final edited form as: J Mol Med (Berl). 2013 March; 91(3): 333–346. Published online 2012 December 18. doi: 10.1007/s00109-012-0982-0
   PMCID: PMC3584201
   ArticlePubReaderPDF–3.5MSupplementary MaterialSelect item 3140604

2. Role of SLC5A8, a plasma membrane transporter and a tumor suppressor, in the antitumor activity of dichloroacetate.

   Oncogene. Author manuscript; available in PMC 2012 March 22. Published in final edited form as: Oncogene. 2011 September 22; 30(38): 4026–4037. Published online 2011 April 18. doi: 10.1038/onc.2011.113   PMCID: PMC3140604
   ArticlePubReaderPDF–1.9MSelect item 3155251

3. The inhibition of pyruvate dehydrogenase kinase improves impaired cardiac function and electrical remodeling in two models of right ventricular hypertrophy: resuscitating the hibernating right ventricle

   Lin Piao, Yong-Hu Fang, Virgilio J. J. Cadete, Christian Wietholt, Dalia Urboniene, Peter T. Toth, Glenn Marsboom, Hannah J. Zhang, Idith Haber, Jalees Rehman, Gary D. Lopaschuk, Stephen L. Archer
   J Mol Med (Berl) Author manuscript; available in PMC 2011 August 12.
4. Dichloroacetate inhibits aerobic glycolysis in multiple myeloma cells and increases sensitivity to bortezomib


Br J Cancer. 2013 April 30; 108(8): 1624–1633. Published online 2013 March 26. doi: 10.1038/bjc.2013.120  PMCID: PMC3668464

5. Dichloroacetate alleviates development of collagen II-induced arthritis in female DBA/1 mice

Li Bian, Elisabet Josefsson, Ing-Marie Jonsson, Margareta Verdengh, Claes Ohlsson, Maria Bokarewa, Andrej Tarkowski, Mattias Magnusson


PMCID: PMC2787291


Pediatrics. Author manuscript; available in PMC 2013 September 19.

Published in final edited form as: Pediatrics. 2008 May; 121(5): e1223–e1228. Published online 2008 April 14. doi: 10.1542/peds.2007-2062

PMCID: PMC3777225
7. Modulation of Astrocytic Mitochondrial Function by Dichloroacetate Improves Survival and Motor Performance in Inherited Amyotrophic Lateral Sclerosis

Ernesto Miquel, Adriana Cassina, Laura Martínez-Palma, Carmen Bolatto, Emiliano Trias, Mandi Gandelman, Rafael Radi, Luis Barbeito, Patricia Cassina


8. Regulation of Muscle Pyruvate Dehydrogenase Complex in Insulin Resistance: Effects of Exercise and Dichloroacetate

Dumitru Constantin-Teodosiu

Diabetes Metab J. 2013 October; 37(5): 301–314. Published online 2013 October 17. doi: 10.4093/dmj.2013.37.5.301

PMCID: PMC3816130

9. Dichloroacetate modulates cytokines toward T helper 1 function via induction of the interleukin-12–interferon-γ pathway

Mujtaba M Badr, Nidal A Qinna, Fadi Qadan, Khalid Z Matalka


PMCID: PMC3923616

10. Peripheral Neuropathy in Rats Exposed to Dichloroacetate


J Neuropathol Exp Neurol. Author manuscript; available in PMC 2010 September 1. Published in final edited form as: J Neuropathol Exp Neurol. 2009 September; 68(9): 985–993. doi: 10.1097/NEN.0b013e3181b40217    PMCID: PMC2741559
11. Antitumor activity of dichloroacetate on C6 glioma cell: in vitro and in vivo evaluation
   Yu Duan, Xin Zhao, Wei Ren, Xin Wang, Ke-Fu Yu, Dan Li, Xuan Zhang, Qiang Zhang

12. Dichloroacetate induces apoptosis and cell-cycle arrest in colorectal cancer cells
   B M Madhok, S Yeluri, S L Perry, T A Hughes, D G Jayne
   Br J Cancer. 2010 June 8; 102(12): 1746–1752. Published online 2010 May 18. doi: 10.1038/sj.bjc.6605701  PMCID: PMC2883702

13. Role of Dichloroacetate in the Treatment of Genetic Mitochondrial Diseases
   Peter W. Stacpoole, Tracie L. Kurtz, Zongchao Han, Taimour Langaee
   Adv Drug Deliv Rev. Author manuscript; available in PMC 2013 August 19.
   PMCID: PMC3746325

14. Metabolic response of glioma to dichloroacetate measured in vivo by hyperpolarized 13C magnetic resonance spectroscopic imaging
   Jae Mo Park, Lawrence D. Recht, Sonal Josan, Milton Merchant, Taichang Jang, Yi-Fen Yen, Ralph E. Hurd, Daniel M. Spielman, Dirk Mayer

15. Dichloroacetate effects on glucose and lactate oxidation by neurons and astroglia in vitro and on glucose utilization by brain in vivo
16. Two mixed-NH3/amine platinum (II) anticancer complexes featuring a dichloroacetate moiety in the leaving group

Weiping Liu, Jia Su, Jing Jiang, Xingyao Li, Qingsong Ye, Hongyu Zhou, Jialin Chen, Yan Li

PMCID: PMC3746205

17. Human Polymorphisms in the Glutathione Transferase Zeta 1/Maleylacetoacetate Isomerase Gene Influence the Toxicokinetics of Dichloroacetate

Mr. Albert L. Shroads, Dr. Taimour Langaee, Ms. Bonnie S. Coats, Ms. Tracie L. Kurtz, Mr. John R. Bullock, Mr. David Weithorn, Dr. Yan Gong, Dr. David A. Wagner, Dr. David A. Ostrov, Dr. Julie A. Johnson, Dr. Peter W. Stacpoole

J Clin Pharmacol. Author manuscript; available in PMC 2013 September 30.
Published in final edited form as: J Clin Pharmacol. 2012 June; 52(6):
10.1177/0091270011405664. Published online 2011 June 3. doi:
10.1177/0091270011405664
PMCID: PMC3786668

18. Dichloroacetate (DCA) as a potential metabolic-targeting therapy for cancer

E D Michelakis, L Webster, J R Mackey

Br J Cancer. 2008 October 7; 99(7): 989–994. Published online 2008 September 2. doi:
10.1038/sj.bjc.6604554 PMCID: PMC2567082

ArticlePubReaderPDF–202KSelect item 3362455
19. Cotreatment with dichloroacetate and omeprazole exhibits a synergistic antiproliferative effect on malignant tumors

TATSUAKI ISHIGURO, MIYU ISHIGURO, RYUMEI ISHIGURO, SAYURI IWAI


PMCID: PMC3362455

ArticlePubReaderPDF–335KSelect item 3043319

20. Synergistic Antitumor Effect of Dichloroacetate in Combination with 5-Fluorouracil in Colorectal Cancer

Jingtao Tong, Ganfeng Xie, Jinxia He, Jianjun Li, Feng Pan, Houjie Liang


ArticlePubReaderPDF–1.0M
Tab 3b

Sodium Dichloroacetate

FDA Review
DATE: May 31, 2016

FROM: Ben Zhang, Ph.D.
ORISE Fellow, Office of New Drug Products,
Office of Pharmaceutical Quality

Haw-Jyh Chiu, Ph.D.
Pharmacology/Toxicology Reviewer, Division of Hematology, Oncology,
Toxicology, Office of Hematology and Oncology Products

Michael Brave, M.D.
Clinical Reviewer, Division of Oncology Products 1, Office of Hematology and
Oncology Products

THROUGH: Ramesh Sood, Ph.D.
Senior Scientific Advisor (Acting), Office of New Drug Products, Office of
Pharmaceutical Quality

Todd Palmby, Ph.D.
Supervisory Pharmacologist/Toxicologist, Division of Hematology, Oncology,
Toxicology, Office of Hematology and Oncology Products

Kathy Fedenko, M.S., C.R.N.P.
Deputy Director for Safety, Division of Oncology Products 1, Office of
Hematology and Oncology Products

Geoffrey Kim, M.D.
Director, Division of Oncology Products 1, Office of Hematology and Oncology
Products

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Dichloroacetate Sodium for Inclusion on the 503A Bulk Drug
Substances List
I. INTRODUCTION

Dichloroacetate sodium has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for oral (capsule) and injectable (intravenous) use as an adjunct treatment for cancer.

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 do not recommend that dichloroacetate sodium be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

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

The drug substance is a small molecule. It is a dichloro analogue of sodium acetate with the following molecular structure:

\[
\text{Cl} \quad \text{O} \quad \text{Cl} \quad \text{Na}
\]

This substance is currently marketed as a dietary supplement.

Databases searched for information on dichloroacetate sodium in regard to Section A of this consultation included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and USP/NF.

1. Stability of the API and likely dosage forms

Dichloroacetate is very sensitive to heat in aqueous solutions. It readily decomposes with dehalogenation, especially in lower pH environments (Chu et al., 1992). The substance also undergoes hydrolysis reactions under basic conditions to yield oxalic acid or acetic acid. One study on the stability of an oral drug formulation of dichloroacetate sodium

---

1 This review focuses primarily on the salt, dichloroacetate sodium, because it is the substance most often used in the medical setting. Some references reviewed herein discuss “dichloroacetate sodium.” Other references discuss “dichloroacetate” and do not specify the associated cation. “Dichloroacetic acid,” which is not a salt form, is also discussed in some references. The text of this review reflects the term used in the reference. We expect “dichloroacetate” and “dichloroacetic acid” data are generally pertinent to “dichloroacetate sodium.”
also suggests that the decomposition of this substance is significantly accelerated when stored at room temperature compared with when stored at 4°C (Henderson et al., 1994). Therefore, dichloroacetate sodium is likely to be stable in the proposed oral capsule dosage forms only when stored at lower temperature and kept away from moisture. When formulated as an injection solution, this substance is unlikely to be stable.

It was nominated for use in oral capsules and solutions for injection.

2. **Probable routes of API synthesis**

Current synthesis of dichloroacetate sodium is mainly based 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. Dichloroacetic acid is then isolated from the mixture and then reacted with the base to yield dichloroacetate sodium (Pragt et al., 2015).

\[
\begin{align*}
\text{O} & \quad \text{Cl}_2 \\
\text{O} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad \text{Cl} \\
\end{align*}
\]

3. **Likely impurities**

Based on the likely manufacturing process, likely impurities include:

a. Byproduct for the chlorination reaction: Monochloroacetate and trichloroacetate;
b. Residual starting materials, such as acetic acid.

4. **Toxicity of those likely impurities**

Impurities are unlikely to be toxic. Further toxicity issues are discussed in section B.

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

Dichloroacetate sodium is a white solid and highly soluble in water. No further information on the influence of particle size and polymorphism on bioavailability were 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**

Dichloroacetate sodium is easily characterized with proton nuclear magnetic resonance (\(^1\)H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (\(^{13}\)C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and mass spectrometry (MS).
**Conclusions:** Dichloroacetate sodium is a small molecule. In a solid oral dosage form, the substance is likely to be stable under ordinary storage conditions at lower temperatures. When formulated as an injectable solution, it is unlikely to be stable. Dichloroacetate sodium is easily characterized with various analytical techniques, and the preparation of the substance has been well developed.

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

1. **Nonclinical Assessment**

PubMed was the public database consulted in the preparation of the nonclinical portion of this review.

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

Dichloroacetate is an organohalide and a byproduct of water chlorination and industrial solvents, and metabolites of drugs (Stacpoole et al., 1998a).

Studies have shown that the concentration of dichloroacetate in drinking water ranged from 19 to 160 µg/L (Uden et al., 1983; Krasner et al., 1989). Dichloroacetate has been shown to activate the pyruvate dehydrogenase complex in mammalian cells (Stacpoole et al., 1970). Pyruvate dehydrogenase catalyzes the irreversible oxidation of pyruvate to acetyl CoA. The commonly proposed mechanism of action for the anti-tumor activity of dichloroacetate is the redirection of glucose metabolism from glycolysis to oxidative phosphorylation, leading to inhibition of proliferation and induction of apoptosis (Kankotia et al., 2014).

As discussed above, likely impurities include monochloroacetate, trichloroacetate and acetic acid. Monochloroacetate is also a metabolite of both dichloroacetate and trichloroacetate in mice, rats, and humans (Larson et al., 1992; Stacpoole et al., 1998b). In healthy volunteer subjects, plasma concentration of monochloroacetate may reach 10% of the dichloroacetate Cmax on a molar basis following a 25 mg/kg IV infusion (dichloroacetate Cmax = 129 ± 73 µg/mL) (Stacpoole et al., 1998b). In vitro, cytotoxicity of monochloroacetate has been observed in mouse and rat hepatocytes (at ≥ 5 mM) (Bruschi et al., 1993) and opossum kidney and human liver cell lines (EC50 = 100 µg/mL) (Dartsch et al., 2000). The LD99 of monochloroacetate has been reported to be approximately 77 mg/kg following a single subcutaneous injection to Sprague-Dawley rats. Toxicities observed at the lethal dose were severe hypoglycemia and lactic acidosis in Sprague-Dawley rats (Shimizu et al., 2002), possibly through inactivation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and inhibition of liver gluconeogenesis (Sakai et al., 2005). In an oral 90-day, repeat-dose toxicity study in Sprague-Dawley rats, mortality was noted at 120 mg/kg. The liver and kidneys were identified as the target organs of toxicity. The lowest observed adverse effect level (LoAEL) of 15 mg/kg was identified in this study (Daniel et al., 1991).
Trichloroacetate has been shown to be hepatocarcinogenic in B6C3F1 mice (Herren-Freund et al., 1987; Bull et al., 1990). Overall, literature reports suggest that trichloroacetate appears to have a similar toxicity profile when compared to dichloroacetate, but trichloroacetate causes less hepatotoxicity and oxidative stress when compared to dichloroacetate (Larson et al., 1992).

Acetic acid is a Class 3 residual solvent, with a permissible daily exposure (PDE) of 50 mg per day (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Impurities: Guideline for Residual Solvents Q3C(R5), 2011).

b. Safety pharmacology

No information available.

c. Acute toxicity

The oral LD$_{50}$ of dichloroacetate has been reported to be ~ 5 g/kg in rodents (Katz et al., 1981).

d. Repeat dose toxicity

The liver, kidney, nervous system, and testes have been identified as the major target organs of dichloroacetate.

In rodents, administration of dichloroacetate in drinking water caused hepatocellular injury, hypertrophy, and hyperplasia. In the kidney, degenerative changes in the renal tubular epithelia and glomeruli were observed in rats administered dichloroacetate for 90 days (Stacpoole et al., 1998a).

In a 90-day repeat-dose toxicity study in juvenile beagle dogs (0, 12.5, 39.5, or 72 mg/kg/day orally via gelatin capsules), mortality was noted at 72 mg/kg/day – possibly due to pneumonia and dehydration. Major target organs were the bone marrow, brain, liver, and testes. Major findings included vacuolization of myelinated white tracts of the cerebrum, cerebellum, and/or spinal cord, degeneration of testicular germinal epithelium and syntial giant cell formation at >12.5 mg/kg/day, dyspnea, body weight loss, deceased erythrocytes and hemoglobin, hepatic vacuolar changes and chronic hepatitis, and suppurative bronchopneumonia and chronic pancreatitis at >39.5 mg/kg/day, and increased LDH and hindlimb paralysis at 72 mg/kg/day (Cicmanec et al., 1991).

e. Mutagenicity

Dichloroacetate did not induce mutation in the bacterial reverse (Ames) test and was not genotoxic in the in vitro mouse lymphoma thymidine kinase (Tk) gene mutation assay, in vitro micronucleus assay in Chinese hamster ovary cells, or the in vivo rat micronucleus assay (Fox et al., 1996).
f. Developmental and reproductive toxicity

In a study assessing the effects of dichloroacetate on fertility, decreased number of viable implants on day 14 of gestation was observed when male rats treated with 125 mg/kg/day dichloroacetate orally for 10 weeks were mated overnight (Toth et al., 1992). Adverse effects on fertility correlated with findings of decreased preputial gland and epididymis weights, reduced epididymal sperm counts, sperm morphology, spermiation inhibition, reduction in percentage of motile sperm, curvilinear and straight-line velocity, linearity, and amplitude of lateral head displacement. Embryofetal toxicity consisting of heart malformations have been observed in rats (Epstein et al., 1992).

Administration of 14 – 2400 mg/kg/day dichloroacetate to pregnant Long-Evans rats on gestation days 6 to 15 caused increased resorptions per litter at ≥900 mg/kg/day. Statistically significant increases in soft tissue malformation were noted at ≥140 mg/kg/day and consisted of defects between the ascending aorta and the right ventricle (Smith et al., 1992).

g. Carcinogenicity

Dichloroacetate is a byproduct of drinking water that has been disinfected with chlorine. Dichloroacetate is also a metabolite of the environmental contaminant trichloroethylene. Because of its presence in the environment, the U.S. Environmental Protection Agency conducted carcinogenicity studies in mice which showed dichloroacetate to be a hepatic carcinogen (Carter et al, 2003). Other carcinogenicity assessments have been conducted as well.

In male B6C3F1 mice, administration of >0.5 g/L dichloroacetate in the drinking water for 60 or 61 weeks resulted in significant increases in hepatocellular carcinomas (Herren-Freund et al., 1987; DeAngelo et al., 1991). In a two-year carcinogenicity study in male Fisher (F344) rats, statistically significant increases in hepatocellular carcinoma was noted at 1.6 g/L dichloroacetate administered in drinking water. The no-observed-effect-level (NOEL) for carcinogenicity in Fisher rats was 0.05 g/L (3.6 mg/kg/day) (DeAngelo et al., 1996).

In a 41-week carcinogenicity study in Tg.AC hemizygous mice, no carcinogenicity was observed at a dose level up to 2000 mg/L in the drinking water (National Toxicology Program, 2007; Kissling et al., 2009).

In a 41-week carcinogenicity study in p53 haploinsufficient mice, a modest non-dose-related increase in pulmonary adenomas was observed in males exposed to 1000 mg/L dichloroacetate in the drinking water (National Toxicology Program, 2007; Kissling et al., 2009). In a 39-week carcinogenicity study in Tg.AC mice, increased dermal papillomas at the site of dermal application was observed at a dose level up to 500 mg/kg (National Toxicology Program, 2007; Kissling et al., 2009).
h. Toxicokinetics

No information available.

Conclusions: Nonclinical studies in mice, rats, and dogs identified the liver, kidney, nervous system, and testes have as the major target organs of dichloroacetate. The oral LD$_{50}$ of dichloroacetate has been reported to be $\sim 5$ g/kg in rodents.

Treatment of male rats with dichloroacetate resulted in decreased fertility. Treatment of pregnant female rats with dichloroacetate resulted in increased fetal resorptions and embryofetal soft tissue malformations, including findings in the aorta and ventricle. Carcinogenicity studies in mice and rats showed that dichloroacetate caused increases in hepatocellular carcinomas and pulmonary adenomas when administered via the drinking water, and dermal papillomas when administered via the dermal route of administration. The toxicity profile of dichloroacetate in animal studies weighs against its inclusion on the 503A bulks list.

2. Human Safety

The following public database(s) were consulted using the search term dichloroacetate in the preparation of the clinical portions of this review: Pubmed, Google, and proceedings of the American Society of Clinical Oncology and the American Association for Cancer Research.

a. Reported adverse reactions

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for dichloroacetic acid and dichloroacetate. This search yielded four reports, but none of these four reports contained sufficient information to establish reasonable evidence of causality.

The Center for Food Safety and Nutrition (CFSAN) was also consulted to search their adverse event data base, CFSAN Adverse Events Reporting System (CAERS), for adverse events associated with dichloroacetate. No safety reports were found.

b. Clinical trials assessing safety

Section II.B.1.g. discusses animal carcinogenicity studies undertaken in part because of concerns about dichloroacetate in human drinking water. Human carcinogenicity of this substance remains a concern.

In a randomized, controlled clinical trial of dichloroacetate in patients with mitochondrial encephalopathy, lactic acid, and stroke like episodes (MELAS), Kaufmann et. al., (2006) showed oral doses of 25 mg/kg BID to be poorly tolerated due to sensory and motor neuropathy.
Chu et al., (2015) conducted a Phase 1 trial of dichloroacetate in 24 patients with advanced solid tumors. Toxicities included fatigue, nausea, vomiting, diarrhea, and neuropathy. The recommended phase 2 dose was 6.25 mg/kg BID.

Dunbar et al., (2014) conducted a Phase 1 trial of dichloroacetate in 15 adults with recurrent high-grade glioma or brain metastases from a primary cancer outside the central nervous system. Dosing was based on haplotype variation in GSTZ1/MAAI. No dose-limiting toxicities were reported. Two patients experienced paresthesias requiring dose modification.

Garon (2014) reported results of an open-label trial of oral dichloroacetic acid 6.25 mg twice daily in patients with previously treated metastatic breast cancer and advanced stage non-small cell lung cancer (NSCLC). Twenty-nine patients were planned for the NSCLC cohort, and the breast cancer cohort was to enroll 18 patients with expansion to 43 patients if three of the first 18 patients responded. The primary end point was response rate. After the first seven patients (six with NSCLC and one with breast cancer) were enrolled, the data safety monitoring board closed the trial because of safety concerns. Two patients died suddenly within one week of starting dichloroacetic acid, one from a fatal pulmonary embolism and the other attributed to a cerebrovascular accident. The most frequent adverse events were lower extremity edema and abdominal pain, both of which were seen in three patients. Grades ≥3 adverse events were abdominal pain (1), lower extremity edema (1), elevated AST (1), pulmonary embolism (2), hyponatremia (1), volume depletion (1), and sudden death (1). Due to the lack of clinical benefit observed, along with the two deaths, the Jonsson Comprehensive Cancer Center Data Safety and Monitoring Board closed the study.

c. Pharmacokinetic data

Dichloroacetate bioavailability in healthy human volunteers varied widely, from 27 to 100% in a study by Schultz et al., (2006). Stacpoole et al., (1998b) found that dichloroacetate is dehalogenated by glutathione transferase zeta (GSTz1)/maleylacetoacetate isomerase (MAAI) in the liver to monochloroacetate and glyoxylate, which are then further catabolized to glycolate, glycine, oxalate, and carbon dioxide. Shroads et al., (2012) identified four human polymorphisms of GSTz1, one of which has a 10-fold higher binding affinity for dichloroacetate than others. After single infusions in healthy volunteers, Cmax was dose proportional up to 30 mg/kg, after which clearance decreased, likely due to inhibition of GSTz1 by dichloroacetate, leading to drug accumulation. Shangraw et al., (1999) established that plasma dichloroacetate clearance is markedly decreased in patients with cirrhosis.

