FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

October 27 and 28, 2015

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

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I. 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).

A. Withdrawn and Removed List

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drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective" ("the withdrawn or removed list") (section 503A(b)(1)(C)).

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

Another of the conditions that must be met for a compounded drug product to qualify for these exemptions is that a licensed pharmacist or licensed physician compounds 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 may 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.

No single one of these criteria is dispositive. Rather, 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.

II. Quinacrine – Drug Proposed Both for the Withdrawn or Removed List and for the Section 503A Bulk Drug Substances List

Information on this topic to be supplied later in an updated version of the briefing document (Tab 1)

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

A. Methylsulfonylmethane (MSM) (Tab 2)

1. Nominations (**Tab 2a**)
   (a) American College for Advancement in Medicine
   (b) Alliance for Natural Health USA
   (c) Integrative Medicine Consortium
   (d) American Association of Naturopathic Physicians
   (e) McGuff Compounding Pharmacy Services, Inc.
   (f) Professional Compounding Centers of America (PCCA)
   (g) International Academy of Compounding Pharmacists (IACP)

2. FDA Review (**Tab 2b**)

B. Curcumin (Tab 3)

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

2. FDA Review (**Tab 3b**)

C. Germanium Sesquioxide (Tab 4)

1. Nominations (**Tab 4a**)
    (a) IACP
    (b) Integrative Medicine Consortium
    (c) Alliance for Natural Health USA
    (d) McGuff Compounding Pharmacy Services, Inc.
    (e) American Association of Naturopathic Physicians
    (f) American College for Advancement in Medicine

2. FDA Review (**Tab 4b**)

D. Rubidium Chloride (Tab 5)

1. Nominations (**Tab 5a**)
    (a) Integrative Medicine Consortium
    (b) Alliance for Natural Health USA
    (c) McGuff Compounding Pharmacy Services, Inc.
    (d) American Association of Naturopathic Physicians
    (e) American College for Advancement in Medicine

2. FDA Review (**Tab 5b**)

E. Deoxy-D-Glucose (Tab 6)

1. Nominations (**Tab 6a**)
    (a) Fagron, Inc.
    (b) National Community Pharmacists Association (NCPA)
    (c) PCCA
    (d) IACP

2. FDA Reviews (**Tab 6b**)

F. Alanyl-L-Glutamine (Tab7)

Information on this topic to be supplied later in an updated version of the briefing document

G. Glutaraldehyde (Tab 8)

1. Nominations (Tab 8a)
   (a) PCCA
   (b) NCPA
   (c) IACP

2. FDA Review (**Tab 8b**)

H. Glycyrrhizin (Tab 9)

1. Nominations (**Tab 9a**)
   (a) Integrative Medicine Consortium
   (b) Alliance for Natural Health USA
   (c) McGuff Compounding Pharmacy Services, Inc.
   (d) American Association of Naturopathic Physicians
   (e) American College for Advancement in Medicine

2. FDA Review (**Tab9b**)

I. Domperidone (Tab 10)

1. Nominations (**Tab 10a**)
   (a) Fagron, Inc.
   (b) NCPA
   (c) PCCA
   (d) IACP

2. FDA Review (**Tab 10b**)

Tab 1

Quinacrine

Materials on Quinacrine To Be Supplied Later

Tab 2

Methylsulfonylmethane (MSM)

Tab 2a

Methylsulfonylmethane (MSM) Nominations

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September 30, 2014

Division of Dockets Management (HFA-305)
Food And Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Re: Docket FDA-2013-N-1525

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

To Whom It May Concern:

The American College for Advancement in Medicine (ACAM) is a prominent and active medical education organization involved in teaching physicians in the proper use of oral and intravenous nutritional therapies for over forty years. We have also been involved in clinical research sponsored by the National Heart Lung and Blood Institute. As such, we have a vested interest in maintaining the availability of compounded drug products.

We appreciate 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. To meet what appear to be substantial requirements involved in this submittal, the FDA has given compounding pharmacists (in general a small business operation) and physicians very limited time to comply with onerous documentation. The Agency has requested information for which no single pharmacy or physician organization can easily provide in such a contracted time frame. As such this time consuming process requires significant coordination from many practicing professionals for which adequate time has not been allotted.

This issue is of great importance and has the potential to drastically limit the number of available compounded drugs and drug products thus limiting the number of individualized treatments that compounded medicines offer to patients.
ACAM and its physician members have not had the time to collect, review and assess all documentation necessary to submit for the intended list of compounded drugs required to assure all patient therapies are represented in our submission. We respectfully seek an additional 120 day period to educate and coordinate our physicians on the issue at hand and to gather the essential information necessary to provide the Agency with the most comprehensive information.
In an attempt to comply with the current timeframe established, a collaborative effort resulted in the attached nominations prepared for bulk drug substances that may be used in pharmacy compounding under Section 503A.

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It is not clear whether the current submission will be the final opportunity to comment or communicate with the Agency. Will a deficiency letter be provided if the initial nomination information was inadequate or will a final decision to reject a nominated substance be made without the opportunity to further comment? ACAM respectfully requests that the FDA issue a deficiency letter should the submitted documentation for a nomination be considered inadequate.

Sincerely,

Neal Speight, MD
(Immediate Past President) for
Allen Green, MD
President and CEO
The American College for Advancement in Medicine

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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.

As discussed in detail below, in the interest 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.,[1] 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.

VIA WWW.REGULATIONS.COM

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

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,[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

[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:

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
Glutiathone
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

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.

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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?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Methylsulfonylmethane
Is the ingredient an active ingredient that meets the definition of ‘‘bulk drug substance’’ in § 207.3(a)(4)?	Yes. There is ample information regarding the active properties of methylsulfonylmethane on Pubmed. Key word: methylsulfonylmethane. Or: see section "safety and efficacy data" below.
Is the ingrdient listed in any of the three sections of the Orange Book?	Not for methylsulfonylmethane, MSM
Were any monographs for the ingredient found in the USP or NF monographs?	Dietary monograph for methylsulfonylmethane available in the USP. Dietary monograph for methylsulfonylmethane tablets available in the USP.
What is the chemical name of the substance?	Sulfonylbismethane
What is the common name of the substance?	MSM, Methylsulfonylmethane, Dimethyl sulfone, Methyl sulfone, DMSO2
Does the substance have a UNII Code?	9H4PO4Z4FT
What is the chemical grade of the substance?	This bulk drug substance is labeled for Food and Cosmetic Use Only by the manufacturer.
What is the strength, quality, stability, and purity of the ingredient?	This bulk drug substance is non-GMO, Kosher. The manufacturer is ISO certified and FDA-registered as dietary and/or nutritional supplement manufacturing establishment. A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Methylsulfonylmethane is supplied as a white flake or crystalline solid.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	Dietary monograph for this bulk drug substance available in the USP. Dietary monograph for Methylsulfonylmethane tablets available in the USP. EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.
Has information been submitted about the substance to the USP for consideration of monograph development?	There is a Dietary USP monograph for methylsulfonylmethane
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	Methylsulfonylmethane 150 mg/mL in normal saline or in sterile water for injection, preservative free

What are the anticipated route(s) of administration of the compounded drug product(s)?	Slow intravenous
Are there safety and efficacy data on compounded drugs using the nominated substance?	1. Engelke UF, Tangerman A, Willemsen MA, et al. Dimethyl sulfone in human cerebrospinal fluid and blood plasma confirmed by one-dimensional (1)H and two-dimensional (1)H-(13)C NMR. NMR Biomed. 2005;18(5):331-336.[PubMed 15996001] 2. Richmond VL. Incorporation of methylsulfonylmethane sulfur into guinea pig serum proteins. Life Sci. 1986;39(3):263-268.[PubMed 3736326] 3. Bertken R. "Crystalline DMSO": DMSO2. Arthritis Rheum. 1983;26(5):693-694.[PubMed 6847737] 4. Usha PR, Naidu MU. Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. Clin Drug Investig. 2004;24(6):353-363.[PubMed 17516722] 5. Ebisuzaki K. Aspirin and methylsulfonylmethane (MSM): a search for common mechanisms, with implications for cancer prevention. Anticancer Res. 2003;23(1A):453-458.[PubMed 12680248] 6. Alam SS, Layman DL. Dimethyl sulfoxide inhibition of prostacyclin production in cultured aortic endothelial cells. Ann N Y Acad Sci. 1983;411:318-320.[PubMed 6410965] 7. Beilke MA, Collins-Lech C, Sohnle PG. Effects of dimethyl sulfoxide on the oxidative function of human neutrophils. J Lab Clin Med. 1987;110(1):91-96.[PubMed 3598341] 8. Kim LS, Axelrod LJ, Howard P, Buratovich N, Waters RF. Efficacy of methysulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial. Osteoarthritis Cartilage. 2006;14(3):286-294.[PubMed 16309928] 9. Xie Q, Shi R, Xu G, Cheng L, Shao L, Rao J. Effects of AR7 joint complex on arthralgia for patients with osteoarthritis: results of a three-month study in Shanghai, China. Nutr J. 2008;7:31.[PubMed 18954461] 10. O'Dwyer P, McCabe DP, Sickle-Santanello BJ, Woltering EA, Clausen K, Martin EW Jr. Use of polar solvents in chemoprevention of 1,2-dimethylhydrazine-induced colon cancer. Cancer. 1988;62(5):944-948.[PubMed 3409175] 11. McCabe D, O'Dwyer P, Sickle-Santanello B, Woltering E, Abou-Issa H, James A. Polar solvents in the chemoprevention of dimethylbenzanthracene-induced rat mammary cancer. Arch Surg. 1986;121(12):1455-1459.[PubMed 3098207] 12. Klandorf H, Chirra AR, DeGruccio A, Girman DJ. Dimethyl sulfoxide modulation of diabetes onset in NOD mice. Diabetes. 1989;38(2):194-197.[PubMed 2914623] 13. Berardesca E, Cameli N, Cavallotti C, Levy JL, Piérard GE, de Paoli Ambrosi G. Combined effects of silymarin and methylsulfonylmethane in the management of rosacea: clinical and instrumental evaluations. J Cosmet Dermatol. 2008;7(1):8-14.[PubMed 18254805] 14. Fleck CA. Managing ichthyosis: a case study. Ostomy Wound Manage. 2006;52(4):82-86, 88, 90.[PubMed 16636365] 15. Traub-Dargatz JL, McKinnon AO, Thrall MA, et al. Evaluation of clinical signs of disease, bronchoalveolar and tracheal wash analysis, and arterial blood gas tensions in 13 horses with chronic obstructive pulmonary disease treated with prednisone, methyl sulfonmethane, and clenbuterol hydrochloride. Am J Vet Res. 1992;53(10):1908-1916.[PubMed 1456540] 16. Marañón G, Muñoz-Escassi B, Manley W, et al. The effect of methyl sulphonyl methane supplementation on biomarkers of oxidative stress in sport horses following jumping exercise. Acta Vet Scand. 2008;50:45.[PubMed 18992134] 17. Magnuson BA, Appleton J, Ryan B, Matulka RA. Oral developmental toxicity study of methylsulfonylmethane in rats. Food Chem Toxicol. 2007;45(6):977-984.[PubMed 17258373] 18. Horváth K, Noker PE, Somfai-Relle S, Glávits R, Financsek I, Schauss AG. Toxicity of methylfulfonylmethane in rats. Food Chem Toxicol. 2002;40(10):1459-1462.[PubMed 12387309] 19. Jacob, SW, Appleton J, MSM: The Definitive Guide, Freedon Press, 2003.
Has the bulk drug substance been used previously to compound drug product(s)?	Yes. Methylsulfonylmethane 150 mg/mL in normal saline or in sterile water for injection, preservative free
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Methylsulfonylmethane (MSM) is commonly used for osteoarthritis and disorders with collagen defects. It may also benefit in alleviating GI upset, musculoskeletal pain, and allergies; boosting the immune system; and fighting antimicrobial infection.

What is the reason for use of a compounded drug product rather than an FDA-approved product?	There is no FDA-approved drug product containing methylsulfonylmethane. MSM is a normal oxidation product of dimethyl sulfoxide (DMSO). Unlike DMSO, MSM is odor free and is a dietary factor. MSM has been referred to as "crystalline DMSO." MSM provides a dietary source of sulfur for methionine.MSM's medicinal properties are theorized to be similar to DMSO, without the odor and skin irritation complications.MSM is not an organic solvent like DMSO; MSM is safer to handle than DMSO. The sulfur content of MSM can be used by the body to maintain normal connective tissues. MSM has also exhibited possible anti-inflammatory, antiatherosclerotic, and chemopreventative activities along with free radical scavenging. MSM has been reported to alleviate allergies, arthritis, GI upset, musculoskeletal pain, and to boost the immune system. It also possesses antimicrobial effects against organisms such as Giardia lamblia, Trichomonas vaginalis, and some fungi. The suggested mechanism is that MSM may bind to surface receptor sites, blocking the interaction of parasite and host. MSM is indicated in patients whom FDA-approved drug products fail or are not appropriate.
Is there any other relevant information?	MSM is found in green plants such as Equisetum arvense, certain algae, fruits, vegetables, and grains. Other sources include the adrenal cortex of cattle, human and bovine milk, and urine. MSM is also found in human cerebral spinal fluid and plasma at 0 to 25 mcmol/L concentrations.Ref1 MSM is naturally occurring in fresh foods; however, it is destroyed with only moderate food processing, such as heating or dehydration. Research was extensively conducted at Oregon Health Science University (OHSU) Medical school. Studies at OHSU typical infusion of 100 gms with no negative outcomes or toxcicity (no LD 50 could be established). MSM has been suggested for use as a food supplement and is available in the United States as a dietary supplement under the Dietary Supplement Health and Education Act.

September 30, 2014

Submitted electronically via www.regulations.gov

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

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

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

Dear Sir or Madam:

PCCA respectfully submits the following list of nineteen chemicals to be considered for the List of Bulk Drug Substances that may be used in Pharmacy Compounding in accordance with Section 503A.

PCCA provides its more than 3,600 independent community compounding pharmacy members across the United States with drug compounding ingredients, equipment, extensive education, and consulting expertise and assistance.

Regarding the specific nominations, we would like to reference the attached spreadsheet and point out a couple of facts regarding our research. To the best of our knowledge, all items submitted:

- Do not appear in any of the three sections of the Orange Book.
- Do not currently have a USP or NF monograph.
- Meet the criteria of a "bulk drug substance" as defined in § 207.3(a)(4).

In regards to the request for chemical grade information, we would like to point out that many of the items submitted do not currently have a chemical grade. PCCA believes that pharmacists should use the highest grade chemical available on the market for all aspects of pharmaceutical compounding and we continue to actively source graded chemicals from FDA-registered manufacturers. However, in the current marketplace, some graded chemicals cannot be obtained for various reasons. PCCA actively tests all products received to ensure they meet our required standards to ensure our members receive the highest quality chemicals possible.

We would like to echo the concerns, voiced by NCPA and others in our industry, the strong recommendation to formalize the process by which the list is updated and communicated to the pharmacy industry. We also recommend an annual process to ensure understanding and adherence to the list. All submissions and updates to the list should be reviewed by the Pharmacy Compounding Advisory Committee (PCAC) and no changes to the list should occur with input and review by the PCAC.

We are also dismayed in the fact that no appointments have been made to the PCAC despite the call for nominations closing in March 2014. Without these appointments, FDA is unable to consult the Committee regarding this list, as outlined in the Act. PCCA, along with industry partners, strongly recommends that the FDA consult with the PCAC related to every single submission the Agency received in relation to FDA-2013-N-1525.

We appreciate this opportunity to submit this list for consideration and we look forward to continuing to work with the FDA in the future on this and other important issues as they relate to the practice of pharmacy compounding.

Sincerely,

Aaron Lopez
Senior Director of Public Affairs
PCCA

John Voliva, R.Ph.
Director of Legislative Relations
PCCA

PCCA Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations	
Ingredient Name	Methylsulfonylmethane
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	Dimethyl Sulfone
Common Name(s)	Methanesulfonylmethane, methyl sulfone, methylsulfonylmethane, sulfonylbismethane, DMSO2, MSM
UNII Code	9H4PO4Z4FT
Chemical Grade	N/A
Strength, Quality, Stability, and Purity	Assay, Description, Melting Point, Solubility; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmcopeias or registered in other countries	OTC in US as a dietary supplement; USP as a dietary supplement; Used in ten other countries
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Capsule, cream/gel, solution
Compounded Strengths	Capsule: 25-500 mg; Topical: 1 – 20%; Solution: 0.1 – 20%
Anticipated Routes of Administration	Oral, topical, injectable, ophthalmic
Saftey & Efficacy Data	Ezaki J, et al. Assessment of safety and efficacy of methylsulfonylmethane on bone and knee joints in osteoarthritis animal model. J Bone Miner Metab. 2013 Jan;31(1):16-25. [http://www.ncbi.nlm.nih.gov/pubmed/23011466]
	Caron JM, et al. Methyl sulfone induces loss of metastatic properties and reemergence of normal phenotypes in a metastatic cloudman S-91 (M3) murine melanoma cell line. PLoS One. 2010 Aug 4;5(8):e11788. [http://www.ncbi.nlm.nih.gov/pubmed/20694196]
	Caron JM, et al. Methyl sulfone manifests anticancer activity in a metastatic murine breast cancer cell line and in human breast cancer tissue--part 2: human breast cancer tissue. Chemotherapy. 2013;59(1):24-34. [http://www.ncbi.nlm.nih.gov/pubmed/23816712]

Used Previously to compound drug	Osteoarthritis, snoring, inflammation
Proposed use	Osteoarthritis, snoring, inflammation
Reason for use over and FDA-approved product	Treatment failures and/or patient unable to take FDA approved product
Other relevant information - Stability information	Unless other studies performed / found: Topical: USP <795> recommendation of BUD for water containing topical formulations – “no later than 30 days.” Oral Solution: USP <795> recommendation of BUD for “water-containing oral formulations” – “not later than 14 days when stored at controlled cold temperatures.” Capsules: USP <795> recommendation of BUD for nonaqueous formulations – “no later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier. Ophthalmic: USP <797> recommendations for high risk level compounded sterile products.

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CERTIFICATE OF ANALYSIS

PRODUCT: DIMETHYL SULFONE
ITEM NUMBER: 30-2998
LOT NUMBER: C153709
MFG. DATE: 04/30/2012
EXPIRATION: 02/29/2016

CAS: 67-71-0
MW: 94.1300000000
FORMULA: C2H6O2S

TEST	SPECIFICATIONS	RESULTS
Assay	>=99.0 %	100.04 %
Description	pass *WHITE TO OFF-WHITE CRYSTALS OR CRYSTALLINE POWDER*	pass *White crystals*
E.Coli	pass *Negative*	pass
Heavy Metals	>=10 ppm max	10 ppm max
Identification	pass *IR*	pass
Melting point	108-110 celsius	108.3 celsius
Moisture	<=1.0 %	0.18 %
Particle Size	pass *NLT 95% thru 40 mesh NLT 70% thru 60 mesh*	pass
Salmonella	pass *Negative*	pass
Solubility	pass *SOLUBLE IN WATER, ACETONE, METHANOL, AND ETHANOL WITH GENTLE HEAT*	pass
Total Plate Count	<1000 cfu/gm	100 cfu/gm
Yeast/Mold	<100 cfu/gm	10 cfu/gm

QC APPROVED
PRINT DATE: 3/3/2

The above test results have been obtained by our supplier or in our quality control laboratory.
This analysis is not to be construed as a warranty, expressed or implied.

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

Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Dimethyl Sulfone
Chemical/Common Name	Methylsulfonylmethane; MSM; DMSO2
Identifying Codes	67-71-0
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 *(including foreign recognition)*	USP has monograph for Dimethyl Sulfoxide

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

Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Methyl Sulfone
Chemical/Common Name	MSM; Dimethyl Sulfone; Methylsulfonylmethane
Identifying Codes	75-75-2
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 *(including foreign recognition)*	USP CAS # is 67-71-0

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)*	
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 2b

Methylsulfonylmethane (MSM)
FDA Review

DEPARTMENT OF HEALTH & HUMAN SERVICES

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SUBJECT: Review of Methylsulfonylmethane (MSM) for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

Methylsulfonylmethane (MSM), also known as dimethyl sulfone (CAS Number 67-71-0) 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). Nominator submissions state that the proposed uses of MSM are for the treatment of osteoarthritis, disorders with collagen defects, snoring, and inflammation. One of the nominations states that MSM may also provide benefit in alleviating gastrointestinal upset, musculoskeletal pain, and allergies; boosting the immune system; and fighting microbial infection. The dosage forms proposed in the nominations are injection, capsules, topical creams or gels, and solutions, with the anticipated routes of administration of oral, topical, injectable, and ophthalmic. This review focuses on the use of MSM in osteoarthritis, which appears to be its most common use, and of the variety of uses referenced in the nominations, was the use for which the most scientific support was provided.

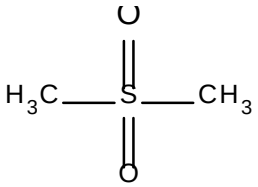
We have reviewed available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons

discussed below, we **do not recommend** that MSM 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?

MSM is a small molecule, containing only two carbons, two oxygens, and a sulfur. It is well characterized by physical and spectroscopic means.



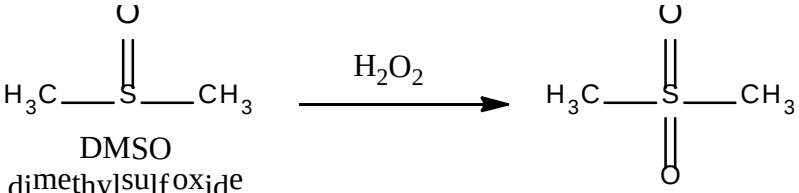
MSM
methylsulfonylmethane
methylsulfone
dimethylsulfone

1. Stability of the API and likely dosage forms

Based on its chemical structure, and on reported data, MSM is expected to have very good stability as an API and in formulated products, e.g., it is reported that chemical reactions can be usefully conducted in molten MSM (Hareau et al., 2001). As it is stable under these extreme conditions, it is likely to be very stable in all dosage forms.

2. Probable routes of API synthesis

It seems likely that MSM is most commonly produced by hydrogen peroxide oxidation of dimethylsulfoxide (DMSO).



DMSO
dimethylsulfoxide

MSM

3. Likely impurities

Given its stability, the most likely impurities are the starting materials, DMSO and hydrogen peroxide. As MSM is a white crystalline solid (m.p. = 109 °C), it is likely to contain very low amounts of either of the starting materials, both of which are liquids. The presence of these and other impurities would result in a lower melting point, and the presence of either liquid starting material would result in a non-crystalline semi-sold.

4. Toxicity of those likely impurities

DMSO and hydrogen peroxide have relatively low toxicities. However, without knowing the specific amounts in a product, it is not possible to state that there are no risks for these compounds for all proposed routes of administration. As such, a comprehensive review of the toxicological properties of possible impurities has not been completed to support this memorandum.

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

There appear to be no polymorphs, with only one crystalline form reported (FDA Response Letter, 2008). It is also reported to have an aqueous solubility of 150 mg/mL (Remizov et al., 1980). Consequently physicochemical characteristics are not expected to influence its performance when administered as a powder or solid oral dosage form.

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

There is no additional relevant information.

Conclusions: From the viewpoint of characterization and physicochemical properties, MSM is suitable for use in compounding.

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

1. Nonclinical Assessment

The following public sources were used to gather information for the nonclinical assessment below: PubMed, ToxNet, ToxLine, MicroMedex, Hazardous Substances Database (HSDB), and Google Scholar.

a. Pharmacology of the drug substance

MSM is an organic sulfur-containing compound that is an oxidized metabolite of DMSO. MSM is found in a number of foods including milk, grains, meat, eggs, fish and vegetables (Richmond, 1986). The mechanism(s) of action of MSM have not been fully characterized. However, MSM has been reported to possess anti-oxidant, anti-apoptotic, and anti-inflammatory properties (Karabay et al., 2014; Ahn et al., 2015; Amirshahrokhi et al., 2013). MSM has also been shown to exert beneficial effects in rodent models of osteoarthritis due to its sulfur concentration, which contributes to cysteine, a

sulfur-containing amino acid required for the production of keratin (Ezaki et al., 2013).

b. Safety pharmacology

No safety pharmacology studies (i.e., information regarding the impact of MSM on the central nervous system (CNS), cardiovascular, or respiratory system,) of MSM were found in the literature.

Note: MSM has been shown to accumulate in brains of human subjects, and is detectable in rat brain following a single oral dose (see toxicokinetics section below), although the pharmacological and toxicological effects of MSM in the CNS have not been studied to date to the best of our knowledge.

c. Acute toxicity

Hovarth et al. (Hovarth et al., 2002) conducted an acute toxicity study in which Sprague-Dawley rats (10/sex/group) were administered a single dose of vehicle control or 2 g/kg MSM by oral gavage. Rats were observed twice daily for clinical signs and mortality, and body weights were recorded on Days 1, 5, 8, 12, and 15 (prior to sacrifice). On Day 15, all surviving rats were euthanized. Necropsy examination included a gross inspection of all external surfaces, organs, and orifices. No mortality, clinical signs of toxicity, or differences in body weight gain were observed. No gross lesions were observed at necropsy. The LD_{50} of MSM in rats was considered to be greater than 2 g/kg in this study, due to the lack of adverse findings.

The following table, excerpted from a publically available Generally Recognized As Safe (GRAS) notice for MSM submitted to the Center for Food Safety and Applied Nutrition (CFSAN) on July 25, 2007 (GRAS Notice No. 000229) by the Burdock Group, contains a summary of acute toxicology studies conducted with MSM. The majority of these studies are not publically available and, although the GRAS notice summarizes the studies, detailed information is not available. Therefore, the table below is provided as a general summary of toxic dose estimates. For references, see link to GRAS notice. Overall, the acute and subacute oral LD_{50} doses for MSM in nonclinical species appear to be high. In a response letter to the GRAS notice dated February 18, 2008, CFSAN replied that they had no questions regarding the submitter's conclusion that MSM is GRAS for use in foods under the conditions of use stated in the notice (for use as an ingredient in meal supplement and meal replacement foods, fruit smoothie-type drinks, and fruit-flavored thirst quencher-type beverages at levels up to 4,000 mg/kg and in food bars such as granola bars and energy-type bars at levels up to 30,000 mg/kg). However, the Agency stated that it has not made its own determination regarding the GRAS status of the subject use of MSM in food. For details see link to Agency response letter to GRAS notice.

Species	Route	Duration of exposure	LD_{50} (mg/kg)	Reference
Mouse	Oral	Acute	>2000	Yu and Peano (2000a)
Mouse	Oral	Acute	>5000	Kocsis *et al* (1975)
Mouse	Intraperitoneal	Acute	>5000	Kocsis *et al.* (1975)
Rat	Oral	Acute	>2000	Horvath *et al.* (2002)
Rat	Oral	Acute	>2000	Yu and Peano (2000b)
Rat	Oral	Acute	>20,000	Hixson (1958)
Rat	Oral	Acute	≥17,020	Schoenig *et al* (1968)
Rat	Oral	Acute	>5000	De Crescente (1981, 2004b)
Rat	Inhalation	Acute	>600	Yu and Peano (2000c)
Rat	Intraperitoneal	Acute	>5000	Kocsis *et al.* (1975)
Rat	Oral	42 days	>20,000	Herschler (1981, 2004c)
Dog	Oral	Acute	>2000	Zheng and Lee (2004c)
Dog	Intravenous	Several weeks*	>2000	Herschler (1981)
Cow	Oral	30 days	>1200	Schmoling *et al* (2001)

*No additional information was stated

d. Repeat-dose toxicity

One report of a repeat-dose toxicology study of MSM is available in the published literature (Hovarth et al., 2002). In this study, Wistar rats (20/sex/group) received 1.5 g/kg of MSM or vehicle control in a volume of 10 mL/kg once daily for 90 days. Animals were observed twice daily for mortality and clinical signs, and body weights were assessed weekly along with food consumption. Clinical pathology samples from retro-orbital bleeds of a subset of animals (5/sex/group) were obtained prior to treatment, once on week 7, and from all animals prior to necropsy. Urinalysis parameters were obtained from a subset of animals (5/sex/group) prior to treatment and on week 7. Organ weights were recorded and gross necropsy was performed on all animals. The study included microscopic evaluation of the following tissues: liver, kidneys, adrenals, left testicle, spleen, brain, thymus, heart, mesenteric lymph nodes, submandibular lymph nodes, stomach, duodenum, pancreas, lungs, pituitary, trachea, esophagus, thyroids, parathyroids, left epididymis, prostate, uterus, and ovaries. No deaths or adverse clinical signs were observed. The authors stated that body weights, food consumption, clinical pathology parameters, and organ weights were unchanged, with the exception of kidney weights which were significantly increased in males receiving MSM (although no values are provided in the publication). Upon microscopic histopathological examination of kidneys from males and females (using Hematoxylin and Eosin, Periodic Acid Schiff, and Sudan Fat Red stains), no treatment-related lesions were observed. A no observed adverse effect level (NOAEL) of >1.5 g/kg was identified by the authors (this corresponds to a human equivalent dose (HED) of 14.5 g/60 kg person/day based on a body surface area comparison).

No other repeat-dose toxicology studies were found in the published literature. Specifically, we have not been able to find any topical, intravenous, or ophthalmic toxicology data.

e. Mutagenicity

Lee et. al. (Lee et al., 2006) investigated the potential genotoxicity of MSM in in vitro bacterial reverse mutation (Ames) and chromosomal aberration assays, and an in vivo mouse micronucleus test. The Ames assay tested MSM doses of 0, 2500, 5000 and 10000 mcg/plate in the following strains of Salmonella typhimurium: TA98, TA100, TA1535, and TA1538, along with appropriate positive controls. In the in vitro chromosomal aberration assay MSM was tested at concentrations of 0, 1.25, 2.5, and 5 mg/mL without S9 for 24 hours and with S9 for 6-18 hours. Appropriate positive controls were included. MSM was considered to be negative in both in vitro assays. In the in vivo micronucleus assay, mice were administered a single dose of MSM via oral gavage at doses of 0, 1250, 2500, and 5000 mg/kg. Positive control mice received an intraperitoneal injection of mitomycin C at 4 mg/kg. Animals were sacrificed after 48 hours and bone marrow smears were prepared. MSM was considered to be negative in the in vivo micronucleus assay (no significant increases in micronucleated polychromatic erythrocytes at any of the doses tested). Overall, MSM was considered to be non-genotoxic by Lee et. al. (Lee et al., 2006).

A number of genetic toxicology tests are listed in the table below, excerpted from the GRAS notice No. 000229 submitted by the Burdock Group. With the exception of Lee et. al. (Lee et al., 2006) those reports are not found in the published literature and, therefore, further details are not available.

Type of assay	Test organism	Concentration	Results	Reference
		In vitro		
Reverse mutation assay*	*Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537	50 – 5000 µg/plate	No significant increase in reversions	Fassio and Barone (2000)
Reverse mutation assay*	*S typhimurium* strains TA97A, TA98, TA100, TA102, TA1535	50 – 5000 µg/plate	No significant increase in reversions	Summers (2005)
Reverse mutation assay*	*S typhimurium* strains TA98, TA100, TA1535, TA1537; *Escherichia coli* strain WP2uvrA	312 5 – 5000 µg/plate	No significant increase in reversions	Zheng and Lee (2004d)
Reverse mutation assay*	S. typhimurium strains TA98, TA100, TA1535, TA1538	2500 – 10,000 µg/plate	No significant increase in reversions	Lee *et al* (2006)
Mouse lymphoma forward mutation assay*	L5178Y tk+/- mouse lymphoma cells		No significant increase in forward mutations	Hall (2005)
Chromosome aberration assay*	Chinese hamster lung cells	1250 – 5000 µg/ml	No significant induction of chromosomal aberrations	Zheng and Lee (2004a)
		In vivo		
Mouse micronucleation assay	Mouse	500 – 2000 mg/kg acute dose	No significant increase in micronucleated polychromatic erythrocytes	Zheng and Lee (2004b)

* With and without metabolic activation

f. Developmental and reproductive toxicity

Magnuson et. al. (Magnuson et al., 2007a) conducted an OECD-compliant study to investigate the developmental toxicity of MSM in rats. Timed-bred

primiparous dams were administered 0 (vehicle), 50, 500, or 1000 mg/kg MSM via oral gavage (24 – 25 rats/group). Dosing was conducted on Gestational Days 6 – 20 and dams were euthanized on Gestational Day 21. Body weights and food consumption were recorded on multiple days through the study. All dams underwent gross examination of the brain and all organs in the thoracic and abdominal cavities. Pregnancy status, number of corpora lutea, number and status of fetuses, pup weights and sex were recorded for each dam. Uteri and ovaries were weighed. All fetuses were given gross external, skeletal and visceral examination. Maternal feed consumption, body weight, body weight gain, uterus weight, and corrected body weight/body weight gain were not significantly affected by treatment. No evidence of maternal toxicity, and no significant differences in litter viability, litter size, or litter body weight were detected. No evidence of fetal mortality, alterations to growth, or structural alterations were observed in the fetuses of dams administered 50-1000 mg/kg/day. The authors concluded that under the conditions of the study, the NOAEL for maternal and fetal toxicity was 1000 mg/kg/day MSM (corresponds to a HED of 9677 mg/60 kg person based on body surface area).

Goldstein et. al. (Goldstein et al., 1992) investigated the effects of MSM on gametogenesis in the nematode *Caenorhabditis elegans* (*C. elegans*). Briefly, young (5 – 7 days of age) nematodes were treated with 0, 0.5, 1, 2, or 5 % MSM in culture media and the number of offspring were counted and examined at up to 11 days of age. Overall, the authors observed dose-dependent decreases in fertility, increased number of abnormal gametes and loss of viability. However, the relevance of this model to human risk assessment is questionable.

g. Carcinogenicity

No studies investigating the potential carcinogenicity of MSM are available in the published literature. Two studies in the literature have shown that MSM can delay the onset of chemically-induced tumors in rats (McCabe et al., 1986; O'Dwyer et al., 1988). In addition, various studies have shown that MSM is cytotoxic in vitro in a number of cancer cell lines and in vivo in implanted tumor models (Caron et al., 2010; Jafari et al., 2012; Lim et al., 2012), suggesting MSM may have anti-tumor properties. Further studies would be required to be completed to determine the effects of MSM on tumor growth and development.

h. Toxicokinetics

Magnuson et. al. (Magnuson et al., 2007b) investigated the pharmacokinetics of MSM following oral administration in rats. 500 mg/kg of [^{35}S]MSM (identical to MSM, except for the addition of a sulphur-35 radiolabel tag) was administered to 8 male Sprague-Dawley rats. Blood samples were collected from 5 rats via the jugular vein predose and at various time points postdose.

Urine and feces samples were collected from 3 rats postdose and at various intervals postdose. Animals were sacrificed 48 hours postdose and a select panel of tissues was collected for radioactivity determinations. The same tissues were collected from 3 untreated rats. Following oral administration, [^{35}S]MSM was rapidly absorbed, was detectable within 15 minutes postdose and remained detectable for 48 hours (sacrifice time). A C_{max} of 618 I g equiv/mL was reached approximately 2 hours postdose and maximal blood concentrations persisted (> 80 % of C_{max}) for up to 8 hours postdose. $AUC_{0\text{-}48hr}$ was approximately 14052 I g equiv/mL. Radioactivity was detected in all organs 48 hours postdose, but not detected in any organ at 120 hours postdose. Highest levels of radioactivity were found in the blood, kidneys, testes, and eyes. Significant levels of MSM were detected in brain (similar to those found in liver, indicating that MSM readily crosses the blood brain barrier). The majority of radioactivity was found to be excreted in the urine (85.8 %), with only 3 % recovered in feces. The majority of total radioactivity (79 %) was excreted by 48 hours postdose.

Otsuki et. al. (Otsuki et al., 2002) reported similar observations to those of Magnuson et. al. following oral gavage of [^{35}S]MSM in rats. In addition Richmond (Richmond, 1986) reported that the majority of [^{35}S]MSM is excreted in urine following oral administration to guinea pigs.

Conclusions: The limited nonclinical toxicology studies that exist in the published literature have not identified any specific safety concerns for oral MSM. However, the literature provides only a single 90-day oral repeat-dose toxicology study, a genetic toxicology battery, and a single oral embryo-fetal development study in the rat. Pharmacology studies have shown that significant levels of MSM are present in the brain following oral administration in humans and rats. The clinical significance of MSM crossing the blood brain barrier is uncertain as there are limited toxicology data in the published literature and very little detail regarding the histopathological evaluations of brain tissue.

From the nonclinical perspective, there do not appear to be any data suggesting adverse effects; however, the data for oral toxicity is limited, and there are no data for the other routes of administration. Therefore, the existing nonclinical data are inadequate to support including MSM on the 503A compounding list.

2. Human Safety

Identification and selection of the literature

Sources cited in the 503A nominations for MSM were consulted. In addition, an independent systematic literature search was performed to identify all human randomized clinical trials (RCTs) related to MSM use in OA. Computer databases used were Medline and Embase (searched from their respective inceptions to January 2015). The search was not restricted to a particular route of administration.

Medline was searched by using the following strategy: (((safety OR toxicity OR effective* OR efficacy* OR pharmacokinetic OR adverse OR "side effects" OR "side effect"))) AND (("dimethyl sulfone"[Supplementary Concept] OR "dimethyl sulfone"[All Fields] OR "methylsulfonylmethane"[All Fields])).

Embase was searched with the following key words:

#3 #1 AND #2

#2 Methylsulfonylmethane

#1 'safety'/exp OR safety OR 'toxicity'/exp OR toxicity OR effective* OR efficacy* OR 'pharmacokinetic'/exp OR pharmacokinetic OR adverse OR 'side effects' OR 'side effect'/exp OR 'side effect'

After the identical studies were eliminated, the 34 remaining studies were individually screened for their eligibility to fulfill the following criteria: (a) human studies, (b) include a treatment arm that investigates solely MSM, (c) investigate OA (if other diseases included, reported the results related to OA separately). Five articles, cited under the references for clinical safety and efficacy, qualified for inclusion.

a. Reported adverse reactions

There are limited safety data for MSM and no long-term safety assessments beyond 12 weeks. Minor and transitory adverse events (AEs) were reported in the literature with oral administration of MSM in humans when taken for short time periods and include: gastrointestinal (GI) upset, fatigue, insomnia, and headache (for details, see Section b, *Clinical trials assessing safety*).

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for MSM through March 19, 2015. Sixteen unique adverse event reports were identified, nine of which were serious. The most commonly reported events were fatigue, nausea, cough, drug ineffective, drug interaction, dyspnea, hematoma, headache, increased international normalized ratio (INR), product quality issue, and somnolence.

Four cases reported bleeding or INR increase. Doses of MSM were not provided. In two of these cases, patients had been on stable doses of warfarin and MSM was added for joint pain. Both patients had an INR increase following the addition of MSM. The precise timing of events is not known. A third case reported deep red blood in the urine three days after use of glucosamine with MSM for back pain. Bleeding stopped when medication was discontinued, and occurred again when medications were restarted a week later. The fourth case was a patient who experienced thrombocytopenia and a hematoma at the site of a needle biopsy while being treated with celecoxib and MSM. There were multiple other concomitant medications. Two cases described hepatitis or transaminase elevation but both were confounded by concomitant medications labeled for hepatotoxicity.

FAERS is a database of unsolicited, spontaneous, adverse event and medication error reports for approved drug and therapeutic biologic products, and may include reports for

compounded products. Due to the nature of postmarketing adverse event reporting, FDA does not receive all adverse event reports that may potentially occur with a product. In addition, FDA does not have sales data on MSM, so it is not possible to estimate a denominator in order to calculate an adverse event rate. These confounders make it difficult to draw definitive conclusions based on these data in regard to the safety of MSM.

The Center for Food Safety and Nutrition was also consulted to search their adverse event data base, CAERS, for adverse events associated with MSM supplements. The search yielded over 400 reports, most of which were for products that included MSM as one of many other supplements. The types of adverse events were varied and occurred in all body systems. There was no information on dose, concomitant medications or underlying illnesses, which severely limited the ability to establish causality related to MSM.

b. Clinical trials assessing safety

The safety of MSM beyond 12 weeks has not been investigated in clinical studies, either controlled or open-label. MSM doses of 500 mg orally three times daily (Usha et al., 2004), 1.125 grams orally three times daily (Debbi et al., 2011), and 3 grams twice daily (Kim et al., 2006) were investigated in randomized controlled trials. No serious adverse events were reported. Dropout rates from the studies due to adverse events were low.

In general, the quality of the adverse event reporting was poor. Usha et. al. (Usha et al., 2004) reported minor gastrointestinal (GI) side effects in 5% of patients but did not state in which treatment group the events occurred. Kim et. al. (Kim et al., 2006) found a comparable incidence of adverse events in the MSM and placebo treatment groups. GI events (bloating, constipation, indigestion), headaches, insomnia, fatigue and/or concentration problems were reported by 57% of the patients in the MSM group. Bloating and insomnia had a higher incidence compared to placebo (25% vs. 18% and 17% vs. 9%, respectively). Debbi et. al. (Debbi et al., 2011) reported no adverse events. Other adverse events reported in the literature for MSM include increased blood pressure, increased effectiveness of anticoagulants, and elevated liver function tests, however, the relation of these adverse events to MSM is unknown.

c. Pharmacokinetic data

There were no systemic pharmacokinetic data for MSM reported in the literature. There are studies in humans that report distribution of MSM in brain tissues, which suggests that MSM can cross the blood brain barrier (Cecil et al., 2002, Lin et al. 2001).

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

Approved therapies for osteoarthritis and joint pain include the following drugs and drug classes: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), duloxetine, opioids and opioid combination products. All of these therapies carry risks (GI, cardiovascular, renal, and hepatic toxicities, abuse and addiction), especially with long-term administration. The safety profile of MSM reported in the literature is poorly

characterized and includes minor symptoms, but more notably, both the literature and the FAERS search suggest that there may be an interaction with warfarin and risk for bleeding, even with relatively short-term exposure, as well as a risk for hypertension (literature only). This is important because the treatment of osteoarthritis can be chronic and there are no safety data to indicate whether risk increases over time. The lack of long-term safety data for MSM makes it difficult to reliably compare the safety of MSM relative to approved therapies.

Conclusions

There are limited safety data for MSM and no long-term assessment or dose-response studies.

The safety of short-term MSM administered orally is poorly characterized based on available literature. There is a possible risk for an interaction with warfarin leading to an increased risk of bleeding. Overall, the more common events were minor and included primarily GI upset, fatigue, and insomnia. There were cases of bleeding and increased INR reported in FAERS which somewhat corroborates the risk identified in the literature, although the causality of these events cannot be determined due to the nature of the reports.

There was no literature describing intravenous or topical administration of MSM. The lack of safety data on these two routes of administration does not support the use of MSM in compounding products intended for intravenous or topical administration.

There are a number of approved therapies for osteoarthritis and joint pain with well-known safety profiles.

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

<u>Identification and selection of the literature</u>

The articles from the literature search (described under *Human Safety*) selected for review of the efficacy of MSM for the treatment of OA pain met the following inclusion criteria:

- Randomized controlled clinical trials (Usha et al., 2004; Kim etal., 2006; and Debbi et al., 2011) and meta-analysis (Ameye et al. 2006; Brien et al., 2011)
- Conducted in patients with osteoarthritis
- Outcome measures included an assessment of pain based on validated and reliable instrument: Disease specific WOMAC,[1] VAS[2] pain, Likert pain[3] or assessment of pain relief

[1] WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; an assessment tool that consists of 24 items divided into three subscales: Pain, Stiffness, and Physical Function. The purpose of

1. *Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance*

The optimum dosage for MSM has not been determined and no dose-ranging studies have been reported in the literature. The suggested oral therapeutic dose is 4-6 g/d, although doses of up to 20 g/d have also been used; over-the counter-preparations are typically 1-5 g daily.

Usha et. al. (Usha et al., 2004) found that patients with knee OA treated with 500 mg MSM three times daily for 12 weeks showed a 33% pain reduction on the visual-analogue-scale (VAS). Kim et. al. (Kim et al., 2006) found that knee OA patients treated with MSM 3 g twice daily for 12 weeks showed a 25% reduction in WOMAC pain score. Debbi et. al., (Debbi et al., 2011) in a study of patients with knee OA dosed with MSM 1.125 grams three times daily vs. placebo for 12 weeks showed a mean pain decrease of 21% on the WOMAC that did not reach statistical significance and a decrease of 5.5% of the VAS pain scale that was statistically significant. There were trends in all studies in favor of MSM in physical function. None of the changes noted in these studies were considered to represent clinically significant improvements according to the criteria set forth by the Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International groups.

> **The criteria for a clinical response to a treatment have been defined by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) and Osteoarthritis Research Society International (OARSI). These definitions are specific to visual-analogue-scales graded from 0-100 mm that can stand-alone or as part of a larger scale such as the WOMAC questionnaire. A clinical response is considered either an improvement in pain or in function of at least 50% with a decrease of 20 mm on the VAS for pain or function, or an improvement in both pain and function of at least 20% with a decrease of 10 mm on the visual-analogue-scales.*

Brien et. al. (Brien et al., 2008) discussed the limitations of two of the studies. Usha et. al. (Usha et al., 2004) and Kim et. al. (Kim et al., 2006) were small trials, enrolling a total of 52 patients treated with MSM alone. The MSM dosage varied, ranging from 500 mg 3 times daily to 3 g twice a day for 12 weeks. It is not clear how the use of rescue medication was addressed in the primary analysis of any of the studies and whether its use affected the efficacy outcome, and there were concerns about the statistical analyses

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the WOMAC is to assess these characteristics in patients with hip and or knee osteoarthritis. This is a commonly used outcome measure in clinical trials of osteoarthritis treatments.

[2] VAS: Visual Analog Scale is a unidimensional (i.e., a line) measure of pain intensity that is composed of a horizontal line, usually 10 cm in length, anchored by two verbal descriptors, one for each symptom extreme (i.e., no pain and worst pain). The patient is asked to make a mark on the line that represents their pain level.

[3] Likert pain scale: The Likert is a verbal numeric rating scale in which a patient is asked to rate their pain on a 5 or 10 point rating scale, where the numbers are assigned pain levels, i.e., 0=no pain, 1=mild pain, 2=moderate pain, 3= a lot of pain, and 4= worst pain imaginable.

employed in the studies. Debbi et. al. (Debbi et al., 2011) studied an intermediate dose, 3.375 g/d, also for 12 weeks, in which 25 patients received MSM.

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

Pain is considered a serious condition, as it interferes with the quality of life. Untreated pain has been associated with suicide.

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

The alternative therapies, described under *Human safety (d)*, have been shown to be efficacious for the treatment of OA pain. There are no head to head studies comparing the efficacy of approved OA pain medications to MSM. Due to differences in study designs, cross study comparisons do not provide insight into comparative efficacy of MSM with approved treatments.

Conclusions

There appears to be, at best, a suggestion of possible efficacy in reducing pain based on differences in pain-related outcomes, in support of the use of MSM in patients with joint pain associated with OA. However, the reductions in pain are small, failed statistical tests, and it is not clear whether they are of clinical significance. In addition, the number of subjects studied in these trials is small, with a total of 77 patients administered MSM. Pain is a serious condition for which there are a number of approved alternative therapies. These alternatives have been shown to effectively treat OA pain.

D. Has the substance been used historically in compounding?

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

No information was found for the historical use of MSM in pharmacy compounding.

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

MSM has been used for the treatment of joint pain associated with osteoarthritis, chronic pain, rheumatoid arthritis, osteoporosis, bursitis, tendinitis, muscle cramps, eye inflammation, allergic rhinitis, interstitial cystitis, along with a myriad of other conditions.

3. *How widespread its use has been*

Use of MSM has been reported in North and South America, Australia, and European and Asian countries.

Proprietary names in other countries:
Altocerin-GM (Acto, India), Aptivium Optimum Joint Formula (Cynergen, Indon.), Arthron-Triactive (Unipharm, Ukr.), Artriox (Medikon, Indon.), Artritin (Teguhsindo, Indon.), Artritosamin (Healthyway, Ukr.), Artro Plus (Ikapharmindo, Indon.), Artrosulfur (Laborest, Ital.), Baknil (Psychotropics, India), Bonic Plus (Ethica, Indon.), Bonjo Aid (Winsome, India), Broncosulfur (Laborest, Ital.), Cartiflex (Galenium, Indon.), Cartigen Plus (Pharmed, India), Cartivit (Apex, India), Cartiwel (Serum Institute, India), Cartizole Plus (Pulse, India), Compensate (Kamakshi, India), Condrorexil (Amnol, Ital.), Conjoint (Medley, India), Cool-Joint (Invision, India), DN Plus (Sain, India), Flex-A-Min Complex (NBTY, Ukr.), Fremov (East West, India), Fremov-ME (East West, India), GCM (Simex, Indon.), Glucometil 3 (Empresa de Nutricion, Arg.), Glucometil K Duo (Empresa de Nutricion, Arg.), GlucOsamax (Health Perception, UK), Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets USP 36, Glucosamine and Methylsulfonylmethane Tablets USP 36, Glucosamine Joint & Muscle Cream with MSM (Nutravite, Canad.), Jointace (Vitabiotics, Indon.), Jointace-DN (Meyer, India), Joint Care Plus (Tempo Scan Pacific, Indon.), Joint Formula Advanced with MSM Booster (Blackmores, Austral.), Joint Guard (Psychotropics, India), Jointop (Intra-Labs, India), Jonty (Alkem, India), Lungcaire Plus (Macropharma, Philipp.), Maxitrin (Dipa, Indon.), Mecocas-Ortho (Casca, India), Mega Gluflex with MSN (Teva, Israel), Methylsulfonylmethane Tablets USP 36, Mex-Amina (Remexa, Mex.), Mobijoint (Psychotropics, India), NatraFlex (Nutralife, UK), Necare (Meridian, India), Neosulfur (Laborest, Ital.), Nurokind Ortho (Mankind, India), OA Plus (Interbat, Indon.), OA Plus (Solitaire, India), Orbone (Ordain, India), Orthocerin-G (Mediez, India), Osicare (Systopic, India), Ositin (Gracia, Indon.), Ostawin (Novaduo, India), Osteoaid (Trianon, Philipp.), Osteoclar (Amnol, Ital.), OsteoEze Active + MSM (Herron, Austral.), Osteoflam (Soho, Indon.), Osteojoin-D (Oxytech, India), Osteokom (Lapi, Indon.), Osteokom Forte (Lapi, Indon.), Osteolip Crema (Amnol, Ital.), Osteo-Relief Plus MSM (Cenovis, Austral.), Osteor Plus (Pyridam, Indon.), Ostiwel Forte (Sanat, India), Ostrimix (Dipa, Indon.), Osvion Plus (Solas, Indon.), Paclo-GMD (Daksh, India), PainEaze (Blue Ocean, UK), ProFLEX 750 (MZL, S.Afr.), Rebone (Puspa, Indon.), Reumafort (Amnol, Ital.), Rhumadol (Naturactive, Fr.), Rino Get (Laborest, Ital.), Risteon (Yarindo, Indon.), Stopain Cold Extra Strength (Troy, USA), Synchrorose (General Topics, Ital.), Synchrorose Intensivo (Dermoteca, Port.), Triflexor (Combiphar, Indon.), Triostee (Tropica Mas, Indon.), Viopor-M (Otto, Indon.), Viopor-M Forte (Otto, Indon.,Viostin-X (Pharos, Indon.)

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

MSM is being sold as a single agent or in combination products for oral or topical use in many countries. We are not aware of any jurisdiction approving MSM as a drug.

Conclusions

The use of MSM has been reported in many countries and appears widespread. It has been used for the indications of the joint pain associated with osteoarthritis, allergic rhinitis, interstitial cystitis, and a myriad of other conditions. Information regarding the history and use of MSM in compounding was not found.

III. RECOMMENDATION

We have reviewed the physicochemical characteristics, safety, effectiveness, and historical use of MSM in compounding, and based on those factors, do not recommend inclusion of MSM on the 503A bulks list. Although MSM is well-characterized physically and chemically and has been used widely in many countries, the non-clinical safety profile of MSM has not been adequately characterized by standard pharmacology and toxicology studies.

The safety of MSM as described in the literature consists mostly of non-serious adverse events, with the most common side effects consisting of gastrointestinal upset, fatigue, insomnia, and headache. However, there have been adverse events of concern reported in the literature that include increased blood pressure, increased effectiveness of anticoagulants, and elevated liver function tests. A search of the FAERS database showed four reports of either bleeding or increased INR. Limitations of the literature reports as well as the FAERS database severely limit the ability to determine causality of the adverse events, but reports of a possible interaction with anticoagulants such as warfarin both in the literature and in FAERS cases provide corroboration for the finding. Notably, there are a number of approved alternative treatments for osteoarthritis that have been demonstrated to be safe and effective.

From the clinical perspective, there is limited evidence from controlled clinical trials, based on pain-related outcomes, that orally administered MSM may be minimally effective for the reduction of joint pain associated with osteoarthritis. The optimal dose of MSM is unknown, and there have been no dose-finding studies reported in the literature.

Based on the minimal evidence of efficacy, the possibility of a potentially serious interaction with anticoagulants and risk of bleeding, and the availability of approved alternatives, MSM should not be included on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

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Tab 3

Curcumin

Tab 3a

Curcumin
Nominations

ACAM
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September 30, 2014

Division of Dockets Management (HFA-305)
Food And Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Re: Docket FDA-2013-N-1525

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

To Whom It May Concern:

The American College for Advancement in Medicine (ACAM) is a prominent and active medical education organization involved in teaching physicians in the proper use of oral and intravenous nutritional therapies for over forty years. We have also been involved in clinical research sponsored by the National Heart Lung and Blood Institute. As such, we have a vested interest in maintaining the availability of compounded drug products.

We appreciate 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. To meet what appear to be substantial requirements involved in this submittal, the FDA has given compounding pharmacists (in general a small business operation) and physicians very limited time to comply with onerous documentation. The Agency has requested information for which no single pharmacy or physician organization can easily provide in such a contracted time frame. As such this time consuming process requires significant coordination from many practicing professionals for which adequate time has not been allotted.

This issue is of great importance and has the potential to drastically limit the number of available compounded drugs and drug products thus limiting the number of individualized treatments that compounded medicines offer to patients.
ACAM and its physician members have not had the time to collect, review and assess all documentation necessary to submit for the intended list of compounded drugs required to assure all patient therapies are represented in our submission. We respectfully seek an additional 120 day period to educate and coordinate our physicians on the issue at hand and to gather the essential information necessary to provide the Agency with the most comprehensive information.
In an attempt to comply with the current timeframe established, a collaborative effort resulted in the attached nominations prepared for bulk drug substances that may be used in pharmacy compounding under Section 503A.

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It is not clear whether the current submission will be the final opportunity to comment or communicate with the Agency. Will a deficiency letter be provided if the initial nomination information was inadequate or will a final decision to reject a nominated substance be made without the opportunity to further comment? ACAM respectfully requests that the FDA issue a deficiency letter should the submitted documentation for a nomination be considered inadequate.

Sincerely,

Neal Speight, MD
(Immediate Past President) for
Allen Green, MD
President and CEO
The American College for Advancement in Medicine

VIA WWW.REGULATIONS.COM

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

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,[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

[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:

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
Glutiathone
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

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.

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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.

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ANH-USA is a regional office of ANH-Intl
INTERNATIONAL
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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.

As discussed in detail below, in the interest 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.,[1] 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.

Column A—What information is requested?	**Column B—Put data specific to the nominated substance**
What is the name of the nominated ingredient?	Curcumin
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please access this article: CNS Neurol Disord Drug Targets. 2014 Sep 17. Natural Compounds and Plant Extracts as Therapeutics against Chronic Inflammation in Alzheimer's Disease - A Translational Perspective. Apetz N, Münch G1, Govindaraghavan S, Gyengesi E. http://www.ncbi.nlm.nih.gov/pubmed/25230232
Is the ingredient listed in any of the three sections of the Orange Book?	No
Were any monographs for the ingredient found in the USP or NF monographs?	There are USP Dietary Supplement monographs for: Curcuminoids, Curcuminoids capsule and tablet, Turmeric, Powdered Turmeric, Powdered Turmeric Extract.
What is the chemical name of the substance?	Curcumin
What is the common name of the substance?	Turmeric or Curcuminoids
Does the substance have a UNII Code?	IT942ZTH98
What is the chemical grade of the substance?	Dietary Supplement
What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of analysis accompanies every lot of material received.
How is the ingredient supplied?	Yellow powder or powdered extract.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	WHMIS (Canada): Not controlled under WHMIS (Canada). DSCL (EEC): This product is not classified according to the EU regulations.
Has information been submitted about the substance to the USP for consideration of monograph development?	There are USP Dietary Supplement monographs for: Curcuminoids, Curcuminoids capsule and tablet, Turmeric, Powdered Turmeric, Powdered Turmeric Extract.
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 strength can range from 50 mg to 1000 mg per capsule. Injection 1mg,10mg/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?	**Safety:** LIKELY SAFE ...when used orally or topically and appropriately. Turmeric and its constituent curcumin have been used safely in several clinical trials lasting up to 8 months (10453,11144,11148,11149,11150,17096,17952,17953). Doses of turmeric or turmeric extract used were up to 2.2 grams daily (10453,11144,11150,17953). Curcumin in a single 12 gram dose, or in doses up to 4 grams daily for 30 days, has also been used safely (18204). PREGNANCY: LIKELY UNSAFE ...when used orally in medicinal amounts; turmeric might stimulate menstrual flow and the uterus (12). LACTATION: There is insufficient reliable information available about the safety of using turmeric in medicinal amounts during lactation. **Effectiveness:** POSSIBLY EFFECTIVE Dyspepsia. Some clinical research shows that taking turmeric orally can relieve symptoms of dyspepsia (11144). Osteoarthritis. Some clinical research shows that some turmeric extracts can improve symptoms of osteoarthritis. In one clinical trial, taking a specific turmeric extract (Meriva, Indena) 500 mg twice daily significantly reduced pain and improved functionality compared to baseline after 8 weeks of treatment in patients with osteoarthritis of the knee. Patients taking this extract also had significantly reduced usage of analgesics and NSAIDs. The extract used in this study was standardized to contain 20% curcuminoids (providing 75% curcumin) complexed with phosphatidylcholine (17953). Turmeric has also been compared to conventional treatment. In one clinical trial, a non-commercial turmeric extract 500 mg four times daily was comparable to the anti-inflammatory drug ibuprofen 400 mg twice daily for reducing knee pain in patients with osteoarthritis after 6 weeks of treatment (17952). INSUFFICIENT RELIABLE EVIDENCE to RATE Alzheimer's disease. Preliminary clinical research shows that taking the turmeric constituent, curcumin, 1-4 grams daily for 6 months does not significant change mental state examination scores compared to placebo in people with Alzheimer's disease (17096). Anterior uveitis. Preliminary clinical research suggests taking the turmeric constituent, curcumin, might improve symptoms of chronic anterior uveitis (11150). Colorectal cancer. Preliminary clinical research suggests that taking turmeric extract might stabilize some markers of colorectal cancer in some patients with treatment refractory colorectal cancer (10453). There is also preliminary research suggesting that the turmeric constituent, curcumin, 4 grams daily for 30 days can reduce numbers of precancerous rectal aberrant crypt foci in people at high risk, such as those who smoke (18204). Rheumatoid arthritis (RA). Preliminary clinical research suggests that the turmeric constituent, curcumin, might reduce some symptoms of rheumatoid arthritis (RA) (11149). In one clinical trial, a specific formulation of the turmeric constituent, curcumin (BCM-95®, Arjuna Natural Extracts, India), 500 mg twice daily reduced RA symptoms more than diclofenac sodium 50 mg twice daily after 8 weeks of treatment (18205), Skin cancer. Preliminary clinical research suggests that an ethanol extract of turmeric in combination with turmeric ointment might relieve odor and itching associated with skin cancers (11148). More evidence is needed to rate turmeric for these uses.
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?	Familial adenomatous polyposis (FAP): curcumin reduces polyp size and number. Oral leukoplakia: high-dose curcumin is effective at reversing this precancerous condition (Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemo preventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 2001;21:2895-90.). Gastric metaplasia: high-dose curcumin is effective at reversing this precancerous condition (Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemo preventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 2001;21:2895-90.). Familial adenomatous polyposis (FAP): curcumin reduces polyp size and number.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There is no FDA-approved drug for polyp reduction in FAP. Celecoxib was formerly approved for this but this approval was rescinded in 2012 (https://www.federalregister.gov/articles/2012/06/08/2012-13900/pfizer-inc-withdrawal-of-approval-of-familial-adenomatous-polyposis-indication-for-celebrex). Even if used off-label, this drug has been shown to increase the risk of heart attacks and other problems. Various corticosteroids and amino-levulinic acid have been approved by the FDA to treat oral leukoplakia. Corticosteroids have significant potential for systemic adverse effects including oral and/or esophageal candidiasis, thinning of mucous membranes, Cushing's syndrome, and many others. Amino-levulinic acid is coupled with phototherapy which is time consuming and expensive, and may be carcinogenic. There is no FDA-approved treatment for gastric metaplasia.
Is there any other relevant information?	Orally, turmeric is used for osteoarthritis, rheumatoid arthritis, dyspepsia, abdominal pain, hemorrhage, diarrhea, flatulence, abdominal bloating, loss of appetite, jaundice, hepatitis, and liver and gallbladder conditions. It is also used for headaches, bronchitis, common cold, respiratory infections, fibromyalgia, leprosy, fever, amenorrhea, and cancer. Other uses include depression, Alzheimer's disease, anterior uveitis, edema, worms, kidney inflammation, and cystitis. Topically, turmeric is used for analgesia, ringworm, bruising, leech bites, eye infections, inflammatory skin conditions, inflammation of the oral mucosa, and infected wounds.

Tab 3b

Curcumin
FDA Review

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: September 30, 2015

FROM: Sandra Casak, M.D., Medical Officer, DOP2

Shawna L. Weis, Ph.D., Pharmacologist, DHOT

Stacy Shord, Pharm.D., Clinical Pharmacologist, DCPV

Rajiv Agarwal, Ph.D., CMC Reviewer, DNDPI

THROUGH: Ramesh Sood, Ph.D., Acting Senior Scientific Advisor, ONDP

Whitney S. Helms, PhD, Supervisory Pharmacologist, DHOT

John K. Leighton, PhD, DABT, Division Director, DHOT

Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, DCPV

Steven Lemery, M.D., M.H.S., Clinical Team Leader, DOP2

Patricia Keegan, M.D., Director, DOP2/OHOP

TO: Pharmacy Compounding Advisory Committee

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

I. INTRODUCTION

Curcumin 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) to treat familial adenomatous polyposis (FAP), gastric metaplasia, and oral leukoplakia.

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 curcumin be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

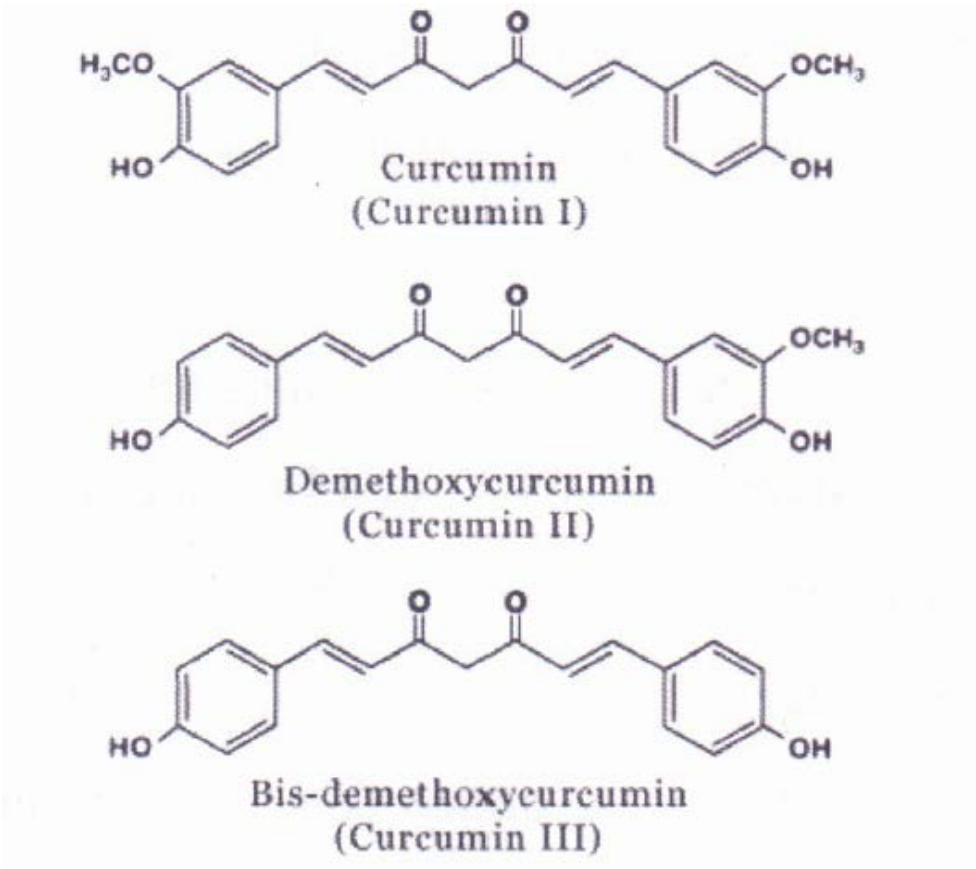
II. EVALUATION CRITERIA

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

1. Stability of the API and likely dosage forms

Curcumin (Diferuloylmethane, turmeric yellow, IUPAC: 1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione,UNII IT942ZTH98, CID 969516, Molecular formula: $C_{21}H_{20}O_6$, Molecular weight: 368.37) is a yellow-orange dye obtained from turmeric, the powdered root of *Curcuma longa* (turmeric). Curcumin may be the active ingredient of turmeric that has been consumed as a dietary spice (Pouri et al., 2013) and is widely used in traditional Indian medicine.

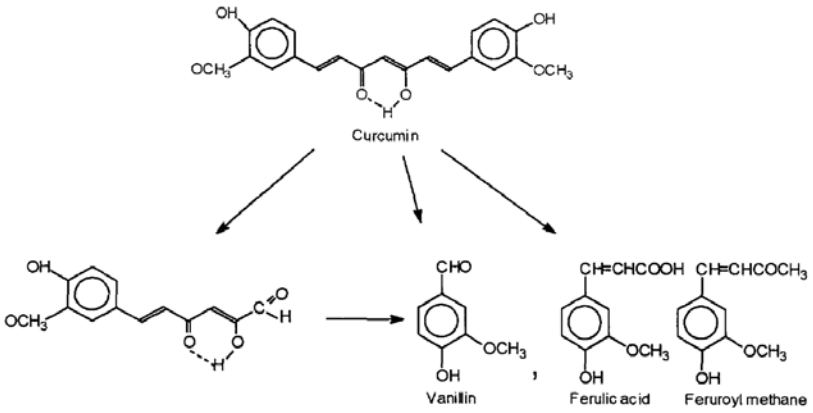
Curcumin (Curcumin I) occurs naturally along with desmethoxycurcumin (Curcumin II) and bisdesmethoxycurcumin (Curcumin III) in the root of the herb *Curcuma longa*, and these are collectively known as curcuminoids. The chemical structure of three curcuminoids are shown below[1]:



[1] It should be noted that the studies generally describe the drug as "curcumin" and are not specific as to which curcuminoid or mixture curcuminoids is being used in the study.

Curcumin and its major components (the three curcuminoids identified above) are well-characterized (both physically and chemically). However, the term “curcumin” is used to define a range of substances with different combinations of curcuminoids that may have different physical and chemical characteristics.

Curcumin is unstable at basic pH and undergoes alkaline hydrolysis in alkali/higher pH solution (Shen et al., 2012). The degradation kinetics of curcumin under various pH conditions and the stability of curcumin in physiological matrices have been investigated. When curcumin was incubated in 0.1 M phosphate buffer and serum-free medium, pH 7.2 at 37°C, about 90% decomposed within 30 minutes. A series of pH conditions ranging from 3 to 10 were tested and the results showed that decomposition was pH-dependent and occurred faster at neutral-basic conditions. Trans-6-(4’-hydroxy-3’-methoxyphenyl)-2,4-dioxo-5-hexanal was predicted as major degradation product and Vanillin, Vanillic acid, ferulic acid, and Feruroyl methane were the minor degradation products (Wang et al., 1997). Curcumin was subjected to acid and alkali hydrolysis, oxidation and photodegradation. Curcumin undergoes degradation under acidic, basic, light and oxidation conditions. It undergoes photodegradation when exposed to light in solution as well as in solid form, but the information on the degradants is not available (Ansari, et al., 2005). Even in the solid state, photodegradation can be seen; therefore, the solid dosage form should be protected from light.



Several USP dietary supplement monographs (U.S. Pharmacopeial Convention online publication, 2015: USP 38) contain mixtures of curcuminoids. Curcumin (as a mixture) is available in the marketplace as a dietary ingredient in oral dosage forms (capsules, tablets, powders).

USP Dietary Supplement: Turmeric
USP Dietary Supplement: Curcuminoids Capsules
USP Dietary Supplement: Curcuminoids Tablets
USP Dietary Supplement: Powdered Turmeric
USP Dietary Supplement: Powdered Turmeric Extract

USP Dietary Supplement: Curcuminoids

2. Probable routes of API synthesis

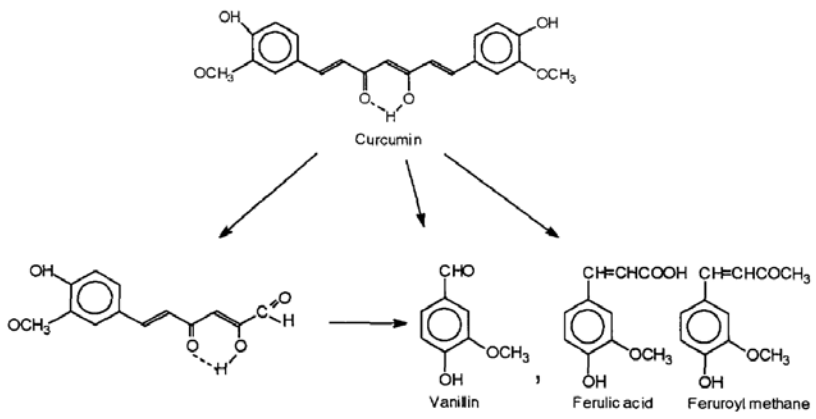
There is no likely commercially viable synthetic pathway for this botanical API.

Curcumin can be isolated by steam distillation. However, there are other extraction methods in different media reported in the literature. Curcumin is a lipophilic compound and is easily dissolved into organic solvents such as methanol, ethanol, and acetone. In these organic solvent extracts, the total of curcuminoids is about 4-6%. Turmeric also contains 2-4% essential oil and 2-3% various volatile oils including turmerone, atlantone, and zingiberone. Other constituents include sugars, proteins and resins.

The essential oil of *Curcuma longa* is obtained by steam distillation, with yields ranging between 1.3 and 5.5%. The oil contains, in addition to turmerone (~60%), free acids, cineol, borneol, zingerone, phellandrene, 3 to 4% of curcumin as a mixture of curcuminoids.

3. Likely impurities

A series of pH conditions ranging from 3 to 10 were tested and the results showed that decomposition of curcumin was pH-dependent and occurred faster at neutral-basic conditions. Trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexanal was a major degradation product and Vanillin, Vanillic acid, ferulic acid, and Feruroyl methane were the minor degradation products.



Heavy metals, pesticides, aflatoxins, residual solvents and microbes are likely impurities in the preparation of extract from the whole root of *Curcuma longa* (turmeric).

4. Toxicity of those likely impurities

The impurity limits for heavy metals, pesticides, aflatoxins, and microbe classes of impurities which have been demonstrated to be present in curcuminoids extracted from turmeric and are listed in the USP Dietary Supplement Monographs are typical of

botanicals. Curcumin used as API in a drug product would likely have the same possible impurities.

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

Curcumin is unstable in aqueous solution and undergoes rapid hydrolysis followed by molecular fragmentation at physiological pH. Therefore, oral solutions and topical preparations that include the use of water should be avoided (see section A.3).

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

As for any botanical preparation, identification of active constituents is difficult. However, degradation products from the structural entities from curcumin (Curcumin I) are identified in section A.1.

Conclusions: The major components of curcumin are well-characterized, both physically and chemically. However, the heterogeneous nature of curcumin (i.e. it is a combination of varying curcuminoidsat varying percentages), and uncertainty about the specific activities of each of the curcumins, prevents us from concluding that the substance "curcumin" is well characterized both physically and chemically. For example, the studies cited in this review do not identify the formulations or preparations of curcumin used, making it difficult compare the clinical data. The compounding of water-based dosage forms is particularly concerning because of the instability of the major components in an aqueous media.

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

1. Nonclinical Assessment

a. Pharmacology of the drug substance

Curcumin, a bioactive polyphenol present in turmeric, has been evaluated clinically as a potential antioxidant, anti-inflammatory, anti-microbial (antibacterial, antifungal, antiviral), and anticancer substance. Because turmeric is commonly used as a flavoring, food additive, coloring agent, and a natural remedy in the Ayurvedic tradition, cumulative daily oral exposure of turmeric and its constituent polyphenols is relatively high. In many parts of Asia, daily exposure to curcumin in food is ≥ 200 mg/day (3 mg/kg/day for 60 kg adults; Somasundaram et al., 2002).

Many of the biological activities ascribed to curcumin may be attributable to its anti-inflammatory properties. In animal models of spinal cord injury, curcumin was found to inhibit activation of the JAK/STAT signaling pathway (Zu et al., 2014), which mediates many effects of pro-inflammatory cytokines such as IL-6 and IFN-γ. In vitro, curcumin was also found to inhibit lipid peroxidation (linoleic acid) and to neutralize peroxides at potencies similar to, or greater than butylated hydroxyanisole (BHA), α-tocopherol (vitamin E) and trolox (a vitamin E analogue; Ak et al., 2008). Because oxidative stress has been associated in some reports with carcinogenesis, its antioxidant properties are of particular interest for potential chemoprevention.

Importantly, while some studies have suggested that curcumin may restore apoptotic signaling in cancer cells via its inhibition of p53-target genes such as BAX, Bcl2 family members (e.g., Bim) and FasL (Heger et al., 2013), other studies suggest that administration of curcumin may inhibit the pharmacodynamic activity of chemotherapeutic agents that act by inducing apoptosis via reactive oxygen species (ROS) and/or DNA damage (Somasundaram et al., 2002).

Curcumin exhibits poor aqueous solubility and low gastrointestinal absorption (Anand et al., 2007). Following absorption, the majority is biotransformed and eliminated via biliary/fecal excretion. The remaining portion circulates as a glucuronide conjugate; thus, it is likely that the biological activities associated with curcumin are in large part the result of the biological activity of its metabolites (in rats, tetrahydrocurcumin-glucuronide and tetrahydrocurcumin-glucuronide; Ireson, et al., 2001).

To improve its bioavailability, a number of modified formulations have been developed, such as nanoparticles, cyclodextrin solutions, lipid-based delivery vehicles, and ethanolic extracts. Limited data are available on the tolerability, toxicity, and biological activity(ies) of the modified curcumin delivery systems, which represents a potential concern for its use as a bulk drug substance for pharmacy compounding.

b. Safety pharmacology

No information is available.

c. Acute toxicity

The acute toxicity of a curcumin-containing solid lipid preparation was evaluated in the Swiss albino mouse and the Wistar rat. Following a single oral dose of up to 2000 mg/kg, there were no mortalities and no effects on body weight over the 15-day post dose interval; thus, the median lethal dose (LD_{50}) was considered to be greater than 2,000 mg/kg in both species (Dadhaniya et al., 2011). Because the authors did not assess systemic exposure to curcumin in the animals treated in this study, the study's determination of LD50 is difficult to interpret in light of the compound's poor oral bioavailability and the dependence of bioavailability on aspects of the formulation, such as particle size and excipient composition.

d. Repeat dose toxicity

The toxicology profile of turmeric oleoresin (containing 79-85% curcumin) was evaluated in a 13-week study by the National Toxicology Program (NTP) for the purposes of dose-setting for a planned carcinogenicity assessment. Groups of 10 male and 10 female animals (F344/N rats and B6C3F1 mice) received turmeric oleoresin by dietary exposure (0, 1,000, 5,000 10,000, 25,000, or 50,000 ppm) for 13 weeks (Lilja et al., 1993).

In the rat, average daily doses based on feed consumption were 0, 50, 250, 480, 1300, or 2600 mg/kg in the male and 0, 60, 300, 550, 1450, and 2800 mg/kg in the female. There were no preterm deaths. There was a 5% decrease in mean male body weight at the end of the study in high dose animals; however, there was no corresponding decrease in mean feed consumption. There were no effects on hematology in males. In females, there was an increase in mean segmented neutrophils at doses of 2600/2800 mg/kg/day. Treatment-associated increases in phosphorous (480 mg/kg/day), total bilirubin (≥250 mg/kg/day) and cholinesterase (≥250 mg/kg/day) were observed in males and/or females. Treatment-associated histological changes ($p < 0.01$) included hyperplasia of the cecum in males and females in the 2600/2800 mg/kg/day dose group. The doses achieved in this study were equivalent to 8-454 mg/kg in humans, which for a 60 kg individual is up to 27-fold greater than those proposed for use in compounding, assuming a maximum curcumin dose of 1000 mg/day.

In the mouse, average daily doses based on feed consumption were 0, 150, 750, 1700, 3850, or 7700 mg/kg in males and 0, 200, 1000, 1800, 4700, or 9300 mg/kg/day in females. There were no preterm deaths. There was an increase in the absolute and relative liver weights in animals that received doses of ≥ 750 and ≥1000 mg/kg/day in males and females, respectively. A decrease in leukocytes was observed in males at doses of ≥ 750 mg/kg/day and in lymphocytes at ≥ 150 mg/kg/day. Phosphorous and serum cholinesterase levels were increased in males at doses of ≥ 1700 mg/kg/day. Urinary specific gravity was increased in all male dose groups.

Absolute and relative mean liver weights were increased in animals at doses of ≥750 and 1000 mg/kg/day in males and females, respectively. No biologically significant histopathological changes were attributed to the test article. The doses achieved in this study were between 12.2-754 mg/kg in humans, which for a 60 kg individual is up to 45-fold greater than those proposed for use in compounding, assuming a maximum curcumin dose of 1000 mg/day.

e. Mutagenicity

The following results of the Ames bacterial mutagenicity study were summarized in the NTP study of turmeric oleoresin (Lilja et al., 1993).

Turmeric oleoresin was negative in the Ames bacterial mutagenicity assay (Strains: TA100, TA1535, TA1537, and TA98 ± S9 metabolic activation) at concentrations of up to 333 µg/plate (a toxicity-limited dose).

In the sister chromatid exchange assay in Chinese hamster ovary (CHO) cells, there was a concentration-related increase in SCEs/cell, which reached statistical significance at the 1.6 and 5.0 µg/mL dose levels (S9). In addition, a positive result was obtained in one of the two replicate assays at the 0.16 µg/mL dose level when tested in the presence of S9 activation; however, as there was no apparent relationship with dose in this replicate, this finding is of unknown biological significance.

In the chromosomal aberration assay (CHO cells), there was an increase in the number of chromosome aberrations/cell which reached statistical significance at the 16 µg/mL dose level at 12 hours both in the presence and absence of metabolic activation (S9 extracts). This suggests that the compound has the potential to induce structural changes in chromosomes at high concentrations. These results may explain the weakly carcinogenic findings observed in the two year bioassays in the rat (increases in clitoral gland adenoma in females) and mouse (potential increases in hepatocellular adenoma in males and females, carcinomas of the small intestine in males) (see section 2.g, below).

f. Developmental and reproductive toxicity

A two-generation reproductive toxicology study of curcumin was conducted in Wistar rats and published in the journal *Food and Chemical Toxicology*. Animals were dosed in feed. The study claims compliance with the 1997 OECD principles of Good Laboratory Practice for the Testing of Chemicals (OECD,C(97)186/Final).

Based on daily feed consumption, mean daily doses (~mg/kg) were as provided below:

Curcumin consumption in the 2-generation reproductive toxicology study in Wistar rats

Generation, interval	1,500 PPM	3,000 PPM	10,000 PPM
F0 males, premating	126.4	253.9	847.4
F1 males, premating	144.0	289.9	958.5
F0 females, premating	138.20	275.7	909.9
F0 females, gestation	109.0	221.1	724.0
F0 females, lactation	282.4	565.1	1913.2
F1 females, premating	154.1	308.1	1017.1
F1 females, gestation	109.0	212.1	743.10
F1 females, lactation	267.2	518.6	1717.9

There was a statistically-significant and dose-related increase in mean body weights of F1 pups in the 10,000 ppm dose level at birth. This effect persisted through F1 postnatal day (PND) 7. On F2 PNDs 7, 14, and 21, there was a decrease in mean body weights compared with concurrent controls in the 3,000 and/or 10,000 ppm dose levels.

There was an apparent treatment-related decrease in F1 litter sizes; however, this effect did not reach statistical significance. There was an apparent increase in the live birth index in 3,000 and 10,000 ppm litters in the F1 generation; however, there was a decrease in the live birth index in 3,000 and 10,000 (not statistically significant at this dose level) in the F2 generation. There was also a dose-related decrease in mean number of implantation sites in F0 dams at all dose levels; however, no decrease was observed in F1 dams.

g. Carcinogenicity

A 2-year carcinogenicity study was conducted by the NTP using Wistar rats. Based on feed consumption, daily doses of turmeric oleoresin were 80, 460, or 2000 mg/kg/day in males and 90, 440, or 2400 mg/kg/day in females.

Ingestion of turmeric oleoresin at doses of up to 2400 mg/kg/day was associated with a significant ($p < 0.05$) increase in clitoral gland adenoma in all exposed female groups (Lilja et al., 1993). Non-neoplastic findings included ulceration, hyperplasia and inflammation of the forestomach in high-dose male and female rats (i.e. 2000/2400 mg/kg/day in the male and female, respectively) at the 15-month and 2-year timepoints, and ulceration, hyperplasia and inflammation of the cecum and colon in in high-dose males and females at the 2-year timepoint. Based on the increased incidence of clitoral gland adenoma, *there is equivocal evidence of carcinogenic activity in the female rat*.

A 2-year carcinogenicity study was conducted by the NTP using B6C3F1 mice. Based on feed consumption, daily doses of turmeric oleoresin were 0, 220, 520, or 6000 mg/kg/day for males and 0, 320, 1620, or 8400 mg/kg/day for females.

Mean body weights were slightly lower in high-dose females than controls (~12%) from Week 25 of the study. Feed consumption in treated groups was comparable to controls throughout the study. There was an increase in absolute and relative liver weights in males and females at the mid- and high-dose levels relative to controls.

A non-dose-related increase in the incidence of hepatocellular adenoma was observed at the mid- and high-dose levels in males and females. The incidence of hepatocellular carcinoma among treated groups were comparable to controls. There was also an increase in the incidence in adenomas of the small intestine in low- and mid-dose males but no increased incidence of small intestine carcinomas were observed in control or high-dose males.

There was an increased incidence of thyroid gland follicular cell hyperplasia in females at all dose levels. As opposed to the rat, there were no increases in the incidence of non-neoplastic gastrointestinal changes in the mouse, suggesting that the rat is a more

sensitive species for these events.

Based on the increased incidence of hepatocellular adenoma in mid-dose males and females and in the incidence of carcinomas of the small intestine in low- and mid-dose males, *there is equivocal evidence of carcinogenic activity in B6C3F1 mice*.

h. Toxicokinetics

Toxicokinetic data were not provided in the GLP 13-week or carcinogenicity studies in the rat and mouse; however, data in a number of species suggest that unformulated curcumin exhibits low oral bioavailability (Anand et al., 2007).

In contrast, a number of studies have demonstrated the potential for substantially enhanced bioavailability when curcumin is reformulated with excipients that enhance its solubility and/or permeability (Prasad et al., 2014); thus, the present review likely underestimates the potential toxicity of these formulations.

Conclusions: From a nonclinical perspective, unformulated curcumin appears to be reasonably safe when administered by the oral route, probably because it is poorly bioavailable; however, preparations that have the potential to greatly enhance the oral bioavailability of curcumin would require additional nonclinical safety evaluation, as studies in rats and mice have indicated that curcumin may have carcinogenic properties.

2. Human Safety

a. Reported adverse reactions

Most literature reports reviewed stated that below 8 grams/day, curcumin is mostly well tolerated.[2] Adverse reactions related to oral curcumin use (regardless of the dose) are nausea and diarrhea, although data from long-term use are scarce. In addition, as most studies are small and non-comparative, there are no descriptions of the frequency and type of assessments used to determine the safety profile of curcumin, nor the grading dictionary used to assess adverse events.

In a study conducted in Thailand (Kuptniratsaikul et al., 2014), 367 patients with primary knee osteoarthritis with a pain score of 5 or higher were randomized to receive ibuprofen 1,200 mg/day or C. domestica extracts 1,500 mg/day for 4 weeks. Subject-incidence of adverse events was slightly increased in the ibuprofen arm (35.7% vs. 29.7% in the C. domestica extracts group). Common adverse events were dyspepsia, abdominal pain/distension, nausea, loose stool, and pitting edema. Patients in the extract group had a lower incidence of all side effects, and only loose stools were more frequent in the C. domestica extracts group (11.9% vs 8.8%).

In a small (n = 12), open-label, Simon's two-stage single-arm trial of 4.5 g/d for 12 weeks of oral curcuminoid C3 complex in patients with plaque psoriasis, there were no reported

study-related adverse events that necessitated participant withdrawal (Kurd et al., 2008).

In a small randomized, double-blind, multicenter trial of curcumin in the prevention of relapse of ulcerative colitis conducted in Japan, 45 patients received curcumin (2 grams/day) plus sulfasalazine or mesalamine, and 44 patients received placebo plus sulfasalazine or mesalamine for 6 months (Hanai et al., 2006). A total of 9 mild, transient side effects in 7 of 45 patients were reported while patients were receiving curcumin. Side effects included sensation of abdominal bulging, nausea, transient hypertension, and transient increase in the number of stools. One patient discontinued curcumin as a result of hypertension.

In a randomized, controlled, observer masked trial comparing the clinical effects of curcumin with fluoxetine in 60 patients with major depressive disorder (Sanmukhani et al., 2014) conducted in India, patients were randomized to receive (1:1:1 ratio) fluoxetine (20 mg) and curcumin (1000 mg) individually or in combination for six weeks. The authors reported that "curcumin was well tolerated by all the patients."

Chuengsamarn et. al. (Chuengsamarn et al., 2014) reported results from a randomized, double-blinded, placebo-controlled trial conducted in a single center in Thailand in 240 patients with type 2 diabetes. Patients were randomized to receive 1500 mg of curcuminoid extract or placebo for 6-months. Body weight, blood pressure, creatinine, and transaminases were monitored. The authors found no significant differences in the means of any of these parameters or minor symptoms such as hot flushes, constipation, etc.

In a double-blind, randomized, placebo-controlled study in 40 patients with a first episode of depression (Bergman et al., 2013), patients were randomized to receive either 500 mg/d curcumin or placebo together with antidepressants (escitalopram or venlafaxine) for 5-weeks. The authors reported that none of the patients complained of any adverse effect during the study.