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

Numerous anticancer agents have been granted marketing approval by FDA following demonstration of safety and efficacy in well-controlled clinical trials.

Conclusions: Toxicity, primarily involving the nervous system, was noted in clinical studies. Dichloroacetate also exhibits significant inter-individual variation in absorption and excretion,
and the drug accumulates over time, complicating both dosing and the management of any toxic effects. FDA is aware of one study being closed due to safety concerns and patient deaths. There are numerous FDA-approved agents that have demonstrated safety for the treatment of patients with various cancers.

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

As previously described, Garon (2014) reported results of an open-label trial of oral dichloroacetic acid 6.25 mg twice daily in patients with previously treated metastatic breast cancer and advanced stage non-small cell lung cancer (NSCLC). The data safety monitoring board closed the trial after enrollment of seven patients due to safety concerns. There were no clinical benefits observed.

2. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

This substance was nominated for use as an adjunct treatment of cancer, which is a serious and life-threatening disease.

3. Whether there are any alternative approved therapies that may be as effective or more effective.

Numerous anticancer agents have been granted marketing approval by FDA following demonstration of safety and efficacy in well-controlled clinical trials.

Conclusions: There are insufficient data to assess the efficacy of dichloroacetate in the treatment of cancer. There are numerous FDA-approved products that have been demonstrated to be effective in the treatment of cancer.

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

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

There is insufficient information to determine how long dichloroacetate has been used in pharmacy compounding.

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

Dichloroacetate is sold via the internet, usually as dichloroacetate sodium, often with the implication that it has a role as a treatment for cancer. No clinical trials have been identified that demonstrate a benefit of dichloroacetate in the treatment of cancer.
3. **How widespread its use has been**

There are insufficient data available from which to draw conclusions about the extent of use of dichloroacetate in compounded drug products.

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


**Conclusions:** There is insufficient information to evaluate the historical use of dichloroacetate in pharmacy compounding. The substance does not appear to be used internationally.

**III. RECOMMENDATION**

We have evaluated the physiochemical characteristics, safety, effectiveness, and historical use in compounding of dichloroacetate sodium as a candidate for the list of bulk drug substances under section 503A of the Act and **do not recommend** it be included on the list of bulk drug substances allowed for use in compounding.

Dichloroacetate sodium is a small molecule that is straightforward to characterize using common analytical techniques. It is stable as a solid oral dosage form only when stored at lower temperatures, and is unlikely to be stable in an injectable form.

Its safety, based on both non-clinical and clinical studies, is of significant concern. In non-clinical studies, dichloroacetate shows potential toxicity in multiple organs as well as increased carcinogenicity. It also shows decreased fertility in rats. Toxicity was also noted in clinical studies, primarily involving the nervous system. Dichloroacetate also exhibits significant inter-individual variation in absorption and excretion, and the drug accumulates over time, complicating both dosing and the management of any toxic effects. FDA is aware of one study being closed due to safety concerns and patient deaths.

There is no evidence of the efficacy of dichloroacetate in the treatment of cancer based on clinical studies. In ongoing and published clinical trials of dichloroacetate in patients with cancer, no objective tumor responses have been reported to date. Relying on this type of treatment may have serious health consequences, including peripheral neuropathy and gastrointestinal symptoms.

Treatment with dichloroacetate sodium could also result in a delay in the use of drugs that have been found to be safe and effective in the treatment of cancer and may increase the likelihood of second malignancies.

In addition, there are numerous FDA-approved products that have been demonstrated to be safe and effective in the treatment of cancer.
Based on a balancing of the four evaluation criteria, we do not recommend dichloroacetate sodium for inclusion on the list of bulk drug substance that can be used in compounding under 503A of the FD&C Act.
BIBLIOGRAPHY


DeAngelo AB, Daniel FB, Most BM, Olsen GR. The carcinogenicity of dichloroacetic acid in the male fischer 344 rat. Toxicology 1996;114:207-221.


K National Toxicology Program. NTP report on the toxicology studies of dichloroacetic acid (CAS No. 79-43-6) in genetically modified (FVB Tg.AC hemizygous) mice (dermal and drinking water studies) and carcinogenicity studies of dichloroacetic acid in genetically modified (B6.129-Trp53(tm1Brd) (N5) haploinsufficient) mice (drinking water studies). Natl Toxicol Program Genet Modif Model Rep 2007;11:1-168.


Tab 4

Pyruvic Acid
Tab 4a

Pyruvic Acid

Nomination
Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

"List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act"

Dear Sir or Madam,

Fagron appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

We hereby nominate the bulk drug substances in the attached spreadsheets for FDA’s consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

None of these items appear on an FDA-published list of drugs that present demonstrable difficulties for compounding. In addition, none are a component of a drug product that has been withdrawn or removed from the market because the drug or components of the drug have been found to be unsafe or not effective.

We include references in support of this nomination for your consideration.

Thank you for your consideration. If Fagron can answer any questions, please contact me (j.letwat@fagron.com; 847-207-6100).

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs
Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlxs file)

7-Keto Dehydroepiandrosterone
Acetyl-D-Glucosamine
Aloe Vera 200:1 Freeze Dried
Astragalus Extract 10:1
Beta Glucan (1,3/1,4 –D)
Boswellia Serrata Extract
Bromelain
Cantharidin
Cetyl Myristoleate Oil
Cetyl Myristoleate 20% Powder
Chrysin
Cittruline
Dehydroepiandrosterone
Deoxy-D-Glucose (2)
Diindoylmethane
Domperidone
EGCg
Ferric Subsulfate
Glycolic Acid
Glycosaminoglycans
Hydroxocobalamin Hydrochloride
Kojic Acid
Methylcobalamin
Nicotinamide Adenine Dinucleotide
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)
Ornithine Hydrochloride
Phosphatidyl Serine
Pregnenolone
Pyridoxal 5-Phosphate Monohydrate
Pyruvic Acid
Quercetin
Quinacrine Hydrochloride
Ribose (D)
Silver Protein Mild
Squaric Acid Di-N-Butyl Ester
Thymol Iodide
Tranilast
Trichloroacetic Acid
Ubiquinol 30% Powder
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the name of the nominated ingredient?</td>
<td><strong>Pyruvic Acid</strong></td>
</tr>
<tr>
<td>Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?</td>
<td>Yes, Pyruvic 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. Zeinab Tosson, Enayat Attwa and Sahar Al-Mokadem (2006). Pyruvic acid as a new therapeutic peeling agent in acne, melasma and warts. Egyptian Dermatology Online Journal 2 (2)</td>
</tr>
<tr>
<td>Is the ingredient listed in any of the three sections of the Orange Book?</td>
<td>The nominated substance was searched for in all three sections of the Orange Book located at <a href="http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm</a>. The nominated substance does not appear in any section searches of the Orange Book.</td>
</tr>
<tr>
<td>Were any monographs for the ingredient found in the USP or NF monographs?</td>
<td>Listed in reagent section of USP</td>
</tr>
<tr>
<td>What is the chemical name of the substance?</td>
<td>2-oxoproanoic acid</td>
</tr>
<tr>
<td>What is the common name of the substance?</td>
<td>Pyruvic acid</td>
</tr>
<tr>
<td>Does the substance have a UNII Code?</td>
<td>8558G7RUTR</td>
</tr>
<tr>
<td>What is the chemical grade of the substance?</td>
<td>Reagent</td>
</tr>
</tbody>
</table>
| What is the strength, quality, stability, and purity of the ingredient?   | Description: Clear, golden-yellowish-brown liquid; Odor resembling acetic acid  
Solubility: Miscible in water  
Infrared Spectroscopy: Conforms to standard  
Assay (GC): >= 95.0%  
Assay (Iodometric Titration): >= 95.0%  
Specific Gravity: 1.262 - 1.277  
Refractive Index: 1.4250 - 1.4300                                                                                                                                                                           |
<p>| How is the ingredient supplied?                                          | Liquid                                                                                                                                                                                                                                                                                                                              |
| Is the substance recognized in foreign pharmacopeias or registered in other countries? | Registered in Italy and Portugal.                                                                                                                                                                                                                                                                                                   |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has information been submitted about the substance to the USP for consideration of monograph development?</td>
<td>No USP Monograph Submission found.</td>
</tr>
<tr>
<td>What dosage form(s) will be compounded using the bulk drug substance?</td>
<td>Peel</td>
</tr>
<tr>
<td>What strength(s) will be compounded from the nominated substance?</td>
<td>40-50%</td>
</tr>
<tr>
<td>What are the anticipated route(s) of administration of the compounded drug product(s)?</td>
<td>Topical</td>
</tr>
</tbody>
</table>
| Has the bulk drug substance been used previously to compound drug product(s)? | Yes, used as a peeling agent  
| What is the proposed use for the drug product(s) to be compounded with the nominated substance? | Used as a topical peeling agent in acne, melasma and warts                                                                                                                                                                                                                                                                             |
| What is the reason for use of a compounded drug product rather than an FDA-approved product? | There are no FDA approved are preparations containing pyruvic acid for chemical peels. There are no FDA approved medications for facial peels only FDA approved procedures. Pyruvic acid has been shown to cause minimal adverse reactions in the chemical peeling process. (L.S. Moy, S.Peace, and R.L. Moy (1996) Comparison of the Effect of Various Chemical Peeling Agents in a Mini-Pig Model May;22(5):429) Chemical peels have a faster recovery time as compared to FDA approved techniques. This can lead to less chance of complications. |
| Is there any other relevant information?                                  | All relevant information was expressed in the above questions                                                                                                                                                                                                                                                                         |
Tab 4b

Pyruvic Acid

FDA Review
I. INTRODUCTION

Pyruvic acid 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 acne, melasma, and warts.
We have reviewed available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we recommend that pyruvic acid for topical use be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

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

Pyruvic acid is a small molecule. Its conjugate base, pyruvate, plays an important role in many metabolic pathways.

Databases searched for information on pyruvic acid in regard to Section A of this consultation included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia, USP/NF.

1. Stability of the API and likely dosage forms

Pyruvic acid is an \(\alpha\)-keto acid, and its pK\(_a\) is at 2.45. Under neutral pH conditions, it primarily turns into its conjugate base, pyruvate. Pyruvate can undergo decarboxylation under basic and neutral conditions to yield carbon dioxide and acetic acid (Hardebeck et al., 1968). Furthermore, because of the conjugated carbonyl groups, pyruvic acid is sensitive to sunlight. Multiple studies demonstrated that pyruvic acid is susceptible to photoinduced oligomerization and decomposition (Griffith et al., 2013; Guzman et al., 2006; Zou et al., 1994). Therefore, pyruvic acid is unlikely to be stable in ambient environments. This compound can likely be stored when carefully sealed, isolated from moisture, and kept away from light, but it is unlikely to be stable in the proposed dosage form without proper storage techniques.

2. Probable routes of API synthesis

Current manufacturing processes can be divided into two groups: fermentation with microorganisms or chemical synthesis. Microbiological production process of pyruvic acid has been widely studied recently and has great potential to lower the cost of production. However, the purification and isolation are still problematic when pyruvic acid is produced by this process (Li et al., 2001). Several chemical synthetic strategies of producing pyruvic acid have been proposed, and they are largely based on the oxidation or decomposition of different starting material, such as lactic acid (Kiyoura 1980),
hydroxyacetone (Kiyoura 1981), and tartaric acid (Feldman 1979; Howard et al., 1932). The dehydration and decarboxylation of tartaric acid method (scheme shown below) have been used on an industrial scale.

\[ \text{HO} \quad \text{OH} \quad \text{OH} \quad \text{KHSO}_4 \quad \rightarrow \quad \text{CH}_2 \quad \text{CO}_2 \quad \text{H}_2\text{O} \]

3. **Likely impurities**

Likely impurities from microbiological production processes:

1) Bioburden, such as residual yeast;
2) Byproduct from fermentation, such as lactic acid.
3) Decomposition product of pyruvic acid, such as acetic acid.

Likely impurities from chemical syntheses:

1) Some synthetic strategies involve oxidations catalyzed by metals catalysts like Palladium, Platinum and Rhodium. These metal elements are possible residual impurities in the product;
2) Decomposition products of pyruvic acid, such as acetic acid.

4. **Toxicity of those likely impurities**

The impurities are unlikely to be significantly toxic. Further toxicity issues are discussed in section B.

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

Pyruvic acid is a liquid at room temperature (MP. 13.8 C) and is highly soluble in water. It has mainly been used as a liquid or solution. Therefore, influence of particle size or polymorphism on bioavailability is not relevant.

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

Pyruvic acid has been characterized with proton nuclear magnetic resonance (\(^1\text{H NMR}\)) spectroscopy, carbon-13 nuclear magnetic resonance (\(^{13}\text{C NMR}\)) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), ultraviolet-visible (UV-Vis) spectroscopy, and mass spectrometry (MS).
Conclusions

Pyruvic acid is a small molecule. The substance is unlikely to be stable in ambient environments, but can be stored when carefully sealed, isolated from moisture, and kept away from light. The nominated compound is easily characterized with various analytical techniques, and the synthesis 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 database(s) were consulted in the preparation of this review: PubMed, TOXNET, EMBASE, Google/Google Scholar, and US Pharmacopeia (Searched using key words pyruvic acid or pyruvate)

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

Pyruvic acid is an intermediate compound in the metabolism of carbohydrates, proteins, and fats. Pyruvate is the main metabolite of pyruvic acid and is a product of the glycolysis pathway. Pyruvate can be converted to lactate or to acetyl-CoA in the cytoplasm or mitochondria, respectively. Scientists are beginning to link disruption of pyruvate metabolism to processes in diseases such as cancer, diabetes, Alzheimer’s, and heart failure (Gray et al., 2014).

b. Safety pharmacology

No information/data available.

c. Acute toxicity

Very little is known about potential toxicities of pyruvic acid other than that it causes skin irritation and/or corrosion in humans (www.msds.com). It is also irritating to the eyes and can cause eye damage (www.msds.com). In 1961, it was observed that the LD50 in mice after subcutaneous exposure was 3533 mg/kg (Yakugaku, 1961). In 2000, it was found that pyruvic acid increases leptin secretion in rat adipocytes (Levy et al., 2000).

d. Repeat dose toxicity

Sprague-Dawley rats were nose-only exposed for six hours a day, five days a week to filtered air, saline, nicotine (50 µg/l), sodium pyruvate (33.9 µg/l), or equimolar nicotine/pyruvate mixtures (18, 25 and 50 µg/l). Saline and sodium pyruvate caused no adverse effects (Phillips et al., 2015).
e. Mutagenicity

No information/data available.

f. Developmental and reproductive toxicity

Hunter (1994) found that pyruvate is metabolized during organogenesis and thus improper regulation of pyruvate transport and metabolism can lead to neural tube defects and other developmental toxicities.

Herrick et al., (2007) found that 0.1mM pyruvate is essential to the proper development and metabolism of feline embryos in vitro.

g. Carcinogenicity

No information/data available.

h. Toxicokinetics

No information/data available.

Conclusions

The toxicity of pyruvic acid has not been fully evaluated in nonclinical studies, especially after topical administration.

Newer research suggests that disruption of pyruvate (primary metabolite of pyruvic acid) metabolism may be related to the development of human diseases such as cancer, heart failure, and neurological conditions, suggesting potential roles for therapeutic treatment with pyruvic acid. Topical pyruvic acid is typically compounded for use in facial peels where a certain degree of skin irritation is desired. However, very little is known about the toxicity of exogenous administration of pyruvic acid via any route of administration, as it is naturally occurring in cells of animals. No pharmacokinetic data were identified to assess the extent to which topical absorption occurs or systemic toxicity may be associated with topical application.

The primary known toxicity of pyruvic acid is irritation when applied to the skin or eyes. No adverse respiratory effects were noted in rats exposed to aerosolized pyruvic acid. The subcutaneous LD$_{50}$ in rats is 3533 mg/kg. As it is involved in metabolic processes, it is not surprising that pyruvic acid is important to fetal development; however, very few developmental toxicity studies have been conducted. In addition, there does not appear to be any nonclinical mutagenicity or carcinogenicity data available for pyruvic acid.
2. Human Safety

The following database(s) were consulted in the preparation of this review:

Databases searched include PubMed, Web of Science, EBSCOHost, EMBASE, the Cochrane Library, Pharmaprojects, the Merck Index Online, and Micromedex Solutions.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for pyruvic acid and retrieved zero cases.

FDA’s Center for Food Safety and Nutrition was also consulted to search their adverse event data base (CAERS) for adverse events associated with pyruvic acid and retrieved zero relevant cases.

a. Reported adverse reactions

Ardigo et al., (2010) reported “excessive irritation” and “mildly erythematous areas” following use of 50% pyruvic acid (formulation not otherwise described) in the treatment of melasma.

Berardesca et al., (2006) evaluated a 50% pyruvic acid peel in photodamage, superficial scarring, and melasma in a “non-erythematogenic” formulation (pyruvic acid 50%, dimethyl isosorbide, propylene glycol, ethyl alcohol, dimethyl sulfone, ethyl lactate, water). Subjects reported moderate stinging and burning sensations that faded within minutes after neutralization of the acid with a 10% sodium bicarbonate in water solution. Subjects also reported “mild erythema immediately after the peeling.” The authors did not specify which subjects (with which condition(s)) experienced these effects.

Cotellessa et al., (2004) treated 40 acne patients with a solution of “40-50%” pyruvic acid in an open-label study and observed “no side-effects” during or post-treatment. However, the authors report that pyruvic acid is generally associated with burning and erythema of rapid onset. The burning is readily relieved by sodium bicarbonate solution; erythema typically persists for hours.

In a general discussion of pyruvic acid, Gozali et al., (2015) stated that adverse reactions with pyruvic acid include “intense stinging and burning sensation, mandatory neutralization, and pungent and irritating vapors for the upper respiratory mucosa.”

Shahmoradi et al., (2015) compared pyruvic acid 70% and a salicylic acid formulation for treatment of plantar warts and collected information only on actively assessed adverse reactions: “pain, burning, scar, pigmentation and crust.” The incidence of these adverse reactions was similar between treatment groups.
Van Scott et al., (1989) reported their clinical experience with pyruvic acid “95 to 99 percent” in the treatment of common warts and stated that “discomfort” is a signal for the desired destructive treatment effect.

Zakopoulou et al., (2006) in their overview of superficial peels, described that pyruvic acid as a chemical peel has “a high risk of scarring,” that it is associated with “intense pain” (relieved by neutralization with a 10% sodium bicarbonate solution), erythema that lasts approximately 15 minutes, and pungent vapors that are “irritating to the upper respiratory tract when inhaled.”

b. Clinical trials assessing safety

We found no clinical trials that were specifically undertaken to assess safety. Safety assessments were among the study procedures in several clinical trials. See Section 2.a. above.

c. Pharmacokinetic data

No information/data available.

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

**Acne**

There are numerous approved therapies for acne vulgaris. Approved products are available for systemic and topical administration. Approved products are available by prescription and OTC marketing and in several dosage forms and formulations. Some products are approved for specific lesion types (e.g., inflammatory lesions). Product categories (and examples of each) include:

- **Antibiotics:**
  - Topical: clindamycin phosphate, erythromycin, sodium sulfacetamide
  - Systemic: minocycline
- **Bacteriostatics:** benzoyl peroxide
- **Retinoids:** adapalene, tretinoin, tazarotene, (note: isotretinoin is indicated for severe recalcitrant nodular acne, not acne vulgaris)
- **Combination products:** clindamycin/tretinoin, adapalene/benzoyl peroxide
- **Hormonal:** drospirenone/ethinyl estradiol (hormonal therapy is indicated only if the patient desires an oral contraceptive for birth control)
- **Other:** azelaic acid

**Melasma**

Fluocinolone acetonide (0.01%), hydroquinone (4.0%), and tretinoin (0.05%) Cream (Tri-Luma) is an FDA approved prescription product indicated for the short-term treatment of moderate-to-severe melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens.
FDA allows hydroquinone to be marketed in nonprescription products at concentrations between 1.5 and 2%.

Hydroquinone is a naturally occurring hydroxyphenolic compound that inhibits the activity of tyrosinase. Higher concentrations may be more likely to be associated with irritant contact dermatitis, hypopigmentation of surrounding skin, and more rarely, exogenous ochronosis. This is a rare condition resulting from the deposition of homogentisic acid in the dermis following a prolonged exposure to hydroquinone. Adverse effects of hydroquinone may also include erythema, stinging, and desquamation (Rossi et al., 2011; Goldstein et al., 2015).

**Warts**

Salicylic acid (at various concentrations according to the vehicle) is listed as an active ingredient in the final monograph (21CFR part 358 subpart B), Miscellaneous External Drug Products for Over-the-Counter Human Use: Wart Remover Drug Products.

Cutaneous warts are frequently treated via initial physical destruction with cryotherapy and paring or excision. There are no approved prescription therapies for warts outside of the genital area. There are some unapproved therapies used to treat warts, including cantharidin, silver nitrate, bleomycin, formaldehyde, and contact sensitizers.

For the treatment of genital warts, there are approved drugs (podofilox gel and solution, imiquimod cream, and polyphenon E ointment), but pyruvic acid is not a suitable treatment for such warts because of the risks for contact dermatitis and ulceration in these sensitive cutaneous and mucosal areas.