Curcumin has been studied in combination with gemcitabine in patients with pancreatic carcinoma in a study investigating the safety and pharmacokinetics of a curcumin formulation designed with the intent to increase curcumin's solubility (Kanai et al., 2013). The formulation (called Theracurmin) consisted of 10% curcumin, 2% other curcumins such as demethoxycurcumin and bisdemethoxycurcumin, 46% glycerin, 4% gum ghatti, and 38% water. In this study, 10 patients received 200 mg daily and 6 patients received 400 mg daily of the formulation in combination with standard gemcitabine. The authors reported "no unexpected adverse events" and 3 patients continued receiving curcumin for more than 9 months. In another study (Epelbaum et al., 2010), 17 patients with pancreatic cancer were enrolled and received 8 grams/daily of curcumin orally concurrently with gemcitabine. Five patients (29%) discontinued curcumin after a few days to two weeks due to intractable abdominal fullness or pain, and the dose of curcumin was reduced to 4 grams/day because of abdominal complaints in 2 other patients. The authors concluded that low compliance with curcumin at a dose of 8 grams/day taken together with systemic gemcitabine may prevent the use of high doses of oral curcumin needed to achieve a systemic effect. In a third study (Kanai et al., 2011) in

21 gemcitabine-resistant patients receiving 8 grams/day, no dose limiting toxicities (DLTs) were observed in the run-in "Phase 1" portion, and this dose was selected for the "Phase 2" portion. The study achieved its primary endpoint of no withdrawal due to curcumin intolerability. The most common Grade 3-4 hematological toxicity was neutropenia (38%) and Grade 3-4 non-hematological toxicity included fatigue (10%); both were reported as not related to curcumin. Other Grade 3-4 non-hematological adverse events were drowsiness, anorexia, obstruction of the gastrointestinal tract, and edema (one patient each).

In a pilot study to assess patient acceptability of curcumin as a cancer prevention agent (Irving et al., 2013), curcumin C3 complex (2.35 g) was administered to patients once daily for 14 days before endoscopic biopsy or colonic resection. Twenty-four of 26 patients commencing curcumin completed the course. Six patients reported mild gastrointestinal adverse events. In a study (Carroll et al., 2011) in patients with colonic polyps, 44 patients received oral curcumin 2 grams or 4 grams per day for 30 days. The authors reported that curcumin was well tolerated at both 2 g and 4 g.

Curcumin as an intravaginal agent has been studied in a trial that randomized 287 women with cervical HPV positive smears (but without high grade cervical neoplasias) to four intervention arms to be treated with vaginal Basant cream (polyherbal cream), vaginal placebo cream, curcumin vaginal capsules and placebo vaginal capsules respectively. All subjects were instructed to use one application of the assigned formulation daily for 30 consecutive days except during menstruation and recalled within seven days of the last application for repeat HPV test, cytology and colposcopy. No serious adverse events were noted (Basu et al., 2013).

A curcumin mouthwash formulation has been studied in pediatric cancer patients receiving doxorubicin for the prevention of oral mucositis. Seven children received standard prevention care (chlorhexidine 0.2% mouthwash for 30 seconds twice per day) and 10 drops of Curcumall twice per day in a mouthwash during treatment with high-dose chemotherapy. No oral adverse events were documented. No systemic adverse events that could possibly be related to the use of the curcumin mouthwash were reported (Elad et al., 2013).

b. Clinical trials assessing safety

See response to question 2a.

c. Pharmacokinetic data

Several published studies indicate that curcumin has relatively poor oral bioavailability; however, it is difficult to compare the available pharmacokinetic (PK) data across studies due to differences in product, dose, or curcumin source. Therefore, the literature review focused on curcumin given as a capsule or as a tablet as a mixture of curcuminoids. Two PK studies found no curcumin in human serum or plasma after administration of oral curcumin (maximum dose, 12 g) as a powder in capsule made using the same curcumin commercial source (PMID: 18559556; 16545122). Curcumin glucuronides and sulfates

were detected in the plasma of all subjects in one of these studies, suggesting that curcumin is absorbed and extensively conjugated; however, the activity of these metabolites relative to curcumin is not known. Another study similarly failed to identify curcumin in human plasma (PMID: 11448902). In this study, oral curcumin was administered as capsule that contained curcuminoids suspended in 200 mg of essential oils derived from curcuma spp. at doses up to 2200 mg/day to patients with colorectal cancer. In contrast, Cheng et al (PMID: 11712783) reported peak serum concentrations following the administration of tablets containing 500 mg of curcumin. Average peak serum concentrations after oral intake of 4, 6, and 8 g of curcumin were 0.5 ± 0.1, 0.6 ± 0.1 and 1.8 ± 1.9 μM, respectively. The concentrations of curcumin peaked at 1–2 hours after oral intake of curcumin and gradually declined within 12 hours. The reasons for the differences in exposure between a capsule and a tablet may stem from different curcumin commercial sources or formulations. These PK studies collectively suggest that curcumin exposure is very limited following oral administration.

It has been suggested that the low bioavailability is secondary to poor absorption, extensive metabolism, or rapid elimination (PMID: 22996406). Curcumin is practically insoluble in water at acidic or neutral pH, but it becomes very susceptible to degradation at higher pHs (pH > 6.5) (PMID: 12204572, 24368738). The effect of food does not appear to have been studied. The metabolism of curcumin is discussed below. The poor systemic exposure limits the ability to determine how curcumin is eliminated.

Because curcumin demonstrates relatively low bioavailability, other formulations, such as liposomes, nanoparticles and phospholipid complexes, have been evaluated. Other studies have coadministered piperine with curcurmin to improve its oral bioavailability. The PK data from these studies was not reviewed. PK studies of intravenous curcumin in humans cannot be found.

Drug Interactions

Curcumin appears to undergo reduction and conjugation (e.g., sulfation and glucuronidation) (PMID: 24368738; 239337173; 17999464). It does not appear to undergo metabolism by the major cytochrome P450 enzymes. Ireson et al (PMID: 11815407) demonstrated curcumin can be metabolized by SULT1A1 and SULT1A3. The individual UGTs that can metabolize curcumin have not been identified. Nonclinical studies suggest that these metabolites may undergo renal and hepatic elimination (PMID: 24368738). It is not known if curcumin exposure will be affected in patients with organ impairment.

In vitro studies suggested that curcumin inhibits multiple cytochrome P450 enzymes, sulfotransferase and glucuronyltransferases (PMID: 18480186). Appiah-Opong et al (PMID: 17433521) states that curcumin inhibited CYP1A2 (IC_{50}, 40.0 μM), CYP3A4 (IC_{50}, 16.3 μM), CYP2D6 (IC_{50}, 50.3 μM), CYP2C9 (IC_{50}, 4.3 μM) and CYP2B6 (IC_{50}, 24.5 μM). Curcumin showed competitive inhibition towards CYP1A2, CYP3A4 and CYP2B6, whereas non-competitive inhibition was observed with respect to CYP2D6 and CYP2C9. Another study suggested that some curcuminoids, including curcumin, can inhibit UGT and SULT, as well as some cytochrome P450 enzymes (PMID: 18480186).

Since curcumin has limited systemic exposure following single doses up to 12 g, it is unlikely that curcumin will inhibit most cytochrome P450 enzymes, with the exception of CYP3A in the gastrointestinal tract. Curcumin has the potential to inhibit CYP3A in the gastrointestinal tract assuming a gastric concentration of 8 mg/mL (following a clinical dose of 2 grams per day based on clinical review of curcumin), because the ratio of the gastrointestinal concentration to the IC_{50} values exceeds 11 (Guidance for Industry: Drug Interactions, February 2012). In vitro studies also suggest that curcumin induces human CYP3A enzymes (PMID: 25300360). Based on this in vitro data, a drug interaction may occur in humans when curcumin is coadministered with an oral sensitive CYP3A substrate or CYP3A4 substrate with a narrow therapeutic index.

Curcumin decreased human P-glycoprotein mRNA levels and transport activity in an in vitro study (PMID: 18439772). Insufficient information is available to determine the likelihood of an interaction with oral P-glycoprotein substrates in humans. Curcumin is not a P-glycoprotein substrate in vitro (PMID: 22930441). Its interaction with other transporters has not been reported.

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

There is no evidence-based use of curcumin. Therefore, for the multiple conditions investigated and for those in which curcumin is being used, any treatment for which a different drug (on- and off-label) or other treatment modality (i.e., surgery) showed an evidence-based effect (i.e., efficacy) is safer, as it will (a) treat the condition, and (b) not expose patients to any potential toxicities of curcumin.

In terms of a toxicity profile, with the limitations described, it appears that curcumin is well tolerated for short duration, with mostly gastrointestinal mild reaction when orally ingested and some local irritation when topically administered.

Conclusions: Curcumin's poor bioavailability, lack of exposure-response for safety, and lack of uniformity of products and doses used (extracts, powders, concentrates, multi-herbal preparations, creams, mouthwashes, oral formulations, etc.), as well as limited well-designed clinical trials, limit the ability to firmly conclude that curcumin is safe. It appears that it is mostly well tolerated for short durations and the most common adverse events related to its use are gastrointestinal, and of mild intensity. Additionally, specific safety concerns related to different curcumin products could include product impurities (e.g., heavy metals), especially when administered at high doses or for prolonged duration.

A number of nonclinical studies have demonstrated the potential for substantially enhanced bioavailability when curcumin is reformulated with excipients to enhance its solubility. Therefore the literature review described here likely underestimates the potential toxicity of these formulations. Furthermore, carcinogenicity studies in 2 species (rat, mouse) indicate a potential carcinogenicity signal.

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

Although curcumin administration results in biological effects that may be important in certain disease pathways (decreased IL-6, TNF-α, and endothelin-1 levels in diabetic patients, improved body weight, reduced serum TNF-α, and induced p53 expression in patients with colorectal cancer [Subash C., 2014], etc.), an extensive review of the literature did not support a conclusion that curcumin is effective for treatment of any disease or condition (familial adenomatous polyposis, gastric metaplasia, oral leukoplakia, dementia, depression, cancer prevention, cancer treatment, mucositis, arthritis).

A systematic review of curcumin as a therapeutic agent in dementia (Brondino et al., 2014) concluded that based on the three randomized controlled trials, there is insufficient evidence to suggest the use of curcumin in patients with dementia.

In a small study conducted in India (Sanmukhani et al., 2014), 60 patients with major depressive disorders were randomized to receive fluoxetine, curcumin (1000 mg) or a combination of both for 6 weeks. Observers were masked to study arm, and the study failed to show a difference between arms (reviewer's comment: the fluoxetine dose was fixed; in clinical practice, the dose is titrated as per the patient's response). In the Bergman paper described above (Bergman et al., 2014), the addition of curcumin to escilatopram or venlafaxine did not result in an improvement in the depression assessments when compared to placebo combined with the antidepressants.

A meta-analysis of 5 randomized controlled studies in 123 patients evaluating the effects of curcumin on blood lipid levels did not indicate a significant effect of curcumin on any of the lipid parameters, and there was significant heterogeneity for the impact of curcumin on total cholesterol, LDL-C and triglycerides but not HDL-C (Sahebkar et al., 2014). In a randomized, double-blinded, placebo-controlled trial conducted in a single center in Thailand (Chuengsamarn et al., 2014), 240 patients with type 2 diabetes were randomized to receive 1500 mg of curcuminoid extract or placebo for six months. Although the authors concluded that the curcumin intervention lowered the atherogenic risks, there were no significant differences in the means of systolic/diastolic blood pressure, levels of creatinine, and AST between the two study groups (curcumin r placebo).

The effect of curcumin on osteoarthritis was explored in a multicenter study in which 367 patients with knee osteoarthritis with a pain score of 5 or higher were randomized to receive ibuprofen 1200 mg/day or C. domestica extracts 1500 mg day for 4 weeks (Kuptniratsaikul et al., 2014). The authors concluded that treatment with C. domestica is not inferior to ibuprofen.

In the small study (Kurd et al., 2008) in 12 patients with psoriasis described above, only 2 responses were reported and therefore the study was terminated early.

In a randomized, double-blind, multicenter trial of curcumin for the prevention of relapse of ulcerative colitis conducted in Japan, 45 patients received curcumin (2 grams/day) plus sulfasalazine or mesalamine, and 44 patients received placebo plus sulfasalazine or mesalamine for 6 months (Hanai et al., 2006). The relapse rate during the 6-month period in the curcumin arm was 4.65% and 20.51% in the placebo group (p=.049). Curcumin was reported to improve the morbidity associated with ulcerative colitis. However, the rate of relapses at 12 months was not significantly different. Although curcumin is postulated to have a protective role in ulcerative colitis through modulation of the release of TNF-α and nitric oxide, the data are insufficient to support the use of curcumin in ulcerative colitis.

One open-label study evaluated the effects of curcumin in five patients with ulcerative proctitis and in five patients with Crohn's disease (Holt et al., 2005). The patients with ulcerative proctitis were given 550 mg of curcumin twice daily for 1 month and then 550 mg three times daily for another month. In the patients with Crohn's disease, curcumin was administered at a dose of 360 mg three times a day for 1 month and then 360 mg four times a day for another 2 months. Improvements in symptoms as well as in inflammatory indices (erythrocyte sedimentation rate and CRP) were reported in the five patients with proctitis in this *open label* study; however, one of the five patients did not complete the study. There was a mean reported reduction of 55 points in the Crohn disease activity index, and reductions in erythrocyte sedimentation rate and CRP were observed in these patients. Further studies would be needed to confirm the preliminary findings in these small studies. Additionally, effects on ESR or CRP would be insufficient to recommend an agent for clinical use.

In a position paper, the American College of Rheumatology (ACR) stated "The ACR recognizes the interest in complementary and alternative medicines (CAM) modalities. The ACR supports rigorous scientific evaluation of all modalities that improve the treatment of rheumatic diseases. The ACR understands that certain characteristics of some CAMs and some conventional medical interventions make it difficult or impossible to conduct standard randomized controlled trials. For these modalities, innovative methods of evaluation are needed, as are measures and standards for the generation and interpretation of evidence. The ACR supports the integration of those modalities proven to be safe and effective by scientifically rigorous clinical trials published in the biomedical peer review literature. The ACR advises caution for those not studied scientifically. The ACR believes healthcare providers should be informed about the more common CAM modalities, based upon appropriate scientific evaluation as described above, and should be able to discuss them knowledgeably with patients."

In the clinical study described above in patients with HPV positive cervical lesions but with no signs of neoplasia treated with topical curcumin, patients in the curcumin arm had a reported higher rate of clearance of HPV than patients in the placebo arm, but this difference was not significant (Basu et al., 2013).

In a small randomized, double-blind, placebo-controlled clinical trial to assess the ability of curcumin to reduce radiation dermatitis severity in 30 patients with breast cancer,

patients were randomized to receive 2 grams of curcumin or placebo orally three times per day (i.e., 6.0 grams daily) throughout their course of radiotherapy. Weekly assessments included Radiation Dermatitis Severity (RDS) score, presence of moist desquamation, redness measurement, McGill Pain Questionnaire-Short Form and Symptom Inventory questionnaire. Standard pooled variances t test showed that curcumin reduced RDS at end of treatment compared to placebo (mean RDS = 2.6 vs. 3.4; P = 0.008). Fisher's exact test reported by the author revealed that fewer curcumin-treated patients had moist desquamation (28.6% vs. 87.5%; P = 0.002). No significant differences were observed between arms for demographics, compliance, radiation skin dose, redness, pain or symptoms. The authors concluded that oral curcumin 6.0 g daily during radiotherapy reduced the severity of radiation dermatitis in breast cancer patients (Ryan JL et al., 2013). However, this was a small study and requires confirmation.

Curcumin has been extensively studied in patients with cancer, mostly in early phase studies to assess tolerability and safety or changes in biomarkers. Although preliminary activity was reported in some studies, no conclusions can be drawn from them. The following table (Gupta et al., 2013), summarizes clinical studies in cancer patients (outcomes are based on the publication and not this reviewer's opinion). As shown in the table, the majority of outcomes appeared to be related to effects on biomarkers and not clinical outcomes.

Disease	Pts (#)	Dosage; duration	Outcome [reference]
Cancer			
Colorectal cancer	15	0.036–0.18 g/day; 4 months	Reduced glutathione S-transferase activity (13)
	15	0.45–3.6 g/day; 4 months	Reduced PGE_2 production (14)
	12	0.45–3.6 g/day; 7 days	Reduced the levels of M_1G (15)
	5	1.44 g/day; 6 months[a]	Reduced the number and size of polyps without any appreciable toxicity (16)
	44	2 and 4 g/day; 1 month	Reduced ACF formation in smokers (17)
	126	1.08 g/day; 10–30 days	Improved body weight, reduced serum TNF-α, and induced p53 expression (18)
Pancreatic cancer	20	1.5 g/day; 6 weeks [a]	Reduced the lipid peroxidation and increased GSH content in patients(19)
	25	8 g/day	Well-tolerated, limited absorption, and showed activity in some patients (12)
	17	8 g/day; 4 weeks[a]	Not feasible for combination therapy (20)
	21	8 g/day[a]	Safe and well-tolerated in patients (11)
Breast cancer	14	6 g/day; 7 day, every 3 weeks[a]	Safe, well-tolerated, and efficacious (21)
Prostate cancer	85	0.1 g/day; 6 months[a]	Reduced the serum PSA content in combination with isoflavones(22)
Multiple myeloma	26	4 g/day; 6 months	Decreased paraprotein load and urinary N-telopeptide of type I collagen (23)
	29	2–12 g/day; 12 weeks[a]	Safe, bioavailable, and efficacious against multiple myeloma (24)
Lung cancer	16	1.5 g/day; 30 days[c]	Reduced the urinary excretion of mutagens in smokers (25)

In an extensive review of the therapeutic roles of curcumin, (Gupta et al., 2013), the authors reviewed multiple studies reporting the effects of curcumin in other diseases and conditions such as irritable bowel syndrome, uveitis, post-operative inflammation, peptic ulcer, H. pylori infection, vitiligo, acute coronary syndrome, lupus, renal transplantation, thalassemia, biliary dyskinesia, recurrent respiratory tract infection, alcohol intoxication, chronic bacterial prostatitis, diabetes, HIV, and chronic arsenic exposure. The authors concluded that curcumin has shown therapeutic potential against a number of human diseases. Common to all of these studies have been the tolerability and low toxicity of this polyphenol. However, poor bioavailability and limited adverse effects reported by some investigators are a major limitation to the therapeutic utility of curcumin.

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

Curcumin 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 to be used in the treatment of familial adenomatous polyposis (FAP), metaplastic atrophic gastritis, and oral leukoplakia.

Familial adenomatous polyposis

Familial adenomatous polyposis and its variants are caused by germline mutations in the tumor suppressor gene, adenomatous polyposis coli (APC), located on chromosome 5q21-q22 (autosomal dominance inheritance). FAP is characterized by the presence of multiple colorectal adenomatous polyps and occurs in approximately 1/10,000 to 1/30,000 live births.

Patients with FAP may present with gastrointestinal bleeding, abdominal pain, and diarrhea but the majority of patients are asymptomatic until they present with symptoms of colorectal cancer (unless they undergo colectomy). When fully developed, patients with classic FAP can have hundreds to thousands of colorectal adenomas. Polyposis typically develops in the second or third decade of life. The mean age of polyp emergence is 16 years. Colorectal cancer occurs in nearly 100 percent of individuals if untreated, with an average age of 45 years at cancer diagnosis (Winawer et al., 1997).

Given the predictable development of colorectal cancer in patients with FAP, treatment is surgical resection of the colon when polyposis develops. The two main prophylactic surgeries are colectomy with ileorectal anastamosis and proctocolectomy with ileal pouch-anal anastomosis. Colectomy with ileorectal anastamosis is a straightforward operation with less functional side effects compared to proctocolectomy with ileal pouch-anal anastomosis. However, patients who undergo colectomy with ileorectal anastamosis are at a 25% risk of developing cancer in the retained rectum after 20 years (Kim et al., 2011).

Chemopreventive strategies have been studied in FAP patients to delay the development of adenomas in the upper and lower gastrointestinal tract, as well as to prevent recurrence of adenomas in the retained rectum of patients after prophylactic surgery with colectomy and ileorectal anastomosis. Although celecoxib has shown to reduce the adenomas in FAP (Steinbach et al., 2000), celecoxib is a COX2 inhibitor with serious and potentially fatal cardiovascular and gastrointestinal risks, and therefore not recommended for treatment of AFP. Sulindac is another NSAID that has been reported to induce regression of adenomas, but no evidence exists that the drug delays or prevents the development of malignancy in these rectal segments and it is used only in conjunction with strict endosopic surveillance and not currently recommended as a primary chemopreventive regimen (Kim et al., 2011).

A small single arm, unblinded study evaluated whether the combination of curcumin and quercetin could suppress adenomas in patients with FAP (Cruz-Correa et al., 2006). Five

patients with FAP who had undergone prior colectomy received combinations of curcumin (480 mg) and quercetin (20 mg) orally three times a day, and the number and size of polyps were assessed at baseline and after therapy. The number and size of polyps was reported to have decreased after 6 months of combination treatment in the five patients. Although the combinations seemed to reduce the adenomas, randomized controlled trials are needed to further validate these findings. Weaknesses of the Cruz-Correa study in relation to the consideration in the bulk substances list include the following: (1) unblinded, small study; (2) the study did not isolate the effect of curcumin (e.g., any effects, if real, could have been caused solely by quercetin or some other factor [e.g., Mizuno et al., Digestive Endoscopy, 2014 indicated that a small percentage of diminutive polyps can shrink or completely regress]); (3) the study did not report on concomitant use of NSAIDS that have also been reported to have effects on polyps (the study stated that patients were instructed to not take NSAIDS; however, the study did not report on compliance with this request); (4) the study enrolled a population post-colectomy and did not enroll patients with FAP with intact colons; and the assessment was performed by one observer without biopsy of polyps to ensure pathological diagnosis.

Oral Leukoplakia

Oral leukoplakia is a precancerous lesion that presents as white patches or plaques of the oral mucosa. It represents hyperplasia of the squamous epithelium, which is believed to be an early step in the transformation of clonally independent premalignant lesions from hyperplasia, to dysplasia, to carcinoma in situ, to invasive malignant lesions (Lee et al., 2000). Leukoplakia is also seen in purely inflammatory conditions not associated with malignancy. An association exists between leukoplakia and human papillomavirus.

Leukoplakia itself is a benign reactive process. However, between 1 and 20 percent of lesions will progress to carcinoma within 10 years. The clinical significance and natural history of oral leukoplakia depends upon the presence and degree of dysplasia. Lesions with high degree of dysplasia require ablation, and for other lesions the removal of the chronic inflammatory stimuli (such as tobacco) induces regression of the lesion. In a Phase 1 study of curcumin as a chemopreventive agent (Cheng et al., 2001), one of four patients with uterine cervical intraepithelial neoplasia (CIN), and one of the seven patients with oral leukoplakia developed malignancy and two patients experienced histological improvement. Because 14% of the population with oral leukoplakia (and 25% with uterine CIN developed frank malignancy during the short study, we would not recommend use of curcumin as an agent to prevent cancer noting that the rate of malignancy could theoretically be increased (in addition to reduced or having no effect).

Metaplastic atrophic gastritis

The terms “gastric metaplasia”, “metaplastic atrophic gastritis”, “atrophic gastritis” and “gastric atrophy” have been used to describe a chronic gastritis that, in addition to inflammation, is associated with mucosal metaplasia (Dixon et al., 1996).

There are two main subtypes, autoimmune (AMAG) and environmental (EMAG)

metaplastic atrophic gastritis. Intestinal metaplasia is the hallmark of atrophic gastritis. Although intestinal metaplasia can be further subdivided into three histologic subtypes, they have been reported to be associated with an increased risk of gastric adenocarcinoma (Antonioli, 1990; Conchillo et al., 2001; Cassaro, 2000).

AMAG is a form of metaplastic atrophic gastritis that is associated with an immune response in the gastric mucosa directed against parietal cells and intrinsic factor. Affected patients are at high risk for developing pernicious anemia, with the subsequent hypergastrinemia, achlorydia, iron deficiency, B12 deficiency, and in later stages, subacute combined degeneration of the dorsal and lateral spinal columns. If detected, the pernicious anemia can be easily treated with vitamin B12.

Patients with AMAG are at increased risk for the development of gastric carcinoid tumors and adenocarcinoma. Gastric adenocarcinoma develops in 1 to 3 percent of patients with autoimmune gastritis (Fenoglio-Preiser, 2008). The magnitude of the risk is variable in the literature, with estimates ranging from 3 to 18 times greater than an age-matched population (Kato et al., 1992; Jedrychowski et al., 1997; Hsing et al., 1993; Tatsuta et al., 1993); nevertheless, the absolute risk of gastric carcinoma in the West is low.

The pathogenesis of EMAG appears related to environmental factors, such as diet and H. pylori infection. In EMAG, gastric acid production does not disappear entirely, parietal cell and intrinsic factor autoantibodies and pernicious anemia are absent, and the risk for gastric ulcer is higher compared with AMAG. Patients with EMAG also may be at increased risk for gastric cancer (Antonioli, 1990).

Although intestinal metaplasia may be an intermediate stage in the development of gastric cancer, there is no consensus as to the magnitude of risk in individual patients with intestinal metaplasia (Akiyama et al., 2009). Risk factors for the development of gastric carcinoma may include pernicious anemia, severity of atrophy, length of disease duration, family history of gastric cancer, dysplastic features in biopsies, and age older than 50 years (Park et al., 2013; Islami et al., 2011). An association between atrophic gastritis and esophageal squamous cell carcinoma has also been reported. In a meta-analysis that included seven studies of esophageal SCC, the overall relative risk for developing esophageal SCC in patients with atrophic gastritis was 1.94 (Islami et al., 2011).

There is no treatment for metaplastic atrophic gastritis. A guideline issued by the American Society for Gastrointestinal Endoscopy suggests (Hirota et al., 2006) that patients at increased risk for gastric cancer due to either background or family history may benefit from surveillance, and if high-grade dysplasia is confirmed, gastrectomy should be considered.

An international consensus developed evidence-based guidelines on the management of pre-cancerous lesions of the stomach. The guidelines recommended endoscopic surveillance every three years after diagnosis in all patients with extensive mucosal atrophy and/or intestinal metaplasia in the antrum and corpus (Dinis-Ribeiro et al., 2012).

Regarding gastric carcinoid tumors, the European Neuroendocrine Tumor Society (ENETS) guidelines suggest endoscopic follow-up every 6 to 12 months after a gastric carcinoid diagnosis. This interval allows for identification of new or recurrent lesions at an early stage when they can be easily removed by polypectomy (Arnold et al., 2009).

The experience of curcumin in patients with metaplastic gastritis is limited and there are no dedicated reports in the literature. However, in the above mentioned chemoprevention study conducted by Cheng, one of the 6 patients with metaplastic gastritis developed gastric cancer during the conduct of the study.

The clinical significance and natural history of metaplastic gastritis depends upon the risk factors and presence and degree of dysplasia. In a Phase 1 study of curcumin as a chemopreventive agent (Cheng et al., 2001), one of six patients with metaplastic gastritis, one of six patients with uterine cervical intraepithelial neoplasia (CIN), and one of the seven patients with oral leukoplakia developed malignancy (two patients experienced histological improvement). Based on this short study in which patients developed frank malignancy, we would not recommend use of curcumin as an agent to prevent cancer, noting that the rate of malignancy could theoretically be increased (in addition to reduced or having no effect).

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

Treatment for FAP is colectomy. Patients with ileorectal anastomosis are subjected to endoscopic surveillance for the early detection of rectal cancer. Although several chemoprevention strategies have been evaluated, the risk of cancer has not decreased and both sulindac and celecoxib are drugs with high risk of serious, potentially fatal adverse events.

Although colectomy is a treatment with serious sequelae, it prevents the development of colon cancer, which would occur in 100% of patients with the classical form of AFP. In fact, without colectomy, multiple cancers would likely occur further increasing the risk of subsequent metastatic disease. Ultimately, it would not be appropriate treatment to forgo frequent endoscopies/monitoring and colectomy (when needed) and instead treat with a chemopreventative agent based only on data showing that some adenomas may decrease in size.

Oral leukoplakia may or may not need treatment. Eliminating the exposure to local irritants and treatment of infections may result in regression of some lesions. For lesions that are already showing signs of dysplasia, ablation is the treatment that would result in the prevention of oral cancer.

Gastric metaplasia also may or may not need treatment. Pernicious anemia should be assessed in these patients, and vitamin B12 should be administered as clinically indicated. Treatment for H. pylori with antibiotics and proton pump inhibitors may also be administered to some patients if there symptoms are related to H. pylori. Some patients

may undergo surveillance for gastric cancer [although this practice is more common in certain countries (i.e., Japan and Korea) with a much higher incidence of gastric cancer compared to the U.S.].

Conclusions: According to published reports, preliminary signs of activity related to curcumin were reported in different diseases and disorders; however, despite numerous clinical trials, there is no conclusive evidence of its effectiveness. In general, the preliminary signs of activity involved effects on biomarkers, or effects on disease processes observed in uncontrolled or small studies. For the conditions for which curcumin has been nominated to be included on the list of bulk drug substances that can be compound in accordance with section 503A, there is insufficient evidence that curcumin is effective. Furthermore, curcumin use may delay the effective treatment of these conditions. Familial adenomatous polyposis is a serious condition because virtually all patients will develop colon cancer if left untreated (treatment is surgical). Use of curcumin outside of a clinical trial setting, where monitoring of the polyps is regimented, may increase the risk of these patients of developing an undetected cancer if they use curcumin in lieu of monitoring. Although not all oral leukoplakia lesions are pre-cancerous, medical supervision, diagnosis, and biopsies may be needed to determine if a particular lesion is non-malignant, pre-malignant, or malignant. Any treatment without clinical monitoring increases the risk of the patients to further develop a malignant lesion, increasing the morbidity and potentially impairing the curability of an oral cancer. Finally, limited data exist regarding the prolonged administration of curcumin that would be necessary for cancer prevention indications and at least one small trial reported development of malignancies in patients with CIN, oral leukoplakia, and gastric metaplasia; therefore, irrespective of any effects on biomarkers, an increased risk of malignancy could not be ruled out.

D. Has the substance been used historically in compounding?

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

We have no information regarding how long curcumin has been used in compounding. Based on a literature search, it appears that curcumin has been studied for clinical use since the early to mid-2000s.

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

See answer to question D1. The medical conditions for which curcumin has been studied are discussed above.

3. How widespread its use has been

We do not have information on the frequency with which curcumin is used as a drug. It is available as a dietary supplement.

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

DOP2 does not have the information to comment on this.

Conclusions: We have insufficient information to provide a conclusion regarding the historical use of curcumin in compounding at this time.

III. RECOMMENDATION

We have evaluated curcumin for use in compounding based on its physicochemical characteristics, safety, effectiveness, and evidence of historical use in compounding. We cannot say that curcumin is well-characterized physically and chemically as a wide range of substances comprised of different amounts of the different curcuminoids and other components are described as curcumin. While we understand that the related substance turmeric has been used traditional Indian medicine, we lack information about the historical use of curcumin in compounding. Although the substances identified as as curcumin appear to be reasonably safe when administered at doses reported in the literature and when admininistered for a limited duration, curcumin's poor bioavailability, lack of exposure-response for safety, and lack of uniformity of the curcumin used in these products and doses used (e.g., extracts, powders, concentrates, multi-herbal preparations, creams, mouthwashes, oral formulations), as well as limited information from well-designed clinical trials, hinder our ability to firmly conclude that curcumin is safe. It appears that it is mostly well tolerated for short duration and the most common adverse events related to its use are gastrointestinal, and are of mild intensity; however, for the proposed uses, curcumin may need to be administered to patients for years. Additionally, specific safety concerns related to different preparations could include product impurities (e.g., heavy metals), especially when administered at high doses or for prolonged duration.

More importantly, the use of curcumin may delay effective treatment of the serious conditions curcumin was nominated for. Familial adenomatous polyposis is a serious condition because virtually all patients with this condition will develop colon cancer if left untreated (treatment is surgical). Use of curcumin outside of a clinical trial setting, where monitoring of the polyps is regimented, may increase the risk of these patients of developing an undetected cancer. Although not all oral leukoplakia lesions are pre-cancerous, medical supervision, diagnosis, and biopsies may be needed to determine if a particular lesion is non-malignant, pre-malignant, or malignant. Any treatment without adequate clinical monitoring increases the risk of the patients to further develop a malignant lesion, increasing the morbidity and potentially impairing the curability of an oral cancer. And, in at least one study, patients with certain preexisting conditions that were given curcumin were actually observed during the study to develop cancer. We are concerned that large numbers of patients may be exposed to potential harm related to the administration of curcumin as a drug.

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Tab 4

Germanium Sesquioxide

Tab 4a

Germanium Sesquioxide Nominations

September 30, 2014

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

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

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

Dear Sir or Madam:

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

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

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

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

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

Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Germanium sesquinoxide
Chemical/Common Name	Germanium sesquinoxide
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 germanium *(including foreign recognition)*	USP Dimethicone monograph talke about an assay procedure for

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)*	
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.

VIA WWW.REGULATIONS.COM

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

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,[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

[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.

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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.

As discussed in detail below, in the interest 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.,[1] 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:

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.

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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

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 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
Glutiathone
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

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American College for Advancement in Medicine

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September 30, 2014

Division of Dockets Management (HFA-305)
Food And Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Re: Docket FDA-2013-N-1525

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

To Whom It May Concern:

The American College for Advancement in Medicine (ACAM) is a prominent and active medical education organization involved in teaching physicians in the proper use of oral and intravenous nutritional therapies for over forty years. We have also been involved in clinical research sponsored by the National Heart Lung and Blood Institute. As such, we have a vested interest in maintaining the availability of compounded drug products.

We appreciate 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. To meet what appear to be substantial requirements involved in this submittal, the FDA has given compounding pharmacists (in general a small business operation) and physicians very limited time to comply with onerous documentation. The Agency has requested information for which no single pharmacy or physician organization can easily provide in such a contracted time frame. As such this time consuming process requires significant coordination from many practicing professionals for which adequate time has not been allotted.

This issue is of great importance and has the potential to drastically limit the number of available compounded drugs and drug products thus limiting the number of individualized treatments that compounded medicines offer to patients.
ACAM and its physician members have not had the time to collect, review and assess all documentation necessary to submit for the intended list of compounded drugs required to assure all patient therapies are represented in our submission. We respectfully seek an additional 120 day period to educate and coordinate our physicians on the issue at hand and to gather the essential information necessary to provide the Agency with the most comprehensive information.
In an attempt to comply with the current timeframe established, a collaborative effort resulted in the attached nominations prepared for bulk drug substances that may be used in pharmacy compounding under Section 503A.

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It is not clear whether the current submission will be the final opportunity to comment or communicate with the Agency. Will a deficiency letter be provided if the initial nomination information was inadequate or will a final decision to reject a nominated substance be made without the opportunity to further comment? ACAM respectfully requests that the FDA issue a deficiency letter should the submitted documentation for a nomination be considered inadequate.

Sincerely,

Neal Speight, MD
(Immediate Past President) for
Allen Green, MD
President and CEO
The American College for Advancement in Medicine

Column A—What information is requested?	**Column B—Put data specific to the nominated substance**
What is the name of the nominated ingredient?	Germanium sesquioxide
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	There are multiple studies and research information regarding the active properties of germanium sesquioxide on Pubmed. Key word: germanium sesquioxide. See section"safety and efficacy data" below or access this link http://www.ncbi.nlm.nih.gov/pmc/?term=germanium
Is the ingrdient listed in any of the three sections of the Orange Book?	Not for germanium, germanium sesquioxide
Were any monographs for the ingredient found in the USP or NF monographs?	Not for germanium, germanium sesquioxide
What is the chemical name of the substance?	Bis (2-carboxyethyl germanium sesquioxide)
What is the common name of the substance?	Germanium, Dipropionic acid germanium sesquioxide, Carboxyethylgermanium Sesquioxide, Ge-132, Organic Germanium, Germanio, Germanium-132, Germanium Organique, spirogermanium.
Does the substance have a UNII Code?	96WE91N25T
What is the chemical grade of the substance?	This bulk drug substance is graded as a nutritional supplement by the manufacturer.
What is the strength, quality, stability, and purity of the ingredient?	No USP/NF monograph for this bulk drug substance. This bulk drug substance is graded as a nutritional supplement by the manufacturer. Prior to purchasing of Germanium sesquioxide, it is verified that it is made in the US and not foreign made. A certificate of US origin is provided. A valid Certificate of Analysis accompanies each lot of raw material received.

How is the ingredient supplied?	Germanium sesquioxide is supplied as a grayish-white powder form.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	TSCA Chemical Inventory: (EPA) This compound is ON the EPA Toxic Substances Control Act (TSCA) inventory list. WHMIS Classification (Canada): On NDSL EINECS Number (EEC): 235-800-0
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	Germanium sesquioxide 100 mg/mL mulitple dose or preservative free
What are the anticipated route(s) of administration of the compounded drug product(s)?	Slow intravenous

Are there safety and efficacy data on compounded drugs using the nominated substance?	1. Massey P. Dietary supplements. Medical Clinics of North America 2002;86:127-147. 2. Maskarinec G, Murphy S, Shumay DM, Kakai H. Dietary changes among cancer survivors. Eur J Cancer Care 2001;10:12-20. 3. Gerber GB, Leonard A. Mutagenicity, carcinogenicity and teratogenicity of germanium compounds. Mutation Research 1997;387(3):141-146. 4. Jao S-W, Lee W, Ho Y-S. Effect of germanium on 1, 2-dimethylhydrazine-induced intestinal cancer in rats. Diseases of the Colon and Rectum 1990;33:99-104. 5. Sato I, Yuan BD, Nishimura T, Tanaka N. Inhibition of tumor growth and metastasis in association with modification of immune response by novel organic germanium compounds. Journal of Biological Response Modifiers 1985;4(2):159-168. 6. Komuro T, Kakimoto N, Katayama T, Hazato T. Inhibitory effects of Ge-132 (carboxyethyl germanium sesquioxide) derivatives on enkephalin-degrading enzymes. 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	34. Unakar NJ, Tsui J, Johnson M. Effect of pretreatment of germanium-132 on Na(+)-K(+)-ATPase and galactose cataracts. Current Eye Research 1997;16(8):832-837. 35. Fujii A, Kuboyama N, Yamane J, Nakao S, Furukawa Y. Effect of organic germanium compound (Ge-132) on experimental osteoporosis in rats. General Pharmacology 1993;24(6):1527-1532. 36. Fujita H, Kurono M, Toyoshima S. Effect of 3-oxygermylpropionic acid polymer (SK-818) on the incidence of spontaneous leukemia in AKR mice. Pharmacometrics 1990;39(4):389-395. 37. Aso H, Suzuki F, Ebina T, Ishida N. Antiviral activity of carboxyethylgermanium sesquioxide (Ge-132) in mice infected with influenza virus. Journal of Biological Response Modifiers 1989;8(2):180-189. 38. Aso H, Shibuya E, Suzuki F, et al. Antitumor effect in mice of an organic germanium compound (Ge-132) when different administration methods are used. Gan To Kagaku Ryoho 1985;12(12):2345-2351. 39. Kumano N, Ishikawa T, Koinumaru S, et al. 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Phase II trial of spirogermanium in central nervous system tumors: A Southwest Oncology Group study. Cancer Treatment Reports 1987;71(1):99 – 100. 63. Ettinger DS, Finkelstein DM, Donehower RC, et al. Phase II study of N-methylformamide, spirogermanium, and 4-demethoxydaunorubicin in the treatment of non-small cell lung cancer (EST 3583): An Eastern Cooperative Oncology Group study. Med Pediatr Oncol 1989;17(3):197-201. 64. Vogelzang NJ, Gesme DH, Kennedy BJ. A phase II study of spirogermanium in advanced human malignancy. American Journal of Clinical Oncology 1985;8(4):341-344 65. McMaster M, Greco F, Johnson D, Hainsworth J. An evaluation of combination 5-fluorouracil and spirogermanium in the treatment of advanced colorectal carcinoma. Investigational New Drugs 1990;8:87-92. 66. Mirabelli C, Badger A, Sung C, et al. Pharmacological activities of spirogermanium and other structurally related azaspiranes: Effects on tumor cell and macrophage functions. Anticancer Drug Design 1989;3:231-242. 67. Import Alert IA #54-07. Germanium Products Rev. September 13, 1995.
Has the bulk drug substance been used previously to compound drug product(s)?	Germanium sesquioxide has been used to compounded 100 m/mL multiple dose or preservative free.

What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Germanium is important for its role in cellular oxygenation. The supposed therapeutic attributes of germanium include: aid in proper immune system functioning, may help the body detoxify toxins, may treat food allergies, oxygen enrichment, free radical scavenging, analgesia, heavy metal detoxification and may promote wound healing. Animal studies of germanium have also shown to have anti-viral and immunological properties.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There is no FDA-approved drug product containing germanium sesquioxide.
Is there any other relevant information?	Germanium sesquioxide (GS) has great potential in the Tx of patients with cancer and chronic illnesses. It has been studied in Asia and Russia for many decades and has had safe intravenous use in the USA for over twenty years. In studies, it has been shown to induce inteferon-gamma (IFN-gamma) [1], enhance natural killer cell activity [1,2], and inhibit tumor and metastatic growth [1]. In addition, oral consumption of GS has been reported to be readily assimilatled and rapidly cleared from the body without evdence of toxicity. Our own published clinical experience is that as an IV additive it is safe when infused under standard dose and safety guidlines [3]. 1. Kaplan BJ, Parish WW, Andrus GM, Simpson JS, Field CJ. Germane facts about germanium sesquioxide: I. CHemistry and anticancer properties. J Altern Complement Med. 2004 Apr;10(2):337-44. PMID:15165414. 2. Tanaka N. et al. Augmentation of NK activity in peripheral bllod lymphocytes of cancer patients by intermittent GE-132 administration. Gan to Kagaku Ryoho. 1984 Jun;11(6):1303-6. PMID:6732257. 3. Anderson P, Cochcran B. Personal experiences with the clinical use of intravenous germanium sesquioxide. AMSA, BIORC and Private clinic data. Seattle Washington, 2014.

Tab 4b

Germanium Sesquioxide
FDA Review

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: September 28, 2015

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Norman Schmuff, Ph.D.
Associate Director for Science, Office of Pharmaceutical Quality/Office of Process and Facilities, CDER, FDA

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Germanium Sesquioxide for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

Germanium sesquioxide 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 a variety of uses related to its role in cellular oxygenation. The nomination focuses on the use of germanium sesquioxide in the treatment of cancer and chronic illnesses.

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 germanium sesquioxide 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.

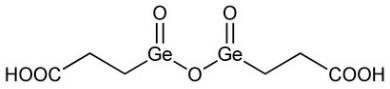
II. EVALUATION CRITERIA

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

NOTE: Currently there is an active import alert for all germanium compounds, except those used for semiconductors. See the FDA webpage[1] for further information.

1. Stability of the API and likely dosage forms

Fig 1. Structure of germanium sesquioxide



Germanium sesquioxide (FDA UNII: 96WE91N25T; CAS 12758-40-6) is also called propagermanium, bis(2-carboxyethylgermanium) sesquioxide, 2-carboxyethylgermanium sesquioxide, carboxyethylgermanium sesquioxide, 2-carboxyethylgermasesquioxane, proxigermanium, repagermanium, organic germanium, Ge-132, and SK-818 (see Figure 1). Germanium sesquioxide has been used as a dietary ingredient However, as described in Import Alert #54-07, any dietary supplement containing germanium sesquioxide is considered adulterated due to safety concerns and cannot be sold legally. Germanium sesquioxide is typically supplied as colorless, monoclinic crystals or crystalline powder.[2] According to the Material Safety Data Sheet of Sigma-Aldrich[3], germanium sesquioxide is stable when stored in a dry and well-ventilated place in a tightly closed container. Germanium sesquioxide is also stable upon exposure to light, heat and humidity, except during storage at 100% relative humidity (Kurono et al., 1989). However, germanium sesquioxide is not compatible with strong oxidizing agents, strong acids or strong bases. No degradation has been reported in liquid or solid form of germanium sesquioxide.

2. Probable routes of API synthesis

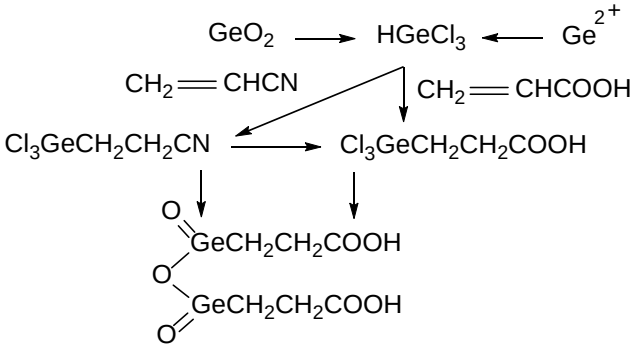
Germanium sesquioxide was originally synthesized by Mironov and coworkers in Russia and popularized by Asai and his colleagues in Japan. Acrylonitrile (also called vinyl

[1] http://www.accessdata.fda.gov/cms_ia/importalert_139.html
[2] https://www.rsc.org/Merck-Index/monograph/mono1500007909/
[3] Sigma-Aldrich manufactures chemicals for use in scientific research, biotechnology, and pharmaceutical development.

cyanide) and trichlorogermane were the starting materials (Tsutsui et al., 1976; Asai et al., 1974; Kaplan et al., 2004). This method is cited in the Merck Index and remains the most probable synthetic route for producing germanium sesquioxide.

From a literature search, many similar methods have been developed for the synthesis of germanium sesquioxide using acrylonitrile or acrylic acid as starting materials, and key reaction intermediate trichlorogermane was synthesized using GeO_2, $Ge(OH)_2$, $GeCl_2$, GeS (most probably GeO_2) as starting materials (see Figure 2) (Chang et al., 1985; Arnold, 1996; Sun et al., 1995; Zhang et al., 2000).

Fig 2. Probable synthetic routes of germanium sesquioxide



3. Likely impurities

The likely impurities are the starting materials, inorganic germanium salts (Kaplan et al., 2004), acrylonitrile, and acrylic acid, and the reaction intermediates 3-(trichlorogermyl)propanoic acid and 3-(trichlorogermyl)propionitrile. In the manufacturing process, the contamination of germanium sesquioxide with dangerous levels of inorganic germanium salts (e.g., GeO_2) occurs, and some of the excess acrylonitrile is converted to acrylamide during the hydrolysis step of synthesis.

4. Toxicity of those likely impurities

Inorganic forms of germanium (e.g., GeO2; Germanium lactate citrate, Ge-lac-cit) can accumulate in the body and cause toxicity (Tao et al., 1997; Luck et al., 1999; Sanai et al., 1991). It was reported that chronic GeO_2 intake causes progressive renal dysfunction (Sanai et al., 1990). Acrylonitrile, acrylamide, and acrylic acid contain structural alerts for genotoxicity. In the U.S. National Library of Medicine's (NLM) Toxicology Data Network (TOXNET), acrylonitrile and acrylamide are classified as Group B1 and B2 Probable Human Carcinogen respectively (USEPA, 1994; USEPA, 2006).

Acrylic acid is not classifiable as to its carcinogenicity in humans, but it may cause skin allergy and lung and kidney damage (Sittig, 2002). Based on a literature search in PubMed, SciFinder and TOXNET, no toxicity data were available on the reaction intermediates 3-(trichlorogermyl)propanoic acid and 3-(trichlorogermyl)propionitrile.

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

Germanium sesquioxide is soluble in water at 20°, insoluble or very slightly soluble in almost all organic solvents, and very soluble in water under alkaline conditions.[4] Germanium sesquioxide is nominated for injection compounding. There are no concerns related to particle size or polymorphism.

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

Germanium sesquioxide is a physicochemically well-characterized, small molecular weight API. It can be quantified using liquid chromatography-mass spectrometry (LC-MS) or inductively coupled plasma mass spectrometry (ICP-MS) (Yamaguchi et al., 2015; Krystek et al., 2004).

Conclusions: From physicochemical point of view, germanium sesquioxide can be easily characterized. From a product quality standpoint, due to the toxicity of likely impurities, germanium sesquioxide is not recommended for inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

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

1. Nonclinical Assessment

The following information is summarized based on a literature search of PubMed and TOXNET.

a. Pharmacology of the drug substance

Published reports have shown that germanium sesquioxide (GS, CEGS, Ge-132) induced IFN-gamma, enhanced NK-cell activity in vitro and in vivo, and inhibited tumor and metastasis growth in animal models (Kaplan BJ, et al., 2004).

b. Safety pharmacology

Intraperitoneal (IP) administration of a water-soluble organogermanium compound, 2-carboxyethyl germanium sesquioxide (Ge-132), produced a dose-related reduction in either the mean arterial pressure or the heart rate in anesthetized rats (HO CC, et al., 1990).

Oral administration and IP injection of Ge-132 resulted in enhancement of 0.5 mg/kg morphine analgesia in the Tail-Flick test, the effect of which was completely abolished by 0.5 mg/kg Naloxone, a stereospecific opiate antagonist.

[4] See https://www.rsc.org/Merck-Index/monograph/mono1500007909/

IP administration of Ge-132 at 250 mg/kg did not show any antinociceptive action by assessing the Tail-Flick test and the Hot-Plate test. Intracerebral injection of Ge-132 (100-1000 micrograms) prolongated Tail-Flick latency (Hachisu M, et al., 1983).

c. Acute toxicity

The median lethal dose (LD50) for acute intraperitoneal administration of GE-132 in mice was 1250 mg/kg. Behavioral changes, including somnolence and muscle contraction or spasticity, were the major adverse effects.

The LD50 for acute intravenous administration of GE-132 in mice was 233mg/kg.

The LD50 for oral administration of GE-132 in mice was greater than 4000 mg/kg with hypermotility, diarrhea, nausea, and vomiting.

LD50 for intraperitoneal administration of GE-132 in rats was 1700mg/kg. The LD50 for acute intravenous administration of GE-132 in rats was greater than 200 mg/kg.

d. Repeat dose toxicity

Male and female rats were administered 1 mg/kg/day of GE-132 orally for 28 days or 6 months. No particular clinical signs and no behavior changes were observed. A small decrease in body weight was observed in males rats after oral administration of GE-132 at 1 mg/day for 6 months. A slight decrease in erythropoiesis and a general stimulation of cellular metabolism was observed after 28 days. A moderate renal deficiency characterized by a tubular disease with presence of cylinders, swelling of tubulus cells, and floculus amounts was observed after 6 months (Anger F1, et al., 1991).

e. Mutagenicity

Germanium compounds, including germanium sesquioxide, did not have mutagenic activity in the in vitro reverse mutation assay in bacterial cells (Gerber GB and Leonard A., 1997).

f. Developmental and reproductive toxicity

No study reports on the developmental and reproductive toxicity of germanium sesquioxide have been identified. The organic compound, dimethyl germanium oxide, has been reported to be teratogenic in chick embryos causing limb abnormalities, umbilical hernias and anophthalmia. Doses of 40 and 100 mg/kg of germanium trioxide (sodium metagermanate; $Na2GeO3 \cdot 7H2O$) injected intravenously into pregnant hamsters on day 8 of gestation resulted in an increased embryonic resorption, but did not produce obvious malformations (Gerber GB and Leonard A., 1997).

g. Carcinogenicity

Germanium compounds, including germanium sesquioxide, were not carcinogenic in mice or rats (Gerber GB and Leonard A., 1997).

h. Toxicokinetics

No information was available.

Conclusions: Germanium sesquioxide does not appear to be mutagenic or carcinogenic. However, there are inadequate nonclinical data to otherwise characterize the safety profile of germanium sesquioxide at a high dose level. The nephrotoxicity of inorganic forms of germanium (such as germanium dioxide or germanium citrate lactate) is well established. The potential nephrotoxicity from organic germanium compounds cannot be excluded due to lack of conclusive findings. Developmental and reproductive toxicity were observed in the studies with other germanium compounds (e.g., dimethyl germanium oxide, sodium metagermanate; Na2GeO3·7H2O).

2. Human Safety

The PubMed database, FAERS, Micromedex, ADIS R&D Insight, ADIS Clincal Trials Insight, Web of Science were used to research this section.

a. Reported adverse reactions

A clinical trial reported in 1990 (Ettinger, D.S et al., 1990) included the use of an intravenous germanium compound (spirogermanium) for the treatment of advanced small cell lung cancer. There were no responses reported, with overall survival of 12.6 weeks in the germanium arm, while four patients experienced severe and life-threatening toxicity (three neurologic, one thrombocytopenia). These findings were consistent with other studies of this form of organic germanium. Several additional reports in the 1980s of early-phase intravenous spirogermanium at escalating doses have been reported (e.g.,Vogelzang, 1985; Ettinger 1989), in which safety manifestations varied from no safety concern at low doses, to neurological (blurred vision, ataxia, dysesthesias) and hepatic (Falkson, 1983) toxicities that appear to resolve within a few days of infusion, with toxicity attenuated by slow infusion. These reports are listed as references in the application for germanium sesquioxide but pertain only to spirogermanium, a different API. A search of the FAERS database did not return any results for this API.

b. Clinical trials assessing safety

There are no clinical trials assessing the safety of germanium sesquioxide.

As above, spirogermanium, an infusional agent explored in the 1980s for the treatment of cancer, was evaluated for safety and efficacy in a few early-phase trials; these data are not germane to the case of germanium sesquioxide (the substance nominated for inclusion on the list of bulk drug substances that may be used to compound under section 503A of the FD&C Act).

The Natural Products Association website states: "The concern with use of Ge-132 is not primarily the organic compound itself, but rather the potential for contamination of a product with the toxic inorganic forms of various germanium salts, such as the highly toxic germanium dioxide." In addition, according to a 1997 article, "at least 31 reported human cases linked prolonged intake of germanium products with renal failure and even death" (Tao, S.-H. et al., 1997).

c. Pharmacokinetic data

No information was available.

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 germanium sesquioxide gives rise to significant concern about its use in compounding. It seems likely that the substance could be contaminated with highly toxic inorganic forms of germanium salts. Prolonged intake of germanium products has been associated with at least 31 cases of renal failure, some of which led to death. 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

As described above, germanium sesquioxide is a form of organic germanium. Little clinical data exist for this form of germanium; published reports in the medical literature are limited to a single case report (Mainwaring, M.G. et al., 2000), in which a woman with spindle cell carcinoma of the lung reported complete resolution of radiographic findings after self-treating with 7.2 grams/day of germanium sesquioxide (the bis-betacarboxyethygermanium sesquioxide form). Conclusions should be limited, however; the patient had just completed treatment with radiation therapy (4500 cGy) and chemotherapy.

An additional clinical trial, "A Phase II, Pilot, Randomized, Double-blind Study Comparing the Effectiveness Organic Germanium to Placebo in Decreasing the Severity of Fatigue in Patients Undergoing Radiation Therapy for Prostate and Breast Cancers," was opened in 2005 (clinicaltrials.gov), but results have not been reported; attempts at contacting the sponsor went unanswered.

Additional clinical reports, including those cited in the nomination, are clinical trial reports from the 1980s and 1990s documenting the use of spirogermanium, a different, infusional form of germanium, for the treatment of patients with cancer. These references are not germane to the evaluation of the clinical merits of germanium sesquioxide for the treatment of patients with malignant diseases. Clinical evaluation of that compound was terminated, with insufficient evidence of clinical activity (Goodwin, 1987; Eisenhower, 1985; Ettinger, 1990; Ettinger, 1989; Falkson, 1983; Saiers, 1987; Vogelzang, 1985).

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

The intended application of this substance is in the treatment of cancer, a serious and life-threatening disease. Although the nomination also referenced "chronic conditions," and several other possible therapeutic attributes of germanium sesquioxide were listed in the nomination, the nomination provided insufficient information about the use of germanium sesquioxide for those conditions to evaluate whether the underlying disease states are serious or life-threatening.

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 after demonstration of safety and efficacy in well-controlled clinical trials.

Conclusions: There is no evidence available in the literature that would indicate that germanium sesquioxide is effective for the treatment of cancer. We located only a single case report that involved a patient who had completed radiation and chemotherapy. 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 in compounding?

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

There is insufficient information available from which to make this determination. Links from some compounding pharmacy webpages point to the NPA webpage (cited above), which cautions against the use of germanium sesquioxide.

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

A single case report describes the use of germanium sesquioxide in cancer as an alternative treatment by the patient following her chemoradiation therapy. Further clinical data for the use of germanium sesquioxide for the treatment of cancer were not publicly available.

3. How widespread its use has been

There are insufficient data to determine the extent of the use of germanium sesquioxide in compounded drug products.

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

We searched the British pharmacopoeia, 2015 edition; update 1/7/2015; European pharmacopoeia, 2015, Online 8.5 and 2016, Online 8.6; Japanese pharmacopoeia, 16th edition and found no information about the recognition of germanium sesquioxide in other countries or foreign pharmacopeias.

Conclusions: There is little information available to assess the historical use of germanium sesquioxide in compounding.

III. RECOMMENDATION

We have evaluated germanium sesquioxide for use in compounding based on its physicochemical characteristics, safety, effectiveness, and evidence of historical use in compounding. Although it is physically and chemically well characterized, it can include impurities with significant toxicities. The nephrotoxicity of inorganic forms of germanium (such as germanium dioxide or germanium citrate lactate) is well established.

Clinical evidence for the efficacy of germanium sesquioxide in oncology is lacking. Furthermore, there are significant risks associated with long-term use and possible contamination by inorganic germanium. The possible uses for germanium sesquioxide in the oncology setting, in which only life-threatening illnesses are included, could delay the administration of FDA-approved products that have well-established safety and efficacy profiles for oncology indications. Given the seriousness of the condition and the high risk of disease progression without effective treatment, delaying administration of approved products raises significant patient safety concerns.

A number of the new oncology agents approved since the last published report for use of germanium sesquioxide in oncology in 2000 argues against the addition of germanium sesquioxide in compounding formularies, given the known safety and efficacy of alternative therapies. Based upon our evaluation of the four criteria identified above, we ***do not recommend*** that germanium sesquioxide be included on the list of bulk drug substances that can be used in compounding in accordance with section 503A.

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Tab 5

Rubidium Chloride

Tab 5a

Rubidium Chloride Nominations

VIA WWW.REGULATIONS.COM

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

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,[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

[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.

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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.

As discussed in detail below, in the interest 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.,[1] 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:

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.

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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

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 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
Glutiathone
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

ACAM
American College for Advancement in Medicine

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September 30, 2014

Division of Dockets Management (HFA-305)
Food And Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Re: Docket FDA-2013-N-1525

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

To Whom It May Concern:

The American College for Advancement in Medicine (ACAM) is a prominent and active medical education organization involved in teaching physicians in the proper use of oral and intravenous nutritional therapies for over forty years. We have also been involved in clinical research sponsored by the National Heart Lung and Blood Institute. As such, we have a vested interest in maintaining the availability of compounded drug products.

We appreciate 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. To meet what appear to be substantial requirements involved in this submittal, the FDA has given compounding pharmacists (in general a small business operation) and physicians very limited time to comply with onerous documentation. The Agency has requested information for which no single pharmacy or physician organization can easily provide in such a contracted time frame. As such this time consuming process requires significant coordination from many practicing professionals for which adequate time has not been allotted.

This issue is of great importance and has the potential to drastically limit the number of available compounded drugs and drug products thus limiting the number of individualized treatments that compounded medicines offer to patients.
ACAM and its physician members have not had the time to collect, review and assess all documentation necessary to submit for the intended list of compounded drugs required to assure all patient therapies are represented in our submission. We respectfully seek an additional 120 day period to educate and coordinate our physicians on the issue at hand and to gather the essential information necessary to provide the Agency with the most comprehensive information.
In an attempt to comply with the current timeframe established, a collaborative effort resulted in the attached nominations prepared for bulk drug substances that may be used in pharmacy compounding under Section 503A.

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It is not clear whether the current submission will be the final opportunity to comment or communicate with the Agency. Will a deficiency letter be provided if the initial nomination information was inadequate or will a final decision to reject a nominated substance be made without the opportunity to further comment? ACAM respectfully requests that the FDA issue a deficiency letter should the submitted documentation for a nomination be considered inadequate.

Sincerely,

Neal Speight, MD
(Immediate Past President) for
Allen Green, MD
President and CEO
The American College for Advancement in Medicine

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Rubidium chloride
Is the ingredient an active ingredient that meets the definition of ‘‘bulk drug substance’’ in § 207.3(a)(4)?	Yes. [The pharmacological action of rubidium chloride in depression]. Brundusino AO, Cairoli S. Minerva Psichiatr. 1996 Mar;37(1):45-9. Italian. PMID:8926857[PubMed - indexed for MEDLINE] Or please see section "safety and efficacy data" below.
Is the ingredient listed in any of the three sections of the Orange Book?	No for Rubidium chloride. Yes for radioactive Rubidium as Cardiogen-82.
Were any monographs for the ingredient found in the USP or NF monographs?	No USP/NF/Dietary monograph available for rubidium chloride. Yes for radioactive rubidium-82.
What is the chemical name of the substance?	Rubidium Chloride=B2
What is the common name of the substance?	Rubidium
Does the substance have a UNII Code?	N3SHC5273S
What is the chemical grade of the substance?	High purity
What is the strength, quality, stability, and purity of the ingredient?	Rubidium chloride, High Purity A Certificate of Analysis accompanies every lot of raw material received.
How is the ingredient supplied?	Rubidium chloride is a white to off white powder or crystal.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	TSCA 8(b) inventory: Rubidium chloride OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR WHMIS (Canada) CLASS D-2A: Material causing other toxic effects (VERY TOXIC).1910.1200). DSCL (EEC) R38- Irritating to skin. R41- Risk of serious damage to eyes.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	Compounded injectable products containing Rubidium chloride can be formulated in strengths of Rubidium chloride ranging from 0.564 mcg/mL (141 mcg/250 mL) to 282 mcg/mL (8.46 mg/30 mL).
What are the anticipated route(s) of administration of the compounded drug product(s)?	Slow intravenous

Are there safety and efficacy data on compounded drugs using the nominated substance?	1. The concentrations of trace elements in blood from healthy newborn infants. Meurling S, Plantin LO. Acta Chir Scand. 1981;147(6):481-5.MID:7324778[PubMed - indexed for MEDLINE] 2. Trace elements in children on total parenteral nutrition (T.P.N.). Ricour C, Gros J, Mazière B, Comar D. Acta Chir Scand Suppl. 1976;466:22-3. PMID:828398[PubMed - indexed for MEDLINE] 3. Serum levels of certain trace elements (Fe, Rb, Se, Zn) in healthy humans (part III). Masiak M, Skowron S, Maleszewska H, Koziorowski L, Herzyk D. Acta Physiol Pol. 1982 Jan-Apr;33(1-2):75-81. PMID:7158384[PubMed - indexed for MEDLINE] 4. The effect of age on Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn contents in intact human prostate investigated by neutron activation analysis. Zaichick S, Zaichick V. Appl Radiat Isot. 2011 Jun;69(6):827-33. doi: 10.1016/j.apradiso.2011.02.010. Epub 2011 Feb 12. PMID:21354803[PubMed - indexed for MEDLINE] 5. Neutron activation analysis of the trace elements cobalt, iron, rubidium, selenium, zinc, chromium, silver, cesium, antimony and scandium in surgical specimens of human brain tumors. 1]. Schicha H, Müller W, Kasperek K, Schröder R. Beitr Pathol. 1974 Mar;151(3):281-96. German. No abstract available. PMID:4365800[PubMed - indexed for MEDLINE] 6. Selenium and rubidium changes in subjects with pathologically altered thyroid. Kvícala J, Havelka J, N ěmec J, Zeman V. Biol Trace Elem Res. 1992 Jan-Mar;32:253-8. PMID:1375062[PubMed - indexed for MEDLINE] 7. Trace element concentration in human brain. Activation analysis of cobalt, iron, rubidium, selenium, zinc, chromium, silver, cesium, antimony and scandium. Höck A, Demmel U, Schicha H, Kasperek K, Feinendegen LE. Brain. 1975 Mar;98(1):49-64. PMID:1122375[PubMed - indexed for MEDLINE] 8. Elemental composition of platelets. Part III. Determination of Ag, Au, Cd, Co, Cr, Cs, Mo, Rb, Sb, and Se in normal human platelets by neutron activation analysis. Kasperek K, Iyengar GV, Kiem J, Borberg H, Feinendegen LE. Clin Chem. 1979 May;25(5):711-5. PMID:436238[PubMed - indexed for MEDLINE] Free Article 9. Simultaneous determination of iron, zinc, selenium, rubidium, and cesium in serum and packed blood cells by neutron activation analysis. Versieck J, Hoste J, Barbier F, Michels H, De Rudder J. Clin Chem. 1977 Jul;23(7):1301-5. PMID:872376[PubMed - indexed for MEDLINE 10. Pharmacologic role of rubidium in psychiatric research. Williams RH, Maturen A, Sky-Peck HH. Compr Ther. 1987 Sep;13(9):46-54. Review. PMID:3311597[PubMed - indexed for MEDLINE] 11. The trace elements cobalt, iron, rubidium, selenium and zinc in serum and in different regions of the human brain. Demmel U, Höck A, Kasperek K, Freundlieb C, Feinendegen LE. Folia Morphol (Praha). 1980;28(2):150-3. No abstract available. 12. PMID:7390317[PubMed - indexed for MEDLINE] 13. Selenium, rubidium and zinc in human semen and semen fractions. Behne D, Gessner H, Wolters G, Brotherton J. Int J Androl. 1988 Oct;11(5):415-23. PMID:3235210[PubMed - indexed for MEDLINE] 14. How should dietary guidance be given for mineral elements with beneficial actions or suspected of being essential? Nielsen FH. J Nutr. 1996 Sep;126(9 Suppl):2377S-2385S. Review. PMID:8811801[PubMed - indexed for MEDLINE] Free Article 15. Trace elements and chronic liver diseases. Loguercio C, De Girolamo V, Federico A, Feng SL, Cataldi V, Del Vecchio Blanco C, Gialanella G. J Trace Elem Med Biol. 1997 Nov;11(3):158-61. PMID:9442462[PubMed - indexed for MEDLINE] 16. Trace elements (zinc, cobalt, selenium, rubidium, bromine, gold) in human placenta and newborn liver at birth. Alexiou D, Grimanis AP, Grimani M, Papaevangelou G, Koumantakis E, Papadatos C. Pediatr Res. 1977 May;11(5):646-8. PMID:859726[PubMed - indexed for MEDLINE] 17. Trace element concentration in the human pineal body. Activation analysis of cobalt, iron, rubidium, selenium, zinc, antimony and cesium. Demmel U, Höck A, Kasperek K, Feinendegen LE. Sci Total Environ. 1982 Jun;24(2):135-46. PMID:7112096[PubMed - indexed for MEDLINE] 18. Pharmacologic action of rubidium chloride. Antidepressive effect: comparison with imipramine]. Carolei A, Sonsini U, Casacchia M, Agnoli A, Fazio C. Clin Ter. 1975 Dec 15;75(5):469-78. Italian. PMID:767038[PubMed - indexed for MEDLINE] 19. The effect of rubidium in schizophrenia. Chouinard G, Annable L. Commun Psychopharmacol. 1977;1(4):373-83. No abstract available. PMID:28202[PubMed - indexed for MEDLINE] 20. Effects of rubidium chloride on the course of manic-depressive illness. Paschalis C, Jenner FA, Lee CR. J R Soc Med. 1978 May;71(5):343-52. PMID:349155[PubMed - indexed for MEDLINE] 21. Cerebrospinal fluid rubidium metabolism in depression. Dunner DL, Meltzer HL, Fieve RR. Psychopharmacologia. 1974 Jun 18;37(1):7-13 PMID:4606322[PubMed - indexed for MEDLINE] 22. Wright, J. One Program, Two Months, Lasting Relief – From Almost Any Symptom...And the Older You Are, the Better it Works, Townsend Letter for Doctors & Patients. 2006 Apr:80-2.
Has the bulk drug substance been used previously to compound drug product(s)?	Rubidum chloride has been used to compound injectable products in strengths of Rubidium chloride ranging from 0.564 mcg/mL (141 mcg/250 mL) to 282 mcg/mL (8.46 mg/30 mL).

What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Rubidium chloride has been used to compound injectable products in strengths of Rubidium chloride ranging from 0.564 mcg/mL (141 mcg/250 mL) to 282 mcg/mL (8.46 mg/30 mL). Rubidium chloride 200 mcg/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, "Tumor-selective modification of cellular microenvironment in vivo: effect of glucose infusion on the pH in normal and malignant rat tissues." 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 rubidium was taken up efficiently by cancer cells, in the presence of other nutrients. This, in combination with other nutrients, 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 rubidium found that tumor masses shrunk 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. Rubidium 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 rubidium chloride in their fight against cancer.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There is no FDA-approved drug product containing rubidium chloride. No existing drug matches the advantages of rubidium 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.

Is there any other relevant information?	No approved drug product exists that addresses the condition adequately. No existing drug matches the unique therapeutic effect of rubidium 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 rubidium chloride are a viable alternative. Rubidium 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 rubidium chloride in their fight against cancer. There is a need to compound rubidium chloride, in order to serve the patient population for whom chemotherapy is no longer effective. As an estimate of such patient population, we expect the number of cancer patients choosing rubidium chloride as part of their adjunctive 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 rubidium chloride. It is estimated that over 50% of all cancer patients use integrative, 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.)

Tab 5b

Rubidium Chloride
FDA Review

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: September 28, 2015

FROM: Sanjeeve Balasubramaniam, M.D., M.PH., Clinical Reviewer, Division of Oncology Products 1, Office of Hematology and Oncology Products, CDER, FDA

Wei Chen, Ph.D., Pharmacologist/Toxicologist Reviewer, Division of Hematology, Oncology, Toxicology, Office of Hematology and Oncology Products, CDER, FDA

Norman Schmuff, Ph.D.
Associate Director for Science, Office of Pharmaceutical Quality/Office of Process and Facilities, CDER, FDA

THROUGH: Amy McKee, M.D., Clinical Team Leader, Division of Oncology Products 1, Office of Hematology and Oncology Products, CDER, FDA

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

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

TO: Pharmacy Compounding Advisory Committee

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

I. INTRODUCTION

Rubidium chloride 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 use in cancer therapy.

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 rubidium 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?

1. Stability of the API and likely dosage forms

Rubidium chloride (RbCl, 7791-11-9) is also called rubidium monochloride or rubinorm. It is supplied as white-to-off-white powder or crystal. Solid rubidium chloride has three arrangements or polymorphs (Kopecky et al., 2005; Pyper et al., 2006). According to the Material Safety Data Sheet (MSDS) of Acros Organics, rubidium chloride is stable under normal temperatures and pressures. It is recommended that rubidium chloride l be stored in a cool, dry, and well-ventilated place in a tightly closed container that protects from moisture (e.g., using a desiccator) due to its hygroscopicity.

2. Probable routes of API synthesis

Rubidium chloride can be synthesized from rubidium oxide (Rb_2O) or rubidium hydroxide (RbOH). The most common preparation method of rubidium chloride is the reaction of rubidium hydroxide (RbOH) with hydrochloric acid (HCl) and the following recrystallization (**Fig 1**).

$$RbOH + HCl \rightarrow RbCl + H_2O$$

Fig 1. Probable synthetic routes of rubidium chloride.

3. Likely impurities

Rb_2O is hygroscopic and reactive and can react exothermically with water to form stable RbOH. The likely impurity in the rubidium chloride product is RbOH when Rb_2O or/and RbOH are used as starting materials.

4. Toxicity of those likely impurities

Rubidium compounds are only slightly toxic on an acute toxicological basis, but would pose an acute health hazard when ingested in large quantities (Johnson et al., 1975). In the U.S. National Library of Medicine's (NLM) Toxicology Data Network (TOXNET), RbOH is designated more toxic than other salts of this metal, and it is designated a pneumotoxin, hepatotoxin, and dermatotoxin (Johnson et al., 1975). In humans, the minimum toxic concentration was 5.75 mg RbOH/m^3; the recommended maximum permissible concentration for occupational exposure is 0.5 mg RbOH/m^3 (Hamidulina, 1987).

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

Rubidium chloride is hygroscopic, as noted above, and very soluble in water. One gram of rubidium chloride dissolves in 1 ml cold water, 0.7 ml boiling water, 90 ml methanol, and 1650 ml alcohol. The aqueous solution of rubidium chloride is neutral.[1] Rubidium chloride is nominated for use in injections, and there are no concerns related to particle size or polymorphism with this use.

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

Rubidium chloride is a physicochemically well-characterized, inorganic API. It can be quantitated using ICP-MS (Jensen et al., 2015).

Conclusions: Rubidium chloride is physicochemically well characterized. From the product quality point of view, rubidium chloride is suitable to be compounded.

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

1. Nonclinical Assessment

Based on searches on PubMed and TOXNET, the following information has been summarized below and in Table 1.

a. Pharmacology of the drug substance

Rubidium is an alkali metal belonging to the same periodic series as sodium, potassium, lithium, and cesium. Rubidium is used for cancer treatment as a high-pH therapy. Mass spectrographic and isotope studies have shown that alkali metals, including rubidium and cesium, are most efficiently taken up by cancer cells where the pH is raised to a range of 8, and cell mitosis ceases. In mouse tumor models, shrinkage of tumor masses was shown after 2 weeks in mice fed a diet containing cesium and rubidium (1.11 mg/day) (Brewer AK., et al., 1984; Brewer AK, et al., 1979). In addition, rubidium could replace potassium in the Na+K-ATPase (sodium-potassium pump) system. Depletion of intracellular potassium ions (K+) induced DNA fragmentation, activated caspases, resulted in apoptosis, and caused tumors to shrink (Britta A, et al., 2005).

b. Safety pharmacology

Rubidium was found to decrease locomotion and rearing in the exploratory box test. It also decreased locomotion in the open field test (Syme GJ, et al., 1979).

Long-term treatment of rats with rubidium produced a condition of behavioral hypo-reactivity accompanied by a decreased dopamine output in the nucleus accumbens at the lowest dose tested of 0.008 mEq/kg (Gambarana C, et al., 1999).

[1] Merck Index. https://www.rsc.org/Merck-Index/monograph/m9687.

c. Acute toxicity

In addition, rubidium chloride, given acutely, enhanced the sleeping time caused by diazepam. (Männistö PT and Saarnivaara L, 1976).

Table 1: Acute toxicity and LD50 values in animals

Organism	Study Type	Route	Reported Dose (Normalized Dose)	Effect	Source
mouse	LD50	IP	1149mg/kg		Comptes Rendus Hebdomadaires des Seances, Academie des Sciences. Vol. 256, Pg. 1043, 1963.
mouse	LD50	IV	233mg/kg		Nippon Yakurigaku Zasshi. Japanese Journal of Pharmacology. Vol. 56(4), Pg. 118S, 1960.
mouse	LD50	oral	3800mg/kg		"Novye Dannye Po Toksikologii Redkikh Metalov Ikh Soedinenii," New Data on the Toxicology of Rare Metals and Their Compounds, Izrael'son, Z.I., ed., Moscow, Izdatel'stvo "Meditsina," 196Vol. -, Pg. 56, 1967.
rat	LD50	IP	1700mg/kg	Peripheral nerve and sensation: spastic paralysis with or without sensory change behavioral: somnolence (general depressed activity) behavioral: convulsions or effect on seizure threshold	Gigiena Truda i Professional'nye Zabolevaniya. Labor Hygiene and Occupational Diseases. Vol. 31(9), Pg. 55, 1987.
rat	LD50	oral	4440mg/kg		Gigiena i Sanitariya. For English translation, see HYSAAV. Vol. 53(5), Pg. 76, 1988.

d. Repeat dose toxicity

Diets containing 0.02% of rubidium or less were not toxic to rats, but diets containing 0.1% of rubidium or more were toxic. Toxicity, as measured by decreased growth, general condition, reproductive performance, and survival time, increased with increasing concentrations of rubidium in the diet. Other

evidence of toxicity when diets contained 0.1% or more of rubidium included poor hair coat, sore noses, red deposits on whiskers, sensitivity, extreme nervousness leading to convulsions in advanced stages, and death. The inclusion of sodium in diets containing rubidium increased early growth of rats, but decreased survival time. The presence of potassium in diets containing rubidium caused better growth of rats and longer survival than rubidium alone. (Glendening BL, et al., 1956).

Substitution of drinking water by a 50 mM rubidium chloride solution for 9 to 11 days led to significant hypokalemia in rats. Chronic rubidium administration was associated with preferential accumulation of rubidium in all renal tubule cells relative to potassium. (Franz-X Beck, et al., 1989)

In a large number of animal experiments in which rubidium was administered chronically, toxicity occurred when more than 40% of total body potassium was replaced by rubidium; toxicity never occurred when replacement value was less than 30%. (Meltzer HL and Lieberman WK, 1971)

e. Mutagenicity

No mutagenicity information on rubidium chloride is available.

f. Developmental and reproductive toxicity

No long-term studies have been performed to evaluate the developmental and reproductive toxicity of rubidium.

It was reported that no rats receiving 0.2% of rubidium or more in the diet reproduced. Generally, when parents were fed diets containing 0.1% of rubidium, the progeny did not survive to weaning age (Glendening BL, et al., 1956).

g. Carcinogenicity

No carcinogenicity information on rubidium chloride is available.

h. Toxicokinetics

No toxicokinetic studies were identified. It is reported that plasma rubidium rapidly reaches a steady-state distribution with the extracellular space. The time it takes to reach half of steady-state for this process is about 5 minutes. Rubidium accumulates preferentially in the intracellular space by using the same membrane channels that are available to potassium. Rubidium chloride has a long biological half-life (50-60 days). (Meltzer HL, 1991)

Conclusions: Administration of rubidium to rats affected their growth and survival times and resulted in behavioral changes. Available nonclinical data are inadequate to determine whether rubidium would be safe to use in compounding.

2. Human Safety

a. Reported adverse reactions

There are no data with which to assess the safety of rubidium chloride for the treatment of cancer. In a case series reported by A. Keith Brewer (Brewer, 1984), patients treated with so-called high-pH therapy using either cesium or rubidium experienced nausea and diarrhea. Other toxicities and other data pertaining to these two listed toxicites, including severity (i.e. grade) and duration, were not reported on. OSE search of the FAERS database did not return any results for rubidium chloride except when used as an imaging agent for positron imaging tomography.

b. Clinical trials assessing safety

There are no modern clinical trials assessing the safety of rubidium chloride for the treatment of cancer. The only trial reported in the medical literature, from 1984 (Brewer, 1984), presented aggregated data on 30 cancer patients treated with either cesium or rubidium and reported nausea and diarrhea, as mentioned above. No supporting clinical trials published in peer-reviewed journals were submitted in the nomination to support use of rubidium chloride for the treatment of cancer.

c. Pharmacokinetic data

No data were found on this topic.

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: There is insufficient information about the human use of rubidium chloride from which to draw a conclusion regarding its safety. There are numerous FDA-approved products for cancer that have demonstrated safety and efficacy for the treatment of various malignancies.

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

All reports of rubidium use in the treatment of cancer can be traced to A. Keith Brewer, a physicist, who noted that Hopi Indians in Arizona had lower malignancy rates compared to the rest of the U.S. population and that their soil was high in rubidium content. He theorized that rubidium and cesium would compete with the potassium efflux through gated channels and result in a pH-dependent lysis of cancer cells. His studies were

conducted in mice in the 1960s and 1970s, followed by a report on the treatment of 30 human subjects with either cesium or rubidium. Data were reported in aggregate, thus the role of rubidium in these results is uncertain. His claims, however, were not supported by any further evidence, and in some cases, the heavy metal compounds were co-administered with the substance laetrile. He reported that "In addition to the loss of pains, the physical results are a rapid shrinkage of the tumor masses. The material comprising the tumors is secreted as uric acid in the urine, the uric acid content of the urine increases many fold. About 50% of the patients were pronounced terminal, and were not able to work. Of these, a majority have gone back to work." However, these anecdotal data are not interpretable outside of the context of a controlled clinical trial conducted with independent scientific oversight according to modern drug development principles that prioritize patient safety and the accurate assessment of efficacy.

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

This product is intended for 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 attest to the safety or efficacy of rubidium 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 in compounding?

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

There are no data from which to draw conclusions. However, Brewer began his study of the use of the substance in the 1960s.

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

There are no significant reports in the medical literature citing the use of rubidium chloride for the treatment of cancer, other than the case series reported briefly, mentioned above (Brewer, 1984). Rubidium (Rb 82) is a nuclear imaging agent for cardiac positron emission tomography (PET) imaging.

3. How widespread its use has been

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

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

We searched British Pharmacopoeia, 2015 ed., update 1/7/2015; European pharmacopoeia, 2015, Online 8.5 and 2016, Online 8.6; Japanese pharmacopoeia, 16th edition and found no information about the recognition of rubidium chloride in other countries or foreign pharmacopeias.

Conclusions: Although Rubidium chloride was first discussed by Brewer in the 1960s, insufficient data are available to assess the historical use of rubidium chloride in compounding.

III. RECOMMENDATION

We have evaluated rubidium chloride for use in compounding based on its physicochemical characteristics, safety, effectiveness, and evidence of historical use in compounding. The substance is physically and chemically well-characterized. There is insufficient information available to assess the historical use of rubidium chloride in compounding, as the only historical information accessible is that of Brewer's own experiments; since that time, there have been no documented clinical trials assessing the safety and efficacy of rubidium chloride for the treatment of cancer, whether in a traditional clinical trial context or in literature regarding compounding. Non-clinical studies of this substance give rise to concern, since administration of rubidium to rats affected their growth and survival times and resulted in behavioral changes.

Data are also insufficient to attest to the safety or efficacy of rubidium chloride in the treatment of cancer. The proposed use of rubidium chloride in the oncology setting, in which all of the illnesses are serious and life-threatening, could potentially delay the administration of FDA-approved products that have well-established safety and efficacy profiles. Moreover, a number of new oncology agents approved since the last published report for use of rubidium chloride in oncology in 1984 argues against the addition of rubidium chloride to the list of bulk drug substances allowed for use in compounding, given the known safety and efficacy of alternative therapies. Therefore, we ***recommend against*** the addition of rubidium chloride to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.

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Tab 6

Deoxy-D-Glucose

Tab 6a

Deoxy-D-Glucose Nominations

FAGRON

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

Dear Sir or Madam,

We hereby nominate the drugs listed below for inclusion on the list of bulk drug substances that may be used in compounding developed by FDA through regulation (section 503A(b)(1)(A)(i) of the FDCA).

No USP monograph exists for these drugs currently, nor are they components of an FDA-approved human drug product. The drugs do not appear on an FDA-published list of drugs that present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product (section 503A(b)(3)(A) 141 of the FD&C Act). In addition, they are not 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.

Camphor Oil White
Cantharidin
Chondroitin Sulfate
Citrulline
Copper Gluconate
Croton Oil
Docusate Sodium 85%
Ferric Subsulfate Pwd
Glycolic Acid
Hydroxytryptophan (L-5-)
Indole-3-Carbinol
Lutein 5% Powder
Melatonin
Methyl Sulfone (MSM)
Nettle Root Powder
Oxyphencyclimine HCl
Peruvian Balsam
Phenyl Salicylate
Phenylalanine (DL-)
Phosphatidyl Serine 20%
Pregnenolone
Pyruvic Acid
Silver Protein Mild
Squaric Acid
Thymol Iodide
Trichloroacetic Acid
Wheat Germ Oil
Threonine (L-)
Glutamine (L-)

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

Respectfully submitted,
Yours truly,

Marije van Dalen
General Manager and President
Fagron, Inc

Fagron
2400 Pilot Knob Road
St. Paul, Minnesota 55120 - USA
(800) 423 6967
www.fagron.us

What is the name of the nominated ingredient?	**Deoxy-D-Glucose (2)**
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?	Yes, Deoxy-D-Glucose is an active ingredient as defined in 207.3(a)(4) because when added to a pharmacologic dosage form it produces a pharmacological effect. References for Deoxy-D-Glucose powder pharmacological actions are provided Ludwig H, Rott R. Effect of 2-deoxy-D-glucose on herpesvirus-induced inhibition of cellular DNA synthesis. J Virol. 1975 Aug;16(2):217-21. PubMed PMID: 168399; PubMed Central PMCID: PMC354657. http://www.ncbi.nlm.nih.gov/pubmed/?term=168399 Ludwig H, Becht H, Rott R. Inhibition of herpes virus-induced cell fusion by concanavalin A, antisera, and 2-deoxy-D-glucose. J Virol. 1974 Aug;14(2):307-14. PubMed PMID: 4858786; PubMed Central PMCID: PMC355516. http://www.ncbi.nlm.nih.gov/pubmed/4858786 Stafstrom CE, Roopra A, Sutula TP. Seizure suppression via glycolysis inhibition with 2-deoxy-D-glucose (2DG). Epilepsia. 2008 Nov;49 Suppl 8:97-100. doi: 10.1111/j.1528-1167.2008.01848.x. Review. PubMed PMID: 19049601. http://www.ncbi.nlm.nih.gov/pubmed/19049601 Stafstrom CE, Ockuly JC, Murphree L, Valley MT, Roopra A, Sutula TP. Anticonvulsant and antiepileptic actions of 2-deoxy-D-glucose in epilepsy models. Ann Neurol. 2009 Apr;65(4):435-47. doi: 10.1002/ana.21603. PubMed PMID: 19399874; PubMed Central PMCID: PMC2910719.