**Conclusions**

The available data suggest that topical use of pyruvic acid is associated with local irritancy (e.g., burning and erythema). Reported adverse reactions generally appeared to be readily manageable and temporary in duration. Information was most limited on what may potentially represent the most significant safety issue: irritancy to the upper respiratory tract from inhaled vapors. Patients and providers (and assisting staff) may be at risk for this adverse reaction in the absence of appropriate cautionary measures (e.g., adequate ventilation). However, there was no information suggesting serious outcomes from respiratory exposure to vapors, or that any authors had undue concerns regarding this risk. No information was available on long-term outcomes. However, some authors did report scarring as a risk, and scars are permanent (although scars are highly variable in their clinical manifestations). Although limited, the available information did not raise any major safety concerns associated with use of pyruvic acid.
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**

We found limited information meeting the above criteria for use of pyruvic acid for acne, melasma, or warts.

Tosson et al., (2006) evaluated pyruvic acid in 60 patients: papulopustular acne (30 patients), melasma (15 patients), and common warts (15 patients). Patients with acne and melasma were treated with 40-50% pyruvic acid chemical peel every 2 weeks for 1-3 months. Patients with warts were treated with 70% pyruvic acid chemical paint twice daily for 2-3 weeks. Reported results included:

- **Acne**: complete disappearance of acne lesions in 10 patients (33.3%) and disappearance of more than 75% of lesions in 6 (20%).
- **Melasma**: improvement of more than 50% in 3 patients (20%) and improvement of 25-50% in 5 (33.3%).
- **Warts**: total clearing of all warts in 12 patients (80%) and improvement (not defined) in 3 (20%).

**Acne**

Cotellessa et al., (2004) conducted an open-label study in which 40 patients affected by mild to moderate papulo-pustular acne were treated with 40–50% pyruvic acid every two weeks for three–four months. They reported the following outcomes: complete remission (clinical disappearance of cutaneous lesions) in 16 patients (40%); partial remission (improvement of cutaneous lesions, without complete disappearance) in 20 patients (50%); and no improvement in 4 patients (10%). Patients who showed evident erythema and/or white frost, desquamation, and clinical improvement with the first two applications continued to be treated with 40% pyruvic acid, whereas patients who did not show erythema and/or white frost, desquamation, and clinical improvement with 40% pyruvic acid were subsequently treated with 50% pyruvic acid. Outcomes were not presented according to how many patients received which concentration of pyruvic acid.

Marczyk et al., (2014) compared the effect of 50% pyruvic and 30% salicylic peels on facial sebum secretion in 20 patients with acne vulgaris (aged 13–30). Ten patients were treated with 50% pyruvic acid and the remaining 10 with 30% salicylic acid. Each peel was applied on the entire the face for five to seven minutes, preceded by skin degreasing with special tissues and protecting the region of eyes, nostrils, and the mouth with Vaseline. The acids were neutralized with “a neutralizing agent.” The peels were applied five times at two-week intervals. Both peels were reported to have significantly decreased the level of sebum secretion measured on the skin surface after the application of six treatments at two-week intervals. The authors did not evaluate any acne endpoints.
Melasma

Ardigo et al., (2010) conducted a pilot study in which they used reflectance confocal microscopy to evaluate pigment distribution in melasma in 15 patients and to perform a preliminary evaluation of the response to therapy in 7 of the 15 cases. Therapy consisted of six cycles of skin peeling with 50% pyruvic acid every day for two weeks, followed by topical application of a “Kligman’s formula containing 2% hydroquinone,” applied daily for a total of five months of treatment. Treatment outcomes were largely reported in histological terms and included complete disappearance of large keratinocytes in the upper epidermal layer in two patients, with other patients showing trace pigmentation by microscopy. However, treatment outcomes do not reflect use of pyruvic acid solely, since a Kligman’s formula was part of the treatment regimen.

Berardesca et al., (2006) evaluated a “non-erythematogenic” pyruvic acid formulation (pyruvic acid 50%, dimethyl isosorbide, propylene glycol, ethyl alcohol, dimethyl sulfone, ethyl lactate, water) in 20 patients affected by photodamage, superficial scarring, or melasma. The authors did not state how many patients were affected by each condition. The 50% pyruvic acid solution was applied for three to five minutes, then neutralized with a 10% sodium bicarbonate in water solution. Four peeling sessions were performed, once every two weeks. The treatment outcomes included “a significant reduction in the degree of pigmentation in patients with melasma.”

Warts

Halasz (1998) reviewed the charts of 56 patients who had common warts treated with plain 70% pyruvic acid (PA; 18 patients) or a combination formulation of 70% pyruvic acid with 0.5% 5-fluorouracil (PA-5FU; 38 patients). Approximately 75% of patients used the prescribed product for one to four weeks, and 25% used the product for one to two months. Patients were apparently also contacted for information; however, it is unclear from the publication which information was obtained from chart review and which was obtained from patient interviews. The results are presented in the following table (Table 3 from the Halasz publication):

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Cleared (%)</th>
<th>Improved (%)</th>
<th>No Change (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA-5FU</td>
<td>22 (58)</td>
<td>10 (26)</td>
<td>6 (16)</td>
<td>38</td>
</tr>
<tr>
<td>PA</td>
<td>14 (78)</td>
<td>0 (0)</td>
<td>4 (22)</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>36 (64)</td>
<td>10 (18)</td>
<td>10 (18)</td>
<td>56</td>
</tr>
</tbody>
</table>

Cleared=all warts resolved  
Improved=some, but not all, treated warts resolved or warts decreased appreciably in size.  
No change=minimal or no decrease in size.

Shahmoradi et al., (2015) conducted a randomized controlled trial in 60 patients with multiple (≥ 2) plantar warts. Patients were equally randomized to receive either pyruvic acid 70% (70% prepared by dissolving the pyruvic acid in a water/ethanol solution) or a salicylic acid solution (salicylic acid 16.7%, lactic acid 16.7%, and collodion 100%). Patients were instructed to apply the assigned treatment twice a day for four weeks.
Patients were visited every two weeks for one month after starting treatment and then monthly for another two months. Treatment outcomes were measured by the number and size of warts and recurrence. The number of warts was decreased after the treatment in both groups; the percent of change in wart numbers after treatment was not different between the treatment groups: $-13.12 \pm 25.6$ (pyruvic acid) vs. $-23.0 \pm 28.0\%$ (salicylic acid), $P = 0.159$). Wart size was decreased after treatment by $-43.47 \pm 57.0\%$ ($P = 0.017$) and by $-37.40 \pm 32.76\%$ ($P < 0.001$), for pyruvic acid and salicylic acid, respectively. The authors found no difference in efficacy between the products.

Van Scott et al., (1989) reported their experience using “95 to 99 percent” pyruvic acid in the treatment of verruca vulgaris (common warts). The discussion focuses on treatment procedures and does not address efficacy outcomes.

One study was found at ClinicalTrials.gov (status: “recruiting”): Isfahan University of Medical Sciences:

The investigators will compare the efficacy of pyruvic acid and salicylic acid in treating multiple plantar warts. Patients with multiple plantar warts will be randomized to receive either pyruvic acid 70% or compound salicylic acid solution (salicylic acid 16.7%, lactic acid 16.7%, and collodion 100%) applying topically twice a day for 4 weeks. Patients will be visited every two weeks for one month after starting treatment and then every one month for up to three months. The number and size of warts will be evaluated.

This appears to be the trial published by Shahmoradi et al., (2015) discussed above.

2. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Pyruvic acid has been nominated for treatment of acne, melasma, and warts. These are not serious or life-threatening diseases or conditions.

3. Whether there are any alternative approved therapies that may be as effective or more effective.

See discussion of available therapies in Section 2.d.

**Conclusions**

There are no adequate and well-controlled trials evaluating pyruvic acid in the treatment of acne, melasma, or warts. The available information suggests that pyruvic acid may have some efficacy in the treatment of these conditions. However, the limited data are largely from small, open-label trials, allowing only for tentative conclusions regarding efficacy. The available data do not suggest an obvious advantage of pyruvic acid over available approved or monographed treatments for acne, melasma or warts.
D. Has the substance been used historically as a drug in compounding?

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

Fischer et al., (2010) reported that dermatologist Ferdinand von Hebra used unspecified chemical peel(s) to treat melasma in 1874. Pyruvic acid has been used in pharmacy compounding for at least approximately 30 years.

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

Dermatologic conditions that pyruvic acid has been used to treat include acne, melasma, warts, seborrheic keratosis, actinic keratosis, and photoaging.

3. How widespread its use has been

The precise extent of use cannot be determined from the available information. However, in addition to the United States, use has been reported in Italy, Poland, Greece, Iran, and Egypt.

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

Pyruvic acid is listed in the European Pharmacopeia. It was not found in the pharmacopeias of the United Kingdom, Germany, India, China, or Japan.

Conclusions

Pyruvic acid has been used for the treatment of a number of dermatologic indications. The substance has been used in pharmacy compounding for some decades. The extent of use could not be precisely determined, but appears to be worldwide.

III. RECOMMENDATION

We have evaluated pyruvic acid for topical use as a candidate for the list of bulk drug substances under section 503A of the Act and recommend that it be included on the list of bulk drug substances allowed for use in compounding based on the following:

1) Pyruvic acid is well characterized in its physical and chemical properties. Although the substance is unlikely to be stable in ambient environment, it can be stored when carefully sealed, isolated from moisture, and kept away from light.

2) The safety profile of pyruvic acid shows that reported adverse reactions generally appeared to be local, non-serious, readily manageable and temporary in duration. Information was most limited on what may potentially represent the most significant safety issue: irritancy to the upper respiratory tract from inhaled vapors. However, there was no information suggesting serious outcomes from respiratory exposure to vapors, or that any authors had undue concerns regarding this risk. No information
was available on long-term outcomes. However, some authors did report scarring as a risk, and scars are permanent (although scars are highly variable in their clinical manifestations). Although limited, the available information did not raise any major safety concerns associated with use of pyruvic acid.

(3) There are no adequate and well-controlled trials evaluating pyruvic acid in the treatment of acne, melasma, or warts. The available information suggests that pyruvic acid may have some efficacy in the treatment of these conditions. However, the limited data are largely from small, open-label trials, allowing only for tentative conclusions regarding efficacy. Available data do not suggest an obvious advantage of pyruvic acid over available approved or monographed treatments for melasma, acne, or genital warts. There are no approved prescription therapies for warts outside of the genital area.

(4) Pyruvic acid has been used in pharmacy compounding to treat various indications, such as acne, melasma, and warts, for some decades. The extent of use could not be precisely determined, but appears to be worldwide.

Based on a balancing of the four evaluation criteria, we recommend that pyruvic acid for topical use be added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act.
BIBLIOGRAPHY


Tab 5

Tea Tree Oil
Tab 5a

Tea Tree Oil

Nominations
Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation’s retail prescription drugs, and, according to a NCPA member survey, almost 86% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet of 2,403 bulk drug substances submitted by the International Academy of Compounding Pharmacists (IACP) as our formal submission of bulk drug substances that are currently used by compounding pharmacies and do not have a specific USP monograph nor are components of FDA approved prescription drug products.

In addition to the IACP spreadsheet of bulk drug substances referenced above, NCPA would also like to formally submit collectively for review and consideration of the FDA Pharmacy Compounding Advisory Committee the drugs and standards contained within the British Pharmacopeia, the European Pharmacopeia and the Japanese Pharmacopeia. NCPA respectfully requests that all drugs and standards contained within these three pharmacopeias for which no USP corresponding monograph exists be accepted and approved to be used for the preparation of compounded medications under section 503A of the Federal Food, Drug and Cosmetic Act.
NCPA is requesting the recognition of these pharmacopoeias as there are examples of situations when our members need access to these alternative compendia for monograph information. NCPA members may receive requests to compound medications that do not have a USP monograph, nor is the drug substance being used a component of an FDA approved drug product. When these situations arise, the British Pharmacopeia, the European Pharmacopeia and the Japanese Pharmacopeia are used in practice to ensure compounds are made with the highest assurance of quality.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

Steve Pfister
Senior Vice President, Government Affairs

Attachment
<table>
<thead>
<tr>
<th><strong>Ingredient Name</strong></th>
<th>Tea tree oil (Melaleuca alternifolia leaf oil)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical Name</strong></td>
<td>oleum melaleucae; melaleuca alternifolia Leaf Oil</td>
</tr>
<tr>
<td><strong>Common Name</strong></td>
<td>Tea tree oil</td>
</tr>
<tr>
<td><strong>UNII Code</strong></td>
<td>VIF565UC2G</td>
</tr>
<tr>
<td><strong>Description of strength, quality, stability and purity</strong></td>
<td>From PCCA Database MSDS: Product is 100% by weight and stable; should be protected from strong oxidizing agents.</td>
</tr>
<tr>
<td><strong>Ingredient Format(s)</strong></td>
<td>Oil</td>
</tr>
<tr>
<td><strong>Recognition in Pharmacopeias</strong></td>
<td>Not USP unless by another name</td>
</tr>
<tr>
<td><strong>Final Compounded Formulation Dosage Form(s)</strong></td>
<td>Cream, Gel, Solution, Shampoo, Wash, Mouthwash</td>
</tr>
<tr>
<td><strong>Final Compounded Formulation Strength</strong></td>
<td>5-10% tea tree oil in cream, gel, or shampoo</td>
</tr>
<tr>
<td><strong>Final Compounded Formulation Route(s) of Administration</strong></td>
<td>Topical, Oral rinse only (DO Not SWALLOW)</td>
</tr>
<tr>
<td><strong>Final Compounded Formulation Clinical Rationale and History of Past Use</strong></td>
<td>Used in nail fungus treatments combined with other antifungals. Tea tree oil can kill bacteria and fungi. Used as complementary therapy in surgery, burn care, and dental care.</td>
</tr>
</tbody>
</table>
September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA’s request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.
Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

**ISSUE: The Issuance of This Proposed Rule is Premature**

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created an series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency’s activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee prior to the implementation and issuance of regulations including the creation of the bulk ingredient list.

(2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee’s review of any submitted drug, regardless of FDA’s statement in the published revised call for nominations that:

General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

David G. Miller, R.Ph.
Executive Vice President & CEO
**General Background on Bulk Drug Substance**

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Tea Tree Oil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical/Common Name</strong></td>
<td>Melaleuca Oil; Oleum Melaleucae; Melaleuca Alternifolia (Tea Tree) Leaf Oil</td>
</tr>
<tr>
<td>Identifying Codes</td>
<td>68647-73-4</td>
</tr>
<tr>
<td><strong>Chemical Grade</strong></td>
<td>Provided by FDA Registered Supplier/COA</td>
</tr>
<tr>
<td><strong>Description of Strength, Quality, Stability, and Purity</strong></td>
<td>Provided by FDA Registered Supplier/COA</td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
<td>Varies based upon compounding requirement</td>
</tr>
<tr>
<td><strong>Recognition in Formularies</strong></td>
<td>Not Listed in USP/NF for this specific salt/form</td>
</tr>
</tbody>
</table>

**(including foreign recognition)**

**Information on Compounded Bulk Drug Preparation**

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Varies based upon compounding requirement/prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>Varies based upon compounding requirement/prescription</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Varies based upon compounding requirement/prescription</td>
</tr>
</tbody>
</table>

**Bibliography** *(where available)*

Past and Proposed Use

The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA’s request for this information is an insurmountable hurdle that has not been requested by the PCAC.
Tab 5b

Tea Tree Oil

FDA Review
DATE: May 31, 2016

FROM: Jing Li, Ph.D.
Chemist, Botanical Review Team, Office of Pharmaceutical Quality

Jinhui Dou, Ph.D.
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Barbara Hill, Ph.D.
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Edward D. Bashaw, Ph.D.
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Kendall A. Marcus, M.D.
Director, Division of Dermatology and Dental Products, Office of Drug Evaluation III

Julie Beitz, M.D.
Director, Office of Drug Evaluation III

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Tea tree oil (Melaleuca alternifolia leaf oil) for Inclusion on the 503A Bulk Drug Substances List
I. INTRODUCTION

Tea tree oil (Melaleuca alternifolia leaf oil, TTO), 100% by weight (i.e., pure or neat TTO without adding diluents or other components), has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Food, Drug, and Cosmetic Act (FD&C Act) for the topical treatment of nail fungus (onychomycosis). The nominators referenced TTO with two identification/registration numbers/codes, Unique Ingredient Identifier (UNII): VIF565UC2G and Registration Number (RN): 68647-73-4, without providing detailed quality information (such as a certificate of analysis). Because the chemical components of botanicals can vary depending on factors such as growing conditions, extraction methods, etc., this review considers TTO that meets International Organization for Standards (ISO), 4730 (2004) and Standards Association of Australia (AS) 2882-2009, which are industry self-imposed quality standards. Australian TTO (ISO 4730) was the study material referenced in the supporting document submitted with the nomination. The ISO/AS standards are referenced in many of the references cited in this review. However, we have found no information to confirm whether the ISO/AS standards are enforced as regulatory standards in Australia, where the majority of the TTO is produced.

TTO is currently marketed for use topically and as oral rinses. It is available as a component of some cosmetics and antiseptics.

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 do not recommend that TTO be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

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

TTO is not registered in the Analytical Profiles of Drug Substances database. PubMed, SciFinder, and Natural Medicines were searched for tea tree oil and Melaleuca alternifolia.

TTO, produced by steam distillation of the leaves and terminal branches of a native Australian tree, Melaleuca alternifolia (Maiden et Betch) Cheel [Fam. Myrtaceae], chemically contains mono- and sesquiterpenoid small molecules, among which over 90% are well characterized. International standards (e.g., ISO 4730, 1996 and 2004) have been established for the quality control of TTO. Additional background information is available.

1 The Registration Number is listed in ChemIDplus A TOXNET DATABASE (accessed at http://chem.sis.nlm.nih.gov/chemidplus/rn/68647-73-4 on June 1, 2016)
provided below to discuss the physical and chemical properties of TTO and botanical raw material used for producing TTO.

1. Characterization and Quantitative Analysis of TTO Active Pharmaceutical Ingredient (API)

TTO consists of numerous fully characterized monoterpenes, sesquiterpenes, and their associated oxygenated analogues, which account for approximately 90% of the contents in TTO, based on the testing results from over 800 TTO samples (Altman et al., 1988; Brophy et al., 1989; Guenther 1968; and Swords et al., 1978). Among them, terpinen-4-ol (29–45%), γ-terpinene (10–28%), α-terpinene (2.7–13.0%), and 1,8-cineole (4.5–16.5%) are the major components. Their structures are presented in Figure 1.

![Image of terpinen-4-ol, α-terpinene, γ-terpinene, and 1,8-cineole structures]

**Figure 1.** The structures of major components in TTO

Based on the chemical structures of the mono- and sesquiterpenoids, the characterization of these small molecules in TTO samples is simple and can be done by currently available techniques such as gas chromatography (GC) and GC-mass spectrometry (GC-MS) (Brophy et al., 1989). Other techniques can also be applied, such as nuclear magnetic resonance, infrared spectroscopy, ultraviolet, and elemental analysis, when necessary.

1.1 Unified International Quality Standards

Two almost identical TTO quality standards have been adopted by the Standards Association of Australia (Essential oils – oil of Melaleuca, terpinene-4-ol type, AS 2782-2985 (1997)) and the ISO (Oil of Melaleuca, terpinene-4-ol type tea tree oil [ISO 4730:1996 (E)]). The TTO standards were revised in 2009 [AS 2882-2009] and in 2004 [ISO 4730 (2004)] by their respective organizations. Table 1 lists the ISO standard and typical composition of TTO samples with 14 terpenoids accounting for over 93% of neat TTO.
Table 1. Composition of *M. alternifolia* (tea tree) Oil*

<table>
<thead>
<tr>
<th>Component</th>
<th>Type of compound</th>
<th>Chemical formula</th>
<th>ISO 4730 standard</th>
<th>Typical composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terpinen-4-ol</td>
<td>Monocyclic terpene alcohol</td>
<td>C₁₀H₁₈O</td>
<td>≥30(^a)</td>
<td>40.1</td>
</tr>
<tr>
<td>γ-Terpinene</td>
<td>Monocyclic terpene</td>
<td>C₁₀H₁₆</td>
<td>10-28</td>
<td>23.0</td>
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<tr>
<td>α-Terpinene</td>
<td>Monocyclic terpene</td>
<td>C₁₀H₁₆</td>
<td>5-13</td>
<td>10.4</td>
</tr>
<tr>
<td>1,8-Cineole</td>
<td>Monocyclic terpene alcohol</td>
<td>C₁₀H₁₈O</td>
<td>≤15(^d)</td>
<td>5.1</td>
</tr>
<tr>
<td>Terpinolene</td>
<td>Monocyclic terpene</td>
<td>C₁₀H₁₆</td>
<td>1.5-5</td>
<td>3.1</td>
</tr>
<tr>
<td>ρ-Cymene</td>
<td>Monocyclic terpene</td>
<td>C₁₀H₁₄</td>
<td>0.5-12</td>
<td>2.9</td>
</tr>
<tr>
<td>α-Pinene</td>
<td>Dicyclic terpene</td>
<td>C₁₀H₁₆</td>
<td>1-6</td>
<td>2.6</td>
</tr>
<tr>
<td>α-Terpineol</td>
<td>Monocyclic terpene alcohol</td>
<td>C₁₀H₁₈O</td>
<td>1.5-8</td>
<td>2.4</td>
</tr>
<tr>
<td>Aromadendrene</td>
<td>Sesquiterpene</td>
<td>C₁₅H₂₄</td>
<td>Trace-7</td>
<td>1.5</td>
</tr>
<tr>
<td>δ-Cadinene</td>
<td>Sesquiterpene</td>
<td>C₁₅H₂₄</td>
<td>Trace-8</td>
<td>1.3</td>
</tr>
<tr>
<td>Limonene</td>
<td>Monocyclic terpene</td>
<td>C₁₀H₁₆</td>
<td>0.5-4</td>
<td>1.0</td>
</tr>
<tr>
<td>Sabinene</td>
<td>Dicyclic monoterpene</td>
<td>C₁₀H₁₆</td>
<td>Trace-3.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Globulol</td>
<td>Sesquiterpene alcohol</td>
<td>C₁₅H₂₆O</td>
<td>Trace-3</td>
<td>0.2</td>
</tr>
<tr>
<td>Viridiflorol</td>
<td>Sesquiterpene alcohol</td>
<td>C₁₅H₂₆O</td>
<td>Trace-1.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

\(^a\) ISO 4730 (2004).
\(^b\) From reference Brophy et al., 1989.
\(^c\) No upper limit is set, although 48% has been proposed.
\(^d\) No lower limit is set.

1.2 More Advanced Analytical Techniques and Future Trends

New analytical techniques were applied to confirm the identity and quality of TTO. New ISO and Australian quality standards for TTO are being considered to include the enantiomeric fraction (EF) value for at least terpinen-4-ol (Larkman et al., 2015). More sophisticated analyses and application of new standards with EF
of certain chiral compounds may be necessary for TTO combination products containing other botanical/non-botanical ingredients.

New chiral enantioselective analytical methods, such as enantioselective GC (eGC), heart-cutting multidimensional GC (MDGC), and comprehensive two-dimensional GC (GC × GC), have also been applied to analyze the composition of TTO (Kreck et al., 2002; Leach et al., 1993; Sciarrone et al., 2010; and Shellie et al., 2001, 2004). Previously, at least four terpenes in various TTO samples were reported with predominate (+)-enantiomers, viz., α-pinene (60–90%), terpinen-4-ol (65–70%), α-terpineol (70–78%), and limonene (58–62%) (Kreck et al., 2002; Leach et al., 1993; Sciarrone et al., 2010; and Shellie et al., 2001, 2004). Comprehensive analyses of the enantiomeric purity of representative compounds and chemometric profiling of TTO were recently published (Wang et al., 2015; and Wong et al., 2015 a and b).

The EFs of representative monoterpenoids, terpinen-4-ol, α-terpineol and limonene, in 57 pure TTO samples sourced from different Australian plantations were studied using advanced methods, such as eGC-MS or eGC coupled with flame ionization detection (FID) and GC-eGC-MS (Wong et al., 2015 a and b). The relatively constant EFs of limonene, terpinen-4-ol and α-terpineol (61.6 ± 1.5%, 61.7 ± 1.6% and 79.6 ± 1.4%, respectively) with the (+)-antipodes being the predominant enantiomers in all 57 TTO samples, were considered as the chiral signature of pure Australian TTO (Wong et al., 2015 a and b). The EFs of the major terpenoids can be used as reliable benchmarks or standard reference (SR) values for quality control of commercial TTO products.

Lately, strong global demand for TTO has increased the incidence of adulteration in TTO with lower-cost ingredients (Larkman et al., 2014). Chiral analysis of selected isomeric compounds mentioned above (e.g., GC-eGC-MS) combined with chemometrics is available to define the botanical origin or detect possible adulteration in TTO products (Wang et al., 2015; and Wong et al., 2015 a and b).

2. Reasonable Raw Material Control

The identification of the botanical source of TTO, *M. alternifolia*, is straightforward. *M. alternifolia* is an indigenous species to Australia, from Queensland to northeastern New South Wales (Cribb et al., 1981; and Penfold et al., 1950). Commercial farming of *M. alternifolia* was established on large plantations in the same area according to the standardized agricultural and collection practices (e.g., land preparation, seed selection, propagation, pest control) supported by the Australian Tea Tree Industry Association (ATTIA) and the Rural Industries Research and Development Corporation of Australia. Currently, these production facilities not only grow tea trees, but also steam-distill the leaves on site to manufacture TTO product, which will meet the ISO/AS standards.

3. Review on Characteristics of TTO API
3.1. Stability of the API and Likely Dosage Forms

Based on available data, ATTIA recommended that a use-by (best before) date for pure Australian TTO sold in dark glass bottles be set at six months from when first opened or two years in unopened bottles (ATTIA, 2012). The certificate of analysis of TTO from Sigma-Aldrich\(^2\) states that the shelf life of the bulk TTO (No. W390208, 1 kg or 5 kg in glass or stainless steel containers) is five years.

A recent study indicated that prolonged storage (e.g., \(\geq 6\) years) under specific conditions does not significantly affect the chiral compositions of the tested monoterpene (e.g., limonene, terpinen-4-ol and \(\alpha\)-terpineol) (Wong et al., 2015 a). TTO has been used in liquid or cream formulations at a broad range of concentrations, from 1\% to 100\%, as a topical antiseptic and disinfectant and for symptomatic treatment of common skin disorders and wounds. There are no data on the stability of TTO terpenoids in these formulated products, which often contain many other botanical or chemical ingredients. Other botanical oils (e.g., sweet almond oil) and organic solvents (e.g., ethanol) have been used as diluents for TTO.

The likely intended dosage forms are liquids (e.g., TTO 100\%, TTO diluted in other plant seed oils, such as sweet almond oil, or organic solvent, such as ethanol at \(\geq 1\%) and creams (e.g., 5-25\% TTO). The nomination has proposed final compounded dosage forms to be cream, gel, solution, shampoo, body wash, and mouthwash.

3.2. Probable Routes of API Synthesis

TTO is produced by steam distillation of the leaves and terminal branches of a native Australian tree, *M. alternifolia*. Generally speaking, the natural variance of TTO should be minor because it is extracted exclusively from a native Australian tree cultivated in the states of New South Wales and Queensland with standardized cultivation practices in place. Meanwhile, the extraction procedure is quite simple and can be easily repeated. Meanwhile, the relatively mild and stable extraction conditions (e.g., temperature) will not introduce much composition change in TTO (Carson et al., 2006).

3.3. Likely Impurities

For botanical products, *impurities* are typically defined as contaminants, e.g., heavy metals and pesticides. Likely impurities in TTO products include

\(^2\)Sigma-Aldrich manufactures chemicals for use in scientific research, biotechnology, and pharmaceutical development. According to its website, a Sigma-Aldrich specification is “a list of test methods, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use.” See http://www.sigmaaldrich.com/united-kingdom-technical-services/specifications.html.
• heavy metal impurities (such as lead, arsenic, mercury) linked to the source of the starting material used in the process; and
• bioburden (such as microbial content, yeast, or mold).

TTO should not be confused with essential oils obtained from other *Melaleuca* species, such as cajeput oil (from *M. leucodendra* L.), niaouli oil (from *M. viridiflora* Solander ex Gaertner). These two species are produced on a small scale in Australia. The TTO monograph published by EMA accepts the essential oils from multiple *Melaleuca* species as TTO (EMA, 2013). However, the essential oil samples from these species contain higher concentrations of 1,8-cineole, probably a skin irritant, that may decrease the antiseptic activity of the purported major active ingredient (terpinen-4-ol) of TTO. In recent years, cases of TTO adulterated with other oils and/or synthetic terpenoids have been reported (Larkman et al., 2014). For pure TTO samples, the available ISO/AS standards are adequate.

### 3.4. Toxicity of Likely Impurities

Considering that TTO is extracted by steam distillation from the fresh leaves and terminal branches of the *Melaleuca* tree and has antibacterial activities, the levels of bioburden, pesticides, and heavy metals are expected to be low, and any toxicity from those impurities is not considered a significant safety concern for topical applications at relatively low doses.

### 3.5. Physicochemical Characteristics Pertinent to Product Performance, such as Particle Size and Polymorphism

No additional information available for further discussion.

### 3.6. Any Other Information about the Substance that may be Relevant, such as whether the API is Poorly Characterized or Difficult to Characterize

The primary components in TTO are mono- and sesquiterpenoids with 14 major compounds fully characterized and quantified by GC-MS or GC-FID, accounting for over 90% of the contents in a typical TTO sample.

### Conclusions

TTO that meets ISO 4730 is a well-characterized natural product derived from the fresh leaves and terminal branches of a single plant species, *M. alternifolia*, mainly growing in Australia. TTO is produced by a relatively simple extraction process: steam distillation. The primary components in TTO are mono- and sesquiterpenoids with 14 major compounds fully characterized and quantified to account for over 90% of the contents in a typical TTO sample. In addition, almost identical ISO/AS standards are available to control the natural variations of the individual compounds in TTO with specified maxima and/or minima ranges. Overall, characterization and identification of the terpenoid small molecules in TTO using available analytical methods (e.g., GC-FID, GC-MS) are straight
forward. On the other hand, neither complete characterization nor quantitative analysis of all the minor chemical components in TTO is feasible.

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

1. Nonclinical Assessment

The following information is summarized from the references listed below, which are the results of searches on Google, EBSCOHost, EmBase, PubMed, Web of Science, and TOXNET that links to multiple databases such as ChEBI, DrugPortal, EMIC, EPA ACToR, MeSH, NIST, PubChem, TOXLINE, and PubMed including PubMed AIDS, PubMed Cancer and PubMed Toxicology.

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

TTO is a complex mixture of over 100 components, mostly made of terpene hydrocarbons: monoterpenes, sesquiterpenes, and their alcohols.

The antifungal properties of TTO are well documented. A wide range of yeasts, dermatophytes, and other filamentous fungi were susceptible to varying concentrations of TTO in a number of in vitro and in vivo studies. Reported minimum inhibitory concentrations (MICs) range from 0.12% to 2%, but some species (e.g., *Aspergillus niger*) require higher concentrations of up to 8%. It has been suggested that different phases of fungal growth are affected differently by TTO (Bagg et al., 2006; Carson et al., 2006; Crawford et al., 2004; Hammer et al., 2000; Pisseri et al., 2009; and Van Kessel et al., 2003).

One study has identified that most components of TTO have antifungal activity against a range of fungi (Hammer et al., 2003). Components showing the most activity, with MICs and minimum fungicidal concentrations (MFC) of ≤0.25%, were terpinen-4-ol, α-terpineol, linalool (a terpene alcohol), α-pinene and β-pinene, followed by 1,8-cineole. The remaining components showed slightly less activity and had values ranging from 0.5 to 2%, with the exception of β-myrcene, which showed no detectable activity (Hammer et al., 2003). Terpinen-4-ol was found to be more active than TTO and strongly enhanced fluconazole activity against fluconazole-resistant *C. albicans* strains. Both TTO and terpinene-4-ol have a low MIC, ranging from 0.06% to 0.5% for all tested fluconazole-resistant *C. albicans* strains (Mertas et al., 2015).

Data from two studies support the hypothesis that TTO and its components exert their antifungal actions by altering membrane properties and compromising membrane-associated functions (Hammer et al., 2004; and Shao et al., 2013). The results from a recent study confirmed that terpinen-4-ol and 1,8-cineole act mainly on the cell membranes and organelles of *B. cinerea*, respectively, and act similarly to TTO when combined in antifungal activity (Yu et al., 2015). A recent
study also showed that TTO induced a broad spectrum of changes in yeast enzymatic profiles, which, together with loss of ability to assimilate saccharides, could significantly affect \textit{C. albicans} pathogenicity (Rajkowaka et al., 2014).

The antifungal efficacy of nanocapsules and nanoemulsions containing TTO was evaluated in an onychomycosis model. Nail infection models demonstrated the ability of the formulations to reduce \textit{T. rubrum} growth, with the inclusion of oil in nanocapsules being most efficient (Flores et al., 2013).

b. Safety pharmacology

No information available.

c. Acute toxicity

The oral LD$_{50}$ for TTO in the rat is 1.9 - 2.6 ml/kg (equivalent to 1.7 – 2.3 g/kg) (Bolt, 1989; Jenner et al., 1964; and Russell, 1999). Rats dosed with amounts of \leq 1.5 g/kg TTO appeared lethargic and ataxic and showed depressed activity levels 72 h post dosing (Kim et al., 2002).

Dermal application of TTO at 5 g/kg resulted in the death of two out of ten treated rabbits (Fragrance Raw Materials Monograph, 1988). A single, 24-hour dermal application of TTO at 2 g/kg resulted in no overt signs of toxicity in rabbits except for slight diarrhea (Bolt 1989).

Toxicity following dermal application of very high doses of TTO to cats or dogs treated for fleas has been described (Villar et al., 1994). Animals had typical signs of depression, weakness, lack of coordination, and muscle tremors (Villar et al., 1994). For the treatment of fleas, three cats each had 120 ml of 100% pure TTO applied to their shaved but intact skin (Bischoff et al., 1998). All three cats experienced severe symptoms (hypothermia, lack of coordination, dehydration, trembling), and one died after three days. The other two cats recovered within 24 and 48 h, respectively. The authors noted that the cat that died had elevated blood urea and persistent dehydration, which suggests that the animal may have had pre-existing renal damage unrelated to the TTO poisoning (Bischoff et al., 1998).

The ototoxicity of TTO was examined in guinea pigs by measuring the thresholds of the compound auditory nerve action potential (CAP) to tone bursts before and after instillation of the oil into the middle ear (Zhang et al., 2000). After 30 min of instillation, 100% pure TTO caused a partial CAP threshold elevation at 20 kHz. A lower concentration of oil (2% TTO in saline with 0.5% Tween 80 detergent) did not cause any significant lasting threshold change. Although this suggests that concentrations of 2% TTO or less may be safe for use within the ear, a high concentration of TTO applied to the round window for a relatively short time was to some extent ototoxic to the high-frequency region of the cochlea (Zhang et al., 2000).
d. Repeat dose toxicity

No repeat dose toxicity studies have been conducted with TTO.

A skin irritation test in rabbits was conducted with 25% TTO in paraffin oil and the solution was repeatedly applied over 30 days to the shaved rabbit skin. Minor initial irritation at the treatment site declined with repeat dose topical administration. However, some microscopic skin changes at the treatment site were noted at the end of the treatment period. In the patch test under semioinclusive conditions, 12.5% and 25% TTO were not irritating while 50% TTO was minimally irritating and 75% TTO was slightly irritating in rabbits. Undiluted TTO in the patch test triggered severe irritation within 24 hours after application in rabbits (Bolt 1989; and Beckmann et al., 1998).

e. Mutagenicity

TTO and its components, including terpinene-4-ol, α-terpinene, 1,8-cineole, α-terpineol, cymene, limonene, α-pinene, β-pinene, linalool, and β-myrcene, are non-mutagenic in the Ames test or the Bacillus subtilis rec-assay (Connor et al., 1985; Evantri et al., 2005; Fletcher et al., 1980; Gomes-Carneiro et al., 1980; Gomes-Carneiro et al., 2005; Ishidate et al., 1984; Oda et al., 1978; Rockwell et al., 1979; Watabe et al., 1981; and Yoo 1985). Terpineol caused a slight but dose-related increase in the number of revertants with the TA102 tester strain in the Ames test both with and without S9 mixture (+/- metabolism), indicating that terpineol induced a base-pair substitution affecting an A–T base pair (Gomes-Carneiro et al., 1998).

However, since TTO has antibacterial properties, the Ames test may not be appropriate for TTO, and therefore the value of the test is limited.

TTO is not genotoxic in the in vitro human lymphocyte micronucleus and the chromosome aberration tests (Pereira et al., 2014). The components of TTO, including cineole, D-(+)-limonene, linalool, 1-phellandrene, β-pinene, and β-myrcene, are not genotoxic in the in vitro genotoxicity tests conducted with mammalian cells (Aydin et al., 2005; Kauderer et al., 1991; and Sasaki et al., 1989). β-Myrcene was not genotoxic in bone marrow cells of rats after oral administration (Zamith et al., 1993).

Overall, the available data on the mutagenicity of TTO and its individual constituents indicate low mutagenic potential.

f. Developmental and reproductive toxicity

Reproductive and developmental toxicity studies have not been conducted with TTO. However, three reproductive and developmental toxicity studies have been conducted with the components of TTO administered orally.
An oral embryofetal and developmental toxicity study was conducted in female Wistar rats with α-terpinene at the dose levels of 30, 60, 125 and 250 mg/kg/day administered during organogenesis. The α-terpinene component is present at approximately 9% in TTO (Araujo et al., 1996). A reduction in body weight minus uterine weight at term indicated that the two highest doses tested (125 and 250 mg/kg) were maternally toxic. A reduced ratio of pregnant/treated females, a decrease in fetal body weight, and an increase in fetal kidney weights were noted at 250 mg/kg. Delayed ossification and skeletal malformations were observed in the offspring of dams given α-terpinene at 60 mg/kg or higher dose levels. No effects were noted on either dams or offspring at 30 mg/kg. The no-observed-adverse-effect level (NOAEL) for embryofetal toxicity in rats was 30 mg/kg for oral exposure to α-terpinene (Araujo et al., 1996).

In another oral embryofetal toxicity study, β-myrcene, present at approximately 0.5% in TTO, was administered to female Wistar rats at the dose levels of 0.25, 0.5 and 1.2 g/kg/day during organogenesis (Delgado et al., 1993). Decreased weight gain and one death of 29 treated dams indicated that the high dose (1.2 g/kg) is maternally toxic. A higher incidence of signs of retardation and of anomalies in the fetal skeleton indicated that β-myrcene was also toxic to the rat embryo at 1.2 g/kg. No adverse effects were observed with the low and mid doses.

A study on fertility and general reproductive performance was also conducted in Wistar rats with β-myrcene (Paumgartten et al., 1998). β-Myrcene (0, 100, 300 and 500 mg/kg/day) in peanut oil was given by oral gavage to male Wistar rats for 91 days before mating and during the mating period, as well as to females continuously for 21 days before mating, during mating and pregnancy, and throughout the period of lactation up to postnatal day 21. The NOAEL for toxic effects of β-myrcene on fertility and general reproductive performance was 300 mg/kg/day by the oral route based on the data from the study. No sign of maternal toxicity and no increase in externally visible malformations were observed at any dose level. β-Myrcene-related increases in the resorption rate and higher frequency of fetal skeleton anomalies were noted only in the high dose group.

The limited data from these studies conducted with the components of TTO suggest that TTO may pose embryofetal toxicity when ingested orally at relatively high doses.

g. Carcinogenicity

Carcinogenicity studies have not been conducted with TTO. However, three carcinogenicity studies have been conducted with individual components of TTO administered intraperitoneally or orally.

α-Terpineol, present at approximately 1.5 - 8% in TTO, was examined for its potential to induce lung tumors in male and female A/He mice. Animals received
intraperitoneal injections of α-terpineol in tricaprylin three times a week for 8 weeks. Dose levels were set at the maximum tolerated dose (MTD) of 0.4 g/kg and a one-fifth of the MTD (~0.08 g/kg). Therefore, the total cumulative doses for three weeks were 9.6 and 1.9 g/kg. Based on the results from this study, α-terpineol was not considered carcinogenic since no significant difference in lung tumors was observed between the treated and control groups (Stoner et al., 1973).

In a rat carcinogenicity study, β-myrcene was orally administered to male and female F344/N rats once daily, 5 days per week, for 105 weeks at dose levels of 0, 0.25, 0.5, or 1 g/kg/day. Neoplastic and non-neoplastic lesion incidences were not presented for the 1 g/kg-dosed male rats due to high mortality. The authors concluded that under the conditions of this two-year gavage study, there was clear evidence of carcinogenic activity of β-myrcene in male F344/N rats based on increased incidences of renal tubule neoplasms. There was equivocal evidence of carcinogenic activity of β-myrcene in female F344/N rats based on marginally increased incidences of renal tubule adenoma (Natl Toxicol Program Tech Rep Ser, 2010).

In a mouse carcinogenicity study, β-myrcene was orally administered to male and female B6C3F1 mice once daily, five days per week, for 104 or 105 weeks at dose levels of 0, 0.25, 0.5, or 1 g/kg/day. Neoplastic and non-neoplastic lesion incidences were not presented for 1 g/kg-dosed male or female mice due to high mortality. The authors concluded that under the conditions of this two-year gavage study, there was clear evidence of carcinogenic activity of β-myrcene in male B6C3F1 mice based on increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma. There was equivocal evidence of carcinogenic activity of β-myrcene in female B6C3F1 mice based on marginally increased incidences of hepatocellular adenoma and carcinoma (Natl Toxicol Program Tech Rep Ser, 2010).

Oral administration of β-myrcene also induced non-neoplastic lesions in the kidney of male and female rats, the nose of male rats, and the liver of male and female mice (Natl Toxicol Program Tech Rep Ser 2010).

h. Toxicokinetics

No information available.

Conclusions

Available nonclinical acute toxicity data suggest that TTO can be toxic when ingested or topically administered at a high concentration. However, no repeat dose toxicity studies have been conducted with TTO. The overall available data on the mutagenicity of TTO and its individual components indicate low mutagenic potential. Carcinogenicity, reproductive, and developmental toxicity studies have not been conducted with TTO. However, limited data from studies of components of TTO administered orally suggest
that they may pose potential embryofetal toxicity and, when administered intraperitoneally or orally, they may pose carcinogenic risks at relatively high doses.

The toxicities of TTO are responses to exposure to a mixture of over 100 different chemical compounds (Hammer et al., 2006). Limited toxicology data are available for TTO and some of its individual components even though the components of TTO are well characterized chemically. The limited nonclinical safety data available for TTO are not adequate to determine whether neat TTO would be safe to use as a bulk drug substance in compounding from a Pharmacology/Toxicology perspective.