Is the ingredient listed in any of the three sections of the Orange Book?	The nominated substance was searched for in all three sections of the Orange Book located at http://www.accessdata.fda.gov/ scripts/cder/ob/docs/queryai.cfm. The nominated substance does not appear in any section searches of the Orange Book.
Were any monographs for the ingredient found in the USP or NF monographs?	The nominated substance was searched for at http://www.uspnf.com. The nominated substance is not the subject of a USP or NF monograph.
What is the chemical name of the substance?	4R,5S,6R)-6-(hydroxymethyl)oxane-2,4,5-triol
What is the common name of the substance?	2-Deoxyglucose 2-Deoxy-D-mannose 2-Deoxy-D-arabino-hexose 2-DG
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: White or lightly yellow crystalline powder Specific Rotation: 45.5° - 47.5° Melting Point: 146.0°C - 147.0°C Heavy Metal: ≤ 10 ppm Arsenic: ≤ 1 ppm Loss on Drying: < 0.5% Residue on Ignition: < 0.1% Chloride: ≤ 0.05% Sulfate: ≤ 0.05% Assay (Dried): ≥ 98.5% Residual Solvents: Methanol: ≤ 0.03% Total Bacteria ≤ 100/g
How is the ingredient supplied?	Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	No foreign pharmacopeia monographs or registrations found.
Has information been submitted about the substance to the USP for consideration of monograph development?	No USP Monograph submission found.
What dosage form(s) will be compounded using the bulk drug substance?	Cream, gel, Ointment, and lip balm
What strength(s) will be compounded from the nominated substance?	Cream2.5-100mg/ml Gel 2.5-100mg/ml, ointment 2.5-100mg/ml,lip balm 2-20mg/ml

What are the anticipated route(s) of administration of the compounded drug product(s)?	Topical
Are there safety and efficacy data on compounded drugs using the nominated substance?	Ludwig H, Rott R. Effect of 2-deoxy-D-glucose on herpesvirus-induced inhibition of cellular DNA synthesis. J Virol. 1975 Aug;16(2):217-21. PubMed PMID: 168399; PubMed Central PMCID: PMC354657. http://www.ncbi.nlm.nih.gov/pubmed/?term=168399 Ludwig H, Becht H, Rott R. Inhibition of herpes virus-induced cell fusion by concanavalin A, antisera, and 2-deoxy-D-glucose. J Virol. 1974 Aug;14(2):307-14. PubMed PMID: 4858786; PubMed Central PMCID: PMC355516. http://www.ncbi.nlm.nih.gov/pubmed/4858786 Stafstrom CE, Roopra A, Sutula TP. Seizure suppression via glycolysis inhibition with 2-deoxy-D-glucose (2DG). Epilepsia. 2008 Nov;49 Suppl 8:97-100. doi: 10.1111/j.1528-1167.2008.01848.x. Review. PubMed PMID: 19049601. http://www.ncbi.nlm.nih.gov/pubmed/19049601 Stafstrom CE, Ockuly JC, Murphree L, Valley MT, Roopra A, Sutula TP. Anticonvulsant and antiepileptic actions of 2-deoxy-D-glucose in epilepsy models. Ann Neurol. 2009 Apr;65(4):435-47. doi: 10.1002/ana.21603. PubMed PMID: 19399874; PubMed Central PMCID: PMC2910719. http://www.ncbi.nlm.nih.gov/pubmed/19399874
Has the bulk drug substance been used previously to compound drug product(s)?	Lip balm and cream
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Topical cream to treat viral infections,

What is the reason for use of a compounded drug product rather than an FDA-approved product?	No FDA approved Dexoy-D-Glucose preparation. Deoxy-D glucose has actions on many viruses including cytomeglavirus and herpes simplex. It is versitile and used in many forms including but not limited to; Vaginal creams, dental paste, troches,and transdermal gels. There are a few antiviral creams that are FDA approved for herpes simplex, Ayclovir. Ayclovir has several side effects including rash,vision changes,irregular heart beat, sudden severe stomach cramping and the possibility of life threatening kidney issues. It doses not have indications for cyto meglavirus. Deoxy-D-Glucose has a much milder side effect profile with no effects on kidneys. Deoxy-D-Glucose has the ability to reverse sevoflurane induced neuroinflammation. Sevoflurane is one of the most commonly used anesthetics in clinic. It has the most undesirable side effect for cuasing neuroinflammation in some patients. Deox-D-Glucose can prevent and treat this neuroinflammation with no other FDA approved options currently available.(Q. Wang, Y.Zhao, M.Sun, S Liu, B. LI, L. Zhang, and L. Yang(2014) 2-Deoxy-D-Glucose Attenuates Sevoflurane-Induced Neuroinflammation through Nuclear Factor Kappa B Pathway in Vitro Toxicol. In. Vitro Oct;28(7):1183-9)
Is there any other relevant information?	All relevant information was expressed in the above questions

Submitted electronically via www.regulations.gov

September 30, 2014

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

Re: Docket No.: FDA-2013-N-1525: ***Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations***

Dear Sir or Madam:

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

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

100 Daingerfield Road
Alexandria, VA 22314-2888
(703) 683-8200 PHONE
(703) 683-3619 FAX

Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

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

Sincerely,

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Nomination from National Community Pharmacists Association

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format(s)	Recognition in Pharmacopeias	Final Compounded Formulation Dosage Form(s)	Final Compounded Formulation Strength	Final Compounded Formulation Route(s) of Administration	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
2-Deoxy-D-glucose	(3R,4S,5R)-3,4,5,6-tetrahydroxyhexanal	Deoxy-D-glucose	9G2MP84A8W	From PCCA Certificate of Analysis: 96.9% Pure (Pass); From PCCA MSDS: 95% by weight and stable.	Powder	Not yet submitted to USP	Cream Topical Gel Troche Oral Ointment Suspension Lip Balm Lollipop Topical Powder Suppository Nasal Spray Solution	0.016% 0.19% 0.2% 0.29% 2%	Topical Vaginal Oral Ophthalmic Nasal Inhallation (Vet)	Dwarakanath BS, et al. Clinical studies for improving radiotherapy with 2-deoxy-D-glucose: present status and future prospects. J Cancer Res Ther. 2009 Sep;5 Suppl 1:S21-6. [http://www.ncbi.nlm.nih.gov/pubmed/20009289]	Used as an antiviral, antifungal and in chemotherapy; uptake to the viral, virsues to make memories?

September 30, 2014

Submitted electronically via www.regulations.gov

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

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

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

Dear Sir or Madam:

PCCA respectfully submits the following list of nineteen chemicals to be considered for the List of Bulk Drug Substances that may be used in Pharmacy Compounding in accordance with Section 503A.

PCCA provides its more than 3,600 independent community compounding pharmacy members across the United States with drug compounding ingredients, equipment, extensive education, and consulting expertise and assistance.

Regarding the specific nominations, we would like to reference the attached spreadsheet and point out a couple of facts regarding our research. To the best of our knowledge, all items submitted:

- Do not appear in any of the three sections of the Orange Book.
- Do not currently have a USP or NF monograph.
- Meet the criteria of a "bulk drug substance" as defined in § 207.3(a)(4).

In regards to the request for chemical grade information, we would like to point out that many of the items submitted do not currently have a chemical grade. PCCA believes that pharmacists should use the highest grade chemical available on the market for all aspects of pharmaceutical compounding and we continue to actively source graded chemicals from FDA-registered manufacturers. However, in the current marketplace, some graded chemicals cannot be obtained for various reasons. PCCA actively tests all products received to ensure they meet our required standards to ensure our members receive the highest quality chemicals possible.

We would like to echo the concerns, voiced by NCPA and others in our industry, the strong recommendation to formalize the process by which the list is updated and communicated to the pharmacy industry. We also recommend an annual process to ensure understanding and adherence to the list. All submissions and updates to the list should be reviewed by the Pharmacy Compounding Advisory Committee (PCAC) and no changes to the list should occur with input and review by the PCAC.

We are also dismayed in the fact that no appointments have been made to the PCAC despite the call for nominations closing in March 2014. Without these appointments, FDA is unable to consult the Committee regarding this list, as outlined in the Act. PCCA, along with industry partners, strongly recommends that the FDA consult with the PCAC related to every single submission the Agency received in relation to FDA-2013-N-1525.

We appreciate this opportunity to submit this list for consideration and we look forward to continuing to work with the FDA in the future on this and other important issues as they relate to the practice of pharmacy compounding.

Sincerely,

Aaron Lopez
Senior Director of Public Affairs
PCCA

John Voliva, R.Ph.
Director of Legislative Relations
PCCA

PCCA Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations	
Ingredient Name	Deoxy-D-Glucose
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	(3R,4S,5R)-3,4,5,6-Tetrahydroxyhexanal
Common Name(s)	2-Deoxy-D-Glucose, 2-Deoxyglucose, 2-Deoxy-D-arabino-hexose, 2-DG, 2-DDG
UNII Code	9G2MP84A8W
Chemical Grade	N/A
Strength, Quality, Stability, and Purity	Melting Point, Assay, Description, Solubility; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmcopeias or registered in other countries	No; None found unless by other name
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Cream, Suspension, Gel
Compounded Strengths	0.1 – 2%
Anticipated Routes of Administration	Topical, Oral
Saftey & Efficacy Data	Singh D, et al. Optimizing cancer radiotherapy with 2-deoxy-d-glucose dose escalation studies in patients with glioblastoma multiforme. Strahlenther Onkol. 2005 Aug;181(8):507-14. [http://www.ncbi.nlm.nih.gov/pubmed/16044218]
	Dwarakanath BS, et al. Clinical studies for improving radiotherapy with 2-deoxy-D-glucose: present status and future prospects. J Cancer Res Ther. 2009 Sep;5 Suppl 1:S21-6. [http://www.ncbi.nlm.nih.gov/pubmed/20009289]
	Ockuly JC, et al. Behavioral, cognitive, and safety profile of 2-deoxy-2-glucose (2DG) in adult rats. Epilepsy Res. 2012 Sep;101(3):246-52. [http://www.ncbi.nlm.nih.gov/pubmed/22578658]
	Vibhuti A, et al. Differential cytotoxicity of the glycolytic inhibitor 2-deoxy-D-glucose in isogenic cell lines varying in their p53 status. J Cancer Res Ther. 2013 Oct-Dec;9(4):686-92. [http://www.ncbi.nlm.nih.gov/pubmed/24518718]

	Xiao H, et al. Separate and concurrent use of 2-deoxy-D-glucose and 3-bromopyruvate in pancreatic cancer cells. Oncol Rep. 2013 Jan;29(1):329-34. [http://www.ncbi.nlm.nih.gov/pubmed/23076497]
Used Previously to compound drug products	Antiviral, chemotherapy, antifungal
Proposed use	Antiviral, chemotherapy, antifungal
Reason for use over and FDA-approved product	Treatment failures and/or patient unable to take FDA approved product
Other relevant information - Stability information	Unless other studies performed / found: Cream: USP <795> recommendation of BUD for water containing topical formulations – “no later than 30 days” Oral Liquid: USP <795> recommendation of BUD for “water-containing oral formulations” – “not later than 14 days when stored at controlled cold temperatures.”

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Unit 1, 73 Beauchamp
Matraville, NSW 2036
Tel: 02.9316.1500
Fax: 02.9316.7422

CERTIFICATE OF ANALYSIS

PRODUCT: DEOXY-D-GLUCOSE (2)
ITEM NUMBER: 30-1773
LOT NUMBER: C161173
MFG. DATE: 11/25/2013
EXPIRATION: 11/24/2015

CAS: 154-17-6
MW: 164.1600000000
FORMULA: C6H12O5

TEST	SPECIFICATIONS	RESULTS
Arsenic	<=1 mg/kg	0.5 mg/kg
Assay	>=95 %	96.9 %
Chloride	<=0.02 %	0.02 %
Description	pass *WHITE TO OFF-WHITE CRYSTALLINE POWDER (CHECK TEXTURE IF POWDER OF CRYSTALLINE).*	pass *White crystalline powder*
Ethanol	<=3000 ppm	110 ppm
Heavy Metals	<=10 ppm	10 ppm
Identification	pass *ID FOR LIQUID GLUCOSE USP*	pass
Loss on Drying	<=0.5 %	0.1 %
Melting Point	147-151 c	148 c
Methanol	<=5000 ppm	0 ppm
Residue on Ignition	<=0.2 %	0.07 %
Solubility	pass *SOLUBLE IN WATER; SLIGHTLY SOLUBLE IN ALCOHOL;INSOLUBLE IN CHLOROFORM*	pass
Specific Rotation	45.5-47.5 degrees	47.1 degrees
Sulphate	<=0.02 %	0.01 %
Water	<=0.5 %	0.4 %

QC APPROVED
PRINT DATE: 3/3/2
PAGE: 1 of

The above test results have been obtained by our supplier or in our quality control laboratory.
This analysis is not to be construed as a warranty, expressed or implied.

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

Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Deoxy-D-Glucose
Chemical/Common Name	Deoxy-D-Glucose; 2-Deoxy-D-Glucose
Identifying Codes	154-17-6
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 *(including foreign recognition)*	Listed in USP as a Reagent

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)*	
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

Deoxy-D-Glucose
FDA Reviews

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: September 29, 2015

FROM: Sanjeeve Balasubramaniam, M.D., M.PH., Clinical Reviewer, Division of Oncology Products 1, Office of Hematology and Oncology Products, CDER, FDA

Wei Chen, Ph.D., Pharmacologist/Toxicologist Reviewer, Division of Hematology, Oncology, Toxicology, Office of Hematology and Oncology Products, CDER, FDA

Xinming Liu, Ph.D.
OPQ ORISE Fellow

THROUGH: Amy McKee, M.D., Clinical Team Leader, Division of Oncology Products 1, Office of Hematology and Oncology Products, CDER, FDA

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

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

Norman Schmuff, Ph.D.
Associate Director for Science, Office of Pharmaceutical Quality/Office of Process and Facilities, CDER, FDA

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Deoxy-D-glucose for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

2-Deoxy-D-glucose 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 use in antiviral and cancer treatments. This review assesses the use of 2-deoxy-D-glucose in treating cancers.

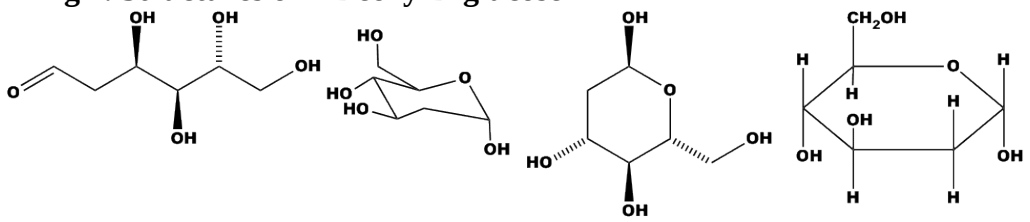
We have reviewed available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we ***do not recommend*** that 2-deoxy-D-glucose be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

II. EVALUATION CRITERIA

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

1. Stability of the API and likely dosage forms

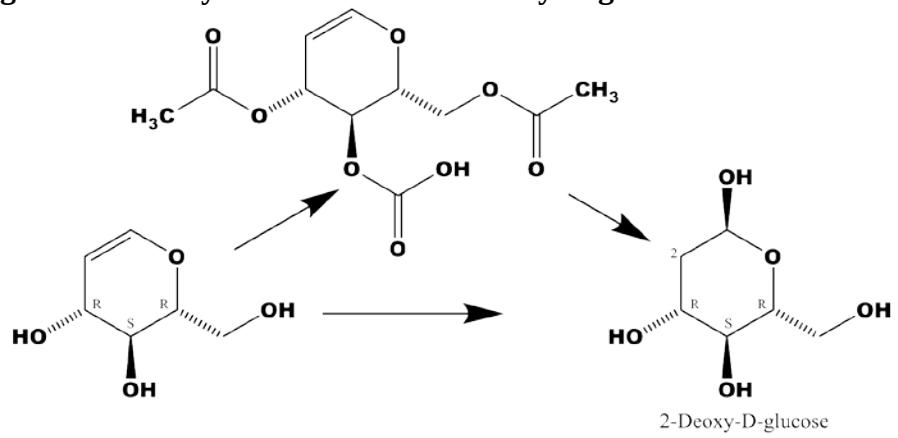
Fig 1. Structures of 2-Deoxy-D-glucose



The substance 2-deoxy-D-glucose is frequently referred to as deoxy-D-glucose. 2-Deoxy-D-glucose (CAS 154-17-6) is also called 2-deoxy-D-arabino-hexose, D-arabino-2-deoxyhexose, 2-deoxyglucose, or 2-DG. It can be represented in a number of structural forms (see Figure 1). It is a rare and naturally occurring monosaccharide, and it is supplied as white or lightly yellow crystalline powder. 2-Deoxy-D-glucose contains an aldehyde group that can easily be oxidized by several oxidizing agents, including the oxygen in air (Tao et al., 2009; Mlakar et al., 1996). According to the Material Safety Data Sheet of Sigma-Aldrich,[1] 2-deoxy-D-glucose is stable when stored in a dry and well-ventilated place in a tightly closed container.

2. Probable routes of API synthesis

Fig 2. Probable synthetic routes of 2-deoxy-D-glucose



[1] Sigma-Aldrich manufactures chemicals for use in scientific research, biotechnology, and pharmaceutical development.

2-Deoxy-D-glucose can be prepared from different methods and starting materials. According to the older literature cited in Merck Index,[2] Sowden, et.al developed a method involving the treatment of D-arabinose with nitromethane and an acetylating agent, which was further treated with diluted sodium hydroxide to prepare 2-deoxy-D-glucose (Sowden et al., 1947). Bergmann, et al. reported the synthesis of 2-deoxy-D-glucose using methylated and brominated D-glucose followed with debromination and hydrolysis with acid, and glucal was the reaction intermediate (Bergmann et al., 1922). Another Merck Index cited the synthetic method as using D-glucose thioethers (e.g. 2-ethylthiotetrabenzoyl-D-glucose di-Et mercaptal) (Bolliger et al., 1951). Based on a literature search, 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol (3,4,6-tri-O-acetyl-D-glucal), D-glucal and 3,4,6-tri-O-benzyl-D-glucal from D-glucose or D-mannose were well documented starting materials or reaction intermediates for the synthesis of 2-deoxy-D-glucose (see Figure 2) (Arita et al., 1972; Monneret et al., 1981; Overend et al., 1949; Arita et al., 1972; Tatsuta et al., 1977; Mereyala et al., 2004; Lu, 2014; Bag et al., 2009).

Other reported methods include using calcium D-gluconate, D-glucosamine hydrochloride, and N-acetyl glucosamine as starting materials (Aspinall et al., 1980; Hong et al., 2013). In summary, there are many ways to prepare 2-deoxy-D-glucose, which vary according to starting materials and chemical reactions. 3,4,6-tri-O-acetyl-D-glucal, D-glucal and D-glucose are the most probable reaction intermediates or starting materials for 2-Deoxy-D-glucose synthesis. Challenges remain to find an ideal method for manufacturing 2-deoxy-D-glucose in high yield and purity.

3. Likely impurities

The likely impurities are the starting materials and reaction intermediates.

4. Toxicity of those likely impurities

D-Glucal and 3,4,6-tri-O-acetyl-D-glucal contain a reactive double bond. D-Glucal can replace glucose 1-phosphate as the glucosyl donor in phosphorylase-catalyzed glucosyl transfer to a suitable oligo- or polysaccharide acceptor (Klein et al., 1982). Based on a the literature search in PubMed, the U.S. National Library of Medicine's (NLM) Toxicology Data Network (TOXNET) and DermNet NZ, no toxicity data were found for D-Glucal and 3,4,6-tri-O-acetyl-D-glucal. There appear to be no structural alerts for genotoxicity for these likely impurities.

[2] See https://www.rsc.org/Merck-Index/monograph/mono1500007909/.

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

2-deoxy-D-glucose is very hydroscopic and soluble in water, partially soluble in hot methanol, ethanol, acetone, and butanol. It is not soluble in ether, chloroform, petroleum ether, or toluene.As is true generally for reducing monosaccharides, it exists in solution in one acyclic, and several cyclic interconverting forms..

2-deoxy-D-glucose is nominated for the compounding of many dosage forms (e.g., powder, solution, cream, gel, ointment, and lip balm). No foreign pharmacopeial monographs (e.g., European Pharmacopeia, British Pharmacopeia, and Japanese Pharmacopeia) or registrations of 2-deoxy-D-glucose were found, and limited information was collected from PubMed about these formulations. From the physicochemical point of view, there are fewer concerns related to the particle size or polymorphism of 2-deoxy-D-glucose for these nominated formulations due to its high aqueous solubility.

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

2-Deoxy-D-glucose is a physicochemically well-characterized substance of small molecular weight. High-performance liquid chromatography (HPLC) is the well-established technique for its quantification (Grounder et al., 2012; Umegae et al., 1990; Hughes, 1985).

Conclusions: 2-Deoxy-D-glucose is a physicochemically well-characterized substance of small molecular weight. No foreign pharmacopeial monographs (e.g., European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopeia) or foreign approvals of 2-deoxy-D-glucose were found.

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

1. Nonclinical Assessment

The following information has been summarized based on searches on PubMed and TOXNET.

a. Pharmacology of the drug substance

2-Deoxy-D-glucose (also called Deoxy-D-glucose or 2DG) is a glucose analog. 2-Deoxy-D-glucose competitively inhibits glucose transport by sharing the same glucose transporters and is phosphorylated by hexokinase (HK) to form 2-DG-6-phosphate, which is not metabolized further to any significant extent. 2-DG-6-phosphate inhibits phosphohexoisomerase and glucose-6-phosphate dehydrogenase thereby reducing the output from glycolysis (ATP) and the

pentose phosphate pathway (NAPDH). Tumors use glucose at high rates to generate metabolic energy (ATP) and as building blocks for macromolecular synthesis to sustain rapid cell proliferation. 2-Deoxy-D-glucose has been shown to deplete cancer cells of energy by inhibiting glucose metabolism. In vitro and in vivo studies evaluating the antitumor activity of 2-Deoxy-D-glucose have shown that deoxy-D-glucose inhibited aerobic glycolysis in cancer cells, decreased cell proliferation, and increased cell apoptosis. In addition, 2-Deoxy-D-glucose has been shown to increase oxidative stress, inhibit N-linked glycosylation, and induce autophagy. 2-Deoxy-D-glucose exhibited a synergistic anticancer effect when combined with other therapeutic agents or radiotherapy (Zhang D et al., 2014).

b. Safety pharmacology

Cardiovascular and respiratory effects: Intravenous administration of 2-deoxy-D-glucose (250 mg/kg, 500 mg/kg, and 1000 mg/kg) in anaesthetised rats showed a time-dependent decrease in mean arterial blood pressure. There was no change in the heart rate in any of the treatment groups. The tidal volume was not changed significantly by oral administration in conscious rats, but a significant decrease in the respiratory frequency at 500 mg/kg and 1000 mg/kg was observed. There was no change in the tidal volume after oral administration, but the respiratory frequency decreased significantly at 2000 mg/kg dose in mice (Vijayaraghavan R, et al., 2006).

Neurological effects: Rats administered 2-deoxy-D-glucose by intraperitoneal injection (IP) at doses up to 1000 mg/kg/day for 14 days had no apparent detrimental effect on spatial learning and memory as assessed by the water maze. In the open field experiments, 2-deoxy-D-glucose, when administered 15 minutes before testing, reduced exploratory activity in a dose-dependent manner, with the effect most marked at the 250 mg/kg dose (Ockuly JC, et al., 2012).

c. Acute toxicity

The oral median lethal dose (LD50) of 2-deoxy-D-glucose was found to be >8000 mg/kg in mice and rats. The LD50 in mice by the intravenous route was found to be 8000 mg/kg. At this dose, 2 out of 4 mice died within 6 h of 2-deoxy-D-glucose administration (Vijayaraghavan R, et al., 2006).

d. Repeat dose toxicity

Dietary supplementation with 2-deoxy-D-glucose elicited physiological changes in rats similar to those seen with caloric restriction (CR). Body weight and food intake declined after 50 weeks in rats on the diets containing 0.4% 2-deoxy-D-glucose (0.2 g/kg). Blood glucose levels in the 2-deoxy-D-glucose groups were reduced at week 13 in the group with 0.4% 2-deoxy-D-glucose in the diet and at week 39 in the groups with 0.25% (0.125 g/kg) or 0.4% 2-deoxy-D-glucose in the diets. Insulin levels were likewise reduced at week 13 in the group with 0.4% of

2-deoxy-D-glucose in the diet and at week 39 in the groups with 0.25% or 0.3% 2-deoxy-D-glucose in the diets. Body temperature was also lowered by 2-deoxy-D-glucose, but this effect was not seen until 39 weeks on the diets with 2-deoxy-D-glucose.

2-deoxy-D-glucose also induced cardiotoxic effects in two different rat strains and increased mortality in F344 rats. F344 rats consuming 0.4% 2-deoxy-D-glucose in the diet showed decreased median survival by 45% (352 vs. 641 days) and maximum lifespan–calculated from the survival of the longest-living 10% of each group–by 43% (487 vs. 859 days). Median survival in rats consuming 0.25% 2-deoxy-D-glucose was not significantly reduced (650 vs. 641 days), although maximum lifespan was reduced by 10%. 2-deoxy-D-glucose delivered in the diet produced cardiac toxicity in rats at doses ranging from 0.02 to 0.3 g/kg (0.04–0.6% 2-deoxy-D-glucose by weight in the diet) and hastened mortality at doses above 0.2 g/kg (0.4% in the diet) as a result of heart failure. Histopathological analysis of the hearts revealed increasing vascularization of cardiac myocytes with dose increases, and tissue staining revealed that the vacuoles were free of both glycogen and lipid. 2-Deoxy-D-glucose-induced cardiac vacuolization was not associated with impaired autophagy. (Minor RK, et al., 2010)

e. Mutagenicity

No information was available.

f. Developmental and reproductive toxicity

IP injections of 2-deoxy-D-glucose (50 mg/kg daily for 7 days) significantly reduced sperm counts in mice after 3-7 days of administration. 2-Deoxy-D-glucose was converted to the 6-phosphate in mouse testis and liver, and myo-inositol levels decreased significantly in both tissues, although lipid-bound myo-inositol levels were normal (Burton Le, et al., 1977).

After 2-deoxy-D-glucose was administered at 120 mg/day to rats from gestational day 9 through 20, the resorption incidence was 69%, and the surviving fetuses were all malformed with anophthalmia, cleft lip and palate, and lesions of the extremities. (Demeyer, 1961, cited by Shepard, T. H. 1980). One g/kg of 2-deoxy-D-glucose administered on days 8, 9, 10, or 11 did not show malformations in surviving rat fetuses (Spielmann et al., 1973).

g. Carcinogenicity

The incidence of pheochromocytoma (both benign and malignant) was approximately 40% in rats given diet supplemented with 0.2% or 0.4% 2-deoxy-D-glucose, compared to about 14% in the untreated controls. The incidence of medullary hyperplasia was also higher in 2-deoxy-D-glucose-treated rats compared to the control group (Minor RK, et al., 2010).

h. Toxicokinetics

Toxicokinetics studies have not been conducted with 2-deoxy-D-glucose. Oral-administered glucose is known to be absorbed rapidly from the upper gastrointestinal tract in rats and humans and 2-deoxy-D-glucose, a glucose analogue, may be absorbed in a similar way. Enteral administration of fluorine-18-fluorodeoxyglucose (F-18 FDG) as a tracer used in positron emission tomography (PET) showed systemic absorption of up to nearly 80% of administered activity in 2 hours in rodents (Higashi T, et al., 2002).

Conclusions: Dietary supplementation with deoxy-D-glucose (2-deoxy-D-glucose) showed cardiac toxicity and decreased median survival in rats. Deoxy-D-glucose caused developmental and reproductive toxicities and carcinogenicity in rats. The toxicity profile of deoxy-D-glucose in animal studies weighs against its inclusion on the 503A list.

2. Human Safety

a. Reported adverse reactions

In a clinical trial from 1958 (Landau, 1958), mild, transient toxicities were observed (flushing, diaphoresis, headache, somnolence, tachycardia, hypoglycemia) similar to hypoglycemia, consistent with one known mechanism of action, inhibition of glycolysis. These toxicities have been reproduced in subsequent clinical trials with this API; the hypoglycemic effect has been routinely dose-limiting in clinical experience (Singh et al., 2005; Dwaraknath et al., 2009). An OSE search of the FAERS database did not retrieve any results for 2-deoxy-D-glucose.

b. Clinical trials assessing safety

Raez et al., (2012) report on a phase 1, dose-escalation trial with 2-deoxy-D-glucose alone and in combination with docetaxel for advanced solid tumors using an oral formulation at three different dosing schedules. Adverse reactions reported were mild, transient, and consistent with severe hypoglycemia. Toxicities associated with *glucopenia* precluded dose escalation beyond 63 mg/kg when given with docetaxel, despite not meeting dose-limiting toxicity criteria, and this dose was not considered to be likely to lead to clinically meaningful efficacy. It was recognized (Dwaraknath, 2009) that high doses would be required to affect the course of malignant diseases, with unacceptable toxicity, prompting the termination of clinical efforts. In later, single-arm trials by the same author using a combination of 2-deoxy-D-glucose with radiotherapy for glioblastoma, toxicity resulted in the inability to complete treatment in a fraction (not reported) of patients; lowering the dose had predictably fewer toxicities.

c. Pharmacokinetic data

From Raez et al., (2012): “The pharmacokinetics of 2-deoxy-D-glucose were linear with dose and did not demonstrate accumulation.... The median maximum plasma concentration at 63 mg/kg was 116 μg/mL. The terminal half-life was 5–6 h and docetaxel did not affect the pharmacokinetics of 2-deoxy-D-glucose.”

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 in well-controlled clinical trials.

Conclusions: Use of 2-deoxy-D-glucose for the treatment of cancer, based on two trials, appears to be beyond the reach of tolerable dosing in both intravenous and oral dosing regimens. Lower doses are being explored in combination treatments with chemotherapy and radiotherapy, with toxicity profiles that appear manageable. The high doses required for single-agent use, based on limited clinical evidence, have led to unacceptable toxicity.

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

Landau et al., (1958) described administration of 2-deoxy-D-glucose intravenously to eight patients with a variety of cancers; no responses were reported, though some mild and transient toxicities were noted. Importantly, the theorized mechanism of action of 2-deoxy-D-glucose in an oncology setting is via the exploitation of the Warburg effect: the observation that malignant cells preferentially use glucose as a carbon source for aerobic glycolysis, with the production of pyruvate even in an oxygen-rich environment. However, the assumption that neoplastic transformation confers a reliance on this single mechanism of energy generation has long been known to be incorrect, and instead, tumor cells can adapt to a variety of biochemical pathways for energy generation from carbon-containing molecules in an oxygen-replete environment (Kurtoglu, 2007). As a result, the putative mechanism for 2-deoxy-D-glucose for the treatment of malignancies is flawed in the presence of oxygen.

Similarly, in the clinical trial reported by Raez et al., (2012), limitation of tolerability of oral regimens of 2-deoxy-D-glucose precluded achieving pharmacodynamically meaningful circulating drug levels.

Dwaraknath et al., (2009) have conducted phase 1/2 trials of oral 2-deoxy-D-glucose in combination with radiotherapy for the treatment of glioblastoma. Results of the phase 2 trial of 60 patients were interpreted to reveal an "increase in survival," but this is in relation to historical controls that appear to have actually had *better* survival based on the table included in the publication. Details of trial conduct, integrity, and results were not publicly available for analysis.

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

It is intended for use in treating cancer, 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 after demonstration of efficacy in well-controlled clinical trials.

Conclusions: Initial interest in this compound appeared in the 1950s. A clinical trial conducted at the National Cancer Institute at that time (Landau, 1958) concluded that the therapeutic window for this agent in an infusional setting precluded the attainment of clinically meaningful drug levels. Similar findings have resulted from combination trials of 2-deoxy-D-glucose in the past decade (Dwaraknath et al., 2009; Raez et al., 2012), though in the setting of combination regimens, 2-deoxy-D-glucose doses were lowered to

minimize the toxicity profile. Based on the available data, 2-deoxy-D-glucose does not appear to be effective for the treatment of cancer. Given the availability of approved products that have been demonstrated to have efficacy, this factor weighs against the use of 2-deoxy-D-glucose in compounding for the treatment of cancer.

D. Has the substance been used historically in compounding?

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

Based on the information available, it appears that the agent has been intermittently in use since the 1950s.

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

Two clinical trials have been reported for use of 2-deoxy-D-glucose as a single agent for the treatment of patients with cancer. In both instances, there were no notable tumor responses, and toxicities outweighed the ability to achieve effective doses via oral and intravenous dosing. Four other single-arm trials have been conducted using 2-deoxy-D-glucose in combination with other anticancer agents for the treatment of patients with advanced solid malignancies and glioblastoma. It has also been used in anti-viral treatments.

3. How widespread its use has been

Three published clinical trials are available in the medical literature (Landau, 1958; Singh, 2005; Raez et al., 2012); three other trials are quoted by Dwaraknath but remain unpublished (Dwaraknath et al., 2009) and appear to have been conducted outside of the United States. We have insufficient information to assess the frequency of use of the substance in compounding. However, several compounding pharmacies currently list products with this substance on their websites.

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

As noted above, we did not locate any entries for this substance in available pharmacopeias.

Conclusions: There is insufficient evidence to evaluate the extent to which deoxy-D-glucose has been used in pharmacy compounding in the US and abroad.

III. RECOMMENDATION

We have evaluated 2-deoxy-D-glucose for use in compounding based on its physicochemical characteristics, safety, effectiveness, and evidence of historical use in

compounding. 2-deoxy-D-glucose is sufficiently well characterized both physically and chemically. Products with this ingredient are listed on the websites of compounding pharmacies, but the extent of historical use of 2-deoxy-D-glucose in pharmaceutical compounding has not been documented. However, there are insufficient data to attest to the safety or efficacy of 2-deoxy-D-glucose in the treatment of cancer. In reported controlled trials, toxicity was reached before clinical efficacy. Given the availability of safe and effective FDA-approved agents for the treatment of cancer, we do not recommend the addition of deoxy-D-glucose to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.

There are a paucity of clinical data for adequately evaluating the safety and efficacy of deoxy-D-glucose in oncology. The possible uses for deoxy-D-glucose in the oncology setting, which only includes life-threatening illnesses, are not advisable given the availability of approved products for oncology indications that have been demonstrated to be safe and effective in well-controlled clinical trials. The number of new oncology agents approved since the initial published report for use of deoxy-D-glucose in oncology in 1958 argues against the use of deoxy-D-glucose in compounding, given the known safety and efficacy of approved therapies. Therefore, we ***recommend against*** the addition of deoxy-D-glucose to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: September 29, 2015

FROM: Jeffrey Murray M.D.
Deputy, Division of Antiviral Products

THROUGH: Norman Schmuff, Ph.D.
Associate Director for Science, Office of Pharmaceutical Quality/Office of Process and Facilities, CDER, FDA

Debra Birnkrant, M.D.
Division Director, Division of Antiviral Products

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Deoxy-D-glucose for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

2-deoxy-D-glucose 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) as a topical product for the treatment of herpes simplex virus (HSV) infections.

This review references a previously prepared review from the Division of Oncology Products 1 (DOP1) for the use of 2-deoxy-D-glucose in the treatment of cancers. The DOP1 review addresses chemistry and nonclinical toxicology issues. In addition, we have reviewed available data on the pharmacology, safety, effectiveness, and historical use in compounding of this substance as it relates to the treatment of HSV infections. For the reasons discussed below, we **do not recommend** that 2-deoxy-D-glucose 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?

Refer to DOP1 review for this section. The DOP1 review concludes the following:

"2-Deoxy-D-glucose is a physicochemically well-characterized substance of small molecular weight. No foreign pharmacopeial monographs (e.g., European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopeia) or foreign approvals of 2-deoxy-D-glucose were found.

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

1. Nonclinical Assessment

Refer to the DOP1 review regarding nonclinical pharmacology, toxicology and safety. According to the DOP1 review, dietary supplementation with 2-deoxy-D-glucose showed cardiac toxicity and decreased median survival in rats. 2-deoxy-D-glucose caused developmental and reproductive toxicities and carcinogenicity in rats with oral administration.

This review addresses the nonclinical pharmacology of the drug substance only as it relates to its potential topical use for treating cutaneous HSV infections. Animal models of HSV infections referred to below include use of 2-deoxy-D-glucose topically.

a. Pharmacology of the drug substance as relates to the treatment of viruses.

2-deoxy-D-Glucose (also called deoxy-D-glucose, or 2DG) is a glucose analog. A possible mechanism of action of 2-deoxy-D-glucose for antiviral activity identified in the literature involves alteration in synthesis of viral glycoproteins or glycolipids (Ray et al. 1978). In cell culture, 2-deoxy-D-glucose has been reported to inhibit the production of HSV type 1 (HSV-1) in a line of green monkey kidney cells (Courtney et al., 1973) and to prevent cell fusion and cytopathic effects (CPE) of baby hamster kidney (BHK-21) cells infected with HSV-1 (Gallaher et al., 1973). Of note, high concentrations of 2-deoxy-D-glucose were used (6 µM - 6 mM in Courtney et al., 1973; 10 mM in Gallaher et al., 1973) in these studies. Cytotoxicity was not evaluated, so it is unclear whether findings are direct antiviral activity or an indirect effect due to cytotoxicity. In a separate report, the half maximal effective concentration (EC50) value of 2-deoxy-D-glucose was reported to be ~274 µM for both HSV-1 and HSV-2 (Kern et al., 1982). 2-deoxy-D-glucose has also been reported to inhibit HSV-induced cellular DNA synthesis as well as cell fusion (Ludwig et al., 1974; Ludwig et al., 1975).

Animal models of 2-deoxy-D-glucose in the treatment of HSV have produced mixed results with more studies showing no beneficial effects. Topical treatment of herpetic keratitis in rabbits resulted in fewer ocular lesions in some animals and reduced the severity in those that developed lesions (Ray et al., 1974). However, no effect on skin lesions, mortality, or latency was observed in a study evaluating the topical treatment of cutaneous HSV-1 infections in mice and genital HSV-2 infections in mice and guinea pigs (Kern et al., 1982). In addition, other investigators have used 2-deoxy-D-glucose in guinea pigs (Shannon et al., 1982) and in mice with herpetic keratitis without any effect (Gordon et al., 1986).

Conclusions:
While there are some in vitro data suggesting 2-deoxy-D-glucose could have antiviral activity, the overall data do not demonstrate antiviral activity of 2-deoxy-D-glucose in the treatment of experimental cutaneous or genital infections due to HSV in animal models.

Direct antiviral activity has not been conclusively demonstrated due to methodologic flaws with the studies such as lack of evaluation for cytotoxicity.

2. Human Safety

a. Reported adverse reactions

As reported in the DOP1 review, patients receiving infusions of 2-deoxy-D-glucose in a clinical trial (Landau, 1958) experienced mild, transient toxicities including flushing, diaphoresis, headache, somnolence, tachycardia, and hyperglycemia. The only report of the safety of topically applied 2-deoxy-D-glucose in the treatment of herpes infection is from a single clinical trial conducted in 1979 as described below.

b. Clinical trials assessing safety

There is only one published clinical trial (Blough and Giuntoli, 1979) of 2-deoxy-D-glucose for the treatment of herpes simplex infection (or any viral infection). Thirty-six women with genital herpes were treated with 2-deoxy-D-glucose as a 0.19% gel for a three week period. The authors report that genital herpes lesions resolved but did not report any specific safety findings. It is not clear whether the authors simply failed to remark on safety or whether there were no substantial safety issues to report.

c. Pharmacokinetic data

There are no data assessing whether 2-deoxy-D-glucose is absorbed systemically after topical administration. Refer to the DOP1 review for the pharmacokinetics of systemically administered 2-deoxy-D-glucose.

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

There are multiple treatments approved in the U.S. for the treatment HSV infections. HSV infections that could be treated with topical products are oral herpes labialis (recurrent HSV infections involving the lips) and genital herpes (primary and recurring infections involving genital areas). The products approved to treat oral HSV infections include:

- Penciclovir cream 1%
- Acyclovir cream 5%
- Famcyclovir, 1500 mg single oral dose
- Valacyclovir, 2g twice daily for one day
- Acyclovir/hydrocortisone cream
- Acyclovir buccal tablets, single dose
- Docosonal cream 10%

All but docosonal cream are available in the U.S. by prescription only; docosonal is available over-the-counter under the brand name Abreva. All of these treatments are well tolerated with minimal adverse effects as topical products or single-day treatments. There are no direct comparisons of the safety of 2-deoxy-D-glucose with any of the above approved treatments for herpes labialis, but given the excellent safety profile of the approved drugs, there is minimal if any room for a significant safety or tolerability advantage of 2-deoxy-D-glucose.

There are also multiple treatments approved in the U.S. for the treatment of genital herpes including:

- Acyclovir ointment
- Acyclovir oral formulations
- Famciclovir oral formulations
- Valacyclovir oral formulations

Acyclovir ointment was first approved in 1982. All drugs listed above are available by prescription only in the U.S. Although multiple days of treatment are required for genital herpes, the approved drugs are well tolerated with few adverse effects. As for treatment of herpes labialis, it is highly unlikely that 2-deoxy-D-glucose could provide a significant safety advantage over approved options. There are no direct comparisons of 2-deoxy-D-glucose with any of the approved treatments.

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 stated above, there is one published trial (Blough 1979) evaluating 2-deoxy-D-glucose as a 0.19% cream for the treatment of genital herpes. The trial was reported to be a double-blind, randomized, placebo-controlled trial in which 36 women received the investigational agent (administered four times daily), and 15 women received placebo. The authors reported a significantly shorter duration of herpetic lesions (10-day difference) and a reduction in the number of recurrences. After the publication of this study, several experts wrote a letter (Corey, 1980) to the editor questioning the trial's validity and conduct for several reasons:

- Questionable randomization processes: more than twice as many women were randomized to 2-deoxy-D-glucose because randomization to placebo was limited due to "ethical issues," as stated in the publication
- Possible toxicity of the placebo: the vehicle used in the placebo which included miconazole may have in fact slowed the healing of herpes lesions according to herpes experts
- The rate of healing on placebo was uncharacteristically long. Healing was more than twice as long as expected according to historical rates and rates

observed in subsequent antiviral trials supporting approved drugs. This suggests that the observed 2-deoxy-D-glucose treatment effect compared to placebo may not have been due to faster healing with 2-deoxy-D-glucose but an adverse effect of placebo slowing the rate of healing.

- Follow-up for recurrences was not well documented in this study with respect to duration of follow-up or mean time until recurrence.

In addition there is a letter to the editor (McCray 1982) and case series (Bierman 1983) which report lack of clinical effectiveness of 2-deoxy-D-glucose for the treatment of herpes simplex infections. The published letter by McCray reports a case series of 22 patients who received 0.19% 2-deoxy-D-glucose in a lanolin base twice daily and a double-blind placebo-controlled trial in 17 patients receiving 0.19% 2-deoxy-D-glucose in a hydroalcoholic vehicle or vehicle alone. The authors report that neither study showed a significant change in clinical symptoms, signs, or frequency of recurrence.

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

Herpes labialis and genital herpes are neither serious nor life-threatening conditions.

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

There are multiple treatments approved in the U.S. for the treatment HSV infections. HSV infections that could be treated with topical products are oral herpes labialis (recurrent HSV infections involving the lips) and genital herpes (primary and recurring infections involving genital areas). The products approved to treat oral HSV infections include:

- Penciclovir cream 1%
- Acyclovir cream 5%
- Famcyclovir, 1500 mg single oral dose
- Valacyclovir, 2g twice daily for one day
- Acyclovir/hydrocortisone cream
- Acyclovir buccal tablets, single dose
- Docosonal cream 10%

All but docosonal cream are available in the U.S. by prescription only; docosonal is available over-the-counter under the brand name Abreva.

There are also multiple treatments approved in the U.S. for the treatment of genital herpes including:

- Acyclovir ointment
- Ayclovir oral formulations
- Famciclovir oral formulations
- Valacyclovir oral formulations

Acyclovir ointment was first approved in 1982. All drugs listed above are available by prescription only in the U.S.

All of the treatments listed above to treat either oral or genital HSV infections were shown to reduce the time to healing of herpes lesions compared to placebo or vehicle. There are no direct comparisons of the efficacy of 2-deoxy-D-glucose with any of the above approved treatments for herpes labialis.

Conclusions: As outlined above, numerous herpes treatments have been granted marketing approval by the Food and Drug Administration after appropriate demonstration of safety and efficacy in multiple, large, well-controlled clinical trials. Given that there are significant deficiencies in the one trial evaluating 2-deoxy-D-glucose for the treatment of genital herpes identified in the literature, there is no basis to conclude that 2-deoxy-D-glucose is as effective as any of the approved options or has any clinical efficacy whatsoever.

D. Has the substance been used historically in compounding?

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

Available data are insufficient to fully evaluate this question, though the agent has been intermittently in use since the 1950s for the treatment of cancers. Its use for herpes simplex appears to have started in the late 1970s around the time of the publication cited above by Blough et al. According to review articles published in the 1980s, the use of 2-deoxy-D-glucose to treat herpes appeared to significantly decline after the approval of acyclovir ointment in 1982, oral acyclovir in 1985 and the approvals of subsequent herpes antivirals. Experts viewed the trial published in 1979 by Blough as flawed and the results highly suspect.

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

As stated in the DOP1 review, two clinical trials have been reported for use of 2-deoxy-D-glucose in cancer. According to internet searches, 2-deoxy-D-glucose has been used for a variety of other conditions in addition to the nominated uses, including warts, diabetic neuropathy, and dental rinses for ulcers.

3. *How widespread its use has been*

Reliable data on the frequency of use in compounding is not available.

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

Not found in available pharmacopeias.

Conclusions: There is insufficient evidence to evaluate the extent to which 2-deoxy-D-glucose has been used in pharmacy compounding in the US and abroad. Literature suggests that it has been used intermittently since the 1950s.