2. Human Safety

The following database(s) were consulted in the preparation of this review: PubMed [key words: tea tree oil AND safety AND efficacy – 15 records, tea tree oil AND (onychomycosis OR nail fungus) – 28 records, tea tree oil/administration and dosage – 92 records], EMBASE [key words: tea tree oil and onychomycosis or shampoo or oral rinse – 5 records, tea tree oil safety and efficacy – 82 records], SciFinder [key words: tea tree oil for onychomycosis – 9 records, tea tree oil in shampoo or mouthwash – 58 records], and Pharmapendium [key words: tea tree oil – 1 record]; the searches were including all dates.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for tea tree oil. Of the 12 reports for TTO, all reported topical use, none described the use of a compounded product and no details of TTO quality were provided. Only one reported use in onychomycosis. The reports included:

- Four cases reporting lack of effect of a variety of products, including TTO, in the treatment of head lice.
- One case of vomiting, stomach cramps, and fever in a child treated with permethrin and TTO for treatment of head lice.
- One case of a brain tumor in a child treated multiple times for head lice with products including lindane, permethrin, and TTO.
- One case of learning disabilities, behavioral, and speech problems in a child treated multiple times for head lice with products including permethrin and TTO.
- One case of eye burning, redness, and blurred vision following use of a commercial TTO-containing product to treat an ingrown eyelash.
- One case of muscle weakness, cramping, decreased energy, exercise intolerance, and increased liver enzymes in a patient using topical terbinafine and TTO for toenail fungus.
- One case reporting misleading labeling on a commercial product containing undecylenic acid and TTO.
- One case of facial and eye swelling in a commercial product containing benzoyl peroxide and TTO.
- One case of dry skin in a patient using topical adapalene 0.3% gel and TTO cleanser for acne.
FDA’s Center for Food Safety and Nutrition was also consulted to search their adverse event database, CAERS, for adverse events associated with tea tree oil. Of the 6 reports from CAERS, none used a compounded product:

- Two reports involved non-topical administration

One case involved internal use of TTO (Doterra) to “combat cancer, cure yeast infection and strengthen immune system” with daily ingestion for multiple episodes, and a second case involved using TTO (100%, Herb Pharm) to clean a G-tube in a 13-month old male child for shortened gut syndrome. The former developed “poisoning,” but manifestations were not specified in the report, and the latter developed botulism.

- One case reported use of “pure TTO” of unknown source on chest, resulting in painful “burns,” with blistering and residual discoloration a month later.

- One case involved using Spring Valley TTO (Nature’s Bounty) for fungal infection; eczematous lesions and life-threatening generalized mucocutaneous candidiasis developed.

- One case involved use of Nature’s Gate Rainwater TTO shampoo (Levlad Laboratories), resulting in irritation, itching, caking of dandruff, and patchy spots forming scab-like patches like pus and dead skin.

- One case reported using TTO drops (Melaleuca Inc.) for pain; reports included difficulty in hearing, water in ear, ear pain, and vision impairment.

  a. Reported adverse reactions

Reported adverse reactions may be considered under the two potential routes of exposure (dermal and oral), and additional special concerns.

**Dermal Exposure**

- Irritant and allergic contact dermatitis reactions

Reactions have been amply documented (Apted 1991; De Groot et al., 1992; Selvaag et al., 1994; van der Valk et al., 1994; De Groot 1996; and Bhushan et al., 1997). These reactions may be in response to pure TTO or lower concentrations of TTO in various formulations. As described above under the CAERS database, there was one report of a case using TTO for fungal infection and developing eczematous lesions resulting in life-threatening generalized mucocutaneous candidiasis. There has also been a report of allergic contact dermatitis with use of TTO presenting as erythema multiforme-like reaction (Khanna et al., 2000). It has been proposed that contact dermatitis reactions are more prone to develop with exposure to outdated TTO due to oxidation of components, but the precise extent of this issue remains to be clarified (Hammer et al., 2006).
One case of immediate hypersensitivity with flushing, pruritus, constricted throat, and lightheadedness occurred in a 38-year-old man after dermal application of TTO (Mozelsio et al., 2003).

**Oral Exposure**

- **Poisoning**

There were reports of poisoning in children, including (a) a 23-month-old child drinking 10 mL of pure TTO resulting in central nervous system depression and unsteady gait (Jacobs et al., 1994), (b) a 17-month-old boy drinking less than 10 mL of pure TTO who developed similar symptoms (Del Beccaro 1995), and (c) a 4-year-old boy ingesting 2 teaspoons of pure TTO leading to ataxia, unconsciousness and unresponsiveness requiring intubation (Morris et al., 2003).

Besides one case of “poisoning” discussed above in the CAERS database, there are two reports in the literature of toxicities in adults via TTO ingestion: (a) a patient who drank half a tea cup of TTO (~ 0.5–1.0 ml/kg body weight) became comatose for 12 hours, and semi-conscious and hallucinatory for the following 36 hours, with subsequent abdominal pain and diarrhea continuing for about 6 weeks (Seawright 1993), and (b) a 60-year-old man who ingested 1½ teaspoonful of TTO to prevent a cold presented with erythema covering his feet, knees, upper body, and arms including palms and elbows, and swelling of hands, feet, and face resolving in about one week (Elliott 1993).

**Special Concerns**

- **Prepubertal gynecomastia**

Henley et al., (2007) published a report on three prepubertal boys who developed gynecomastia coinciding with the topical application of products that contained lavender and/or TTOs. Gynecomastia resolved in each patient shortly after the use of these products was discontinued. They conducted studies in human cell lines indicating that the two oils had estrogenic and anti-androgenic activities. In 2012, Block published a report indicating that 12 out of 31 cases of gynecomastia in prepubertal females and males had documented use of lavender or TTO.

- **Stomatitis and cheilitis**

Biswas et al., (2003) reported a case of angular cheilitis and stomatitis in a woman who used mouthwash containing TTO and resolution of the lesions after stopping its use. Since, as is discussed further below, TTO is contained in many mouthwash preparations for dental care, development of these lesions may be related to TTO content in the mouthwash.

- **Linear IgA disease**
Perrett et al., (2003) described a patient in whom linear IgA disease, a rare acquired subepidermal blistering disorder characterized by basement membrane zone IgA deposition, appears to have been precipitated by a contact reaction to TTO.

b. Clinical trials assessing safety

Dedicated clinical studies assessing safety (irritancy and sensitization) of TTO have been summarized by the European Commission Scientific Committee on Consumer Products (SCCP). The following is an excerpt:

Irritancy

1. Tea Tree Oil has been investigated for skin irritancy using an occlusive patch test on 25 human subjects for 21 days and compared with 1,8-cineole in concentrations of 0%, 3.8%, 8%, 12%, 16%, 19.9%, 24% and 28.1% in soft white paraffin: 8 Tea Tree Oil preparations containing 1,8-cineole concentrations similar to the 1,8-cineole groups (from 1.5% to 28.8%) and the 1,8-cineole-treated groups did not show skin irritation. (see below on sensitization result) (Southwell et al., 1997).

2. In a Danish dermatology clinic, from 2001-2002 (study 1) and in 2003 (study 2) 217 and 160 consecutive patients were patch tested with the European standard series, respectively, and in addition with 10% Tea Tree Oil in petrolatum (study 1) and commercial lotions containing 5% Tea Tree Oil (studies 1 and 2). In the 1st study 44 out of 217 subjects tested (20.3%) showed irritancy from a lotion containing 5% Tea Tree Oil. In the 2nd study 3.1% (5/160) irritant reactions were seen (see below on sensitization result) (Veien et al., 2004).

3. Various concentrations of Tea Tree Oil (5, 25 and 100%) in different vehicles were applied under occlusive patch testing to the skin of healthy human volunteers (n=311) using a protocol based on the Draize human sensitisation test. The mean irritancy score was 0 for 5% and 0.25 for 100% Tea Tree Oil (Aspres et al., 2003).

4. Ten different samples of undiluted Tea Tree Oil were applied under occlusive conditions for 48 hours to 219 subjects. The prevalence of marked irritancy to 100% tea tree oil ranged from 2.4 to 4.3% (without or with the indistinguishable reactions). Any level of irritancy (mild and marked) ranged from 7.2 to 10.1% (Crieg et al., 1999).

Comment of the SCCP on skin irritation

3 European Standard Series of patch test allergens consist of 26 allergens for patch testing for contact allergy (http://www.dermnetnz.org/dermatitis/standard-patch.html)
From these studies it is concluded that neat Tea [sic] Tree Oil as well as formulations containing 5% Tea Tree Oil can exhibit skin irritancy.

Contact Sensitization

1. A study was performed based on the skin sensitization method developed by Draize in 1965: 6 Tea Tree Oil products were investigated, which consisted of 100% Tea Tree Oil and 25% and 5% Tea Tree Oil in cream, ointment or gel formulation. Cream base was used as a negative control. A total of 151 adult male and female panelists were selected. On Day 1, 100 μl of the respective product was placed in Finn chambers onto the upper arm or the back. After 48 h the chambers were removed and the skin was assessed. If needed, the volunteers returned 48 h later for a further assessment. Skin reaction was assessed on a 5-graded scale. The test products were applied to the skin 9 times over a three-week period and any response for irritancy was recorded (induction). After a two-week rest phase the products were applied on a new site (challenge), and two days later and—if necessary—again after four days the skin reaction was assessed. Any doubtful results were repeated two weeks later. Results showed the following.

- **Irritancy**

148 of 151 panelists were evaluated. The average daily score for irritancy was 0.1922 for the neat Tea Tree Oil. The other samples showed scores from 0.0000 to 0.0060.

- **Sensitization:**

150 of 151 panelists were evaluated. 3 out of 150 (2%) became sensitized to Tea Tree Oil.

In a second, follow-up trial the number of panelists was increased to a joint number of 306 (irritancy) and 308 (sensitization). The second study confirmed the results of the first one, but no details were presented. Since different samples of Tea Tree Oil were tested simultaneously on subjects, it was not possible to determine which specific concentrations were responsible for inducing sensitization (Aspres et al., 2003).

2. Various concentrations of Tea Tree Oil (5, 25 and 100%) in different vehicles were applied under occlusive patch testing to the skin of healthy human volunteers (n=311) using a protocol based on the Draize human sensitization test. Three subjects developed Grade 3 skin reactions suggestive of an allergic reaction. Since different samples of Tea Tree Oil were tested simultaneously on subjects it was not possible to determine which concentration was responsible for inducing sensitization (see above, Item #3 under Irritancy: Aspres et al., 2003).
3. For the studies discussed above under Irritancy (Items #1 and #2: Southwell et al., 1997, Veien et al., 2004, respectively), data on sensitization were also collected. The study in Item #1 under Irritancy showed 3 of 28 panelists exhibiting an allergic response. They were further tested for allergic responses with major constituents of Tea Tree Oil: three positive reactions were seen against a sesquiterpenoid hydrocarbon fraction and one positive reaction against α-terpinene (Southwell et al., 1997). For the study in Item #2 under Irritancy (Danish clinic), one person had a relevant positive patch test to 5% and 10% Tea Tree Oil in the initial study, but none in the second study (Veien et al., 2004).

4. The SCCP also summarized patch testing in patients with TTO. However, for healthy individuals, prevalence rates for allergic contact dermatitis reactions to TTO dilutions were cited in an Australian study conducted with 219 volunteers to be 2.9 to 4.8% using patch testing. Within the subjects with previous exposure to Tea Tree Oil the rate rose to 4.3 to 7.2%. The same authors report on personal communications related to a study of the North American Contact Dermatitis Group: 0.5% of patients reacted to oxidized Tea Tree Oil (5% in petrolatum) on patch testing (Crawford et al., 2004).

Excerpt of SCCP Comment on contact sensitization

Neat Tea Tree Oil is a sensitizer in humans. In a human sensitization study with 9 applications, 3 of 150 (2%) volunteers became sensitized (Aspres et al., 2003).

It is not fully understood which of the constituents is responsible for sensitization. Terpinolene, α-terpinene, a sesquiterpenoid fraction, limonene, and/or oxidative degradation products like ascaridole, 1,2,4-trihydroxymethane, peroxides, and epoxides have been discussed. In one study, oxidized Tea Tree Oil was shown to be three times more potent than fresh oil. The sensitizing potency may also be influenced by the content of irritants such as p-cymene and 1,8-cineole.

5. Clinical trials with TTO for various indications have been reported. However, their safety data are minimally descriptive, and the reported adverse effects do not differ from those described above in section II.B.2.a. For example, the safety data in acne and onychomycosis clinical trials are summarized below to illustrate this point. The data on the type of adverse reactions derived from clinical trials for other conditions are similar.

Onychomycosis Clinical Trials

The safety data from two reported onychomycosis clinical trials evaluating various formulations of TTO are summarized below.

- A randomized, double-blind, placebo-controlled study

This study was conducted to examine the clinical efficacy and tolerability of 2% butenafine hydrochloride and 5% TTO in a cream base in onychomycosis, which
included 60 subjects treated under occlusion three times daily for eight weeks. Four out of 40 patients (10%) in the active treatment group experienced subjective mild inflammation without discontinuing treatment (Syed et al., 1999).

- A randomized, double-blind, multi-center trial

Buck et al. (1994) compared efficacy and tolerability of topical 1% clotrimazole solution against 100% TTO administered twice daily for 6 months for the treatment of toenail onychomycosis in a randomized, double-blind, multi-center trial. Adverse reactions included irritation, erythema, and edema, occurring in 3/53 (5.7%) of the subjects treated with clotrimazole and in 5/64 (7.8%) with TTO.

Acne Clinical Trials

The safety data from seven reported acne clinical trials evaluating various formulations of TTO are summarized in Table 2.
Table 2. Summary of Safety Information from Clinical Studies Evaluating TTO Products for the Treatment of Acne

<table>
<thead>
<tr>
<th>Reference and type of study</th>
<th>Treatment groups</th>
<th>Product application</th>
<th>Tolerability (frequency of adverse events)</th>
<th>Type of adverse events with TTO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bassett et al., 1990 Single-blind&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(1) TTO 5% gel (&lt;i&gt;n&lt;/i&gt; = 58) (2) BP 5% (&lt;i&gt;n&lt;/i&gt; = 61)</td>
<td>Twice daily (left on) for 8 weeks</td>
<td>(1) 44% (2) 79%</td>
<td>dryness, stinging and burning</td>
</tr>
<tr>
<td>Darabi et al., 2005 Investigator-blind</td>
<td>(1) TTO 5% gel (&lt;i&gt;n&lt;/i&gt; = 30) (2) Erythromycin 2% gel (&lt;i&gt;n&lt;/i&gt; = 30)</td>
<td>Twice daily (left on) for 6 weeks</td>
<td>Rates not stated; rates for groups not significantly different</td>
<td>[abstract without details]</td>
</tr>
<tr>
<td>Enshaieh et al., 2007 Double-blind</td>
<td>(1) TTO 5% gel (&lt;i&gt;n&lt;/i&gt; = 30) (2) Placebo (&lt;i&gt;n&lt;/i&gt; = 30)</td>
<td>Twice daily (washed off) for 6 weeks</td>
<td>(1) 10% (2) 6.7%</td>
<td>Pruritus, burning, and scaling</td>
</tr>
<tr>
<td>Yadav et al., 2011 Open-label</td>
<td>(1) TTO 5% gel (&lt;i&gt;n&lt;/i&gt; = 46) (2) TTO 5% gel + Perfact tablet (&lt;i&gt;n&lt;/i&gt; = 46) (3) Perfact tablet alone (&lt;i&gt;n&lt;/i&gt; = 48)</td>
<td>Gel applied once daily; tablets taken twice daily for 4 weeks</td>
<td>No serious adverse events reported</td>
<td>Adverse events not described</td>
</tr>
<tr>
<td>Kwon et al., 2014 Double-blind</td>
<td>(1) TTO 5% extract (&lt;i&gt;n&lt;/i&gt; = 34) (2) LFCO 5% extract (&lt;i&gt;n&lt;/i&gt; = 34)</td>
<td>Twice daily for 8 weeks</td>
<td>(1) 31.3% (2) 12.6%</td>
<td>Dryness, erythema, desquamation</td>
</tr>
<tr>
<td>Kim et al., 2013 Not stated</td>
<td>(1) Baseline + mixture of TTO 3% and lavender oil 2% (&lt;i&gt;n&lt;/i&gt; = 27) (2) Baseline only (&lt;i&gt;n&lt;/i&gt; = 27)</td>
<td>Oils applied twice daily (washed off) for 4 weeks. Baseline not stated</td>
<td>(1) 3.7% (2) 0%</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Yoo et al., 2003 Case-controlled</td>
<td>TTO 0.1% + &lt;i&gt;Ramulus mori&lt;/i&gt; extract 0.01% (&lt;i&gt;n&lt;/i&gt; = 20)</td>
<td>4 Weeks</td>
<td>Not stated in English abstract</td>
<td>Not stated in English abstract</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adapted from Hammer KA, 2015

BP, benzoyl peroxide; LFCO, Lactobacillus fermented Chamaecyparis obtusa.

The authors stated that the study was technically single-blinded as patients were likely to be able to identify which product they had received.

c. Pharmacokinetic data

There are no reports of human pharmacokinetic studies documenting systemic exposure following topical application of TTO or its components.

There are several reports of in vivo penetration into the stratum corneum and in vitro penetration into and through the epidermis. Cal et al. (2006) used skin stripping techniques to measure the amount of terpinen-4-ol (the major component of TTO) in the stratum corneum following in vivo application of 5% w/w terpinen-4-ol in grape seed oil or carbomeric hydrogel. The formulations were applied to the forearm in amounts of 100 mg/cm<sup>2</sup> and left on for 1 hour. The author reported that penetration into the stratum corneum was 110 µg/cm<sup>2</sup> and 23 µg/cm<sup>2</sup> for the hydrogel and oil formulations, respectively. Reichling et al. (2006) reported in vitro application of neat TTO and three formulations containing 5% TTO, namely a semisolid oil in water emulsion, an ointment, and a
cream, to heat-separated human epidermis under infinite dosing conditions, which resulted in permeation of terpinen-4-ol into the receptor fluid with flux rates of 0.26, 0.067, 0.051, and 0.022 µl/cm²/h, respectively. Assuming a specific gravity of 0.933, the flux for neat TTO would be equivalent to about 0.28 mg/cm²/h, which suggests there could be substantial systemic absorption if applied to large surface area for extended time.

However, it has been argued that the infinite dosing condition, such as in the report by Reichling et al. (2006) noted above, is not representative of normal use. Therefore, Cross et al. (2008) evaluated in vitro human skin penetration (n=3 donors) of neat TTO and a 20% solution using a finite dose of 10 mg/cm². The authors reported terpinen-4-ol cumulative penetration into the receptor fluid of 140 – 310 µg/cm² or 3.6 – 8.0% of the applied amount over the 24 hour period following application of neat TTO. Following application of the 20% TTO formulation, the cumulative penetration after 24 hours was 18 – 33 µg/cm² or 1.1 – 1.9% of the applied dose. Partial occlusion of the donor chamber with a glass coverslip resulted in approximately 2.5 fold increase in penetration of terpinen-4-ol.

Overall, the data suggest that components of TTO can be absorbed following topical application. Under normal dosing condition of 10 mg/cm², up to 8% of the applied dose penetrated through the epidermis in vitro. There are no available systemic pharmacokinetic data from in vivo human exposure.

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

Pharmacologic treatment of onychomycosis consists of both oral and topical drug products. Approved oral treatments include itraconazole capsules and terbinafine tablets as well as griseofulvin as tablets or oral suspension. These oral treatments are associated with significant potential toxicities, including cardiac, hepatic, hematologic and dermatologic adverse effects as well as potential drug-drug interactions. Approved topical therapies include ciclopirox solution, tavaborole solution, and efinaconazole solution. Their adverse effects are primarily local reactions.

There are no head-to-head comparisons for safety between TTO and the approved therapies. However, based on available information, it appears that TTO would likely be safer when used topically for onychomycosis than the approved oral drugs, but not necessarily safer than the topical solutions of ciclopirox, tavaborole or efinaconazole.

Conclusions

1. TTO is a mixture of mono- and sesquiterpinoids, and the currently available nonclinical safety data are not adequate to determine whether neat TTO would be safe to use as bulk drug substance in compounding.
2. We have not found safety data from use of TTO in compounding. Available human safety data are based on formulations outside of compounding, and they suggest the following safety concerns:

- Oral ingestion may be associated with significant systemic toxicities.
- Topical administration may produce adverse effects including local irritant and allergic reactions, and even systemic hypersensitivity, especially if the TTO components have been oxidized.
- There have been reports, such as prepubertal gynecomastia and linear IgA disease, which may require further exploration to support safety, especially in subpopulations such as pediatric patients.

3. TTO can be absorbed from topical administration resulting in systemic exposure. As previously described, systemic exposure can produce toxic effects. The relationship between topical exposure (e.g., dose, duration) and the development of systemic effects cannot be predicted in the absence of human pharmacokinetic data.

4. Based on the information currently available, there has been no head-to-head comparison of the safety of topical TTO to oral onychomycosis agents. In one clinical trial, the safety of topical TTO was similar to that of topical clotrimazole, a product that is not approved for the treatment of onychomycosis. There are no trials comparing the safety of topical TTO with currently approved topical drug products for onychomycosis.

C. Are there concerns about whether a substance is effective for a particular use?

In addition to treatment of nail fungus, TTO is also known to have been used for numerous conditions, including acne, tinea pedis, bacterial vaginosis, halitosis, dandruff, dental plaques, gingivitis, hemorrhoids, herpes labialis, lice infestation, methicillin-resistant _Staphylococcus aureus_ colonization, nickel-induced contact dermatitis, ocular demodicosis, oropharyngeal candidiasis, skin infection, trichomoniases, and vaginal candidiasis. However, the efficacy of TTO in these conditions has not been well supported and/or the available literature has presented inconsistent efficacy findings across studies. A recent review considers most of these studies lacking in sufficient reliable evidence to rate TTO for effectiveness for these other uses (Natural Medicines database 2015).

1. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance
There are two clinical trials of TTO in the treatment of onychomycosis. These trials are difficult to interpret due to the lack of a control group, use of an unapproved control, or use of endpoints that combine both complete and partial responses.

One of them involves TTO as part of a fixed combination with an antifungal, butenafine.

- A randomized, double-blind, placebo-controlled study

This study was conducted to examine the clinical efficacy and tolerability of 2% butenafine hydrochloride and 5% TTO in a cream base in toenail onychomycosis, which included 60 subjects (40 with active and 20 with placebo cream) treated under occlusion three times daily for 8 weeks, and evaluated at weeks 8, 24, and 36 (Syed et al., 1999). The fungi involved were primarily *Trichophyton rubrum*, with rare *Trichophyton tonsurans* and *Trichophyton mentagrophytes*. Mycological cure was defined as negative fungal culture for dermatophytes and absence of hyphae in wet potassium hydroxide. After 36 weeks, 80% of the subjects using medicated cream had “overall cure,” defined as resolution of all clinical symptoms with respect to global assessment together with mycological cure and progressive growth of normal nail, as opposed to none in the placebo group.