III. RECOMMENDATION

We have evaluated 2-deoxy-D-glucose for use in compounding based on its physicochemical characteristics, safety, effectiveness, and evidence of historical use in compounding. Please see the DOP1 review for conclusions on the physicochemical characteristics and information about safety based on non-clinical evidence as used in the oncology setting. There are insufficient data to fully evaluate the safety or efficacy of 2-deoxy-D-glucose in the treatment of herpes simplex. Results of non-clinical data were mixed with respect to antiviral activity, but most studies in animal models showed no beneficial effect. The only clinical trial identified in the literature was conducted 36 years ago, was of poor quality, and was largely discredited by herpes experts and subsequent clinical reports. Multiple safe and effective FDA-approved agents (oral and topical) are available for the treatment of herpes infections, including one product sold over-the-counter. There is insufficient information about the length and extent of the use of 2-deoxy-D-glucose in compounding to evaluate the significance of its historical use. Based on a balancing of the four evaluation criteria, we find that 2-deoxy-D-glucose 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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Tab 7

Alanyl-L-Glutamine

Materials on Alanyl-L-Glutamine To Be Supplied Later

Tab 8

Glutaraldehyde

Tab 8a

Glutaraldehyde Nominations

September 30, 2014

Submitted electronically via www.regulations.gov

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

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

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

Dear Sir or Madam:

PCCA respectfully submits the following list of nineteen chemicals to be considered for the List of Bulk Drug Substances that may be used in Pharmacy Compounding in accordance with Section 503A.

PCCA provides its more than 3,600 independent community compounding pharmacy members across the United States with drug compounding ingredients, equipment, extensive education, and consulting expertise and assistance.

Regarding the specific nominations, we would like to reference the attached spreadsheet and point out a couple of facts regarding our research. To the best of our knowledge, all items submitted:

- Do not appear in any of the three sections of the Orange Book.
- Do not currently have a USP or NF monograph.
- Meet the criteria of a "bulk drug substance" as defined in § 207.3(a)(4).

In regards to the request for chemical grade information, we would like to point out that many of the items submitted do not currently have a chemical grade. PCCA believes that pharmacists should use the highest grade chemical available on the market for all aspects of pharmaceutical compounding and we continue to actively source graded chemicals from FDA-registered manufacturers. However, in the current marketplace, some graded chemicals cannot be obtained for various reasons. PCCA actively tests all products received to ensure they meet our required standards to ensure our members receive the highest quality chemicals possible.

We would like to echo the concerns, voiced by NCPA and others in our industry, the strong recommendation to formalize the process by which the list is updated and communicated to the pharmacy industry. We also recommend an annual process to ensure understanding and adherence to the list. All submissions and updates to the list should be reviewed by the Pharmacy Compounding Advisory Committee (PCAC) and no changes to the list should occur with input and review by the PCAC.

We are also dismayed in the fact that no appointments have been made to the PCAC despite the call for nominations closing in March 2014. Without these appointments, FDA is unable to consult the Committee regarding this list, as outlined in the Act. PCCA, along with industry partners, strongly recommends that the FDA consult with the PCAC related to every single submission the Agency received in relation to FDA-2013-N-1525.

We appreciate this opportunity to submit this list for consideration and we look forward to continuing to work with the FDA in the future on this and other important issues as they relate to the practice of pharmacy compounding.

Sincerely,

Aaron Lopez
Senior Director of Public Affairs
PCCA

John Voliva, R.Ph.
Director of Legislative Relations
PCCA

PCCA Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations	
Ingredient Name	Glutaraldehyde
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	Yes, but at a 50% concentration. Currently, difficult to source from a FDA-registered manufacturer
Chemical Name	Pentane-1,5-dial
Common Name(s)	Glutaral
UNII Code	T3C89M417N
Chemical Grade	USP (50% Concentration)
Strength, Quality, Stability, and Purity	Assay, Description, pH, Solubility, Specific Gravity; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Solution (25% Concentration)
Recognition in foreign pharmcopeias or registered in other countries	USP (50% Concentration), BP (50% Concentration); Used in ten countries
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Solution
Compounded Strengths	0.1-10%
Anticipated Routes of Administration	Topical, soak
Saftey & Efficacy Data	McElhiney LF. Glutaraldehyde-treated autologous pericardium used in valve repairs. Int J Pharm Compd. 2012 Jan-Feb;16(1):12-6. [http://www.ncbi.nlm.nih.gov/pubmed/23050306]
	Dall'oglio F, et al. Treatment of cutaneous warts: an evidence-based review. Am J Clin Dermatol. 2012 Apr 1;13(2):73-96. [http://www.ncbi.nlm.nih.gov/pubmed/22292461]

	Hirose R, et al. Topical treatment of resistant warts with glutaraldehyde. J Dermatol. 1994 Apr;21(4):248-53. [http://www.ncbi.nlm.nih.gov/pubmed/8056897]
Used Previously to compound drug products	Soaking solution for heart valve repairs, warts

Proposed use	Soaking solution for heart valve repairs, warts
Reason for use over and FDA-approved product	Treatment failures and/or patient unable to take FDA approved product
Other relevant information - Stability information	Soaking solution: USP <797> recommendations for high risk level compounded sterile products; Topical: USP <795> recommendation of BUD for water containing topical formulations – “no later than 30 days”

PCCA USA
9901 South Wilcrest Drive
Houston, TX 77099
Tel:281.933.6948
Fax: 281.933.6627

PCCA Canada
744 Third Street
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Tel: 800.668.9453
Fax: 519.455.0690

PCCA Australia
Unit 1, 73 Beauchamp Road
Matraville, NSW 2036
Tel: 02.9316.1500
Fax: 02.9316.7422

CERTIFICATE OF ANALYSIS

PRODUCT: GLUTARALDEHYDE 25% AQUEOUS SOLUTION (W/W)
ITEM NUMBER: 55-1211
LOT NUMBER: C159268
MFG. DATE: 10/15/2012
EXPIRATION: 10/31/2017
CAS: 111-30-8
MW: 100.1200000000
FORMULA: C5H8O2

TEST	SPECIFICATIONS	RESULTS
Assay (%)	24.0-26.5 %	25.9 %
Color, Pt-Co	0.0-100	5
Description	pass *COLORLESS OR ALMOST COLORLESS SOLUTION; SUBSTANTIALLY FREE FROM DIRT, RUST, AND FOREIGN MATERIAL; A SLIGHT HAZE SHALL NOT BE CAUSE FOR REJECTION*	pass *Colorless*
Identification	pass	pass
PH	3.1-4.5	3.8
Solubility	pass *VERY SOLUBLE IN WATER AND ALCOHOL*	pass
Specific gravity	1.0605-1.0725	1.0655

QC APPROVED
PRINT DATE: 3/4/2014

The above test results have been obtained by our supplier or in our quality control laboratory.
This analysis is not to be construed as a warranty, expressed or implied.

8.50 x 11.00 in

Submitted electronically via www.regulations.gov

September 30, 2014

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

Re: Docket No.: FDA-2013-N-1525: ***Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations***

Dear Sir or Madam:

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

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

100 Daingerfield Road
Alexandria, VA 22314-2888
(703) 683-8200 PHONE
(703) 683-3619 FAX

Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

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

Sincerely,

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Nomination from National Community Pharmacists Association

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format(s)	Recognition in Pharmacopeias	Final Compounded Formulation Dosage Form(s)	Final Compounded Formulation Strength	Final Compounded Formulation Route(s) of Administration	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
Glutaraldehyde	Pentane-1,5-dial	Glutaraldehyde	T3C89M417N	From PCCA MSDS: 25% by weight and stable; avoid exposure to air, excess heat, alkalis and oxidizing agents.	Solution	Not yet submitted to USP	Solution	0.1-10%	Topical, soak	Dall'oglio F, et al. Treatment of cutaneous warts: an evidence-based review. Am J Clin Dermatol. 2012 Apr 1;13(2):73-96. [http://www.ncbi.nlm.nih.gov/pubmed/22292461]; McElhiney LF. Glutaraldehyde-treated autologous pericardium used in valve repairs. Int J Pharm Compd. 2012 Jan-Feb;16(1):12-6. [http://www.ncbi.nlm.nih.gov/pubmed/23050306]	Used as a cold sterilant to disinfect a variety of heat-sensitive instruments, such as endoscopes, bronchoscopes, and dialysis equipment; also used in a Soaking solution for heart valve repairs and for warts.

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

Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Glutaraldehyde solution
Chemical/Common Name	Pentane-1,5-dial
Identifying Codes	111-30-8
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 *(including foreign recognition)*	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)*	
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 8b

Glutaraldehyde
FDA Review

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: September 29, 2015

FROM: Hon Sum Ko, MD
Medical Officer, Division of Dermatology and Dental Products

Jiaqin Yao, PhD
Pharmacology/Toxicology Reviewer, Division of Dermatology and Dental Products

Sukhamaya Bain, PhD
Senior Chemistry Reviewer, Division of New Drug API/Branch II

Doanh Tran, PhD
Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3

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

Kendall A. Marcus, MD
Director, Division of Dermatology and Dental Products

Barbara Hill, PhD
Pharmacology/Toxicology Supervisor, Division of Dermatology and Dental Products

Ramesh Sood, PhD
Senior Scientific Director (Acting), Office of New Drug Products

TO: Pharmacy Compounding Advisory Committee

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

I. INTRODUCTION

Glutaraldehyde 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 use in soaking solution for heart valve repairs and for warts.[1]

[1] Note: USP monograph exists for glutaral concentrate (glutaraldehyde in a 50% aqueous solution), a different concentration than that proposed in the nominations. USP Guidelines state: "[s]ome drug substances are available as concentrated solutions … and are intended to be used as intermediates for final formulations." See USP Nomenclature Guidelines, last revision on Dec. 1, 2014, available at http://www.usp.org/sites/default/files/usp_pdf/EN/2014-12-01_nom_guidelines.pdf, accessed Sept. 2015. Under 21 CFR 207.3(a)(4), the definition of *bulk drug substances*

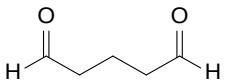
We have reviewed available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we ***recommend that glutaraldehyde for topical use*** be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act. This determination is based on information for use in the treatment of nongenital cutaneous warts and not as a soaking solution for heart valve repairs.

Glutaraldehyde as a soaking solution for heart valve repairs is being used as a crosslinking reagent in the manufacture of a medical device and, therefore, will not be considered in this review for bulk drug substances that can be compounded under section 503A of the Act.

II. EVALUATION CRITERIA

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

Yes, the drug substance is a simple dialdehyde and has the following structure:



The drug substance is well characterized and is easily characterizable via proton nuclear magnetic resonance, infrared and mass spectrometric techniques.

1. Stability of the API and likely dosage forms

Glutaraldehyde is stable in light, oxidizes in air and polymerizes upon heating (Osol A et al., 1975). In alkaline solutions, it readily forms polymeric films via inter- and intra-molecular Aldol condensations. The drug substance is reactive towards both acid and base, but is more stable in acid than in base (Goodman et al., 1975). An American Medical Association finding suggests that glutaraldehyde loses activity within two weeks after preparation (AMA Drug Evaluations Annual, 1994).

According to the Dow Chemicals safe handling and storage guide, if water is evaporated from aqueous glutaraldehyde solutions, the residual material will rapidly polymerize in a nonhazardous reaction, producing a residue that will burn (Online: Dow Chemical Company, 2003). As the reaction is reversible, polymerization is not a problem for dilute solutions. The rate of loss of activity depends on storage temperature, pH, and contamination, with 25-37 ºC being a safe temperature range for storage.

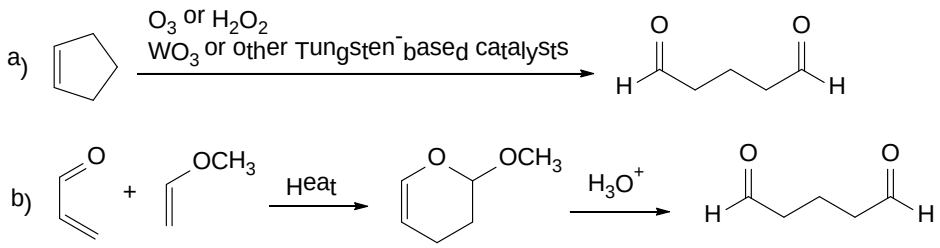
---

excludes intermediates used in the synthesis of the bulk drug substance. Therefore, we are evaluating glutaraldehyde for the list in forms or concentrations other than those provided in the USP monograph.

For the proposed dilute solution compounding, the drug substance is expected to be stable if protected from heat and air.

2. Probable routes of API synthesis

Glutaraldehyde is produced via (a) oxidation of cyclopentene (Kohlpaintner C et al., 2008) or via (b) Diels-Alder reaction of acrolein with methyl vinyl ether (Troy D B, 2005). The latter yields 3,4-dihydro-2-methoxy-2H-pyran, acidic hydrolysis of which leads to glutaraldehyde.



In both cases, the drug substance is obtained from the reaction mixture by multiple extractions with water, in which the drug substance is soluble.

3. Likely impurities

Based on the manufacturing processes, traces of the starting compound, cyclopentene or acrolein could be present in the drug substance as process impurities. The other probable impurities would be the air oxidation products of glutaraldehyde, 1,5-pentanedioic acid (glutaric acid) and 5-oxopentanoic acid.

4. Toxicity of those likely impurities

1,5-pentanedioic acid (glutaric acid) does not contain a structural alert for mutagenicity.

Because 5-oxopentanoic acid is an aldehyde, it is a structural alert for mutagenicity. Acrolein, an α,β-unsaturated carbonyl compound, also contains a structural alert for mutagenicity. However, trace contamination of the drug substance by these impurities is less of a concern because the drug substance itself has a structural alert for mutagenicity. Mutagenicity is discussed further below.

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

The drug substance is a liquid, boiling at about 188 ºC, with decomposition. Because it is a liquid, solid state properties, such as polymorphism and particle size distribution, do not apply for the drug substance.

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

The drug substance is a dialdehyde, thus a structural alert for mutagenicity. Mutagenicity is discussed further, in section B, below.

Conclusions: Glutaraldehyde is well characterized physically and chemically. From chemical synthesis and stability perspectives, the proposal of compounding glutaraldehyde as a topical product is reasonable, when stored protected from heat and air. Note, that some of its likely impurities have identified structural alerts for mutagenicity. However, trace contamination of the drug substance by these impurities is less of a concern because the drug substance itself is a structural alert for mutagenicity, as discussed in section B.

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

1. Nonclinical Assessment

The public database PubMed was consulted for this review.

a. Pharmacology of the drug substance

Glutaraldehyde, a highly reactive chemical, can cause immediate superficial tissue necrosis by chemical dehydration of the affected tissue.

b. Safety pharmacology

Inhalation of glutaraldehyde for 24 hours at 33 ppm caused nervous behavior, and excessive grooming and panting in mice (Varpela et al., 1971). Treatment with a single intravenous dose of 1 to 10 mg/kg glutaraldehyde caused prolongation of the Q-T interval, resulting in ventricular fibrillation in dogs (James and Bear, 1968). A 50% decrease in the respiratory rate was noted in mice following 60-minute oronasal exposure to 2.6 ppm glutaraldehyde (Zissu et al., 1994).

c. Acute toxicity

Acute toxicity of glutaraldehyde has been tested in various species (NTP, 1999). Four-hour inhalation LC_{50} of glutaraldehyde ranged from 24 to 5,000 ppm in rats. The oral LC_{50} was 66 - 820 mg/kg in rats and 15 - 300 mg/kg in mice, and 50 mg/kg in guinea pigs. In rabbits, the oral LC_{50} was 1.59 mL of a 50% aqueous solution/kg body weight and the dermal LC_{50} was 640 - 3,045 mg/kg. The subcutaneous, intraperitoneal, and intravenous LC_{50} of glutaraldehyde was 2,390, 17.9, and 15.3 mg/kg in rats and 1,430, 13.9, and 15.4 mg/kg in mice, respectively. Glutaraldehyde was an irritant to the skin, eye, and respiratory tract of tested rabbits and mice (NTP 1999; Zissu et al., 1994).

d. Repeat dose toxicity

The toxicity of glutaraldehyde has been tested in animals by various routes and exposure durations (NTP, 1993; Greenspan et al., 1985; Zissu et al., 1998; NTP, 1999). In 13-week inhalation studies in which rats and mice were exposed to 0, 62.5, 125, 250, 500, or 1,000 ppb, all 1,000 ppb mice and 20% of the 500 ppb female mice were killed moribund or died before the end of the studies, and one female rat in the 250 ppb group was killed moribund. Local effects, including signs of nasal irritation and cell proliferation in nasal tissue, were observed in treated rats and mice following inhalation of glutaraldehyde at lower doses. The irritant effects are exacerbated by repeated exposure. In 13-week drinking water studies with rats and mice exposed to concentrations up to 1,000 ppm glutaraldehyde and beagle dogs exposed to concentrations up to 250 ppm glutaraldehyde, no systemic toxic effects were observed. There was no systemic toxicity in rats given a diet containing 0.5% - 5% glutaraldehyde for 3 months or 0.25% glutaraldehyde in drinking water for 11 weeks. In a short-term dermal study, cumulative toxicity and mortality occurred in mice after repeated treatment with aqueous solutions containing 25% and 50% glutaraldehyde, but there was no evidence of cumulative toxicity at 5% or less. Skin irritation studies with glutaraldehyde in rabbits resulted in erythema, edema, and necrosis. Glutaraldehyde was a skin sensitizer in guinea pigs (Stern et al., 1989).

e. Mutagenicity

Genotoxicity of glutaraldehyde has been tested extensively, but there is still disagreement in the literature (Zeiger et al., 2005). Glutaraldehyde is a known DNA-protein cross-linker, because of its high reactivity. In vitro, it was mutagenic in Salmonella and E. coli (Zeiger et al., 2005). Glutaraldehyde caused weak, and inconsistent, positive results in cultured mammalian cells (Zeiger et al., 2005). Glutaraldehyde did not induce cell transformation in Syrian hamster embryo (SHE) cells (Yamaguchi and Tsutsui, 2003). However, one study clearly showed that glutaraldehyde was mutagenic in mammalian cells by a clastogenic mode of action (Speit et al., 2008). Glutaraldehyde was generally negative in in vivo genotoxicity tests. Glutaraldehyde was negative in the in vivo rat unscheduled DNA synthesis (UDS) test (Mirsalis et al., 1989). DNA damage was not detected in testis cells of rats orally treated with glutaraldehyde (EPA/OTS, 1991). No clear induction of micronuclei was observed in bone marrow cells of mice treated with glutaraldehyde via short-term inhalation or acute intraperitoneal injection (NTP, 1999; EPA/OTS, 1993). Only increased chromosome aberrations in bone marrow cells were reported in one of eight studies in which rats or mice were treated with glutaraldehyde via gavage, inhalation, or intraperitoneal injection (Zeiger et al., 2005).

f. Developmental and reproductive toxicity

Although repeated oral treatment with glutaraldehyde caused embryo-toxicity and fetal-toxicity in pregnant rats, mice, or rabbits, no teratogenic effects were

observed in pregnant rats, mice, or rabbits treated with glutaraldehyde at concentrations that were less than those that were maternally toxic (Ema et al., 1992; Neeper-Bradley et al., 1995; NTP, 1999). No effects on parental fertility, mating performance, pup viability, or litter size were observed in either generation in a two-generation study in which male and female rats were treated with glutaraldehyde at concentrations of 0, 50, 250, or 1,000 ppm in drinking water (Neeper-Bradley et al., 1995).

g. Carcinogenicity

Inhalation of glutaraldehyde was not carcinogenic in rats or mice (NTP, 1999; Zissu et al., 1998). A 2-year drinking water study showed large granular lymphocytic leukemia (LGLL) present in the livers and spleens of all control and glutaraldehyde treated rats (Van Miller et al., 2002). A slightly, but statistically significantly increased incidence of LGLL was seen in glutaraldehyde-treated females only at all dose levels (50 - 1000 ppm). However, the finding was not conclusive as the strain of rats used in the study had a high natural susceptibility to LGLL, and variation in control data existed within the study laboratory.

h. Toxicokinetics

There was no evidence of systemic toxicity in rats or mice after inhalation of glutaraldehyde, which may be attributed in part to their limited systemic bioavailability due to the high reactivity at the site of contact (NTP, 1999). Following dermal treatment with glutaraldehyde, only approximately 5% of the applied dose was absorbed in rats, but in rabbits, 32% to 53% of the applied dose was absorbed and either excreted or found in tissues (Beauchamp, 1992). The terminal half-lives for elimination are long for both intravenous injection (rat 10 h, rabbit 15 – 30 h) and dermal application (rat 40 – 110 h, rabbit 20 – 100 h), probably due to the strong binding of glutaraldehyde to protein (McGregor et al., 2006). The metabolism of glutaraldehyde probably involves initial oxidation to the corresponding carboxylic acids by aldehyde dehydrogenase.

Conclusions: Glutaraldehyde is a cross-linker with cellular proteins/DNA, because of its highly reactive chemical properties. The toxicity of glutaraldehyde in animals is characterized by local irritation of the skin, eye, and respiratory tract and skin sensitization. The irritant effects are exacerbated by repeated exposure. Glutaraldehyde was mutagenic in vitro, but generally negative in vivo. Glutaraldehyde was not carcinogenic in rats and mice. There is no evidence of reproductive and developmental effects of glutaraldehyde on tested animals. Based on the literature reviewed, from a nonclinical perspective, it appears to be reasonably safe to use glutaraldehyde topically in 0.1% to 10% solutions for the treatment of warts.

2. Human Safety

a. Reported adverse reactions

Potential routes of human exposure to glutaraldehyde include inhalation, ingestion, and dermal contact. From the comprehensive review by Andersen in 1996 and subsequent literature, it is clear that glutaraldehyde may produce the following adverse reactions:

- As an irritant – irritation to respiratory and dermatologic systems via vapor or direct contact, respectively, and thus an occupation hazard to workers exposed to the substance in their environment
- As a sensitizer – allergic contact dermatitis (see below)
- In clinical use – skin ulceration and necrosis (see below)

It should also be noted that the adverse effects are likely dependent on the degree of exposure; the higher the strength of glutaraldehyde for exposure, the more likely the adverse reactions.

b. Clinical trials assessing safety

There have been no dedicated clinical trials assessing the safety of glutaraldehyde used in the treatment of warts. However, dermal safety studies conducted with glutaraldehyde have been reported and were summarized by Andersen in his safety review of glutaraldehyde in 1996. The following tables concerning provocation testing are excerpts from this review.

- Irritancy

Table 5 of Andersen Report: Provocative Tests and Case Studies of Dermal Irritation

Case study/testing	Findings	Reference
657 patients with eczematous dermatitis were patch-tested with 2% Glutaral	One (0.1%) positive reaction occurred	Angelini et al., 1985
160 patients were patch-tested with 1% Glutaral (pH 7.5)	No positive reactions occurred	Juhlin and Hansson, 1968
The chamber-scarification test was used to test the irritancy of 2% Glutaral on 5 subjects	"Marked" irritancy was observed at 72 h	Frosch and Kligman, 1977
The chamber-scarification test was used to test the irritancy of 2% Glutaral on 5 subjects	"Marked" irritancy was observed at 72 h	Frosch and Kligman, 1977
2 patients allergic to Glutaral were patach-tested with fabric treated with a fabric softener containing 550 and 5,500 ppm Glutaral	No adverse reactions occurred	Weaver and Mailbach, 1977
An "open" exaggerated use test was conducted on 2 subjects allergic to Glutaral using undiluted fabric softener containing 550 ppm Glutaral	No signs of cutaneous allergy were observed	Weaver and Maibach, 1977
14 Glutaral-sensitive subjects wore cotton T-shirts treated with fabric softener containing 550 ppm Glutaral for 24 h for 14 days	No irritation occurred	Weaver and Maibach, 1977
13 patients were patch-tested with 1% Glutaral	9 subjects had irritant reactions	Hansen and Menne, 1990
884 patients were patch-tested with 0.1% Glutaral	2 subjects had allergic reactions, 1 of which had clinical relevance; no irritant reactions were observed	Hansen and Menne, 1990
A woman with allergic contact dermatitis to a hair conditioner containing > 1% Glutaral was patch-tested with standard screening trays, the conditioner, and 0.05, 0.1, 0.5, and 1% Glutaral	The woman had positive reactions to all of the Glutaral concentrations except 0.05%	Jaworsky et al., 1987
2 patients with allergic contact dermatitis to Glutaral were patch-tested with 0.25 and 1% aq. Glutaral, moistened Glutaral-tanned leather, and formaldehyde	The patients had positive reactions to both concentrations of Glutaral and most of the leather samples; neither subject reacted to formaldehyde	Jordan et al., 1972
20 subjects suspected to be contact-sensitive to Glutaral were patch-tested with 1% Glutaral	All of the subjects had strong reactions	Maibach, 1975
9 subjects sensitized a year previously to Glutaral were patch-tested with Glutaral	6 subjects (66%) had positive reactions	Maibach and Prystowsky, 1977
Subjects who patch-tested positive to Glutaral were tested in a usage test with 25% Glutaral on soles of feet and antecubital fossae	6/6 subjects were negative on the soles; severe dermatitis on antecubital fossae occurred on 5/5 subjects	Maibach and Prystowsky, 1977

- Sensitization

Table 6 of Andersen Report: Human Dermal Sensitization Studies with Glutaral (glutaraldehyde)

Test	Results	Reference
102 male subjects, induction with 0.1% and challenge with 0.5%	No sensitization was observed	Marzulli and Maibach, 1974
30 male subjects, induction with 5.0% and challenge with 0.5%	7 (23.3%) positive for sensitization	Marzulli and Maibach, 1974
109 male and female subjects, induction and challenge with 0.1%	No irritation or sensitization was observed	Ballantyne and Berman, 1984
109 male and female subjects, induction and challenge with 0.2%	2 doubtful reactions during induction; no reactions at challenge	Ballantyne and Berman, 1984
109 male and female subjects, induction and challenge with 0.5%	9 doubtful and 7 definite erythematous reaction during induction. 1 doubtful and 1 local erythematous reaction with edema during challenge; both failed to react to induction patch	Ballantyne and Berman, 1984
RIPT on 706 individuals using a 4% aq. solution containing either 22 or 220 ppm Glutaral	No signs of irritation or sensitization were observed	Weaver and Maibach, 1977

- Phototoxicity and Photoallergenicity

Human photosafety studies, including those on phototoxicity and photoallergenicity, are usually conducted on topical products containing substances that absorb light in the ultraviolet B (UVB), ultraviolet A, and visible spectrum. Pure glutaraldehyde has a single peak absorption for ultraviolet light at 280 nm. There may be an additional peak at 235 nm due to polymerization. Although these peaks fall below the lower bound for UVB (290 – 320 nm), human studies on photosafety have been performed for glutaraldehyde.

Fifty-two healthy volunteers participated in a standard phototoxicity study and 99 healthy subjects in a standard photoallergenicity study with 0.005, 0.01, 0.02, and 0.05% glutaraldehyde – no evidence of phototoxicity or photoallergenicity was demonstrated (TKL Research, Inc., 1990a and 1990b).

- Clinical Studies Involving Treatment of Nongenital Cutaneous Warts

  - 10% glutaraldehyde solution on plantar and periungal warts in >30 patients – brown or tan discoloration (London, 1971);
  - 25% glutaraldehyde solution on “various types” of warts in >100 patients – irritation “rarely” (London, 1971);

- 10% glutaraldehyde aqueous solution on mosaic plantar warts in 38 patients – no adverse reactions mentioned, but "considerable" problems of dispensing (Bunney et al., 1976);
- 2% aqueous solution of glutaraldehyde on plantar warts in 192 patients, 5% glutaraldehyde in collodion on plantar warts in 28 patients, and 10% glutaraldehyde solution in ethanol on warts of hands and feet in 21 patients – intense brown stain (Allenby, 1977);
- 10% glutaraldehyde gel on plantar warts in 21 patients – brownish discoloration (Scott, 1982);
- 20% aqueous solution of glutaraldehyde applied to periungal, palmer, and plantar warts in 25 patients – brown discoloration which subsided afterwards (Hirose et al., 1994);
- Case report of 20% glutaraldehyde solution to plantar wart of a 7-year-old boy – necrosis of pulp of big toe; author claims that "repeated cases of this type have led to the withdrawal of the product from the market in December 1995" (Prigent et al., 1996);
- Case report of 20% glutaraldehyde solution on warts on leg in a 20-year-old man – allergic contact dermatitis (Martin et al., 1997);
- Case report of glutaraldehyde of unstated strength and dosage form painted onto the plantar wart of a 26-year-old man – deep plantar ulceration with necrotic tissues (Fujisawa et al., 2009).

c. Pharmacokinetic data

There are no reports of human pharmacokinetic studies in vivo. Frantz et al., 1993 reported that following in vitro application of a 7.5% solution of glutaraldehyde to full-thickness human skin (250 µl on 1.77 cm^2 area, breast skin, n=3 females) for 6 hours, a mean (±SD) of 0.20 ± 0.08 percent of the applied dose passed through the skin and 4.56 ± 1.67 percent of the applied dose was present within the skin tissue. Similar results were observed with a lower strength glutaraldehyde 0.75% solution. These results suggest that glutaraldehyde solution can absorb into and bind to skin tissue, but only a small fraction would pass through the skin and be available for systemic distribution.

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

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. Topical salicylic acid in different vehicles has been monographed under Wart Remover Drug Products for over-the-counter use (21 CFR 358 subpart B). There are some unapproved therapies for 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 glutaraldehyde 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 clinical evidence on glutaraldehyde as a drug substance in the treatment of nongenital cutaneous warts suggests potential for irritation and sensitization, but not phototoxicity or photoallergenicity. When used in the treatment of warts, it will cause skin discoloration, which eventually subsides after treatment. Systemic bioavailability is likely limited because of the binding of glutaraldehyde to protein and DNA in the skin. There have been reports of allergic contact dermatitis, skin ulceration and necrosis, especially with high concentrations such as 20% glutaraldehyde. These risks should be managed by the use of strengths of 10% or less.

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

The mechanism of action of glutaraldehyde in the treatment of warts has not been fully determined. Cutaneous warts are caused by human papillomavirus (HPV), which is a non-enveloped, double-stranded DNA virus. Although glutaraldehyde crosslinks proteins and DNA, it is not clear whether this serves as an antiviral activity in wart treatment. Depending on the strength used, glutaraldehyde may not disinfect all HPV types (Meyer et al, 2014). Glutaraldehyde also has keratolytic and anhidrotic effects, which may contribute to its local action in wart treatment.

There are publications on glutaraldehyde compounded for the treatment of nongenital cutaneous warts, but the clinical evidence is primarily based on uncontrolled studies. The only randomized, comparative study is that by Bunney et al., in 1976 involving glutaraldehyde solution and salicylic acid/lactic acid (see Table below). However, a Cochrane review of the available data on wart treatments in 2012 by Kwok et al., states that there are no randomized controlled trials to support glutaraldehyde use in the treatment of cutaneous warts without explanation, although this study was included in the database evaluated.

The following Table is a summary of available data on clinical studies for cutaneous wart treatment with glutaraldehyde. Formulations and treatment regimens vary in these trials.

Reference	Glutaraldehyde Used			Type of Warts Treated	# of Subjects & Comparator	Results
	Strength	Formulation	Frequency			
London, 1971a	10%	solution (aq)	2x/day	plantar and periungal warts	>30 (no comparator)	“cannot claim” 100% cure; failures due to “not paring”
London, 1971b	25%	solution (solvent ?)	Not stated	various types of warts	>100 (no comparator)	“practically” 100% cure
Bunney et	10%	solution	Not	mosaic	38	Cure rates: glutaraldehyde

al, 1976		(aq)	stated	plantar warts	glutaraldehye, 43 SAL*	18/38 (47%) vs SAL 19/43 (44%)
Allenby, 1977	2%	solution (aq)	Daily	plantar warts	192 (no comparator)	14 subjects lost to follow up; cure rate of 137/178 (77%) [71% if including the lost subjects in denominator]
	5%	solution (in collodion)	2x/day	plantar warts	28 (no comparator)	Cure rate of 21/28 (75%)
	10%	solution (in ethanol)	2x/day	warts of hands and feet	21 (no comparator)	Cure rate of 15/21 (71%)
Scott, 1982	10%	gel	2x/day	plantar warts	21 (no comparator)	Cure rate of 15/21 (71%)
Hirose et al, 1994	20%	solution (aq)	Daily	Resistant periungal, palmer, and plantar warts	25 (no comparator)	Cure rate of 18/25 (72%)

*SAL – a paint with 16.7% each of salicylic acid and lactic acid in collodion

Regarding lack of effectiveness, a small trial conducted by Gibson et al., in 1984 compared topical acyclovir vs placebo vs cryotherapy/glutarol (glutaraldehyde) with cure rates of 7/18 (39%), 5/18 (28%), and 1/11 (9%) at 8 weeks, respectively, and no statistically significant differences between the three treatments. However, this trial was not designed to study glutaraldehyde itself.

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

Glutaraldehyde compounded for use in the treatment of nongenital cutaneous warts does not constitute use in a serious or life-threatening disease.

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

See section II.B.2.d for alternative approved therapies for cutaneous warts.

There have been no comparative effectiveness studies between glutaraldehyde and approved therapies for nongenital cutaneous warts. A study of 81 patients compared 10% glutaraldehyde solution to a “SAL paint” consisting of salicylic acid and lactic acid, each of 16.7% strength in collodion (a paint with salicylic acid and lactic acid, each of 16.7%, is now marketed under the name Salactol in the United Kingdom by Dermal laboratories for the treatment of warts) in the treatment of mosaic plantar warts showed that the treatments were of similar efficacy (see Section III.1.; Bunney et al., 1976). However, the comparator is not an approved product in the United States.

Conclusions: Information about the effectiveness of glutaraldehyde in the treatment of nongenital cutaneous warts is primarily based on uncontrolled studies. A comparative study in the United Kingdom showed that the efficacy of glutaraldehyde 10% solution is

similar to that of salicylic acid/lactic acid paint. It appears that the efficacy in wart treatment may be similar over a range of concentrations from 2% up and in various vehicles, but further research would be required for determination of the optimal formulation. In addition, there is no standard regimen for its use for this indication; it is possible that this lack of standard regimen may be due to the variability on the location of the wart and the HPV type involved.

D. Has the substance been used historically in compounding?

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

The use of glutaraldehyde compounded for plantar hyperhidrosis was originally reported by Juhlin and Hansson in 1968. Glutaraldehyde compounded for the treatment of cutaneous warts has been reported since the 1970s.

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

Glutaraldehyde use in pharmacy compounding as a bulk drug substance is primarily for the treatment of cutaneous warts. Although there have been earlier reports of its use in hyperhidrosis, a search in PubMed has not shown publications on this issue after 1995. It has also been used for onychomycosis (Suringa, 1970).

Apart from medical use, glutaraldehyde is also present as an excipient in many cosmetics at concentrations up to 1%, and it is a food additive permitted for direct addition to food for human consumption. Glutaraldehyde is present as a residual excipient in some non-live vaccines (for instance, in the DPT vaccine, DAPTACEL, at a concentration of up to 50 ng per 0.5 mL, i.e., 0.01%).

3. How widespread its use has been

The use of glutaraldehyde in the treatment of cutaneous warts is global.

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

Glutaraldehyde is approved in the United Kingdom as a 10% solution, Glutarol, for the treatment of cutaneous warts. It was approved in France as a 20% solution, Verutal, also for the treatment of cutaneous warts, but this drug was withdrawn in 1995 upon reports of skin necrosis after use on plantar warts, although it is available in Europe as a disinfectant. Glutaraldehyde in lower strengths (up to 3.5%), alone or in combination with other compounds such as isopropanol, phenol, etc., is also cleared under 510(k) in the United States as disinfectant for sterilization of medical devices under various proprietary names.

Glutaraldehyde is included in the United States Pharmacopoeia, European Pharmacopoeia, and British Pharmacopoeia, but not in the Japanese Pharmacopoeia.

Conclusions: Glutaraldehyde has a history of use in pharmacy compounding for over 40 years, primarily in the treatment of nongenital cutaneous warts. Formulations of glutaraldehyde are recognized in the U.S. Pharmacopoeia, as discussed above, and foreign pharmacopoeias. Although in some countries, such as the United Kingdom, glutaraldehyde is used for the indication of wart treatment as an approved drug product, it is compounded for the same indication in other countries where this is not approved. Publications on its use in warts indicate that this practice is widespread and global.

III. RECOMMENDATION

We have evaluated glutaraldehyde as a candidate for the list of bulk drug substances under section 503A of the FD&C Act and ***recommend*** that it be included on the list based on the following:

(1) Glutaraldehyde is well characterized in its physical and chemical properties.

(2) The safety profile of glutaraldehyde shows that:

- Glutaraldehyde is a cross-linking agent on proteins and DNA, but nonclinical studies do not seem to show safety issues in vivo other than local irritation and skin sensitization; therefore it appears to be reasonably safe to use glutaraldehyde topically in 0.1% to 10% solutions for the treatment of warts; and
- When used topically, there is potential for irritation, sensitization, but phototoxicity or photoallergenicity has not been demonstrated. It causes skin discoloration, which eventually subsides; systemic bioavailability is likely limited because of the binding of glutaraldehyde to protein and DNA in the skin. There have been reports of allergic contact dermatitis, skin ulceration and necrosis, especially with high concentrations: these risks should be managed by the use of strengths of 10% or lower.

(3) Glutaraldehyde has been compounded for use in the treatment of nongenital cutaneous warts for over 40 years. Reports on its use in other medical conditions include hyperhidrosis and onychomycosis. Its use in wart treatment is supported in peer-reviewed medical literature, and the practice is world-wide.

(4) There is available evidence from uncontrolled clinical studies and one randomized controlled trial on the effectiveness of glutaraldehyde in nongenital cutaneous wart treatment. However, there is no standard regimen for its use for this indication.

Based on a balancing of the four evaluation criteria, we find that glutaraldehyde is a suitable substance for the bulk drug substance list under 503A of the FD&C Act. Therefore, we ***recommend that glutaraldehyde for topical administration*** be included on this list. We also recommend that the compounded product be prescribed at concentrations of 10% or lower.

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Tab 9

Glycyrrhizin

Tab 9a

Glycyrrhizin Nominations

VIA WWW.REGULATIONS.COM

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

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,[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

[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.

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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.

As discussed in detail below, in the interest 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.,[1] 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:

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.

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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

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 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
Glutiathone
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

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American College for Advancement in Medicine

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September 30, 2014

Division of Dockets Management (HFA-305)
Food And Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Re: Docket FDA-2013-N-1525

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

To Whom It May Concern:

The American College for Advancement in Medicine (ACAM) is a prominent and active medical education organization involved in teaching physicians in the proper use of oral and intravenous nutritional therapies for over forty years. We have also been involved in clinical research sponsored by the National Heart Lung and Blood Institute. As such, we have a vested interest in maintaining the availability of compounded drug products.

We appreciate 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. To meet what appear to be substantial requirements involved in this submittal, the FDA has given compounding pharmacists (in general a small business operation) and physicians very limited time to comply with onerous documentation. The Agency has requested information for which no single pharmacy or physician organization can easily provide in such a contracted time frame. As such this time consuming process requires significant coordination from many practicing professionals for which adequate time has not been allotted.

This issue is of great importance and has the potential to drastically limit the number of available compounded drugs and drug products thus limiting the number of individualized treatments that compounded medicines offer to patients.
ACAM and its physician members have not had the time to collect, review and assess all documentation necessary to submit for the intended list of compounded drugs required to assure all patient therapies are represented in our submission. We respectfully seek an additional 120 day period to educate and coordinate our physicians on the issue at hand and to gather the essential information necessary to provide the Agency with the most comprehensive information.
In an attempt to comply with the current timeframe established, a collaborative effort resulted in the attached nominations prepared for bulk drug substances that may be used in pharmacy compounding under Section 503A.

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It is not clear whether the current submission will be the final opportunity to comment or communicate with the Agency. Will a deficiency letter be provided if the initial nomination information was inadequate or will a final decision to reject a nominated substance be made without the opportunity to further comment? ACAM respectfully requests that the FDA issue a deficiency letter should the submitted documentation for a nomination be considered inadequate.

Sincerely,

Neal Speight, MD
(Immediate Past President) for
Allen Green, MD
President and CEO
The American College for Advancement in Medicine

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Glycyrrhizin
Is the ingredient an active ingredient that meets the definition of ‘‘bulk drug substance’’ in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please access this article: van Rossum TG, Vulto AG, Hop WC, Brouwer JT, Niesters HG, Schalm SW.Intravenous glycyrrhizin for the treatment of chronic hepatitis C: a double-blind, randomized, placebo-controlled phase I/II trial. J Gastroenterol Hepatol. 1999 Nov;14(11):1093-9.
Is the ingredient listed in any of the three sections of the Orange Book?	
Were any monographs for the ingredient found in the USP or NF monographs?	NF monograph for Licorice Fluidextract, available. Dietary monograph for Licorice, Powered Licorice and Powedered Licorice Extract, available in the USP.
What is the chemical name of the substance?	(3β,20β)-20-Carboxy-11-oxo-30norolean-12-en-3-yl 2-O-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid.
What is the common name of the substance?	Glycyrrhizic acid, glycyrrhizinic acid, glycyrrhetinic acid glycoside.
Does the substance have a UNII Code?	6FO62043WK
What is the chemical grade of the substance?	Not graded
What is the strength, quality, stability, and purity of the ingredient?	Licorice is a generally recognized as safe (GRAS) dietary supplement. A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Glycyrrhizin is supplied as a crystalline powder form.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	Information not available.
Has information been submitted about the substance to the USP for consideration of monograph development?	NF monograph for Licorice Fluidextract, available. Dietary monograph for Licorice, Powered Licorice and Powedered Licorice Extract, available in the USP.
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	8 mg/mL multiple dose or preservative free, in various sizes up to 30 mL
What are the anticipated route(s) of administration of the compounded drug product(s)?	Slow intravenous

Are there safety and efficacy data on compounded drugs using the nominated substance?	1. van Rossum TG, Vulto AG, Hop WC, Brouwer JT, Niesters HG, Schalm SW.Intravenous glycyrrhizin for the treatment of chronic hepatitis C: a double-blind, randomized, placebo-controlled phase I/II trial. J Gastroenterol Hepatol. 1999 Nov;14(11):1093-9. 2. van Rossum TG, Vulto AG, Hop WC, Schalm SW. Pharmacokinetics of intravenous glycyrrhizin after single and multiple doses in patients with chronic hepatitis C infection. Clin Ther. 1999 Dec;21(12):2080-90. 3. Anderson P, Cochran B. Personal experiences with the clinical use of intravenous substances. AMSA, BIORC and Private clinic data. Seattle Washington,2014 4. van Rossum TG, de Jong FH, Hop WC, Boomsma F, Schalm SW.'Pseudo-aldosteronism' induced by intravenous glycyrrhizin treatment of chronic hepatitis C patients. J Gastroenterol Hepatol. 2001 Jul;16(7):789-95.
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?	Glycyrrhizin a.k.a. glycyrrhizic acid / glycyrrhizinic acid (GA) has great potential in the treatment of patients who have chronic viral illnesses such as Hepatitis C. Data in humans shows it to be a safe agent [2] and helpful in Hepatitis C [1]. Over a decade of clinical use has revealed no adverse events when used under standard dose and administration guidelines [3].
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There are no FDA approved drugs which provide the same pharmacology and potential therapeutic benefit as Glycyrrhizin.
Is there any other relevant information?	In the US it is estimated that there are 16,000 Acute Hepatitis C cases and 3.2 million people with chronic Hepatitis C. [http://www.cdc.gov/hepatitis/c/cfaq.htm] As there is no commercial alternative to Glycyrrhizin and there is data [1-4 above] to show it can safely and effectively be used for therapy in the Hepatitis C population this compound is a necessary substance to include in section 503a.