This study demonstrates effectiveness of the combination cream with 2% butenafine hydrochloride and 5% TTO. However, in the absence of a treatment arm of butenafine hydrochloride alone, the contribution of 5% TTO is unknown. Thus, the authors have failed to show whether TTO plays any role in the efficacy in the treatment of onychomycosis.

- A randomized, double-blind, multi-center trial

Buck et al. (1994) compared the efficacy and tolerability of 1% clotrimazole solution against 100% TTO administered topically twice daily for 6 months for the treatment of 117 subjects having toenail onychomycosis in a randomized, double-blind, multi-center trial. The fungi involved were primarily *Trichophyton rubrum* and *Trichophyton mentagrophytes*. After six months of therapy, the response rates are given by the authors as follows:

<table>
<thead>
<tr>
<th></th>
<th>Clotrimazole 1%, N=53</th>
<th>TTO 100% N=64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycologic culture negative</td>
<td>4 (11%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Partial or full clinical resolution</td>
<td>22 (61%)</td>
<td>24 (60%)</td>
</tr>
</tbody>
</table>

The percentages for mycologic cure and clinical resolution in the article appear to be exaggerated. There were only five drop-outs (four in the clotrimazole and one in the TTO arm), but the percentages suggest that much lower numbers of subjects were used as denominators (i.e., clotrimazole N=36, and TTO N= 40) in contrast to the number of subjects enrolled. With an intent-to-treat population, the actual mycologic cure rates would be 8% for clotrimazole and 11% for TTO, and the partial or full clinical resolution rates would be 42% for clotrimazole and 38% for TTO.
This study would not be able to demonstrate effectiveness of 100% TTO in the treatment of toenail onychomycosis. The control, clotrimazole 1% solution, is not an approved treatment for onychomycosis and would be inappropriate for comparison unless TTO is statistically superior. In addition, the generally accepted success criterion for onychomycosis therapy is a clear or almost clear nail with documentation of a mycologic cure (using potassium hydroxide and culture). The article has not provided data specifying the occurrence of full resolution or almost cleared nail, apart from the occurrence of partial or full resolution combined while the mycology assessment does not include potassium hydroxide examination.

2. **Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease**

No, onychomycosis is not a serious or life-threatening condition.

3. **Whether there are any alternative approved therapies that may be as effective or more effective.**

Yes, there are approved drug therapies for onychomycosis that have been shown to be effective. [See section II.B.2.d for the approved drug therapies.]

As stated above, there have not been head-to-head comparisons between TTO and the approved drug products for onychomycosis, and it is not known whether it is more or less effective than such drug products.

**Conclusions**

There have not been adequate data supporting the effectiveness of TTO in the treatment of onychomycosis, whether as monotherapy or in combination with another antifungal agent. Specifically, the design of both studies cited above would be unable to provide adequate evidence to support the use of TTO in the treatment of onychomycosis, as monotherapy or in combination with an antifungal.

Although the study by Syed et al. (1999) demonstrates effectiveness of the combination cream with 2% butenafine hydrochloride and 5% TTO, it lacks a treatment arm of butenafine hydrochloride alone to demonstrate the contribution of 5% TTO. Thus, whether TTO plays any role in the efficacy in the treatment of onychomycosis is unknown.

In the study by Buck et al. (1994), the control, clotrimazole 1% solution, is not an approved treatment for onychomycosis and would be inappropriate for comparison unless TTO is statistically superior. In addition, the generally accepted success criterion for onychomycosis therapy is a clear or almost clear nail together with mycologic cure (using both potassium hydroxide and culture). The article provides no data specifying the occurrence of full resolution or almost complete clearing of the treated nail, apart from the occurrence of partial or full resolution combined.
D. Has the substance been used historically as a drug in compounding?

Historically, local people in Australia have used the leaves and leaf preparations of the tea tree plant (M. alternifolia) to help alleviate cuts, bites, burns and other skin ailments. TTO was used during World War II to treat skin injuries of workers in munitions factories and TTO was commonly used in surgery and dentistry in the mid-1920s.

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

It is not clear how long TTO has been used in pharmacy compounding in the United States. It has been used as a topical antiseptic agent for about a century with standardized TTO commercially available since 1982 (ATTIA 2012).

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

TTO has been used as a topical agent for a wide variety of skin, ocular, oral and vaginal conditions, such as toenail onychomycosis, tinea pedis, vaginal infections (yeast and bacterial), herpes labialis, and acne vulgaris, in the absence of sufficient reliable evidence for effectiveness (see section II.C for more details). There is scant information regarding use in compounding for such conditions.

3. How widespread its use has been

In the United States, there are over 210 marketed products containing TTO listed in the Natural Medicines Database (Natural Medicines, 2015), which does not specify whether the TTO meets the ISO 4730 standard. Although many of them can be considered dietary supplements (for oral use) or skin care products (for topical use), the names of some of the following products suggest treatment-related applications: Solaray Yeast Cleanse (TTO 60 mg with other herbs, vitamins and minerals for oral use); Sore Throat Spray Tincture Formulation (two sprays containing 0.1 mL TTO, Hydrastis canadensis extract, Echinacea angustifolia extract, Mentha piperita extract and other ingredients in water and ethanol); and Cut & Burn Ointment.

The websites of two U.S. pharmacy stores, CVS (www.cvs.com) and Walgreens (www.walgreens.com), listed 365 and 52 “tea tree oil” products, respectively (data accessed on 01/19/2016). Most of the products containing TTO are categorized as “health and medicine,” “personal care,” and “beauty” products. For example, there are 25 TTO “health and medicine” products available at CVS, which include 16 first aid products, six for cough, cold and flu, and three for fever and pain (e.g., Tea Tree Therapy Vaginal Suppositories with Tea Tree Oil, Tea Tree Therapy Antiseptic Cream with Tea Tree Oil and Herbal Extracts, Zim's Max-Freeze Gel for pain, CVS 100% tea tree oil). The “personal care” and “beauty” are marketed in various forms, such as toothpaste, foot cream, mouthwash, shampoo, body wash, body oil, and so on. Other pharmacy stores (e.g., Walmart) also have various TTO products. Based on an internet search, TTO is available in compounded drug products from a number of compounding pharmacies.
In Canada, there are 28 licensed natural health products containing TTO as anti-fungal/antiseptic agents for minor infections/wounds or other conditions. In addition to numerous pure TTO (i.e., 100%) products, there are several TTO combination products with treatment-related applications suggested by the product names, such as Natures Harmony Tea Tree Antiseptic Cream (TTO 5% with sweet almond oil and other ingredients), Tea Tree Anti Fungal Gel (TTO 5%), Tea Tree Medicated Gel For Acne (TTO 20% with 0.5% Cinnamomum camphora and other ingredients), and Sore Throat Spray Tincture Formulation (Natural Medicines, 2015).

Topical herbal medicine or drug applications of TTO in Europe, Australia, New Zealand, and other parts of the world have also been recorded (WHO 2002).

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

Herbal medicine monographs of TTO were published by WHO (WHO, 2002) and EMA (EMA 2013). In Australia, pure TTO was registered as a single medicine product “a mild antiseptic for minor cuts, abrasions, bites and stings” (TGAeBS Public Summary 2011).

Although TTO is not listed in the U.S. Pharmacopeia-National Formulary or the Japanese Pharmacopeia, the European Pharmacopeia and the British Pharmacopeia include an entry for TTO (Melaleucae aetheroleum) that defines TTO as essential oil obtained by steam distillation from the foliage and terminal branchlets of Melaleuca alternifolia (Maiden et Betche) Cheel, M. linariifolia Smith, M. dissitiflora F. Mueller and/or other species of Melaleuca. This is a broader definition of TTO, than the one derived from M. alternifolia alone, which is the definition of TTO being considered in this review.

Conclusions

TTO is recognized in the European Pharmacopeia and the British Pharmacopeia, and its usage is worldwide.

Although TTO-containing products are commercially available at least since 1982 for use as topical formulations for a wide variety of skin, ocular, oral and vaginal conditions, there is scant information regarding the use of TTO in pharmacy compounding and insufficiently reliable evidence supporting its effectiveness for such conditions.

III. RECOMMENDATION

We have evaluated TTO as a candidate for the list of bulk drug substances under section 503A of the Act and recommend that it not be included on the list of bulk drug substances allowed for use in compounding based on the following:

1. Pure TTO, an essential oil from a single species (Melaleuca alternifolia) by steam distillation, is well characterized in its physical and chemical properties. Although complete characterization and quantitative analysis of all the minor chemical
components (less than 10%) in TTO may not be feasible, there is assurance of consistency if the TTO used meets one of the two TTO quality standards (AS 2882-2009 and ISO 4730).

2. The safety profile of pure TTO or TTO-formulated products shows that the most common adverse reactions from topical administration of TTO are due to irritation or sensitization resulting in contact dermatitis lesions. However, currently available nonclinical safety data are not adequate to determine whether TTO would be safe to use in compounding. In addition, there are certain safety issues such as prepubertal gynecomastia and linear IgA disease that have not been adequately explored. Thus, although there is a fairly large amount of human data on topical use, there remain sufficient safety concerns to warrant further exploration. In addition, oral ingestion of TTO can be associated with serious toxicities, although it has been available for some time as oral rinses and mouthwash. Lack of adequate safety information weighs against inclusion on the list of bulk drug substances that can be used in compounding under 503A.

3. There is inadequate available evidence from adequate and well-controlled clinical trials to support the effectiveness of pure TTO or TTO-formulated products in the treatment of onychomycosis as monotherapy or in combination with an approved antifungal. The clinical trials in support of this indication either lacked a critical treatment arm to demonstrate TTO having any contribution to the treatment effect in onychomycosis, or did not adequately assess treatment success. Lack of adequate effectiveness information weighs against inclusion on the list of bulk drug substances that can be used in compounding under 503A.

4. Pure TTO and numerous formulated multiple-ingredient products have been used topically in various formulations for onychomycosis and other skin, ocular, oral and vaginal conditions over at least a few decades, but there is scant information on its historical use in pharmacy compounding for these conditions.

Based on a balancing of the four evaluation criteria, we recommend that TTO not be added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act.
BIBLIOGRAPHY


Tab 6

2,3-Dimercapto-1-propanesulfonic acid (DMPS)
Tab 6a

2,3-Dimercapto-1-propanesulfonic acid (DMPS)
Nominations
September 30, 2014

VIA ELECTRONIC SUBMISSION

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

Re: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations

Docket No. FDA-2013-N-1525

Dear Sir/Madam:

The Alliance for Natural Health USA (“ANH-USA”) submits this comment on the Notice: “Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations” published in the Federal Register of July 2, 2014 by the Food and Drug Administration (“FDA” or the “Agency”).

ANH-USA appreciates this opportunity to comment on the list of bulk drug substances that may be used to compound drug products pursuant to Section 503A of the FD&C Act (“FDCA”), 21 U.S.C. §353a (hereinafter the “503A List”). This list of ingredients is crucial to patients who require compounded substances, in particular those substances that are available only across state lines. ANH-USA therefore write to request that the Agency:

A) Extend the deadline for nominations by at least 90 days;
B) Maintain the 1999 List; and
C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List.

“Promoting sustainable health and freedom of healthcare choice through good science and good law”
As discussed in detail below, in the interest of compiling a comprehensive 503B List, more time is needed to provide the required information. This will benefit both FDA, by reducing the subsequent number of petitions for amendments, and consumers, by allowing continued access to important substances.

Organizational Background of Commenter Alliance for Natural Health USA

ANH-USA is a membership-based organization with its membership consisting of healthcare practitioners, food and dietary supplement companies, and over 335,000 consumer advocates. ANH-USA focuses on the protection and promotion of access to healthy foods, dietary nutrition, and natural compounded medication that consumers need to maintain optimal health. Among ANH-USA’s members are medical doctors who prescribe, and patients who use, compounded medications as an integral component of individualized treatment plans.

ANH-USA’s Request and Submissions Regarding Docket No. FDA-2013-N-1525

A) Extend the deadline for nominations by at least 90 days

This revised request for nominations follows the initial notice published in the Federal Register of December 4, 2013. Like the initial notice, this revised request provides only a 90 day response period. However, FDA is requiring more information than it sought originally and yet providing the same amount of time for the submission of nominations. The September 30, 2014 deadline for such a complex and expansive request is unreasonably burdensome and woefully insufficient.

The task set forth by FDA to nominate bulk drug substances for the 503A List places an undue burden on those who are responding. The Agency requires highly technical information for each nominated ingredient, including data about the strength, quality and purity of the ingredient, its recognition in foreign pharmacopeias and registrations in other countries, history with the USP for consideration of monograph development, and a bibliography of available safety and efficacy data, including any peer-reviewed medical literature. In addition, FDA is requiring information on the rationale for the use of the bulk drug substance and why a compounded product is necessary.

For the initial request for nomination, it was estimated that compiling the necessary information for just one nominated ingredient would require five to ten hours. With the revised request requiring more information, the time to put together all of the data for a single nomination likely will be higher. Given that it is necessary to review all possible ingredients and provide the detailed support, or risk losing important therapeutic ingredients, this task requires more time than has been designated by the Agency. While ANH-USA recognizes there will be additional opportunities to comment and petition for amendments after the 503A List is published, the realities of substances not making the list initially makes this request for more time imperative. For example, if a nomination for a substance cannot be completed in full by the current September 30, 2014 deadline, doctors and patients will lose access to such clinically important substances and face the
administrative challenges in obtaining an ingredient listing once the work of the advisory committee is completed. There is no regulatory harm in providing additional time to compile a well-researched and comprehensive initial 503A List.

B) Rescind the withdrawal of the ingredient list published on January 7, 1999

In the revised request for nomination, the Agency references in a footnote its withdrawal of the proposed ingredient list that was published on January 7, 1999. ANH-USA argued against this in its March 4, 2014 comment and would like to reiterate its opposition to the withdrawal. There is no scientific or legal justification to require discarding the work that lead to the nominations and imposing the burden on interested parties to begin the process all over again.

C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List

ANH-USA submits the following ingredients for nomination for the 503B list:

1. The attached Excel spreadsheets for 21 nominated ingredients prepared by IACP in support of its petition for the nomination of these ingredients; and
2. The submissions for Copper Hydrosol and Silver Hydrosol from Natural Immunogenics Corp., with their Canadian Product Licenses as proof of safety and efficacy.

In conclusion, Alliance for Natural Health USA requests that FDA provide a more realistic time frame, adding at least 90 days to the current deadline; rescind the withdrawal of the ingredient list published on January 7, 1999; and accept the ingredient nominations for approval for use.

Sincerely,

Gretchen DuBeau, Esq.
Executive and Legal Director
Alliance for Natural Health USA

1 As of October 1, 2014, the address for Natural Immunogenics Corp. will be 7504 Pennsylvania Ave., Sarasota, FL 34243.
September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

“Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations”

To Whom It May Concern:

The American Association of Naturopathic Physicians (AANP) appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

This is a significant issue for our members and their patients. AANP strongly supports efforts to ensure that the drug products dispensed to patients are safe and effective.

Background: AANP Submissions to Date

On January 30, 2014, we submitted comments to Docket FDA-2013-D-1444, “Draft Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Withdrawal of Guidelines” relating to congressional intent in crafting HR 3204. These comments highlighted the fact that, for compounding pharmacies subject to Section 503A, Congress intended that States continue to have the authority to regulate the availability of safely compounded medications obtained by physicians for their patients. As we further noted, compounded medications that are formulated to meet unique patient needs, and that can be administered immediately in the office, help patients receive the products their physicians recommend and reduce the medical and financial burden on both the patient and
doctor that restrictions on office use would impose. Such medications, we emphasized, provide a unique benefit to patients and have an excellent track record of safety when properly produced and stored.

AANP also (on March 4, 2014) nominated 71 bulk drug substances. We identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring. We estimated, at that time, that at least 6 hours per ingredient would be needed to do so – time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP sought a 90-day extension to more completely respond to the Agency’s request.

In this renomination, we have narrowed our focus to 42 bulk drug substances that are most important for the patients treated by naturopathic doctors. Twenty-one of these bulk drug substances are formally nominated in the attachments as well as noted by name in this letter. Given the limitations imposed by the fact that our physician members spend the majority of their day providing patient care, however, AANP again found that the span of time the Agency provided for renominations was insufficient to prepare the documentation needed for the remaining 21 bulk drug substances.

We now request that FDA extend the deadline for which comments are due by 120 days, so that we may provide this further documentation. We have determined that as much as 40 hours per ingredient will be needed to do so – time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP respectfully seeks an additional 120-day period for the purpose of gathering this essential information.

**Naturopathic Medicine and Naturopathic Physicians**

A word of background on our profession is in order. AANP is a national professional association representing 4,500 licensed naturopathic physicians in the United States. Our members are physicians trained as experts in natural medicine. They are trained to find the underlying cause of a patient’s condition rather than focusing solely on symptomatic treatment. Naturopathic doctors (NDs) perform physical examinations, take comprehensive health histories, treat illnesses, and order lab tests, imaging procedures, and other diagnostic tests. NDs work collaboratively with all branches of medicine, referring patients to other practitioners for diagnosis or treatment when appropriate.

NDs attend 4-year, graduate level programs at institutions recognized through the US Department of Education. There are currently 7 such schools in North America. Naturopathic medical schools provide equivalent foundational coursework as MD and DO schools. Such coursework includes cardiology, neurology, radiology, obstetrics, gynecology, immunology, dermatology, and pediatrics. In addition, ND programs provide extensive education unique to the naturopathic approach, emphasizing disease prevention and whole person wellness. This includes the prescription of clinical doses of vitamins and herbs and safe administration via oral, topical, intramuscular (IM) and intravenous (IV) routes.
Degrees are awarded after extensive classroom study and clinical training. In order to be licensed to practice, an ND must also pass an extensive postdoctoral exam and fulfill annual continuing education requirements. Currently, 20 states and territories license NDs to practice.

Naturopathic physicians provide treatments that are effective and safe. Since they are extensively trained in pharmacology, NDs are able to integrate naturopathic treatments with prescription medications, often working with conventional medical doctors and osteopathic doctors, as well as compounding pharmacists, to ensure safe and comprehensive care.

**Characteristics of Patients Seen by Naturopathic Physicians**

Individuals who seek out NDs typically do so because they suffer from one or more chronic conditions that they have not been able to alleviate in repeated visits to conventional medical doctors or physician specialists. Such chronic conditions include severe allergies, asthma, chronic fatigue, chronic pain, digestive disorders (such as irritable bowel syndrome), insomnia, migraine, rashes, and other autoimmune disorders. Approximately three-quarters of the patients treated by NDs have more than one of these chronic conditions. Due to the fact that their immune systems are often depleted, these individuals are highly sensitive to standard medications. They are also more susceptible to the numerous side effects brought about by mass-produced drugs.

Such patients have, in effect, fallen through the cracks of the medical system. This is why they seek out naturopathic medicine. Safely compounded medications – including nutritional, herbal, and homeopathic remedies – prove efficacious to meet their needs every day in doctors’ offices across the country. Such medications are generally recognized as safe (GRAS), having been used safely for decades in many cases. As patients’ immune function improves, and as they work with their ND to improve their nutrition, get better sleep, increase their exercise and decrease their stress, their health and their resilience improves. This is the ‘multi-systems’ approach of naturopathic medicine – of which compounded drugs are an essential component.

**Bulk Drug Substances Nominated at this Time**

Notwithstanding the concerns expressed and issues highlighted in the foregoing, AANP nominates the following 21 bulk drug substances for FDA’s consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A. Thorough information on these substances is presented in the spreadsheets attached with our comments. The documentation is as complete and responsive to the Agency’s criteria as we can offer at this time.

The bulk drug substances nominated are:

Acetyl L Carnitine
Alanyl L Glutamine
Alpha Lipoic Acid
Artemisia/Artemisinin
Boswellia
Calcium LS Methyltetrahydrofolate
Cesium Chloride
Choline Chloride
Curcumin
DHEA
Dicholoroacetic Acid
DMPS
DMSA
Germanium Sesquioxide
Glutathione
Glycyrrhizin
Methylcobalamin
MSM
Quercitin
Rubidium Chloride
Vanadium

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating the patients of naturopathic doctors. AANP wishes to specify these 21 ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination. The additional bulk drug substances include:

7 Keto Dehydroepiandrosterone
Asparagine
Calendula
Cantharidin
Choline Bitartrate
Chromium Glycinate
Chromium Picolinate
Chrysin
Co-enzyme Q10
Echinacea
Ferric Subsulfate
Iron Carbonyl
Iscador
Pantothenic Acid
Phenindamine Tartrate
Piracetam
Pterostilbene
AANP Objects to Unreasonable Burden

AANP believes it necessary and proper to lodge an objection to FDA’s approach, i.e., the voluminous data being required in order for bulk drug substances to be considered by the Agency for approval. FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of the persons most knowledgeable about and experienced in the application of compounded medications are either small business owners or busy clinicians, and given the extent and detail of information on potentially hundreds of ingredients as sought by FDA, this burden is unreasonable. The approach has no basis in the purpose and language of the Drug Quality and Security Act (“Act”) – particularly for drugs that have been safely used for years, not only with the Agency’s implicit acceptance, but without any indication of an unacceptable number of adverse patient reactions.

The volume of data being required in this rulemaking is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, the Agency contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with the resources to seek regulatory approvals. The FDA’s analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The burden on respondents to this current rulemaking is further aggravated by the FDA’s complete absence of consideration of the harm that will be caused if needed drugs are removed from the market. The “Type 2” errors caused by removing important agents from clinical use could far exceed the “Type 1” errors of adverse reactions, particularly given the strong track record of safely compounded medications. The infectious contamination that gave rise to the Act has little to do with the process set out by FDA for determining which ingredients may be compounded. Yet the Agency has offered little consideration of the respective risks and benefits of its approach. Based on the fact that compounding pharmacies and physicians are carrying the full burden of proof, as well as how much time it is likely to take for the process of documentation and evaluation to conclude, the Agency itself may well find that it has caused more harm to patients’ clinical outcomes than provided a bona fide contribution to patient safety.
Conclusion

AANP appreciates the Agency’s consideration of the arguments and objection presented herein, the request for an extension of time to gather the documentation that FDA is seeking, and the nominations made and referenced at this time.

We look forward to continued dialogue on these matters. As AANP can answer any questions, please contact me (jud.richland@naturopathic.org; 202-237-8150).

Sincerely,

Jud Richland, MPH
Chief Executive Officer
September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525
Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations.

To Whom It May Concern:

The Integrative Medicine Consortium (IMC) appreciates the opportunity to address the Food and Drug Administration’s request for the submission of ingredients to be listed as allowed for compounding by compounding pharmacies pursuant to Section 503A of the Food Drug and Cosmetic Act. IMC represents the interests of over 6,000 medical and naturopathic physicians and their patients. As we noted in our submission of March 4, 2014, we know from extensive experience that the appropriate availability of compounded drugs offers significant clinical benefits for patients and raise certain objections to the manner in which the FDA is proceeding on these determinations.

First, we note that we are in support of and incorporate by reference the comments and proposed ingredients submitted by our member organization, the American Association of Naturopathic Physicians (AANP), as well as the International Association of Compounding Pharmacists (IACP), and the Alliance for Natural Health-USA (ANH-USA). We also write on behalf of the Academy of Integrative Health and Medicine (AIHM), a merger of the American Holistic Medical Association and the American Board of Integrative and Holistic Medicine.

We also write to raise objections to:

A) The ingredient submission process the FDA is following on this docket, which places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the
process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Further, we write to ask that FDA:

D) Keep the record open for an additional 120 days for the submission of additional materials.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

F) Accept the attached nominations.

G) Accept allergenic extracts as a class without requiring individual nominations and approval.

Commenter Organizational Background: The Integrative Medicine Consortium

The Integrative Medicine Consortium (IMC) began in 2006 when a group of Integrative Medicine leaders joined together to give a common voice, physician education and support on legal and policy issues. Our comment is based on the collective experience of over 6,000 doctors from the following seven organizations:

- American Academy of Environmental Medicine (AAEM) www.aaemonline.org
- American Association of Naturopathic Physicians (AANP) www.naturopathic.org
- American College for Advancement in Medicine (ACAM) www.acam.org
- International College of Integrative Medicine (ICIM) www.icimed.com
- International Hyperbaric Medical Association (IHMA) www.hyperbaricmedicalassociation.org
- International Organization of Integrative Cancer Physicians (IOIP) www.ioipcenter.org

The IMC has been involved in the assessment of risk as applied to the integrative field generally, including participation in the design of malpractice policies suited to the practice of integrative care along with quality assurance efforts for the field such as initiating the move toward developing a professional board certification process. IMC and its member organizations have collectively held over a hundred conferences, attended by tens of thousands of physicians, in which clinical methods that involve the proper use of compounded drugs are a not infrequent topic and subject to Category
I CME credit. Our collective experience on these matters is thus profound, well-credentialed and well-documented.

IMC Objections and Requests Regarding Docket FDA-2013-N-1525

A) The ingredient submission process the FDA is following on this docket, inappropriately places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

We wish to lodge our objection to FDA’s approach to its data collection about drugs that will be placed on the list of permitted ingredients. The FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of those knowledgeable and experienced in compounded pharmaceuticals are either small businesses or busy physicians, and given the significant quality and quantity of information on potentially hundreds of ingredients requested by FDA, this burden is unreasonable. This approach has no basis in the purpose and language of the Drug Quality and Security Act (“Act”), particularly for drugs that have been in use for years, not only with FDA’s at least implicit acceptance, but without any indication of an unacceptable level of adverse reactions.

This is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with the resources to seek regulatory approvals.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

Given that the Act arose from Good Manufacturing Practice violations and not concern for any specific drug ingredient, the requirement that ingredients not the subject of a USP monograph or a component of approved drugs be withdrawn pending these proceedings has no legislative basis or rationale. The hiatus in availability and inappropriate shift of burden to the compounding industry is further aggravated by the complete absence of consideration by the FDA of the harm caused by the removal of needed drugs from practice. The “Type 2" errors caused by removing important agents from clinical use could far exceed the “Type 1" errors of adverse reactions, particularly given the
Comments, Integrative Medicine Consortium
Docket FDA-2013-N-1525
September 30, 2014
List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act
Page 4

track record in this industry. This is particularly true given that the infectious contamination that gave rise to the Act has little to do with the approval process for which ingredients may be compounded. Yet FDA has offered little consideration of the respective risks and benefits of its approach, and with pharmacies and physicians carrying the full burden of proof and the time expected for the advisory process to conclude, the FDA will likely itself cause more patient harm than provide a contribution to safety.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The FDA’s analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). While the FDA made this assessment for “Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness,” 79 FR 37687, in which 25 drugs were added to the list of barred drugs, it has not done so for the much broader issue of upending the compounding pharmaceutical industry, which bears costs both in preparation of detailed submissions on potentially hundreds of ingredients, loss of sales of ingredients no longer approved, the economic consequence to physicians of not being to prescribe these drugs, and the economic impacts of health difficulties and added expense that will result from the withdrawal of drugs from clinical use. The Agency needs to address these concerns.

D) Extend the deadline for which comments are due by 120 days.

IMC’s March 4, 2014 submission, along with AANP and ANH-USA nominated 71 bulk drug substances. IMC identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring.1 We had determined that at least 6 hours per ingredient would be needed to do so, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC sought a 90

1 For example, other nominations would include 7 Keto Dehydroepiandrosterone; Asparagine; Calendula; Cantharidin; Choline Bitartrate; Chromium Glycinate; Chromium Picolinate; Chrysin; Co-enzyme Q10; Echinacea; Ferric Subsulfate; Iron Carbonyl; Iscador; Pantothenic Acid; Phenindamine Tartrate; Piracetam; Pterostilbene; Pyridoxal 5-Phosphate; Resveratrol; Thymol Iodide.
day extension to more completely respond to the Agency's request.

In the renomination, we have narrowed our focus to the attached 21 bulk drug substances given restraints on available resources. These bulk drug substances are documented in the attachment. Given the limitations imposed by the fact that our physician members spent the majority of their day providing patient care, however, we have found that the span of time the Agency provided for renominations was insufficient.

We now request that FDA extend the deadline for which comments are due by at least 120 days, so that we may provide additional documentation. The FDA can certainly begin work on those nominations it has received, but nominations should remain open. We have determined that as much as 40 hours per ingredient will be needed to do, particularly given the lack of resources being offered by the Agency, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC respectfully seeks an additional 120 day period - if not greater - for the purpose of gathering this essential information. If such an extension is not granted, we will explore the prospect of submitting a Citizen's Petition along with AANP and other interested parties.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

In our submission of March 4, 2014, we raised a number of additional considerations, in particular citing a number of monographs, compendia and other authoritative sources that should be considered proper sources for authorized compounding in addition to the U.S. Pharmacopeia. We urge FDA to reach this issue as a means of allowing substances in long use on the market without undue delay or ambiguity.

F) Accept the attached nominations.

Notwithstanding the concerns expressed and issues highlighted in the foregoing, IMC nominates the bulk drug substances in the attachment for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

G) Accept allergenic extracts as a class without requiring individual nominations and acceptance.

In addition, we ask the FDA clarify its view of, and accept as appropriate for use, the category of materials that have been long used in the compounding of allergenic extracts for immunotherapy.
This should particularly be the case where such substances are compounded in manner consistent, where appropriate under its terms, with USP Monograph 797. Given both long-standing safe use, the nature of the materials and methods of clinical use, and the safety assurances contained in this monograph, we believe that individual nominations and approval should not be imposed upon this form of treatment.

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating patients. IMC wishes to identify these additional ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination.

Sincerely,

Michael J. Cronin, N.D.
Chair, Integrative Medical Consortium

Enclosures:
Nominations

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2 Such as environmental and body molds, dust mites, grasses, grass terpenes, weeds, trees, foods, as well as hormone, neurotransmitter, and chemical antigens that are used in various forms of immunotherapy and desensitization.
September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

“Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations”

To Whom It May Concern:

McGuff Compounding Pharmacy Services, Inc. (McGuff CPS) appreciates the opportunity to address the FDA’s request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products.

Request for Extension
The Agency has indicated the majority of compounding pharmacies are small businesses. McGuff CPS is a small business and has found that the requirements to assemble the requested documentation have been particularly onerous. The Agency has requested information for which no one particular pharmacy, physician or physician organization can easily assemble and must be sought through coordination with the various stakeholders. To collect the information required is a time consuming process for which many practicing professionals have indicated that the time allotted for comment to the Docket has been too limited.

This is an issue of great importance which will limit the number of available compounded drugs products available to physicians and, therefore, will limit the number of individualized treatments to patients. McGuff CPS and physician stakeholders have not had the time to collect, review, and collate all documentation necessary to submit the intended list of compounded drugs required to assure all patient therapies are represented in our submission. McGuff CPS respectfully seeks an additional 120 day period for the purpose of coordinating the various stakeholders and gathering the essential information necessary to provide the Agency with the most comprehensive information.
The Agency has not announced the process of follow on communication or failure e.g. what happens if a nominated substance needs more detailed information of a particular nature? Will the whole effort be rejected or will a “deficiency letter” be issued to the person or organization that submitted the nomination? The Agency issues “deficiency letters” for NDA and ANDA submissions and this appears to be appropriate for compounded drug nominations. McGuff CPS respectfully requests the FDA issue “deficiency letters” to the person or organization that submitted the nomination so that further documentation may be provided.

Nominations

To comply with the current time limits established by the Docket, attached are the nominations prepared to date for bulk drug substances that may be used in pharmacy compounding under Section 503A.

Sincerely,

Ronald M. McGuff
President/CEO
McGuff Compounding Pharmacy Services, Inc.
### Column A—What information is requested?

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the name of the nominated ingredient?</td>
<td>DMPS sodium salt</td>
</tr>
<tr>
<td>Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?</td>
<td>Yes.</td>
</tr>
<tr>
<td>Is the ingredient listed in any of the three sections of the Orange Book?</td>
<td>Not for dimercaptopropane sulfonic acid sodium</td>
</tr>
<tr>
<td>Were any monographs for the ingredient found in the USP or NF monographs?</td>
<td>Not for dimercaptopropane sulfonic acid sodium</td>
</tr>
<tr>
<td>What is the chemical name of the substance?</td>
<td>(R,S)-2,3-dimercaptopropane-1-sulfonic acid), sodium salt</td>
</tr>
<tr>
<td>What is the common name of the substance?</td>
<td>DMPS</td>
</tr>
<tr>
<td>Does the substance have a UNII Code?</td>
<td>690VN2L7TK</td>
</tr>
<tr>
<td>What is the chemical grade of the substance?</td>
<td>DMPS is not graded</td>
</tr>
<tr>
<td>What is the strength, quality, stability, and purity of the ingredient?</td>
<td>DMPS is manufactured in a 510-FDA Registered facility. A certificate of analysis accompanies every lot of raw material received.</td>
</tr>
<tr>
<td>How is the ingredient supplied?</td>
<td>DMPS is a white to almost white crystalline powder with a weak, characteristic odor.</td>
</tr>
<tr>
<td>Is the substance recognized in foreign pharmacopeias or registered in other countries?</td>
<td>DMPS parenteral dosage form is approved by the German Health Authorities (BfArM).</td>
</tr>
<tr>
<td>Has information been submitted about the substance to the USP for consideration of monograph development?</td>
<td>Information not known</td>
</tr>
<tr>
<td>What dosage form(s) will be compounded using the bulk drug substance?</td>
<td>Oral capsules Injection</td>
</tr>
<tr>
<td>What strength(s) will be compounded from the nominated substance?</td>
<td>Various capsule strengths ranging from 2.5 mg to 500 mg of DMPS per capsule Injection: 50 mg/mL</td>
</tr>
<tr>
<td>What are the anticipated route(s) of administration of the compounded drug product(s)?</td>
<td>Capsules: oral Injection: intravenous or intramuscular</td>
</tr>
</tbody>
</table>

Nominations Submitted by: Alliance for Natural Health USA, American Association of Naturopathic Physicians, Integrative Medical Consortium, and McGuff Compounding Pharmacy Services, Inc.
Are there safety and efficacy data on compounded drugs using the nominated substance?

Bibliographies on Safety and Efficacy Data: Federal Register 1999

**Therapeutic uses:**

**heavy metal poisoning**


**References:**

Has the bulk drug substance been used previously to compound drug product(s)?

Yes
<table>
<thead>
<tr>
<th><strong>What is the proposed use for the drug product(s) to be compounded with the nominated substance?</strong></th>
</tr>
</thead>
</table>
| **Therapeutic uses:**  
**Heavy metal poisoning**  
DMPS is indicated in the treatment of arsenic, bismuth, cadmium, chromium, lead, mercury, uranium, etc. poisoning. Please access and review Heyl - Dimaval (DMPS) Monograph below. |

<table>
<thead>
<tr>
<th><strong>What is the reason for use of a compounded drug product rather than an FDA-approved product?</strong></th>
</tr>
</thead>
</table>
| **Therapeutic uses:**  
**Heavy metal poisoning**  
- BAL is more effective if given 1 to 2 hours after ingestion of mercury salts. BAL is formulated in peanut oil thus can only be given intramuscularly and peanut allergy is possible. Compounded DMPS is an aqueous injection that can be given intravenously for a more rapid onset of action especially in critical emergency cases. BAL is not available in oral dosage forms and is not very effective for chronic mercury poisoning. In these cases, compounded DMPS capsule is preferred due to simple procedure for long-term therapy.  
Dimercapto-1-propanesulfonic acid (DMPS), a chelating agent, is well characterized chemically. DMPS has been used to treat heavy metal poisoning. At doses reported in the literature for this indication, DMPS appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of DMPS's effectiveness for this indication is also reported in the literature.  
- Chemet is indicated for lead poisoning in pediatric patients and only available in oral capsule dosage form. Compounded DMPS is available in oral capsule and injection dosage forms.  
- Versenate CA injection is indicated for lead poisoning and not available in oral dosage forms. Compounded DMPS is available in oral capsule and injection dosage forms. |

<table>
<thead>
<tr>
<th><strong>Is there any other relevant information?</strong></th>
</tr>
</thead>
</table>
Pharmacy Advisory Committee assembled in 1998-2000 to examine 29 drug substances for inclusion on the 503A List. The Committee included DMPS on the list. [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm290713.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm290713.htm) |
September 30, 2014

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA’s request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.
Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

**ISSUE: The Issuance of This Proposed Rule is Premature**

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created an series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency’s activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee prior to the implementation and issuance of regulations including the creation of the bulk ingredient list.

(2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee’s review of any submitted drug, regardless of FDA’s statement in the published revised call for nominations that:

General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

David G. Miller, R.Ph.
Executive Vice President & CEO
General Background on Bulk Drug Substance

**Ingredient Name**  
Dimercapto-1-propanesulfonic acid

**Chemical/Common Name**  
Dimercapto-propanesulfonic acid (DL-2,3)Na salt

**Identifying Codes**

**Chemical Grade**  
Provided by FDA Registered Supplier/COA

**Description of Strength, Quality, Stability, and Purity**  
Provided by FDA Registered Supplier/COA

**How Supplied**  
Varies based upon compounding requirement

**Recognition in Formularies**  
Not Listed in USP/NF for this specific salt/form

Information on Compounded Bulk Drug Preparation

**Dosage Form**  
Varies based upon compounding requirement/prescription

**Strength**  
Varies based upon compounding requirement/prescription

**Route of Administration**  
Varies based upon compounding requirement/prescription

**Bibliography**

*(where available)*  
Federal Register 1999

Past and Proposed Use

The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA’s request for this information is an insurmountable hurdle that has not been requested by the PCAC.
Tab 6b

2,3-Dimercapto-1-propanesulfonic acid (DMPS)

FDA Review
I. INTRODUCTION

Dimercapto-1-propanesulfonic acid (DMPS) 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). Treatment of heavy metal poisoning is the use identified in the nominations. This substance was previously reviewed by the Agency in 1998. It was included on a proposed list of bulk drug substances published in the Federal Register in January 1999 (64 FR 996 at 998). The proposed rulemaking was withdrawn in 2013.

Upon further review of the substance’s physicochemical characteristics, safety, effectiveness, and historical use in compounding, we recommend that DMPS not be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.
II. EVALUATION CRITERIA

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

2,3-Dimercapto-1-propanesulfonic acid:

\[
\text{CAS-74-61-3} \quad \text{DMPS sodium salt, CAS-4076-02-2}
\]

\[
\text{C}_3\text{H}_7\text{O}_3\text{S}_3, 188.289 \text{ g/mol} \quad \text{C}_3\text{H}_7\text{O}_3\text{S}_3\text{Na}, 201.3 \text{ g/mol}
\]

DMPS sodium salt, monohydrate, \text{C}_3\text{H}_7\text{NaO}_3\text{S}_3\text{H}_2\text{O} has a molecular weight of 228.30 and the CAS Registry number is 207233-91-8. DMPS is more commonly supplied as its sodium salt (monohydrate) [CAS-207233-91-8]. There is a current Material Safety Data Sheet (MSDS) for DL-2,3-Dimercapto-1-propanesulfonic acid, sodium salt, monohydrate.

(1) Stability of the API and likely dosage forms

According to the manufacturer’s (Heyl) Scientific Product Monograph, \(^1\) DMPS is stable in the crystalline form, relatively stable in aqueous solutions, but labile to oxidation. The drug product, as manufactured by Heyl and approved by the German authorities (100 mg solid oral capsules), has a listed shelf life of three years with storage at room temperature.

(2) Probable routes of API synthesis

The technical monograph from Heyl lists a three-step linear synthesis starting with allyl bromide. As stated in Heyl’s monograph and references contained within, excerpted below, this is similar to previously published syntheses for DMPS:

\(^1\) Available at http://www.heyl-berlin.de/pdfs/Monographie-DMPS-2008-Eng_klein.pdf. We note that the Heyl Scientific Product Monograph has no official status in the United States, and its DMPS product (Dimaval) is not approved for use in this country. Throughout this review, we rely on information in the Heyl Scientific Product Monograph where necessary to supplement information from other sources. Other sources consulted include the Merck Index, which includes limited background information, We also reviewed the World Health Organization’s (WHO) International Programme on Chemical Safety’s April 2009 draft publication on the health effects of dimercapto-1-propanesulfonic acid (CAS 4076-02-2). We note that the 2009 WHO publication is a draft for review and includes cautionary language about citations to that source.
(3) Likely impurities

As discussed in the Heyl monograph excerpted above, in Heyl’s process, the drug substance is purified by release from the lead salt. Thus, the substance could contain residual metals (specifically, lead). Other potential in-process impurities could include allyl bromide, allyl sulfonic acid, and 2,3-dibromopropane-1-sulfonic acid. Potential contamination with heavy metals can be monitored using USP compendial procedures (USP <231>).

(4) Toxicity of those likely impurities

Several of these intermediates and likely impurities (allyl bromide, allyl sulfonic acid, and 2,3-dibromopropane-1-sulfonic acid) are available commercially. Material Safety Data Sheets (MSDS) are available for allyl bromide and allyl sulfonic acid. Allyl bromide is mutagenic, and the MSDS states that it is possibly carcinogenic. For possible repeated administration of DMPS, genotoxicity and possible carcinogenicity are toxicities of concern related to allyl bromide.

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

DMPS is non-hygroscopic, exists as a monohydrate, is freely soluble in water, is sparingly soluble in methanol, is minimally soluble in ethanol, and is insoluble in non-polar organic solvents such as ether. Its octanol-water coefficient is 0.083; it can be determined using a variety of techniques (iodometric titration of –SH groups, HPLC in comparison with a standard, photometrically at 412 nm, titration (N-bromosuccinimide, copper sulfate), and colorimetrically after forming iron complexes).

Conclusions: DMPS is described in the chemical literature from over 60 years ago, is available from multiple sources world-wide, is described in the Merck Index, and is approved for manufacture and marketing in Germany. The substance is well defined and

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Note that while the Heyl process uses precipitation of 2,3-dimercapto-1-propanesulfonic acid as the lead salt, other syntheses might use a different method of purification that might not raise the same concerns about lead contamination.
can be identified consistently. There are many analytical methods available for detecting and quantifying DMPS. Technical information on the synthesis and properties of DMPS are available in English from Heyl. Although there are some concerns related to the toxicities of allyl bromide, as discussed above, potential contamination with heavy metals can be monitored using USP compendial procedures.

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

1. Nonclinical Assessment

Information contained within this assessment is paraphrased from the World Health Organization’s (WHO) International Programme on Chemical Safety’s April 2009 draft publication on the health effects of dimercapto-1-propanesulfonic acid (CAS 4076-02-2), which, as noted above, is a draft circulated for review and has not been finalized to date. A curated list of references is available in the WHO document. We found no relevant scientific journal articles published after that date. Heyl’s Scientific Product Monograph for DMPS, referenced above, provides supplemental information where necessary.

(1) Pharmacology of the drug substance

The mechanism of action of DMPS has not been fully characterized. The studies on the mechanism of action have focused on the interaction of DMPS with arsenic and mercury. DMPS increases the urinary elimination of arsenic and interferes with arsenic methylation, leading to changes in the concentrations of organoarsenic metabolites in the urine. For mercury, DMPS promotes excretion and protects against mercury-induced renal damage by inhibiting mercury accumulation in renal proximal and distal tubular cells.

(2) Safety pharmacology

According to the Scientific Product Monograph for Dimaval, at therapeutic doses of 5 mg/kg DMPS, no adverse effects on the cardiovascular system were noted. DMPS did not show neurotoxic effects in vitro or in mice.

(3) Acute toxicity

DMPS has relatively low acute toxicity. The LD50 for parenteral administration of DMPS is approximately 1 to 2 g/kg for various species.