Tab 9b

Glycyrrhizin
FDA Review

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: September 30, 2015

FROM: Sarah Connelly, MD; Medical Officer, Division of Antiviral Products (DAVP)

Mark Powley, PhD, Pharmacology/Toxicology Reviewer, DAVP

William Ince, PhD, Clinical Virology Reviewer, DAVP

George Lunn, PhD, Product Quality Reviewer, Office of Pharmaceutical Quality (OPQ)

THROUGH: Debra Birnkrant, MD, Director, DAVP

Ramesh Sood, PhD, Acting Senior Scientific Advisor, Office of New Drug Products, OPQ

Kimberly Struble, Clinical Team Lead, DAVP

TO: Pharmacy Compounding Advisory Committee

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

I. INTRODUCTION

Glycyrrhizin 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 use in the treatment of hepatitis C by intravenous administration.

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 glycyrrhizin be added to the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

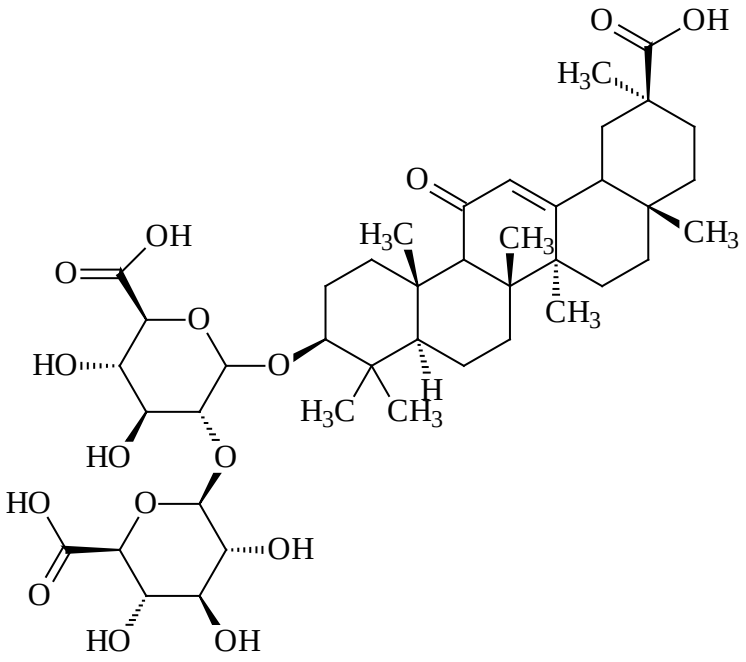
II. EVALUATION CRITERIA

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

1. Introduction

Glycyrrhizin (also known as glycyrrhizic acid or glycyrrhizinic acid) is a triterpene saponin extracted from licorice, the dried rhizome and roots of *Glycyrrhiza glabra* L., and related plant species, such as *G. uralensis* Fischer and *G. inflata* Batalin, of the family Leguminosae. Licorice contains 6-14% glycyrrhizin in addition to asparagine, sugars, and resin (Merck Index 15th Edition, Monographs 4540 and 4541).

The structure of pure glycyrrhizin is as follows:



Molecular Weight	822.94
Molecular formula	$C_{42}H_{62}O_{16}$

There is extensive literature describing licorice and other materials that contain glycyrrhizin (e.g., He et al., 2012; He et al., 2014; Tan et al., 2011; Wu et al., 2013) and many related and unrelated compounds, including some that are known to be pharmacologically active. The nomination cites articles by van Rossum et al., that discuss the use of a finished drug product apparently obtained from Japan. One of the articles states that "Glycyrrhizin was given as SNMC, a clear solution for intravenous use, consisting of 2 mg glycyrrhizin, 1 mg cysteine, and 20 mg glycine per mL in physiologic saline solution (Minophagen Pharmaceutical Company, Tokyo, Japan)."

The USP Dietary Supplement Monographs for powdered licorice and powdered licorice extract describe substances that contain glycyrrhizin. There is no USP Monograph for glycyrrhizin or glycyrrhizic acid. However, there is a USP NF Monograph for the related drug substance ammonium glycyrrhizate [CAS 53956-04-0], which is the ammonium salt of glycyrrhizic acid. Compounders can currently compound the related substance ammonium glycyrrhizate under section 503A if they comply with the specifications of this monograph.

When ammonium glycyrrhizate dissolves (e.g., in the stomach), it will dissociate to glycyrrhizic acid and ammonia. Therefore, when a substance of known purity such as ammonium glycyrrhizate as defined in the NF monograph is used, it can be expected to be pharmacologically equivalent to glycyrrhizic acid. However, glycyrrhizin may refer to a variety of other extracts of licorice, and cannot be described as well-characterized.

2. Probable routes of API synthesis

Glycyrrhizin is extracted from natural sources, specifically from *Glycyrrhiza glabra* and related species.

3. Likely impurities

Licorice and combination products with licorice and other herbs from various sources may contain many other components in addition to glycyrrhizin. The identified glycyrrhizin and other known components with similar structures to glycyrrhizin are present in licorice and its extracts at relatively small percentages.

4. Toxicity of those likely impurities

We have no information about the toxicity of the likely impurities.

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

There are no known physicochemical characteristics relevant to product performance.

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

No other relevant information.

Conclusions: Although the molecular structure of pure glycyrrhizin can be characterized, the characterization of substances described as "glycyrrhizin" is more complicated. The term glycyrrhizin may refer to a variety of other extracts of licorice, and cannot be described as well-characterized. Licorice and combination products with licorice and other herbs from various sources may contain many other components in addition to glycyrrhizin. The concentration of glycyrrhizin in any given substance described as "glycyrrhizin" or any particular licorice extract can vary widely, and we have little information about the likely impurities. Therefore, we cannot conclude that glycyrrhizin is well-characterized, physically or chemically.

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

1. Nonclinical assessment

Several published toxicological summaries are available for glycyrrhizinic acid. The most comprehensive is the World Health Organization's (WHO) monograph on the safety of dietary glycyrrhizinic acid (WHO, 2006). This monograph serves as the primary basis for the review of non-clinical safety related endpoints. Relevant information from other sources is also provided.

However, the terminology used to describe various test compounds is inconsistent. For instance, glycyrrhizin is described by WHO as the crude licorice extract containing glycyrrhizinic acid. Other references appear to use glycyrrhizin and glycyrrhizinic acid interchangeably and it is therefore difficult to know exactly what substance is being used as the test compound.[1]

[1] It should be noted that many of the studies discussed in this document describe the drug as "glycyrrhizin" and are not specific as to the species or mixtures of substances being used in the study.

a. Pharmacology of the drug substance

Primary Pharmacology (i.e., antiviral activity)

Hepatitis C Virus (HCV): Glycyrrhizin has no significant antiviral activity against HCV. Clinical experience with glycyrrhizin for the treatment of chronic HCV is extensive. Glycyrrhizin therapy has no apparent anti-HCV activity as determined by a reduction in plasma HCV RNA levels (van Rossum et al.,1999, and reviewed in Liu et al., 2003, and Liu et al., 2001). The apparent antiviral effect of glycyrrhizin observed in cell culture is most likely a result of the cytopathic or cytostatic effects of the drug. Reported cell culture half maximal effective concentration (EC_{50}) values ranged from 17 µM to 218 µM (extrapolated from the mass concentration), depending on the method of preparation and purity, but selectivity indices (SI) were <10 and were particularly low when assessed using the concentrations required to inhibit cellular proliferation rather than death (Ashfaq et al., 2011; Matsumoto et al., 2013; Adianti et al., 2014).

Other viruses: Glycyrrhizin has not been demonstrated to have a direct antiviral effect on any of the many viruses tested. Some nonclinical studies demonstrate that glycyrrhizin can selectively and directly inactivate herpesvirus (HSV-1 and VZV) when incubated with particles, but at concentrations of drug above those found to be cytotoxic (Pompei et al., 1979, Baba et al., 1987) or with little effect (Wang et al., 2013). In most cases, any apparent antiviral effects measured in animal models of infection (Utsunomiya et al., 1997) or in cell culture are likely due to its inhibition of cellular processes involved in pro-inflammatory cytokine secretion (Utsunomiya et al., 1997; Yoshida et al., 2009; Saidi et al., 2008; Michaelis et al., 2011) or cellular growth and survival (see Table 1) and, thus, indirectly, viral replication. Glycyrrhizin has been reported to reduce cytopathic effect (CPE) induced by vaccinia, HSV-1, NDV and VSV (but not poliovirus) at 8 millimolar (mM), but it also inhibited cellular proliferation at this dose (Pompei et al., 1979). Inhibition and SI data for a range of viruses are listed in Table 1, which collectively indicate a low selectivity index for most viruses and that any apparent antiviral activity is mediated primarily through an inhibitory effect on cellular pathways involved in proliferation or metabolism.

Table 1: EC_{50} values and selectivity indices for glycyrrhizin for a range of viruses.

Virus	Cell line	EC_{50} value[a] (µM)	SI[b]	Notes	Citation
HCV	Huh-7	17-218	<10	Effect on cell proliferation not assessed	Ashfaq et al., 2011, Matsumoto et al., 2013, Adianti et al, 2014
RSV	A549	9[c]	6	Effect on cell proliferation not assessed	Feng et al., 2013
IBDV	CEF	650[d]	>4.52	Effect on cell proliferation not assessed	Sun et al., 2013
CVA16, EV17	Vero	>1000	<7	Effect on cell proliferation not assessed	Wang et al., 2013
VZV	Vero	152[e]	8	Effect on cell proliferation not assessed	Shebl et al., 2012
EBV	Raji (Lymphoid)	30	150	Effect on cell proliferation not assessed	Lin et al., 2008
Non-HCV Flaviviruses	Vero	0.7 (median)	6 (median)	CC_{50} assessed on prolif. cells/protein expression	Crance et al., 2003
Hepatitis A virus	PLC/PRF/5	324	15	CC_{50} assessed on prolif. cells/protein expression	Crance et al., 1990

Measles	Vero	875	>7	Effect on cell proliferation not assessed	Hosoya et al., 1989
HIV-1	MT-4	150	8	Effect on cell proliferation not assessed	Ito et al., 1987

[a]Test compound is glycyrrhizin unless otherwise noted.
[b] A ratio estimated based on the 50% cytotoxic concentration, or the lowest cytotoxic concentration, divided by the EC_{50} value.
[c]Glycyrrhiza uralensis extract.
[d]Dipotassium glycyrrhizinate.
[e]Licorice extract powder (species not specified).

The Division does not generally consider an SI value less than 10 as a demonstration of bona fide antiviral activity. However, it should be noted that in studies that compared the antiviral activity of glycyrrhizin to ribavirin against a panel of flaviviruses (Crance et al., 2003) and picornavirus (HAV) (Crance et al., 1990), selectivity indices for ribavirin were generally 2-3 fold lower, based on inhibition of cellular protein expression. Ribavirin is approved for the treatment of chronic HCV infection, but its mechanism of action is unclear and may not be due to a direct antiviral effect.

The reported anti-inflammatory activity of glycyrrhizin could have a beneficial effect on viral pathogenesis (Utsunomiya et al., 1997; Yoshida et al., 2009; Matsui et al., 2004; Borde et al., 2011; Saidi et al., 2008). Multiple studies indicate that glycyrrhizin inhibits HMGB1, thought to be a cellular co-factor for the replication of some viruses (Moisy et al., 2012; Matsumoto et al., 2012) and a mediator of pro-inflammatory signaling (Kim et al., 2012; Mollica et al., 2007; Borde et al., 2011; Saidi et al., 2008). Glycyrrhizin may potentially reduce HIV replication due to the indirect effect of glycyrrhizin inhibition of HMGB1 in NK cells, which suppresses the secretion of inflammatory cytokines that stimulate HIV replication in DCs, although the clinical significance of this activity is unclear (Yoshida et al., 2009; Saidi et al., 2008).

Secondary Pharmacology

A number of pharmacological actions have been reported for glycyrrhizinic acid and related compounds. Of importance for this review is the inhibitory effect on 11β-hydroxysteroid dehydrogenase-2 (11β-OHSD2) in the kidney. Effects potentially related to this inhibition include “increased potassium excretion, sodium and water retention, body weight gain, alkalosis, suppression of the renin-angiotensis-aldosterone system, hypertension, and muscular paralysis” (Cosmetic Ingredient Review Expert Panel, 2007).

b. Safety pharmacology

<u>From WHO Monograph</u>: “No effects were reported on the nervous system, cardiovascular system, respiratory system, or the gastrointestinal tract of cats given a single dose of glycyrrhetic acid at 125 mg/kg bw [body weight] by intraperitoneal administration (Finney et al., 1958).” Glycyrrhetic acid is the major hydrolysis product of glycyrrhizinic acid (see section II.B.1.h).

c. Acute toxicity

<u>From WHO Monograph</u>: “The [median lethal dose] LD_{50} values for glycyrrhizinic acid and various salts in mice, guinea pigs and dogs were reported to be in the range of 308 to 12,700 mg/kg bw.”

Additional: IV administration of 70 mg/kg glycyrrhizin to mice resulted in convulsions and hemolysis (Segal et al., 1977). The test article described by the authors in this paper appears to be ammoniated glycyrrhizin.

d. Repeat dose toxicity

From WHO Monograph: "The toxicity of glycyrrhizinic acid and/or its monoammonium salt has been evaluated in a number of short-term studies in rats and mice. At high doses, effects reported included those related to apparent mineralocorticoid excess or pseudohyperaldosteronism. Mild myolysis of the heart papillary muscles was reported in female Sprague-Dawley rats treated with glycyrrhizin (crude extract) at 30 mg/kg bw per day or with 18α- or 18β-glycyrrhetic acid at 15 mg/kg bw per day for 30 days (note: glycyrrhizinic acid is not metabolized to 18α-glycyrrhetic acid)."

e. Mutagenicity

From WHO Monograph: "Several glycyrrhizinic acid salts and liquorice extracts and/or various components of liquorice containing glycyrrhizinic acid have been investigated in a number of tests for mutagenicity and/or genotoxicity. Overall, although some positive findings were reported, the available data indicated that glycyrrhizinic acid and its related salts are not genotoxic in vitro or in vivo."

f. Developmental and reproductive toxicity

From WHO Monograph: "Ammonium and disodium salts of glycyrrhizinic acid at doses of ≤1.5 g/kg bw per day have been evaluated in several studies of developmental toxicity in mice, rats, hamsters and rabbits. In one of these studies, embryotoxicity was observed, but overall the data indicated that glycyrrhizinic acid and its salts are not teratogenic."

g. Carcinogenicity

From WHO Monograph: "In a study of carcinogenicity, B6C3F1 mice were treated for 96 weeks with the disodium salt of glycyrrhizinic acid at a dose of ≤229 mg/kg bw per day in males and 407 mg/kg bw per day and observed for an additional 14 weeks. There was a dose-related reduction in the amount of water consumed by the treated animals when compared with the control animals (statistical significance not stated); however, no dose-related increase was reported in the incidence of tumours or in the specific distribution of benign and malignant neoplasms in treated mice compared with controls."

h. Toxicokinetics

From WHO Monograph: "The absorption, distribution, biotransformation and excretion of glycyrrhizinic acid and/or its monoammonium salt have been investigated in rats and humans. In both species, glycyrrhizinic acid, whether in the free form or as the monoammonium salt, is poorly absorbed from the gastrointestinal tract. In the gastrointestinal tract, glycyrrhizinic acid is hydrolysed, mainly by the activity of

intestinal microflora, to 18β-glycyrrhetic acid (the aglycone of glycyrrhizinic acid), a substance that is readily absorbed. 18β-Glycyrrhetic acid is subject to enterohepatic circulation and can be further metabolized by intestinal bacteria to 3-dehydro-18β-glycyrrhetic acid and 3-epi-18β-glycyrrhetic acid."

> "Doses in excess of 25 mg/kg bw may saturate the capacity of intestinal microflora to hydrolyse glycyrrhizinic acid to glycyrrhetic acid. In humans, absorption of glycyrrhetic acid from the gut is virtually complete, regardless of whether it is formed from the hydrolysis of glycyrrhizinic acid or is initially present as either the glycoside or the aglycone in a food matrix (e.g. liquorice)."

> "The results of studies in rats, and inferences that can be drawn from the results of studies in humans indicate that both glycyrrhizinic acid and its hydrolysis product glycyrrhetic acid are largely confined to the plasma. In plasma, glycyrrhizinic acid and glycyrrhetic acid are bound to serum albumin and are not taken up in body tissues to a significant extent."

Additional: Takeda et. al. (Takeda et al., 1996) report similar systemic exposure (e.g., $AUC_{0-\infty}$ and C_{max}) for glycyrrhetic acid following administration of 10 mg/kg glycyrrhizin via oral and intravenous (i.v.) routes.

Conclusions: Glycyrrhizin is not an antiviral compound. Low selectivity indices for most viruses in cell culture indicate that apparent effects on viral replication are due to cytotoxic or cytostatic activity of the compound. Glycyrrhizin may exert some effect on viral replication and pathogenesis through indirect anti-inflammatory activity.

Non-clinical data appear to support the safety of low level exposures to glycyrrhizinic acid and related compounds through oral routes (e.g., diet). The following conclusion is quoted from the WHO monograph:

> The Committee concluded that the safety evaluation of glycyrrhizinic acid should be based on the data from humans. It was observed that there is a sensitive subset of the population who appear to show signs of pseudohyperaldosteronism at lower exposures than those which produce effects in the general population, but the available data did not allow the Committee to adequately characterize this subgroup, and hence the data could not be used to assign an ADI. The available data suggest that an intake of 100 mg/day would be unlikely to cause adverse effects in the majority of adults. The Committee recognized that, in certain highly susceptible individuals, physiological effects could occur at intakes somewhat below this figure.

The European Commission Scientific Committee on Food (SCF) characterized susceptible subgroups as "people with decreased 11-β-hydroxysteroid dehydrogenase-2 activity, people with prolonged gastrointestinal transit time, and people with hypertension or electrolyte-related or water homeostasis-related medical conditions" (Scientific Committee on Food, 2003).

Although a substantial database exists for oral exposure, there is little non-clinical data for i.v. glycyrrhizinic acid administration. This is significant given the relatively high i.v. doses of glycyrrhizinic acid doses previously used in a phase 1-2 clinical trial supporting treatment of HCV (i.e., 80, 160, and 240 mg) (van Rossum et al., 1999). A primary concern is the potential for off-target effects related to inhibition of 11β-OHSD2. Convulsions occurring following i.v. dosing in mice may also be relevant.

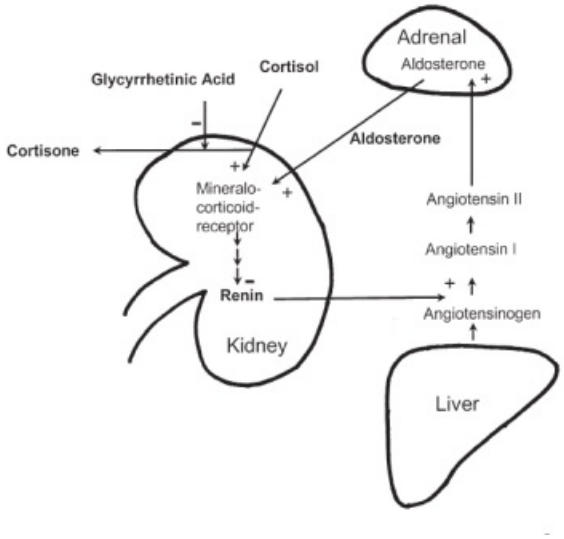
2. Human Safety

a. Reported adverse reactions

The nomination stated that "over a decade of clinical use has revealed no AEs when used under standard dose and administration guidelines." However, the source cited for that statement (Anderson et al., 2014) could not be located. As described in this section, AEs associated with intravenous glycyrrhizin administration have been reported in numerous publications.

An extensive literature search was performed using PubMed, MEDLINE and Embase databases. Published articles describe adverse reactions following administration of licorice extract, glycyrrhizinate compounds, and intravenous glycyrrhizin, with pseudo-hyperaldosteronism effects (or hypermineralocorticoid syndrome) most commonly characterized. These aldosterone-like effects are related to glycyrrhizin's inhibition of conversion of cortisol to cortisone in the kidney. As described in Section II.B.2.c, the metabolite glycyrrhetinic acid inhibits 11-ß-hydroxysteroid dehydrogenase, leading to increased cortisol levels in the kidney, which stimulate the mineralocorticoid receptor with effects such as sodium retention, edema, hypokalemia, and hypertension (Figure 1).

Figure 1: Glycyrrhetinic acid inhibits enzymatic conversion of cortisol to cortisone in the kidney. This results in an increased level of cortisol, which stimulates the mineralocorticoid reception, eventually leading to inhibition of renin formulation and, via the angiotensin system, inhibition of aldosterone formation.



Source: van Rossum TG et al. 'Pseudo-aldosteronism' induced by intravenous glycyrrhizin treatment of chronic hepatitis C patients. Journal of Gastroenterology and Hepatology (2001) 16, 789–795.

In the United States, the estimated consumption of glycyrrhizin (when consumed in licorice) ranges from 1.6 to 215 mg/day (0.027–3.6 mg/kg), with a likely average intake of less than 2 mg/day (Ishbrucker et al., 2006). Acceptable oral glycyrrhizin intake avoiding these pseudo-hyperaldosteronism effects has been stated in various publications as ranging between 0.015-0.229 mg/kg/day or 200 mg/day (1400 mg/week). However, one article states there is great individual variation in susceptibility to glycyrrhizic acid's effects and that it is not possible to precisely determine the minimum level leading to adverse symptoms (Ishbrucker et al., 2006; van Rossum et al., 2001; Stormer et al., 1993). For reference, the glycyrrhizin strength provided in this 503A nomination is 8 mg/mL, up to 30 mL (i.e., 240 mg).

A Medline search for "licorice" reveals over 100 case reports describing events related to pseudo-hyperaldosteronism including hypokalemia, hypertension, edema, myopathies with some further serious cases of rhabdomyolysis, torsades de pointes, paralysis, posterior reversible encephalopathy syndrome, cardiac arrest, including fatal events (Gross et al., 1966; Bannister et al., 1977; Heidemann et al., 1983; Nielsen et al., 1984; Pant P et al., 2010; van Beers et al., 2011; Robles et al., 2013; Panduranga et al., 2013; Bedock et al., 1985). The glycyrrhizin dose in such case reports is typically not available. Instead, there may be a rough estimate of licorice consumption before the event. Heavy licorice consumption has also been associated with an increased risk of preterm birth in cross-sectional and retrospective studies with a postulated mechanism related to pseudo-hyperaldosteronism effects in the mother (Ishbrucker et al., 2006).

Pseudo-hyperaldosteronism effects are similarly reported in patients with chronic HCV infection receiving intravenous glycyrrhizin as part of clinical treatment (Figure 2), including hypokalaemia, hypertension, peripheral edema, paralysis, syncope, paresthesia, increased creatine phosphokinase. Some reports occur with intravenous doses as low as 80 mg/day. One dedicated study by van Rossum et al., on the safety of intravenous glycyrrhizin is described in further detail in Section II.B.2.b. In the European study by Manns et al., 4.2% in the double-blind phase and 6.6% in open-label phase discontinued the study due to treatment-related AEs in patients receiving intravenous glycyrrhizin 200 mg 3-5 times/week (Manns et al., 2012). Hypertension and hypokalaemia were more frequent in patients receiving glycyrrhizin 200 mg 5 times/week than in patients receiving glycyrrhizin 200 mg 3 times/week (Figure 2). Systolic blood pressure (SBP, mean ± SD) changed in the three treatment groups (i.e., 5 times/week GL, 3 times/week GL and 5 times/week placebo) during the double-blind phase by 3.5 ± 16.2 mmHg, 2.8 ± 14.7 mmHg and 0.5 ± 11.1 mmHg, respectively.

Figure 2: Most frequent glycyrrhizin-related adverse events in patients with chronic HCV infection during 12-week double-blind treatment

	5×/week GL *N* = 123	3×/week GL *N* = 127	Placebo *N* = 129
Number of subjects	123	127	129
Number of subjects with AEs	57	48	35
Number of AEs	138	101	82
Relationship possible (*N*, %)			
Hypertension aggravated	12 (8.7%)	1 (1.0%)	4 (4.9%)
Hypertension NOS*	7 (5.1%)	4 (4.0%)	–
Headache	5 (3.6%)	6 (5.9%)	1 (1.2%)
Abdominal pain, upper	1 (0.7%)	2 (2.0%)	6 (7.3%)
Paraesthesia	2 (1.4%)	4 (4.0%)	–
Blood pressure increased	1 (0.7%)	3 (3.0%)	2 (2.4%)
Relationship probable (*N*, %)			
Hypertension NOS	6 (4.3%)	5 (5.0%)	–
Paraesthesia	5 (3.6%)	5 (5.0%)	–
Hypokalaemia	5 (3.6%)	3 (3.0%)	–

SAF: safety analysis set, GL: glycyrrhizin
*NOS: Not otherwise specified.

Source: Manns MP, Wedemeyer H, Singer A, Khomutjanskaja N, Dienes HP, Roskams T, Goldin R, Hehnke U, and Inoue H; European SNMC Study Group. Glycyrrhizin in patients who failed previous interferon alpha-based therapies: biochemical and histological effects after 52 weeks. J Viral Hepat. *2012 Aug;19(8):537-46.*

As noted by the U.S. Centers for Disease Control and Prevention (CDC), approximately three million people are infected with hepatitis C (Smith et al., 2012). The prevalence of HCV antibody among persons born between 1945-1965 is 3.3%, a five times higher prevalence than in other persons. This aging population may have additional medical comorbidities requiring medication treatment and, thus, are at risk for potential drug-drug interactions with HCV therapies. One article regarding glycyrrhizin treatment cautions that patients on concomitant thiazide diuretics, which enhance potassium loss, are at risk

of developing severe hypokalemia (van Rossum et al., 2001). Another article notes that glycyrrhizin-related potassium loss may increase the risk for cardiac toxicity in patients taking digitalis (Levy et al., 2004). Furthermore, it has been suggested that patients with predisposing sodium-retaining conditions such as ascites and hypertension, which occur with chronic HCV, may be more susceptible to glycyrrhizin's pseudo-hyperaldosterone effect (Levy et al., 2004). Monitoring of potassium levels and ECGs in patients on glycyrrhizin therapy has been recommended (Kurisu et al., 2008).

Additional isolated case reports of vesicular drug eruption and drug-induced ductopenia in patients receiving intravenous glycyrrhizin therapy were identified in the literature, the latter case resulting in fatal biliary cirrhosis 26 months after onset (Kurokawa et al., 2005; Ishii et al., 1993).

The Signals Management Branch performed a search for adverse events occurring in patients receiving products or ingredients with glycyrrhizin (or derivative). The data source used in their assessment was the FDA Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS). CAERS is a post-market surveillance system that collects reports about adverse events and product complaints allegedly related to CFSAN-regulated products. This CAERS search identified 370 case reports in patients receiving over approximately 100 different reported brand or product names containing glycyrrhizin (or derivative). The majority of reported brand or product names list multiple ingredients in addition to glycyrrhizin which prevents meaningful causality assessment as related to glycyrrhizin use, as illustrated in selected examples:

Isagenix Cleanse For Life

fructose, i-methionine, potassium citrate, purple carrot (daucus carota), citric acid, lime juice powder, sugars, niacin, vitamin b6, vitamin b12, isagenix ionic alfalfa, aloe vera leaf gel (inner-heart filet) powder, bilberry extract, blueberry extract, ashwagandha extract, raspberry juice extract, paud'arco inner bark extract, burdock root extract, fennel seed extract, rhodiola root extract, yellow dock root extract, deglycyrrhizinated licorice (dgl) root extract, suma root extract, eleutherococcus senticosus root extract, peppermint leaf extract, turmeric root extract, choline bitartrate, inositol, betaine hci, natural flavor

Super Milk Thistle

ultracleanse milk thistle (silybum marianum) fruit one part milk thistle extract, standardized to contain 80% silymarin, bound to two parts phosphatidylcholine (soy) using a proprietary process for improved absorption, artichoke (cynara scolymus) leaf, silicon dioxide, licorice (glycyrrhiza glabra), cellulose, vegetable capsule (modified cellulose), magnesium stearate, dandelion (taraxacum officinale) root

Serious adverse events are listed in these CAERS cases; however, the multiple numbers of ingredients in the administered products confounds causality assessment with glycyrrhizin use. For example, hepatic failure was reported in a 34 year old woman approximately two months after use of Green Tea Fat Burner, which included licorice

(glycyrrhiza glabra) in addition to green tea extract (egg) (leaf), soy, mate (yerba mate) powder (leaf), bladderwrack powder, trimethylglycine (tmg), cayenne extract (hu) (fruit), eleuthero (eleutherosides) (root), ginger extract (gingerols) (root), gotu kola powder (aerial), soy bean oil, gelatin, glycerin, purified water, beeswax, soy lecithin, titanium dioxide, sodium copper chlorophyllin and caffeine. The narrative states the consumer was on no other concomitant medications except ibuprofen and that the pathologist 'believes with no question that it was the GTFB that caused her liver to become in a toxic condition'. Cases identified from the CAERS search in patients with hepatitis C infection include:

> Case 153719: Upper Abdominal Pain: Puritan's Pride Licorice Root 420 mg Rapid Release Capsules (licorice (glycyrrhiza glabra)(root), silica, vegetable magnesium stearate, gelatin)
>
> 36 year old man with a history of hepatitis C who took Puritan's Pride Licorice Root along with multiple additional Puritan's Pride products and tea products for approximately four months to 'improve his hepatitis C' when had liver enzymes two times higher than his baseline which was "slightly elevated" and complaints of "liver pain", upper abdominal pain. All dietary supplements were discontinued; however, dechallenge information was not reported.
>
> Case 163345: Abdominal Pain Upper, Diarrhea, Vomiting, Blood Pressure Increased, Hemorrhoids: Complete Body Cleansing Program 7 Days Gastro Formula - AM Packet (fennel seed powder (foeniculum vulgare), artichoke leaf extract (cynara scolymus) (phenols), ginger root extract (zingiber officinale) (gingerols), licorice root extract (glycyrrhiza glabra), peppermint leaf (mentha piperita), riboflavin, dicalcium phosphate, cellulose, titanium dioxide (natural mineral whitener), vegetable acetoglycerides, calcium carbonate), Complete Body Cleansing Program 7 Days Total Cleanser - AM Packet (garlic bulb powder (allium sativum), clove bud powder (eugenia caryophyllata), pomegranate fruit extract (punica granatum), fructooligosaccharides (fos), curcumin, ginger root extract (zingiber officinale) (gingerols), riboflavin, licorice root powder (glycyrrhiza glabra), dicalcium phosphate, cellulose, titanium dioxide (natural mineral whitener), vegetable acetoglycerides, chamomile flower (matricaria recutita))
>
> 59 year old man with a history of hepatitis C, hypertension, hypercholesterolemia, internal bleeding, esophageal precancerous conditions on concomitant verapamil, lisinopril, metoprolol, lansoprazole began the Complete Body Cleansing program and that day developed vomiting, stomach pain, diarrhea, and 'thought he was going to die'. Blood pressure elevated at 199/119. The consumer went to the emergency department where he was told 'that some people are very sensitive to the effects of this type of product and that he should not take it anymore'. The consumer stopped the Complete Body Cleansing program and later developed hemorrhoids at an unknown

time. Causality assessment is limited by lack of clinical diagnostic assessment, dechallenge information.

In summary, the identified CAERS adverse events occurring in patients receiving products or ingredients with glycyrrhizin (or derivative) are confounded in their role to provide information regarding safety or adverse reactions because one cannot determine the contribution of the multiple additional product ingredients.

b. Clinical trials assessing safety

A study by van Rossum et al., described safety outcomes in 44 patients with chronic HCV infection or compensated cirrhosis receiving intravenous glycyrrhizin for 4 weeks at 200 mg 6 times/week (1200 mg), at 240 mg 3 times/week (720 mg) or placebo 3 times/week (van Rossum et al., 2001). Bodyweight, blood pressure, and plasma concentrations of sodium, potassium, cortisol, DHEA-S (dehydroepiandrosterone sulfate), renin, and aldosterone were measured before and at 0 and 4 weeks after treatment. Approximately 45% patients had compensated cirrhosis. Patients were not allowed to eat licorice during the study. Mean baseline SBP and diastolic blood pressure (DBP) were similar across the three groups, ranging 126-132 mmHg for SBP and 79-82 mmHg for DBP.

The study demonstrated no significant changes in the placebo group. Within the 1200 mg group, reversible symptoms of pseudo-hyperaldosteronism were observed. SBP in the 1200 mg group was significantly higher at the end of treatment (Figure 3), while aldosterone was significantly lower. At the end of the follow-up period, these values had returned to baseline.

Figure 3: Blood pressure changes on intravenous glycyrrhizin treatment versus placebo in patients with chronic HCV infection

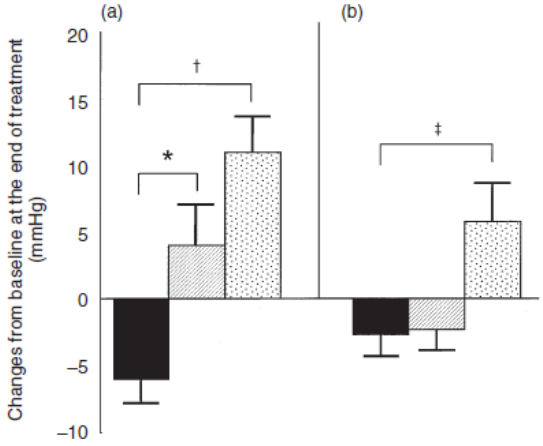


Figure 3 Changes (mean ± SEM) from baseline at the end of treatment in (a) systolic and (b) diastolic blood pressure after 4 weeks therapy with (■) 0, (▨) 720 or (⊡) 1200 mg glycyrrhizin weekly. Significantly different from 0 mg: $^{*}P = 0.03$, $^{\dagger}P = 0.01$, $^{\ddagger}P = 0.04$.

Source: van Rossum TG, de Jong FH, Hop WC, Boomsma F, and Schalm SW.'Pseudo-aldosteronism' induced by intravenous glycyrrhizin treatment of chronic hepatitis C patients. J Gastroenterol Hepatol. 2001 Jul;16(7):789-95.

Decrease in aldosterone and potassium concentrations at the end of treatment increased with increasing dosage, although not significantly. Changes in bodyweight, sodium, cortisol, DHEA-S, and renin did not differ significantly between the three groups.

The authors conclude from their study that patients with chronic hepatitis or compensated cirrhosis should not be treated with a dose exceeding 1200 mg glycyrrhizin weekly due to the risk of developing symptoms of pseudo-hyperaldosteronism and note that at the 1200 mg/week dose “some minor symptoms of pseudo-hyperaldosteronism occur.” They describe that patients with cirrhosis and ascites have increased plasma renin and aldosterone caused by a hyperkinetic circulation in decompensated patients with portal hypertension and that these patients may be at risk for further aldosteronism by glycyrrhizin treatment.

c. Pharmacokinetic data

Glycyrrhizin is a conjugate of glycyrrhetinic acid and glucuronic acid. After intravenous administration, glycyrrhizin is metabolized in the liver to 3-mono-glucuronide-glycyrrhetinic acid, which is then excreted with bile into the intestine and further metabolized into glycyrrhetinic acid (GA) by intestinal bacteria. This GA metabolite can be reabsorbed. GA inhibits 11-ß-hydroxysteroid dehydrogenase, which leads to increased cortisol levels in the kidney (van Rossum et al., 1999). This section focuses on the pharmacokinetics of intravenous glycyrrhizin.

A study by van Rossum et. al. evaluated 80, 160, and 240 mg glycyrrhizin 3 times/week or 200 mg glycyrrhizin 6 times/week for 4 weeks in 35 European patients with chronic HCV infection (van Rossum et al., 1999). Glycyrrhizin was given as intravenous stronger neo-minophagen C (SNMC), consisting of 2 mg glycyrrhizin, 1 mg cysteine, and 20 mg glycine per mL in physiologic saline solution. Overall, 16 patients were cirrhotic and 19 patients were non-cirrhotic. Mean baseline ALT ranged 2.1-3.9 times the upper limit of normal across the groups.

The pharmacokinetic results are displayed in Table 1. Glycyrrhizin's pharmacokinetics were linear up to 200 mg. Terminal elimination half-lives on Day 1 ranged 7.7-10.1 hours. No significant differences between Day 1 and Day 14 were found in any dose group, with the exception of AUC in the 200 mg group, which was significantly higher on Day 14 (574 ± 389 µg/h/mL) compared with Day 1 (468 ± 210 µg/h/mL; P = 0.03). Due to glycyrrhizin's half-life of approximately 9 hours, a dosing interval of 24 hours may lead to accumulation as demonstrated by the higher Day 14 versus Day 1 AUC in the 200 mg 6 times/week dosing group. No significant pharmacokinetic differences were observed between cirrhotic and noncirrhotic patients. Baseline ALT levels did not correlate with half-life or clearance.

Table 2: Pharmacokinetic data with intravenous glycyrrhizin treatment in patients with chronic HCV infection

Table 1. Pharmacokinetic results, by dosage group, on days 1 and 14.

	80 mg 3 times/wk		160 mg 3 times/wk		240 mg 3 times/wk		200 mg 6 times/wk	
	Day 1 (n = 8)	Day 14 (n = 7)	Day 1 (n = 7)	Day 14 (n = 7)	Day 1 (n = 7)	Day 14 (n = 7)	Day 1 (n = 11)	Day 14 (n = 12)
C_{max} (mg/L)	42 ± 16	31 ± 4	70 ± 14	72 ± 11	102 ± 7	106 ± 16	112 ± 39	116 ± 40
V_{ss} (mL/kg)	67 ± 11	66 ± 10	62 ± 13	57 ± 15	66 ± 8	63 ± 10	54 ± 7	53 ± 14
AUC (µg/h/mL)	138 ± 76	112 ± 37	415 ± 156	466 ± 232	319 ± 66	345 ± 99	468 ± 210	574 ± 389
Cl_{tot} (mL/h/kg)	9.9 ± 3.3	10.8 ± 2.9	5.9 ± 2.5	5.7 ± 2.7	10.3 ± 3.1	9.8 ± 3.2	6.0 ± 2.6	5.5 ± 2.6
$t_{1/2}$ (h)	7.7 ± 2.8	6.2 ± 2.7	10.1 ± 1.4	10.2 ± 1.6	8.6 ± 2.1	6.6 ± 2.0	9.0 ± 2.3	9.1 ± 2.2

Values are expressed as mean ± SD.
C_{max} = maximum concentration; V_{ss} = volume of distribution at steady state; AUC = area under the curve; Cl_{tot} = total clearance; $t_{1/2}$ = half-life.

Source: van Rossum TG, Vulto AG, Hop WC, Schalm SW. Pharmacokinetics of intravenous glycyrrhizin after single and multiple doses in patients with chronic hepatitis C infection. Clin Ther. 1999 Dec;21(12):2080-90.

These European data were compared with previously reported data from two small Japanese studies that evaluated the pharmacokinetics of glycyrrhizin in Japanese patients with hepatitis. Tanaka et. al. (Tanaka et. al., 1993) investigated the pharmacokinetic profile of multiple doses of intravenous glycyrrhizin 120 mg in 8 patients with chronic hepatitis of unreported cause. Yamamura et. al. (Yamamura et al., 1995) investigated the same regimen in 4 patients with acute hepatitis and 6 patients with cirrhosis (5 of 6 cases were caused by chronic HCV infection). Comparing the European data and the combined Japanese data, the mean (± SD) AUC was 289 ± 244 µ/h/mL versus 402 ± 372 µ/h/mL, the half-life was 8.2 ± 2.6 versus 8.8 +/- 9.0 hours; and the total clearance was 7.6 ± 3.6 versus 8.5 ± 5.7 mL/h/kg in the European and Japanese studies, respectively. The European pharmacokinetic data seem very comparable to the Japanese findings, although

a correlation between hepatic function and pharmacokinetics was not observed, which may be explained by the European patients having milder liver disease.

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

There are various products that are FDA-approved for treatment of chronic HCV infection. Currently approved and recommended treatments for chronic HCV infection include all oral direct-acting antiviral (DAA) therapies, thereby removing risks of intravenous administration such as phlebitis, infiltration, extravasation, and infections (Dychter et al., 2012). In clinical trials of all oral chronic HCV therapies, discontinuations due to AEs have been low. As stated in the HCV Guidance[2] regarding all oral treatment options including the fixed-dose combination of paritaprevir/ritonavir/ombitasvir plus dasabuvir (Viekira Pak, July 20, 2015) with or without ribavirin, the fixed-dose combination ledipasvir/sofosbuvir (LDV/SOF, Harvoni, March 20, 2015), and sofosbuvir plus simeprevir (SOF+SIM), "(a)cross numerous phase 3 programs, less than 1% of patients without cirrhosis discontinued treatment early, and AEs were mild. Most AEs occurred in RBV-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low." (AASLD/IDSA/IAS-USA HCV Guidance).

Conclusions: Intravenous glycyrrhizin has risks associated with the route of administration (e.g., phlebitis, infection). The association between glycyrrhizin use and pseudo-hyperaldosteronism is well established. Many case reports occur in the setting of excessive licorice consumption. However, serious pseudo-hyperaldosteronism effects such as hypokalemia and hypertension have been reported in patients receiving intravenous glycyrrhizin in the context of hepatitis C treatment. Some authors caution that patients with chronic hepatitis C, particularly with cirrhosis, may be more susceptible to glycyrrhizin's pseudo-hyperaldosterone effect. There are numerous FDA-approved products available to treat chronic HCV infection that have been demonstrated to be safe.

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

Yes, there are concerns about whether intravenous glycyrrhizin is effective for antiviral use, specifically for hepatitis C, as several trials show no effect on HCV RNA. Similar lack of antiviral findings is demonstrated with hepatitis B and HIV.

1. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

<u>Hepatitis C</u>
Several identified clinical trials have evaluated intravenous glycyrrhizin for the treatment of chronic HCV infection. Most of the trials have been conducted in Japan. However,

[2] American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C, are available at http://www.hcvguidelines.org/. Accessed Sept. 4, 2015.

studies by van Rossum et. al., Orlent et. al., and Manns et. al., were conducted in European patients. The literature search did not locate any trials of intravenous glycyrrhizin for the treatment of chronic HCV infection performed in the U.S. population (van Rossum et al., 1999; Orlent et al., 2006; Manns et al., 2012).

The studies were conducted mainly during a time when either interferon (IFN) or pegylated IFN (PEG)/ribavirin (RBV) therapy was the recommended HCV treatment option, with sustained virologic response (SVR) rates in up to only 50% of patients with HCV genotype 1 infection. SVR is defined as a lack of detection of HCV RNA in the blood a certain time period measured in weeks after treatment is completed. The current primary endpoint used in HCV registrational trials is SVR12, which is achieving SVR 12 weeks after completing treatment. Achieving SVR correlates with improved clinical outcomes such as decreased hepatocellular carcinoma (HCC), hepatic events, fibrosis, all-cause mortality, and is, therefore, considered a virologic cure of chronic HCV.

In addition, the studies were conducted when there was no established standard of care treatment for PEG/RBV non-responders. Furthermore, the intolerance to and/or contraindications to IFN-based treatment precluded many patients from being eligible for treatment. Therefore, based on the identified articles, it appears there was hope that intravenous glycyrrhizin could be a therapeutic option for patients who did not respond to, or were intolerant to/ineligible for, IFN-based treatment. The form of intravenous glycyrrhizin administered in these trials was SNMC, containing: 2 mg/mL glycyrrhizin, 1 mg/mL cysteine, 20 mg/mL glycine diluted with saline. Each ampule contained 40 mg glycyrrhizin.

In all identified trials, no clinically meaningful antiviral effect, as measured by HCV RNA, was demonstrated using intravenous glycyrrhizin for the treatment of chronic HCV infection (Table 2). The small study by Abe et. al. (Abe et al., 1994) combined SNMC with IFN, which likely explains the percentage of subjects with on-treatment HCV RNA negativity. Some trials have shown a decrease in ALT levels, which was not sustained following treatment cessation, and the clinical significance of partial reduction in ALT levels was questioned as an appropriate surrogate of clinical outcome (Kang et al., 2006). Glycyrrhizin's effect on decreasing transaminases is not known (Marzio et al., 2014). One possible mechanism is due to its ability to stabilize the hepatocyte's cell membrane.