(4) Repeat dose toxicity

Chronic toxicity of DMPS is relatively low. Oral administration of DMPS (126 mg/kg/day) on 5 days per week for 66 weeks in rats did not produce any adverse effects. In beagle dogs treated for 6 months with doses up to 15 mg/kg/day intravenously or 45 mg/kg/day orally, no changes were observed in body weight gain, hematology (red and white cell parameters), clinical chemistry (i.e., glucose, uric acid, creatinine, total protein, electrolytes, and liver enzymes), or macroscopic and microscopic examination of organs. Intravenous administration of 150 mg/kg/day DMPS for 10 weeks in the dog increased
the iron content of the liver and spleen, and decreased hemoglobin, hematocrit, red blood cells, and alkaline phosphatase activity in the blood.

(5) Mutagenicity
DMPS did not show evidence for mutagenicity in the Ames test.

(6) Developmental and reproductive toxicity
DMPS does not show reproductive toxicity or teratogenicity. No teratogenic effects were reported in the offspring of female rats administered DMPS (126 mg/kg/day) orally 5 days per week from 14, 26, or 60 weeks prior to mating through pregnancy and nursing. Additionally, no teratogenic effects were reported in rabbits administered DMPS at doses up to 100 mg/kg/day intravenously from Days 6 to 18 of gestation.

(7) Carcinogenicity
No information available.

(8) Toxicokinetics
The pharmacokinetics of DMPS has been measured in various animal species. Following oral administration, absorption of the DMPS dose was 30% in rats and 60% in dogs, and peak plasma concentrations were reached after 30 to 45 minutes. Following intravenous administration, DMPS is mainly distributed into the plasma and kidneys, with only small concentrations measured in the brain and other organs. The elimination of DMPS is rapid with a serum half-life of approximately 20 to 60 minutes.

Conclusions: There are no pharmacology/toxicology concerns with the use of DMPS in pharmacy compounding of drug product formulations based on the nonclinical pharmacology and toxicology data summarized in the April 2009 WHO document and Heyl’s Scientific Monograph. As noted above, however, the WHO document is a draft circulated for review and has not been finalized, and the Heyl monograph has no official status in the United States.

2. Human Safety
PubMed was the public database searched in the preparation of the clinical portion of this review.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for DMPS and retrieved two cases.

FDA’s Center for Food Safety and Nutrition was also consulted to search their adverse event data base (CAERS) for adverse events associated with DMPS and retrieved zero relevant cases.
Reported adverse reactions

Most adverse reactions associated with the administration of DMPS generally appear to be relatively mild or moderate in severity, but serious and life-threatening reactions have occurred. The following adverse events have been reported in the literature: dermatologic reactions, including maculopapular skin rash, pruritus and blisters; nausea and vomiting, possibly dose-related; hypotension, when DMPS was given rapidly intravenously (reduced by slowing the infusion); mild increase in serum transaminases; transient bronchospasm; fever; and leucopenia.

An additional concern noted with the use of DMPS is that the drug may chelate a heavy metal from a site of storage, thereby raising plasma levels and possibly allowing re-deposition in another organ, which could impair that organ’s function. Such an event has only rarely been described. DMPS may cause the excretion of trace metals (zinc, copper, magnesium) but the clinical consequence of this is unknown.

Though most events appear to be non-serious, there have been reports in the literature of serious or life-threatening adverse events, and one patient died after starting DMPS therapy. At least one case of Stevens-Johnson and one case of erythema multiforme have been reported (Linde A et al., 2008). Although the patient with Stevens-Johnson recovered, that condition is serious and can be fatal. In 2012, Alhamad et al., reported a second case of severe diffuse desquamation starting two days after start of DMPS. The patient died on the third day after the start of DMPS therapy. Although multiple issues might have led to this patient’s death, the contribution of DMPS cannot be excluded.

One FAERS case was of a 56-year-old female who received intravenous solutions of DMPS and EDTA and experienced low blood pressure (“around” 70/30). The patient received an epinephrine injection and recovered. The second FAERS case is the report of a fatal case of mercury poisoning. The 36-year-old male initially presented to an emergency department (ED) after injecting himself with elemental mercury and received diphenhydramine, and 10 days later re-presented to the ED. He was found to have mercury deposits in his lungs and heart cavities, was hospitalized, received various therapies, including DMPS on day 12 after hospital admission, and died on day 18 after admission.

Clinical trials assessing safety

There are no clinical trials that adequately assess safety. See the Appendix for a full list of studies reviewed. In most publications, there is no description of adverse reactions or methods used to assess adverse reactions. As discussed further below, most of the studies consist of a small number of subjects with no control groups, or included only one or several patients who had received DMPS after exposure to one or another heavy metal. Most of the reports provide some information on the blood levels and urinary excretion of the heavy metal involved, but response of clinical symptoms and clinical laboratory findings are often not included.
(3) Pharmacokinetic data

Oral bioavailability of DMPS is approximately 39% of administered dose but with a very broad range (19-62%) of absorption. $C_{\text{max}}$ occurs at 3-4 hours. The drug is 90% protein bound. The volume of distribution is 2.67-15.4 L/kg. The elimination half-life is between 4.4 and to 9.6 hours. Twelve (12) percent is excreted as the parent compound with the remainder as the disulfide metabolite (which is excreted more slowly). Most of the drug is eliminated via the kidney with about 10% eliminated via the biliary tract (Jekat FW et al., 2009)

(4) The availability of alternative approved therapies that may be as safe or safer

Depending upon the heavy metal being targeted for elimination from the body, the following FDA-approved therapies are available:

- Calcium disodium Versenate (edetate disodium calcium) approved in 1953

  Edetate disodium calcium is indicated for the reduction of blood levels and depot stores of lead in lead poisoning (acute and chronic) and lead encephalopathy, in both pediatric populations and adults.

- Chemet (2,3-dimercaptosuccinic acid; succimer; DMSA) approved in 1991

  Chemet is indicated for the treatment of lead poisoning in pediatric patients with blood lead levels above 45 μg/dL. Chemet is not indicated for prophylaxis of lead poisoning in a lead-containing environment; the use of Chemet should always be accompanied by identification and removal of the source of the lead exposure.

- BAL (British Anti-Lewisite; dimercaprol) approved in 1946

  BAL in Oil (Dimercaprol Injection USP) is indicated in the treatment of arsenic, gold, and mercury poisoning. It is indicated in acute lead poisoning when used concomitantly with Edetate Calcium Disodium Injection USP. Dimercaprol Injection USP is effective for use in acute poisoning by mercury salts if therapy is begun within one or two hours following ingestion. It is not very effective for chronic mercury poisoning. Dimercaprol Injection USP is of questionable value in poisoning caused by other heavy metals such as antimony and bismuth. It should not be used in iron, cadmium, or selenium poisoning because the resulting dimercaprol-metal complexes are more toxic than the metal alone, especially to the kidneys.

- Cuprimine (penicillamine) approved in 1970

  Cuprimine is indicated in the treatment of Wilson's disease, cystinuria, and in patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy. Available evidence suggests that Cuprimine is not of value in ankylosing spondylitis.

- Syprine (trientine dihydrochloride) approved in 1985
It is indicated for the treatment of Wilson’s disease in patients who are intolerant of penicillamine. In contrast to penicillamine, trientine does not appear to be useful in the treatment of cystinuria or rheumatoid arthritis.

**Conclusions:** None of the safety data reported about DMPS is from adequate and well-controlled trials. At best, the data are anecdotal. Reportedly, most adverse reactions associated with its use are not common and are usually mild or moderate in severity. However, there have been reports of severe and fatal dermatologic reactions. Rapid infusion rate may be associated with hypotension. DMPS may also be associated with re-deposition of heavy metals stored in the body, or excretion of heavy metals, the clinical consequences of which are unknown.

**C. Are there concerns about whether the substance is effective for a particular use?**

(1) Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

There are no adequate scientific studies that demonstrate the effectiveness of the bulk drug substance as it is used in drug products. See the Appendix for a full list of the studies reviewed.

Based on the review of various sources as described above, in the United States, the drug products compounded from DMPS bulk drug substance are used for the treatment of presumed mercury toxicity due to amalgam dental fillings and for treatment of persons with autistic disorders. There are no adequate and well-controlled efficacy studies in either of these conditions that support therapeutic use of DMPS. The studies that have been conducted are insufficient to determine the effectiveness of DMPS in its various applications, most of which were for the removal of purported heavy metal excess in humans, due either to acute or chronic exposure, usually in the setting of ingestion of food or water, accidental or intentional heavy metal intake, or the use of mercury-containing amalgam used for dental fillings.

Although there were several studies that included a control group (Guha 2001; Schuurs 2000), most of the publications referenced only one individual (Hohage 1997; Pai 2000; Walshe, 1985; Wax 2000) or a small group (Chisolm 1985; Garza-Ocanus, Torres-Alanis) of affected individuals, all of whom had been treated with DMPS. For efficacy assessment, various methods (change in serum levels of heavy metals (Walshe 1985; Slikkerveer 1998), serum half-life of heavy metal (Clarkson 1981; Toet 1994), urinary excretion of heavy metal (Aposhian 1998; Chisolm 1985; Drasch 2007; Garcia-Ocanus 1997; Guha 2001; San Qing 2013; Schuurs 2000; Slikkerveer 1998; Torres-Alanis 2000; Vannes 2000)) were used even though there was no clear relationship between these parameters and the clinical conditions of the subjects (Schuurs 2000; Vannes 2000).

For many of the studies, there was little description of the clinical status of the subjects and their response to DMPS therapy. Most of the studies showed that DMPS was capable of increasing urinary or biliary excretion of heavy metals above levels that were measured at baseline before therapy, but whether or not survival was improved or
morbidity was diminished remains uncertain since time alone acts to reduce levels of heavy metals in the body when patients are removed from exposure.

It is of note that many of the reports originate outside the United States, possibly because heavy metal exposures are more common in other countries. Also, an oral DMPS product, Dimaval, is available in some countries outside the United States. A review of listings for DMPS in an internet search using Google (accessed November 10, 2014) suggests that, in the United States, the condition most often associated with therapy with DMPS is presumed “mercury intoxication” in persons who have had dental fillings with amalgam, a material that contains significant amounts of mercury. The largest trials of the use of DMPS in this setting (Schuurs 2000; Vammes 2000) do not identify a benefit, either clinical or by measure of excretion of mercury, due to such therapy.

(2) Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

As stated above, a review of various sources found that in the United States, the drug products compounded from DMPS bulk drug substance are predominantly used for the treatment of presumed mercury toxicity due to amalgam dental fillings and for treatment of persons with autistic disorders. Presumed mercury toxicity due to amalgam dental fillings is a situation that has not been substantiated as a medical condition requiring therapy. Summary minutes from a joint meeting of the Dental Products Panel of the Medical Devices Advisory Committee of the Center for Devices and Radiological Health and the Peripheral and Central Nervous System Drugs Advisory Committee of the Center for Drug Evaluation and Research held on September 6-7, 2006, stated, “The Committee’s consensus was that the direct evidence . . . neither supports nor refutes adverse health effects. The studies do not support any finding of adverse effects from dental amalgam. However, the lack of evidence is not a refutation.”

Autistic disorders are serious diseases for which there are no specific treatments available. Concerns about potential neurotoxic effects and possible association with autism of thimerosal (ethyl mercury), which is used as a preservative in multidose vials of some vaccines, have been voiced in the literature and the media, but studies to assess the harms of thimerosal-containing vaccines have failed to find such associations.

(3) Whether there are any alternative approved therapies that may be as effective or more effective

See response to B.2:(4) above regarding treatment of heavy metal poisoning. There have been no trials performed to compare the relative efficacy of DMPS and FDA-approved chelators.

Conclusions: There are no adequate scientific studies that demonstrate the effectiveness of the DMPS bulk drug substance as it is used in any drug product.
D. **Has the substance been used historically in compounding?**

(1) **Length of time the substance has been used in pharmacy compounding**

DMPS has been used in pharmacy compounding for a number of years as evidenced by the Agency’s prior discussion of compounding DMPS at the 1998 PCAC meeting. According to transcripts from the 1998 PCAC meeting, an individual at this meeting stated that DMPS has been used in compounding since the mid-1980s. Results from a Google search using the terms “compounding pharmacy DMPS” indicate that it is currently being compounded. As stated above, DMPS was described in literature over 60 years ago.

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

There are no approved indications for the use of DMPS. However, based on publications and internet listings, it appears that compounding pharmacies have been preparing various formulations of DMPS (capsules, solution for IV/IM use, dermatological preparations, suppositories) mainly for presumed mercury intoxication and for autism spectrum disorders.

(3) **How widespread its use has been**

We have no way of quantifying the degree to which DMPS has been employed for presumed medical uses.

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

Germany (via the Federal Institute for Drugs and Medical Devices or Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)) has granted approval for the use of DMPS in patients with acute and chronic poisoning with mercury or lead. DMPS appears to be used in different countries for acute and chronic poisoning with other heavy metals in addition to mercury and lead (arsenic, copper).

**Conclusions:** DMPS has been used for many years in various parts of the world for the treatment of acute and chronic poisoning with heavy metals. It is marketed in Europe as Dimaval for some of these uses.

**III. RECOMMENDATION**

We recommend that DMPS **not be placed** on the list of bulk drug substances allowed for use in compounding. Although the substance is well characterized physically and chemically and has been used in compounded drug products for a number of years, our recommendation is based on the absence of a clear benefit associated with the use of DMPS, inadequate investigation of safety with the use of the substance, and the availability of approved medications for heavy metal intoxication that are supported by substantial evidence of safety and effectiveness.
Although studies have generally shown that DMPS increases the urinary excretion of various heavy metals with a reported low incidence of adverse reactions, these studies are not considered to have been adequately designed to demonstrate the efficacy and safety of the use of DMPS. At best, the data are anecdotal. As discussed above, serious and life-threatening dermatologic reactions, including one fatality, have been reported.

There are several FDA-approved products on the U.S. market for the treatment of heavy metal intoxication, and there are no trials comparing the safety and efficacy of DMPS with those of the FDA-approved products. Additionally, there are no credible studies supporting the use of DMPS for the treatment of autism, a serious condition where DMPS has been used without credible evidence of benefit.
BIBLIOGRAPHY


## APPENDIX

### Table of References Cited in Support of the Efficacy and Safety of the Use of DMPS

<table>
<thead>
<tr>
<th>Citation</th>
<th>Number of DMPS-treated Subjects</th>
<th>Indications</th>
<th>Dose</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aposhian, 1998</td>
<td>20 adults in Mongolia</td>
<td>High arsenic in drinking water</td>
<td>300 mg single dose orally</td>
<td>Increase in urine arsenic from 50 to 265 micrograms/2 hours</td>
<td>Not reported</td>
<td>Single dose only study</td>
</tr>
<tr>
<td>Chisolm, 1985</td>
<td>12 pediatric subjects in Baltimore</td>
<td>Lead poisoning (serum lead 40-60 micrograms/dL)</td>
<td>200-400 mg/M² for 5 days orally</td>
<td>Increase in urine lead by 1.3-15 fold over baseline</td>
<td>2 subjects with mild increase in AST. No other AEs</td>
<td>No symptomatic AEs. Increase in urinary Zn and Cu</td>
</tr>
<tr>
<td>Clarkson, 1981</td>
<td>10 subjects ages 1.5-55 years in Iraq</td>
<td>Mercury poisoning from insecticide</td>
<td>50 mg/10kg 3x/dx1, 2x/dx1, then 1x/d given IM</td>
<td>Reduction in mercury blood level half time from 60.3 d to 9.8 d</td>
<td>No symptomatic or laboratory AEs</td>
<td>Greater excretion of inorganic mercury than organic mercury</td>
</tr>
<tr>
<td>Drasch, 2007</td>
<td>75 children and adults in Philippines</td>
<td>Occupational/environmental exposure to mercury</td>
<td>200 mg/d orally for 14 days, 5 mg/kg/d for children</td>
<td>20 fold increase in urinary mercury (37.5 to 909 micrograms Hg/g Cr)</td>
<td>Not assessed</td>
<td>Number of therapeutic cycles not specified</td>
</tr>
<tr>
<td>Garza-Ocanus, 1997</td>
<td>8 subjects age 19-35 years from Mexico</td>
<td>Mercury excess from facial cream</td>
<td>200 mg/d for 5 day cycles orally</td>
<td>Increase in urinary Hg 1.5-10 fold</td>
<td>No adverse reactions reported</td>
<td>Number of therapeutic cycles not specified</td>
</tr>
<tr>
<td>Guha, 2001</td>
<td>11 subjects ages 18 years and above in India</td>
<td>Arsenic poisoning due to drinking water</td>
<td>100 mg 4x/d for 1 week, then repeated in weeks 3, 5 and 7 orally; consumption of arsenic-contaminated water also discontinued</td>
<td>Urinary arsenic rose from baseline of 44.05 +/- 21.1 to 110.32 +/- 64.79 micrograms/L in patients receiving DMPS; no change in patients who received placebo; improvement in “clinical scores” in both groups, greater with DMPS compared to placebo.</td>
<td>No adverse reactions based on symptoms or hematology/chemistry data</td>
<td>10 subjects included in placebo group</td>
</tr>
<tr>
<td>Hohage, 1997</td>
<td>Single 39 year old male in Germany</td>
<td>Suicide attempt with IV mercury 3 years earlier</td>
<td>300 mg/d x 6 months orally</td>
<td>Urinary Hg increased from 603 to 2,240 micrograms/L. Blood Hg fell from 96.3 to 46.3</td>
<td>Reportedly had no adverse reactions</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Age</td>
<td>Gender</td>
<td>Method</td>
<td>Blood Hg</td>
<td>Adverse Reactions</td>
</tr>
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<tr>
<td>Pai, 2000</td>
<td>Single 48 year old male</td>
<td>Deliberate ingestion of 10 mL inorganic mercury</td>
<td>250 mg q6h x 7 d, q8h x 1 d, q 12 h x 8d, then daily x 7d IV</td>
<td>Blood Hg decreased from approximately 5,000 to 990 micrograms/L</td>
<td>No report of adverse reactions</td>
<td>Patient also dialyzed for acute renal failure. HD not successful, but CVVH effective</td>
</tr>
<tr>
<td>San-qing, 2013</td>
<td>35 children ages 7-17 years in China</td>
<td>Wilson’s disease</td>
<td>Repetitive alternating courses of PCNamine and DMPS (up to 20 mg/kg/d for 6 days) IV</td>
<td>With DMPS, 24 hr urinary Cu increased from a mean of 677 to 1995 micrograms/d. Improvement in LFTs and neurological function</td>
<td>2 deaths (liver failure, encephalopathy). Skin rash in 2 subjects. Dizziness, nausea, vomiting in 4 subjects (due to too rapid infusion). Decreases in WBC and platelets attributed to PCNamine</td>
<td>Subjects were also treated with PCNamine</td>
</tr>
<tr>
<td>Schuurs, 2000</td>
<td>120 subjects in the Netherlands</td>
<td>Dental amalgams with and without symptoms</td>
<td>Single oral dose of DMPS of 300 mg or placebo</td>
<td>Urinary Hg increased 4 fold in both symptomatic and asymptomatic subjects;</td>
<td>42% of DMPS treated and 27% of placebo treated subjects developed adverse reactions</td>
<td>Symptoms improved after DMPS but causal relationship to drug not likely, as no clear relationship between symptoms reported and amalgam fillings</td>
</tr>
<tr>
<td>Slikkerveer, 1998</td>
<td>24 subjects in the Netherlands</td>
<td>Treated with bismuth for H. Pylori</td>
<td>Half treated with DMPS, half treated with DMSA at a single dose of 30 mg/kg orally</td>
<td>No increase in blood bismuth after DMPS, but increase with DMSA. Both agents increased urine bismuth x 50 compared to control subjects</td>
<td>Treatment was “well tolerated” although 7 subjects experienced diarrhea, headache or nausea (author does not state whether adverse events occurred in the DMPS or DMSA treated persons)</td>
<td></td>
</tr>
<tr>
<td>Toet, 1994</td>
<td>Single 38 year old male from the Netherlands</td>
<td>Non-accidental ingestion of 100 mL Hg chloride</td>
<td>IV 250 mg q4h x12, q6h x8, q 8h thereafter for 4 weeks, then 300 mg tid po for total of 7 weeks</td>
<td>Half-life of Hg initially 2.5 days, then 8.1 days compared to 40-60 days if untreated</td>
<td>Only adverse reaction was erythema</td>
<td>80% of Hg excreted non-renally, probably mostly biliary. No Hg detected in dialysate</td>
</tr>
<tr>
<td>Torres-Alanis, 2000</td>
<td>8 females, 3 males, all adults from Mexico</td>
<td>Mercury dental amalgams</td>
<td>Single IV dose of 3 mg/kg</td>
<td>Urinary excretion of Hg increased from 33.89 to 486.33 micrograms Hg in 1 hour</td>
<td>No adverse reactions reported</td>
<td>Also increased excretion of Zn, Cu, Selenium and Magnesium</td>
</tr>
<tr>
<td>Vammes, 2000</td>
<td>80 subjects from Norway, including healthy</td>
<td>Mercury dental amalgams</td>
<td>Single IV dose of 2 mg/kg</td>
<td>Urinary excretion of Hg increased 4-6 fold in subjects with amalgams</td>
<td>One subject developed bronchospasm 5 minutes after commencement of</td>
<td>The increase in Hg excretion was not related to whether or not the</td>
</tr>
</tbody>
</table>
controls, those without amalgam, those with amalgam without symptoms and those with amalgam with symptoms and in subjects without amalgams, but baseline excretion was lower in subjects without amalgams

| Walshe, 1985 | 13 yr old male in England with Wilson’s disease | Needed alternate chelator after developing lupus on penicillamine | 200 mg bid continuously orally | Normalization of serum copper, symptomatic improvement | No adverse reactions in proband. Author reports fever and leucopenia in 1 treated subject and intense nausea in another |
| Wax, 2000 | 33 yr old female in Rochester, NY | Arsenic poisoning, cause uncertain (possibly well water) | 250 mg q4h orally for 12 days | Symptomatic recovery from polyneuropathy. Urinary arsenic increased 3 fold | None reported | Drug used under emergency IND |