Table 3: Clinical Trials on Effect of Glycyrrhizin as Treatment of Chronic Hepatitis C Virus Infection

Author	Patients – n	Study Design	Treatment	Duration	Main Results	Safety
Abe et al 1994	28	OL, comparative	IFN-alpha 2b+SNMC vs IFN-alpha 2b	12 weeks, no FU	Combination therapy caused non-significant on-treatment ALT normalization (64%) and HCV RNA (-) (38.5%)	Not stated in abstract (article in Japanese) *NOTE: Effect may be due to IFN alone.*

					Histology unaffected	
Van Rossum et al 1999 (Europe)	57 prior IFN failure, IFN-ineligible, unlikely to respond to IFN (cirrhosis, GT1)	DB, placebo-controlled	3x/week SNMC (80, 160, 240 mg) vs placebo	4 weeks, 4 weeks FU	↓ALT 23-29% across SNMC groups vs 6% in placebo; however, not sustained post-treatment. Only 10% with on-treatment ALT normalization. **No effect on HCV RNA**	No reports of HTN, edema, hypokalemia. No D/C due to AE
Tsubota et al 1999	170	OL, comparative	3x/week SNMC (100 mL) vs 3x/week SNMC (100 mL)+UDCA	24 weeks, 8 weeks FU	↓AST and ALT in both groups; however, not sustained post-treatment. **No effect on HCV RNA** No effect on histologic grade or stage	None reported. No D/C due to AE
Van Rossum et al 2001 (Europe)	15	OL, pilot study	SNMC (200 mg) 6x/week Conclude 6x/week treatment more effective than 3x/week treatment.	4 weeks, 4 weeks FU	↓ALT 47%, 20% with on-treatment ALT normalization; not sustained post-treatment **No effect on HCV RNA**	
Iino et al 2001	100 In patients who did not respond with ↓ALT after 2 weeks of daily 80mg SNMC	OL, comparative	SNMC (80mg vs 200mg) daily	3 weeks, no FU	↓ALT 26% vs 52% in 80mg vs 200mg daily groups.	Not reported in abstract
Miyake et al 2002	112	OL, comparative	SNMC (80mg vs 200mg) 3x/week	12 weeks, no FU	↓ALT 29% vs 50% in 80 mg vs 200 mg groups; ALT normalization	4% hypokalemia, 3% HTN, <1% edema with apparent dose-

					in 19% and 32% in 80mg vs 200mg groups.	dependent effect
Orlent et al 2006 (Europe)	121 72/121 Patients determined ineligible for IFN treatment	OL **Patients with Week 4 ↓ALT ≥50% or ALT ≤1.5x ULN randomized to next group* OL, comparative	SNMC (200 mg) 6x/week SNMC 6x/week vs SNMC 3x/week vs SNMC 1x/week	4 weeks 22 weeks	ALT response ≤1.5x ULN) in 60% ALT response maintained in 60%, 24% and 9% of 6x, 3x, 1x/week groups ALT normalization in 30%, 12% and 0% of 6x, 3x, 1x/week groups. **No effect on HCV RNA** No significant effect on histological improvement	SAEs: hypokalemia + tachyarrhythmia (n=1) Other AEs: tachyarrhythmia (n=1), HTN (n=7) with D/C in 2 patients, ascites (n=1) with D/C
Manns et al 2012 (Europe)	379 Patients failed prior IFN-alpha based therapy 363	DB, placebo-controlled OL, comparative	SNMC (200 mg) 5x/week vs SNMC 3x/week vs placebo 5x/week SNMC 5x/week vs SNMC 3x/week	12 weeks 40 weeks, no FU	↓ALT by ≥50% after 12 weeks ~29% in both GL groups vs 7% placebo ~45% improvement and ~38% deterioration in necro-inflammation. Did not reach endpoint of ≥60% improvement **No effect on HCV RNA**	Most frequent related AEs: HTN, hypokalemia, headache, paresthesia, peripheral edema, upper abdominal pain, ↑CPK, nausea. Appears to be a dose/frequency-dependent effect 4.2% in DB phase and 6.6% in OL phase D/C due to treatment related AEs

UDCA-ursodeoxycholic acid

A retrospective study by Arase et al., published in 1997 described a possible beneficial impact of long-term glycyrrhizin on prevention of HCC in patients with chronic HCV

infection. In this study, patients who had received SNMC for up to ~15 years and who kept low ALT serum levels had lower incidence of HCC with ~2.5-fold reduction of the relative risk. The first group received glycyrrhizin up to 7 times per week for a median of approximately 10 years (range 2–16 years), and the control group remained untreated for a median follow-up period of approximately 9 years (1–16 years). The mechanisms leading to lower HCC incidence in the glycyrrhizin group are unclear and uneven randomization cannot be excluded (Stickel et al., 2007). The feasibility of such long-term administration has been questioned due to the need for almost daily dosing (Levy et al., 2004).

Several meta-analyses have concluded that there are scientifically insufficient data on glycyrrhizin therapy to evaluate its usefulness (Coon et al., 2004; Dhiman et al., 2005; Levy et al., 2004; Stickel et al., 2007). In 2004, Levy et al., reviewed published English language trials on hepatitis C using glycyrrhizin and concluded that, based on the available evidence, use for the routine treatment of any chronic liver disease is not recommended. Stickel et. al.'s 2007 paper states the "treatment of liver disease with glycyrrhizin, regardless of the aetiology, cannot be advocated due to the lack of obvious benefit."

Hepatitis B

The 2007 review by Stickel et. al. (Stickel et al., 2007) lists four trials of intravenous glycyrrhizin use in the treatment of chronic hepatitis B infection, and an excerpt from the article's Table 3 is provided below. The studies by Hayashi et. al. (Hayashi et al., 1991) and Tandon et. al. (Tandon et al., 2001) are small pilot studies that also included approved treatments for chronic hepatitis B (interferon, lamivudine) confounding the results. The two studies by Zhang et. al. (Zhang et al., 2000 and 2002), in China describe an effect on aminotransferases, though do not demonstrate an effect on HBV serologies. Therefore, these studies do not provide convincing evidence for use of intravenous glycyrrhizin in the treatment of chronic hepatitis B.

Table 4: Clinical trials on the efficacy of glycyrrhizin preparations in the treatment of hepatitis B infection

Table 3
Clinical trials on the efficacy of glycyrrhizin preparations in the treatment of viral hepatitis and in the prevention of HCC

Author	Patients (*n*)	Study design	Disease	Treatment	Duration (days)	Main results
Studies investigating the effect of glycyrrhizin in the treatment of chronic/subacute hepatitis B						
Hayashi et al. [37]	10	Pilot study	Chronic hepatitis B	Glycyrrhizin + human fibroblast interferon	4 weeks, 36 weeks FU	3/10 patients HBe negative 9/10 ALT levels decreased 1/10 DNA negative
Zhang et al. [46]	107	Open-label, prospective, multicentre	Chronic hepatitis B	SNMC (100 ml) daily for 2 weeks, every other day for 2 weeks, 2–3 tablets 3×/day for 12 weeks	Total treatment duration 16 weeks	Improved aminotransferase and bilirubin levels in 66% of patients
Tandon et al. [47]	7	Open-label pilot study	Subacute hepatitis B	Glycyrrhizin + UDCA for 1 week + LAM	Unclear	All 7 patients seroconverted to anti-HBe, 5/7 had loss of HBs
Zhang et al. [48]	194	Prospective, randomised,	Chronic hepatitis B	SNMC i.v. (100 ml and 40 ml) oral glycyrrhizin	4 weeks i.v. followed by 4 weeks orally	ALT levels normalised in 58% and 57%, respectively

ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; γ-GT, gamma-glutamyl transpeptidase; PT, prothrombin time; IFN, interferon; LAM, lamivudine; SNMC, Stronger Neominophagen C®; UDCA, ursodeoxycholic acid.

Source: Stickel F and Schuppan D. 2007. Herbal medicine in the treatment of liver diseases. Dig Liver Dis. 2007 Apr;39(4):293-304.

HIV

A review article on the antiviral effects of glycyrrhiza species by Fiore et. al. (Fiore et al., 2008) describes two studies of glycyrrhizin use in HIV patients where some patients were stated to have achieved increased CD4 cell counts. Notably, both referenced studies are from Japan and were conducted in the 1980s before the availability of highly active antiretroviral therapy and, thus, do not provide evidence for any beneficial use of intravenous glycyrrhizin in the treatment of HIV (Gotoh et al., 1987; Mori et al., 1989).

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

The intended indication, based on the nomination, is treatment of chronic HCV infection. Chronic HCV infection is a serious and potentially life-threatening illness for which inadequate treatment could pose significant adverse health consequences such as progression of liver disease to cirrhosis, hepatocellular carcinoma, liver failure or death.

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

Hepatitis C

As discussed above, there are alternative approved therapies that are more effective than intravenous glycyrrhizin for treatment of chronic HCV infection. The approved oral direct acting antivirals (DAA) s have demonstrated antiviral efficacy with SVR rates exceeding 90%.

As mentioned in Section II.C.1, achieving SVR is considered a virologic cure of chronic HCV, and patients achieving SVR experience decrease in liver inflammation as reflected by improved ALT, AST levels and reduction in rate of progression of liver fibrosis (AASLD/IDSA/IAS-USA HCV Guidelines). Furthermore, achieving SVR is associated with a greater than 70% reduction in the risk development of hepatocellular carcinoma and 90% reduction in the risk of liver-related mortality and liver transplantation (Morgan et al., 2013; van der Meer et al., 2012; Veldt et al., 2007).

Treatment of chronic HCV infection has advanced rapidly over the past several years and is currently guided by baseline host and viral factors such as HCV genotype, prior HCV treatment history and cirrhosis status. Interferon is no longer recommended as a preferred HCV treatment option due to the availability of approved, effective, all oral HCV DAA treatments. The most common HCV genotype in the United States is genotype 1, which accounts for approximately 70% of all infections in the United States (Manos et al., 2012). For treatment of HCV genotype 1 infection, three highly potent DAA oral combination regimens are recommended with SVR rates exceeding 90% in the registrational trials: LDV/SOF, paritaprevir/ritonavir/ombitasvir plus dasabuvir +/- RBV, SOF+SIM (AASLD/IDSA/IAS-USA HCV Guidelines). The next most common HCV genotypes are genotype 2 and 3, comprising approximately 16% and 12% of U.S. infections, respectively, and the recommended oral DAA combination SOF+RBV regimens for these genotypes also result in high SVR rates (Manos MM et al., 2012; AASLD/IDSA/IAS-USA HCV Guidelines).

Hepatitis B
Approved therapies that are effective for hepatitis B include entecavir, lamivudine, telbivudine, tenofovir, and interferon.

HIV
Numerous approved highly active antiretroviral therapies are effective for treatment of HIV.

Conclusions: Currently approved HCV treatment recommendations consist of highly effective, all oral HCV DAA combination therapies with SVR rates exceeding 90% in most populations. Achieving SVR is considered a virologic cure of chronic HCV, and patients achieving SVR experience improved transaminase levels and reduction in the risk development of HCC, liver-related mortality and liver transplantation. In contrast, intravenous glycyrrhizin has no demonstrable antiviral effect in clinical studies of patients with chronic HCV infection. The effect of glycyrrhizin on ALT is not sustained following treatment cessation, and the clinical significance of partial reduction in ALT levels has been questioned as an appropriate surrogate of clinical outcome. Likewise, data for intravenous glycyrrhizin in the treatment of chronic hepatitis B and HIV have not demonstrated efficacy.

D. Has the substance been used historically in compounding?

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

Use of *Glycyrrhiza* (licorice) dates back to ancient manuscripts from China, India, and Greece and has been in use for curative and flavoring purposes for more than 4,000 years. Licorice is one of the most commonly used herbal medicines in China for a variety of illnesses, ranging from the common cold to liver disease. Licorice has been used, often with several other botanicals, in a number of formulated combination products, also known as patented traditional Chinese medicines, for cough, and other symptoms. In addition to the numerous formulated multiple-herb products listed in the Chinese Pharmacopoeia, a number of papers also refer to various combinations that contain glycyrrhizin from licorice (e.g., He et al., 2012; He et al., 2014; Tan et al., 2011; Wu et al., 2013). Some of the combination products with licorice are reported to also contain other known pharmacologically active compounds. Examples include morphine, ephedrine, pseudoephedrine, methylephedrine, and amygdalin (He et al., 2012). In Chinese medicine, licorice is often used orally at 1.5-9 g/day, and is apparently well tolerated.

Literature suggests that glycyrrhizin has been used for more than three decades to treat chronic hepatitis in Japan (Davis et al., 1991; Fiore et al., 2008). Based on a review of published literature, we were unable to document the history of the use of intravenous glycyrrhizin in pharmacy compounding in the United States.

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

Chronic hepatitis C is the most commonly referenced medical condition associated with intravenous glycyrrhizin treatment, with the majority of literature from Japan. Chronic hepatitis B and HIV are also mentioned as medical conditions that have been treated with intravenous glycyrrhizin.

3. How widespread its use has been

The use of intravenous glycyrrhizin in the United States is unknown, and a reference provided with the 503A nomination template referencing "over a decade of clinical use" could not be located (Anderson et al., 2014). Most of its use for treatment of chronic HCV infection appears to be in Japan.

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

The Chinese Pharmacopoeia does not have a separate entry for glycyrrhizin and identifies glycyrrhizin only as a component of licorice. A licorice monograph in the Chinese Pharmacopoeia stated that the herb acts as a demulcent and an expectorant in helping get rid of phlegm. The Chinese Pharmacopoeia requires testing of glycyrrhizin in licorice raw herb and specifies that licorice should contain no less than 2% of glycyrrhizin. Various other compounds in licorice are not controlled by the Chinese Pharmacopoeia for Chinese medicine use.

A survey of other pharmacopeias (European, British, Indian, Japanese) did not find descriptions of any products that had a minimum assay value of more than 10% glycyrrhizin.

Conclusions: *Glycyrrhiza* (licorice) has been used for curative and flavoring purposes for more than 4,000 years. Based on a literature review, glycyrrhizin appears to have been used to treat chronic hepatitis in Japan for over 30 years. However, based on a review of published literature, the extent of use of intravenous glycyrrhizin in the United States is unknown.

III. RECOMMENDATION

Based on its physicochemical characteristics, safety, effectiveness, and evidence of historical use in compounding, glycyrrhizin is ***not recommended*** to be included on the list of bulk drug substances allowed for use in compounding under section 503A. A review of available resources indicates that most licorice extracts and other licorice-containing substances are complex mixtures that are not sufficiently well characterized to be suitable for use in compounding.

The proposed use for this nominated substance is listed as "treatment of patients who have chronic viral illnesses such as hepatitis C." Glycyrrhizin is not an antiviral

compound, and intravenous glycyrrhizin has no demonstrable antiviral effect in clinical studies of patients with chronic HCV infection, in contrast to the significant efficacy of available, approved all oral HCV DAA combination therapies. Likewise, data for intravenous glycyrrhizin in the treatment of chronic hepatitis B and HIV have not demonstrated efficacy. Regarding safety considerations, the association between glycyrrhizin use and serious pseudo-hyperaldosteronism-related adverse reactions is well established, and patients with chronic HCV infection may be more susceptible to glycyrrhizin's pseudo-hyperaldosterone effects. Although *Glycyrrhiza* (licorice) has been used for curative and flavoring purposes for more than 4,000 years and glycyrrhizin appears to have been used to treat chronic hepatitis in Japan for over 30 years, we were unable to find evidence of the use of glycyrrhizin in compounded drug products in the United States, either to treat chronic HCV infection or for other uses.

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Tab 10

Domperidone

Tab 10a

Domperidone Nominations

FAGRON

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

Dear Sir or Madam,

We hereby nominate the drugs listed below for inclusion on the list of bulk drug substances that may be used in compounding developed by FDA through regulation (section 503A(b)(1)(A)(i) of the FDCA).

No USP monograph exists for these drugs currently, nor are they components of an FDA-approved human drug product. The drugs do not appear on an FDA-published list of drugs that present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product (section 503A(b)(3)(A) 141 of the FD&C Act). In addition, they are not 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.

Camphor Oil White
Cantharidin
Chondroitin Sulfate
Citrulline
Copper Gluconate
Croton Oil
Docusate Sodium 85%
Ferric Subsulfate Pwd
Glycolic Acid
Hydroxytryptophan (L-5-)
Indole-3-Carbinol
Lutein 5% Powder
Melatonin
Methyl Sulfone (MSM)
Nettle Root Powder
Oxyphencyclimine HCl
Peruvian Balsam
Phenyl Salicylate
Phenylalanine (DL-)
Phosphatidyl Serine 20%
Pregnenolone
Pyruvic Acid
Silver Protein Mild
Squaric Acid
Thymol Iodide
Trichloroacetic Acid
Wheat Germ Oil
Threonine (L-)
Glutamine (L-)

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

Respectfully submitted,
Yours truly,

Marije van Dalen
General Manager and President
Fagron, Inc

Fagron

2400 Pilot Knob Road
St. Paul, Minnesota 55120 - USA
(800) 423 6967
www.fagron.us

What is the name of the nominated ingredient?	**Domperidone**
Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?	Yes, Domperidone is an active ingredient as defined in 207.3(a)(4) because when added to a pharmacologic dosage form it produces a pharmacological effect. References for Domperidone powder pharmacological actions are provided Augusto Larrain, Vishesh K. Kapur, Ted A. Gooley, Charles E. Pope, II. Pharmacological Treatment of Obstructive Sleep Apnea with a Combination of Pseudoephedrine and Domperidone. J Clin Sleep Med. 2010 April 15; 6(2): 117–123. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2854696/ J S Shindler, G T Finnerty, K Towlson, A L Dolan, C L Davies, J D Parkes. Domperidone and levodopa in Parkinson's disease. Br J Clin Pharmacol. 1984 December; 18(6): 959–962. http://www.ncbi.nlm.nih.gov/pmc/articlesAugusto Larrain, Vishesh K. Kapur, Ted A. Gooley, Charles E. Pope, II. Pharmacological Treatment of Obstructive Sleep Apnea with a Combination of Pseudoephedrine and Domperidone. J Clin Sleep Med. 2010 April 15; 6(2): 117–123. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2854696/ J S Shindler, G T Finnerty, K Towlson, A L Dolan, C L Davies, J D Parkes. Domperidone and levodopa in Parkinson's disease. Br J Clin Pharmacol. 1984 December; 18(6): 959–962. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1463696/ PMC1463696/ da Silva Silva O, Knoppert D, Angelini M, Forret P. Effect of domperidone on milk production in mothers of premature newborns: a randomized, double-blind, placebo-controlled trial. CMAJ 2001;164(1):17-21 . http://www.ncbi.nlm.nih.gov/pubmed/11202662

Is the ingredient listed in any of the three sections of the Orange Book?	The nominated substance was searched for in all three sections of the Orange Book located at http://www.accessdata.fda.gov/ scripts/cder/ob/docs/queryai.cfm. The nominated substance does not appear in any section searches of the Orange Book.
Were any monographs for the ingredient found in the USP or NF monographs?	The nominated substance was searched for at http://www.uspnf.com. The nominated substance is not the subject of a USP or NF monograph.
What is the chemical name of the substance?	6-chloro-3-[1-[3-(2-oxo-3H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1H-benzimidazol-2-one
What is the common name of the substance?	Domperidon; Domperidona; Domperidonas ;Dompéridone; Domperidoni; Domperidonum
Does the substance have a UNII Code?	5587267Z69
What is the chemical grade of the substance?	BP/EP grade
What is the strength, quality, stability, and purity of the ingredient?	Appearance: White or almost white powder Identification IR, TLC, and HPLC: As per standard Solubility Practically insoluble in water. Soluble in Dimethyl Formamide. Slightly soluble in Ethanol (96%) and Methanol. Appearance of Solution: Clear and not more intensely colored than reference solution Y6 Melting Point: 244.0°C - 248.0°C Related Substances: Impurity A: ≤ 0.25% - Impurity B: ≤ 0.25% - Impurity C: ≤ 0.25% - Impurity D: ≤ 0.25% - Impurity E: ≤ 0.25% - Impurity F: ≤ 0.25% Total Impurities: ≤ 0.5% Heavy Metals: ≤ 20 ppm Loss on Drying: ≤ 0.5% Sulphated Ash: ≤ 0.1% Assay: 99.0% - 101.0%
How is the ingredient supplied?	Powder

Is the substance recognized in foreign pharmacopeias or registered in other countries?	Pharmacopoeia European monograph 1009; BP Argentina: Ecuamon; Euciton; Moperidona; Motilium; Peridon; Australia: Motilium Belgium: Motilum;Zilium; Docdomperi; Domperitop Brazil: Motilium; Domperol; Peridal Chile: Docivin; Dompesin; Donegal; Dosin; Gasdol; Idon; Restol; Siligaz Czech Republic: Motilium; Oroperidys Denmark: Motilium France: Biperidys; Motilium; Oroperidys; Peridys Germany: Motilium;Domitilium Japan:Nauzelin United the Kingdon: Motilum; Vivadone It is also licensed in Greece; Hong Kong; Hungary; India; Indonesia; Italy; Israel; Malaysia; Mexico; Netherlands; New Zealand; Philippines; Portugal; Russian Federation; South Africa;Singapore; Thailand; Turkey;Ukraine; Venezuela.
Has information been submitted about the substance to the USP for consideration of monograph development?	No USP Monograph submission found.
What dosage form(s) will be compounded using the bulk drug substance?	Capsules
What strength(s) will be compounded from the nominated substance?	10-30mg
What are the anticipated route(s) of administration of the compounded drug product(s)?	Oral

Are there safety and efficacy data on compounded drugs using the nominated substance?	Augusto Larrain, Vishesh K. Kapur, Ted A. Gooley, Charles E. Pope, II. Pharmacological Treatment of Obstructive Sleep Apnea with a Combination of Pseudoephedrine and Domperidone. J Clin Sleep Med. 2010 April 15; 6(2): 117–123. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2854696/ J S Shindler, G T Finnerty, K Towlson, A L Dolan, C L Davies, J D Parkes. Domperidone and levodopa in Parkinson's disease. Br J Clin Pharmacol. 1984 December; 18(6): 959–962. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1463696/ Saurav Shome, Tapasi Rana, Subhalakshmi Ganguly, Biswarup Basu, Sandipan Chaki Choudhury, Chandrani Sarkar, Debanjan Chakroborty, Partha Sarathi Dasgupta, Sujit Basu. Dopamine Regulates Angiogenesis in Normal Dermal Wound Tissues. PLoS One. 2011; 6(9): e25215. Published online 2011 September 20. doi: 10.1371/journal.pone.0025215 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3176820/ Osamu Kano, Yoshihisa Urita, Hirono Ito, Takanori Takazawa, Yuji Kawase, Kiyoko Murata, Takehisa Hirayama, Ken Miura, Yuichi Ishikawa, Tetsuhito Kiyozuka, Jo Aoyagi, Yasuo Iwasaki. Domperidone effective in preventing rivastigmine-related gastrointestinal disturbances in patients with Alzheimer’s disease. Neuropsychiatr Dis Treat. 2013; 9: 1411–1415. Published online 2013 September 18. doi: 10.2147/NDT.S50135 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3788693/ Comparison of antiemetic efficacy of domperidone, metoclopramide, and dexamethasone in patients receiving outpatient chemotherapy regimens. D Cunningham, C Evans, J C Gazet, H Ford, A Pople, J Dearling, D Chappell, C Coombes. Br Med J (Clin Res Ed) 1987 July 25; 295(6592): 250. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1247086/
Has the bulk drug substance been used previously to compound drug product(s)?	Capsules and Suspensions

What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Antiemetic; dyspepsia; Gastro- oesophageal reflux disease; migraine; Parkinson's Disease; Breast feeding
What is the reason for use of a compounded drug product rather than an FDA-approved product?	No FDA approved preparation for Domperidone. Domperidone inceases prolactin levels in humans. Prolactin is best known for its ability to increase milk production. It has many effects in the body on functions as eating, mating, estrogen production, and ovulation . There are no current FDA approved medications to increase prolactin levels. Studies of Domperidone against metoclopramide have shown equal effectiveness in improving gastric emptying. Metoclopramide is FDA approved for gastric emptying but with its increased use runs risk of Tardive Dyskensia. (D. Shaffer, M. Butterfield, C. Palmer, and A.C. Mackey(2004) Tardive Dyskensia Risks and Metoclopramide Use Before and After U.S. Market withdrawl of Cisapride J.Am.Pharm.Assoc. Nov-Dec;44(6):661-5) There are several medications for Parkinson' disease Levodopa and Bromcriptine are two standards of treatment. Bromocriptine can be helped by the addition of Domperidone due to its ability to help with G.I. side effects of bromocriptine. It can help with increased bioavailabity of Levodopa administration and still have added benefits on GI side effects. (N. Nishikawa, M. Nagai,T. Tsujii,H.Iwaki,H. Yabe, and M. Nomoto(2012) Coadministration of Domperidone Increases Plasma Levodopa Concentration in Patients with Parkinson's Disease Clin Neuropharmacol Jul-Aug:35(4) :182-4). Altough Domperidone has seen continued use for increase milk production all over the world, it has many other benefits that make it a needed choice for 503A.
Is there any other relevant information?	All relevant information was expressed in the above questions

Submitted electronically via www.regulations.gov

September 30, 2014

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

Re: Docket No.: FDA-2013-N-1525: ***Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations***

Dear Sir or Madam:

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

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

100 Daingerfield Road
Alexandria, VA 22314-2888
(703) 683-8200 PHONE
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Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

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

Sincerely,

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Nomination from National Community Pharmacists Association

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format(s)	Recognition in Pharmacopeias	Final Compounded Formulation Dosage Form(s)	Final Compounded Formulation Strength	Final Compounded Formulation Route(s) of Administration	Bibliographies on Safety and Efficacy Data	Final Compounded Formulation Clinical Rationale and History of Past Use
Domperidone	5-chloro-1-(1-(3-(2-oxo-1-benzimidazolinyl)propyl)-4-piperidyl)-2-benzimidazolinone	Domperidone (Motilium)	5587267Z69	From PCCA Certificate of Analysis: 99.3% assay with 0.37% total impurities; From PCCA MSDS: >95% by weight and stable.	Powder	BP, USP monograph in progress	Capsule	10mg	Oral	Motilium in other countries; Committee on drugs. The transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108(3):776-89. [http://bit.ly/1fX9Gnp] – reports no "Reported Sign or Symptom in Infant or Effect on Lactation" (p.780); Patterson D, et al. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am J Gastroenterol. 1999 May;94(5):1230-4. [http://www.ncbi.nlm.nih.gov/pubmed/10235199]	Gastroparesis, nausea, vomitting, lactation

September 30, 2014

Submitted electronically via www.regulations.gov

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

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

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

Dear Sir or Madam:

PCCA respectfully submits the following list of nineteen chemicals to be considered for the List of Bulk Drug Substances that may be used in Pharmacy Compounding in accordance with Section 503A.

PCCA provides its more than 3,600 independent community compounding pharmacy members across the United States with drug compounding ingredients, equipment, extensive education, and consulting expertise and assistance.

Regarding the specific nominations, we would like to reference the attached spreadsheet and point out a couple of facts regarding our research. To the best of our knowledge, all items submitted:

- Do not appear in any of the three sections of the Orange Book.
- Do not currently have a USP or NF monograph.
- Meet the criteria of a "bulk drug substance" as defined in § 207.3(a)(4).

In regards to the request for chemical grade information, we would like to point out that many of the items submitted do not currently have a chemical grade. PCCA believes that pharmacists should use the highest grade chemical available on the market for all aspects of pharmaceutical compounding and we continue to actively source graded chemicals from FDA-registered manufacturers. However, in the current marketplace, some graded chemicals cannot be obtained for various reasons. PCCA actively tests all products received to ensure they meet our required standards to ensure our members receive the highest quality chemicals possible.

We would like to echo the concerns, voiced by NCPA and others in our industry, the strong recommendation to formalize the process by which the list is updated and communicated to the pharmacy industry. We also recommend an annual process to ensure understanding and adherence to the list. All submissions and updates to the list should be reviewed by the Pharmacy Compounding Advisory Committee (PCAC) and no changes to the list should occur with input and review by the PCAC.

We are also dismayed in the fact that no appointments have been made to the PCAC despite the call for nominations closing in March 2014. Without these appointments, FDA is unable to consult the Committee regarding this list, as outlined in the Act. PCCA, along with industry partners, strongly recommends that the FDA consult with the PCAC related to every single submission the Agency received in relation to FDA-2013-N-1525.

We appreciate this opportunity to submit this list for consideration and we look forward to continuing to work with the FDA in the future on this and other important issues as they relate to the practice of pharmacy compounding.

Sincerely,

Aaron Lopez
Senior Director of Public Affairs
PCCA

John Voliva, R.Ph.
Director of Legislative Relations
PCCA

PCCA Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations

Ingredient Name	Domperidone
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	5-Chloro-1-{1-[3-(2-oxobenzimidazolin-1-yl)propyl]-4-piperidyl}benzimidazolin-2-one
Common Name(s)	Domperidone; Motilium
UNII Code	5587267Z69
Chemical Grade	BP, EP & JP
Strength, Quality, Stability, and Purity	Assay, Description, Melting Point, Solubility; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmcopeias or registered in other countries	BP, EP & JP; Available in 112 countries
Submitted to USP for monograph consideration	Yes
Compounded Dosage Forms	Capsule
Compounded Strengths	1 - 20 mg
Anticipated Routes of Administration	Oral
Saftey & Efficacy Data	Package insert for domperidone 10 mg tablets (AUS) [http://bit.ly/1gOdDJ2]
	Committee on drugs. The transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108(3):776-89. [http://bit.ly/1fX9Gnp] – reports no “Reported Sign or Symptom in Infant or Effect on Lactation” (p.780)
	Patterson D, et al. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am J Gastroenterol. 1999 May;94(5):1230-4. [http://www.ncbi.nlm.nih.gov/pubmed/10235199]

	Johannes CB, et al. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. Pharmacoepidemiol Drug Saf. 2010 Sep;19(9):881-8. [http://www.ncbi.nlm.nih.gov/pubmed/20652862]
	Knoppert DC, et al. The effect of two different domperidone doses on maternal milk production. J Hum Lact. 2013 Feb;29(1):38-44. [http://www.ncbi.nlm.nih.gov/pubmed/22554679]
	Vieira MC, et al. Effects of domperidone on QTc interval in infants. Acta Paediatr. 2012 May;101(5):494-6. [http://www.ncbi.nlm.nih.gov/pubmed/22226330]
	Barone JA. Domperidone: a peripherally acting dopamine2-receptor antagonist. Ann Pharmacother. 1999 Apr;33(4):429-40. [http://www.ncbi.nlm.nih.gov/pubmed/10332535]
	Reddymasu SC, et al. Domperidone: review of pharmacology and clinical applications in gastroenterology. Am J Gastroenterol. 2007 Sep;102(9):2036-45. [http://www.ncbi.nlm.nih.gov/pubmed/17488253]
Used Previously to compound drug products	Gastroparesis, Nausea, Vomiting, Lactation
Proposed use	Gastroparesis, Nausea, Vomiting, Lactation
Reason for use over and FDA-approved product	Treatment failures and/or patient unable to take FDA approved product
Other relevant information - Stability information	USP <795> recommendation of BUD for nonaqueous formulations – “no later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.

September 30, 2014

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

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

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

Dear Sir or Madam:

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

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

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

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

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

Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Domeperidone
Chemical/Common Name	Domeperidone
Identifying Codes	57808-66-9
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies *(including foreign recognition)*	BP, USP monograph in progress

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)*	Motilium in other countries
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 10b

Domperidone
FDA Review

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: September 29, 2015

FROM: Ben Zhang, Ph.D. ORISE Fellow, Office of Pharmaceutical Quality (OPQ), CDER

Sushanta Chakder, PhD, Pharmacology/Toxicology Supervisor
Division of Gastroenterology and Inborn Errors Products (DGIEP), Office of Drug Evaluation III (ODE III), Office of New Drugs (OND)

Miriam Chehab, PharmD, Safety Evaluator
Ali Niak, MD, Medical Officer
Division of Pharmacovigilance II (DPV II), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)

Joel L. Weissfeld, MD, MPH, Medical Officer
Jie Jenni Li, PhD, MBBS, Team Leader
Division of Epidemiology II (DEPI II), OPE, OSE

Mohamed A. Mohamoud, PharmD, MPH, BCPS, Team Leader
Drug Utilization, DEPI II, OPE, OSE

Anil Rajpal, MD, Clinical Team Leader, DGIEP, ODE III, OND

Leslie McKinney, PhD, Pharmacology/Toxicology Reviewer
Catherine Sewell, MD, MPH, Clinical Reviewer
Christina Chang, MD, Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products (DBRUP), ODE III, OND

THROUGH: Norman Schmuff, PhD, Associate Director for Science, Office of Process and Facility, OPQ, CDER

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Joyce Korvick, MD, Deputy Director for Safety
Donna Griebel, MD, Director
DGIEP, ODE III, OND

Lynnda Reid, PhD, Pharmacology/Toxicology Supervisor
Christine Nguyen, MD, Deputy Director for Safety
DBRUP, ODE III, OND

Julie Beitz, MD, Director, ODE III, OND

TO: Pharmacy Compounding Advisory Committee

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

I. INTRODUCTION

Domperidone 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 various uses, including the treatment of gastroparesis, nausea/vomiting, and lactation, which are the subject of this review.

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 domperidone 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?

Domperidone is a synthetic small molecule which acts as a selective antagonist of the peripheral dopamine receptor.

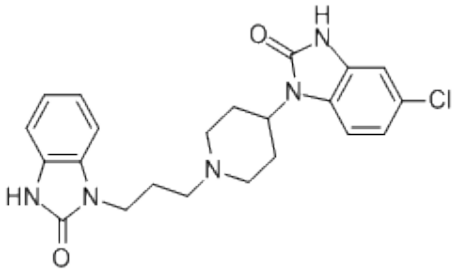


Fig. 1 Structure of Domperidone

Databases searched for information on domperidone in regard to Section A of this consultation included PubMed, SciFinder, Analytical Profiles of Drug Substances, the

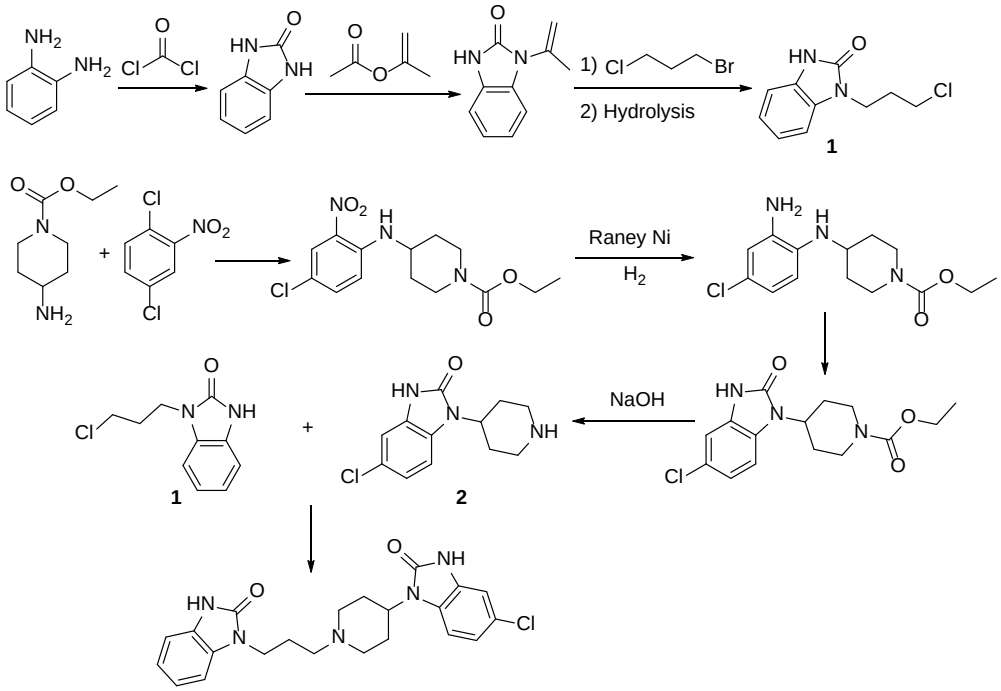
European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia, USP/NF, and Google.

1. Stability of the API and likely dosage forms

Domperidone is stable as a solid at room temperature when isolated from strong oxidants. The aqueous solution is also stable at room temperature under acidic, basic and neutral conditions and the neutral solution is stable up to 100°C. But exposure to strong oxidants like H_2O_2 or sunlight may cause degradation and oxidation of the compound (Thanikachalam et al., 2008).

2. Probable routes of API synthesis

The current industry manufacturing procedures of domperidone mainly follow the synthetic route shown below:



The original synthetic procedure was patented by Janssen Pharmaceutica N.V. (Vanderberk et al., 1978) in 1978. There have been multiple reports on the modifications of the reaction conditions, reagents and synthetic strategies in the literature trying to improve the yield and quality of the product (Li et al., 2006; Henning et al., 1987). The yield and purity of the product may vary depending on the reagents and reaction conditions that have been used in the synthesis.

3. Likely impurities

Possible impurities may include:

1) Trace amounts of the synthetic precursors: compounds 1-(3-chloropropyl)-2-benzimidazolidinone and 5-Chloro-1-(4-piperidyl)-2-benzimidazolinone.
2) Trace amounts of reagents involved in the synthesis like Ni, 1-bromo-3-chloropropane, and phosgene.
3) Trace amounts of residual solvent such as MeOH and ethyl acetate.

4. Toxicity of those likely impurities

Depending on the specific reaction conditions, some of the impurities resulting from the reagents used in the synthesis might be genotoxic, especially the halogenated compounds like phosgene and 1-bromo-3-chloropropane. However, as these reagents are used in early steps, such substances are likely to be removed, if there are subsequent purifications. The two synthetic precursors 1-(3-chloropropyl)-2-benzimidazolidinone and 5-Chloro-1-(4-piperidyl)-2-benzimidazolinone are unlikely to exhibit high toxicity. Other toxicity issues can be found in section B.

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

Domperidone is a white powder with very low solubility in water (0.986 mg/L). It has usually been administered as a solid or a suspension. No further report on the impacts of the physicochemical properties on the product performance was 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

Domperidone is well characterized. Based on the molecular structure, the characterization of the API is simple and can be done by currently available techniques such as proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), Ultraviolet-visible (UV-Vis) spectroscopy and high performance liquid chromatography (HPLC).

Conclusions: Domperidone is a small synthetic molecule that is easily characterized. The synthesis of this compound involves 9 steps, and the overall yield reported in the literature is usually low (Li et al, 2006), suggesting that there could be many impurities in the final API depending on intermediate and final purification steps. The compound is very stable when stored in the dark and separated from strong oxidants.

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

The following information is summarized from the references listed below.

1. Nonclinical Assessment

a. Pharmacology of the drug substance:

Domperidone is a dopamine receptor antagonist. The gastric prokinetic effects of domperidone are due to the blockade of dopamine receptors in the gastrointestinal tract (Reddymasu et al, 2007). Domperidone acts on the pituitary to block the dopamine-mediated inhibition of prolactin secretion, thus allowing release of prolactin (Besser et al, 1980, and Cocchi et al., 1980). Prolactin is necessary for galactopoiesis, maintenance of the lactocyte, and maintenance of milk synthesis in the lactocyte.

b. Safety pharmacology:

The literature contains extensive information regarding the safety of domperidone in various systems.

Cardiac safety: Domperidone is a potent potassium channel (Kv11.1 or hERG) blocker (nanomolar (nM) range, see table 1 below). In whole heart preparations (guinea pig or rabbit), it prolongs the action potential duration (APD), making domperidone potentially proarrhythmic. More definitively, domperidone has been found to be proarrhythmic by TRIaD criteria, also in the nM range. TRIaD stands for triangulation (of the cardiac action potential), reverse use dependence, instability (beat-to-beat variation) and dispersion (of repolarization throughout the heart). The use of TRIaD allows for a more robust analysis of drug action on the electrical parameters of the heart, and is a better predictor of proarrhythmic potential than hERG channel block alone.

Table 1. Effect of domperidone on cardiac parameters

Assay	Prep	Effective Dose	Ref / Yr
hERG	CHO cells	IC_{50} = 162 nM	Drolet et al., 2000
	HEK293	IC_{50} = 57 nM	Claassen et al., 2005
APD (repolarization)	Guinea pig heart	100 nM*	Drolet et al., 2000
	Guinea pig heart	100 nM*	Hreiche et al., 2009
	Rabbit heart	30 nM*	Hondegehm, 2011 and 2013
TRIaD	Rabbit heart	100 nM*	Hondegehm, 2011 and 2013

*Effect did not saturate at doses tested; no IC_{50} (drug concentration producing 50% current inhibition) was determined

Taken together, the dose-response data from the various nonclinical assays show that the 'no effect' level for domperidone on cardiac parameters is in the range of 10 nM.

Central Nervous System (CNS) safety: Domperidone does not cross the blood brain barrier and does not have significant CNS effects when administered orally (Laduron et al., 1979).

Respiratory safety: In animals, domperidone increases ventilation rate and ventilatory function (Delphert et al., 1985; Hsaio et al., 1989).

c. Acute toxicity

Domperidone has no acute toxicity in the therapeutic range. LD_{50} values for oral administration in rats and mice are high (5243 and 800 mg/kg respectively) (Material Safety Data Sheer, ScienceLab.com).

d. Repeat dose toxicity

Chronic toxicity studies have been conducted in rat and dog. These studies have not been published but summaries of the results are available in monograph form (Teva Canada Limited, 2012). In the rat, at doses up to 160 mg/kg/d, there was no treatment-related mortality, and the main target organ of toxicity was the mammary gland. In the dog, at doses up to 40 mg/kg/d, there was no treatment-related mortality and the target organs of toxicity were testes and prostate, which showed histological changes.

e. Mutagenicity

Domperidone was found to be negative for mutagenicity in vitro and in vivo (VanParys et al., 1982; VanParys et al., 1985).

f. Developmental and reproductive toxicity

Animal reproduction studies have not shown any teratogenic or embryotoxic effects (See Domperidone monograph (Teva Canada Limited, 2012). Domperidone was not found to be teratogenic in animals at doses greater than 100 times the recommended human dose (Magee et al., 2002; Shepard, 1992).

g. Carcinogenicity

Carcinogenicity studies have been conducted in mouse and rat. Mammary carcinomas, which are expected for a dopamine antagonist given at high doses, were observed in both species. Other findings are reported in the domperidone monograph (Teva Canada Limited, 2012).

h. Toxicokinetics

Nonclinical toxicokinetics have been investigated in rats and dogs (Heykants et al., 1981; Michiels et al., 1981; Meuldermans et al., 1981), and results are similar to those from investigations of human toxicokinetics. Following oral administration to rats, domperidone was rapidly absorbed, and the peak plasma concentrations were reached in 30 minutes. The half-life of elimination ranged from 8 to 10 hours. Toxicokinetics were similar following single and repeated oral dosing for 11 months, and there was no evidence of accumulation. The route of excretion was primarily via the feces.

Distribution to the rat brain was limited. In the pregnant rat, there was minimal transfer across the placenta. There was little excretion into milk in the lactating rat.

Conclusions:

The proarrhythmic properties of domperidone have been well-characterized in a variety of nonclinical preparations. In the nonclinical assays, domperidone blocks cardiac potassium channels, prolongs action potential duration, and alters the stability of the heart rate at very low concentrations..

2. Human Safety

The chief safety concern outlined in this section is the cardiac risk of domperidone, specifically the drug's effect on the electrical activity of the heart (QT interval prolongation), which could pre-dispose patients to develop life-threatening ventricular arrhythmias, such as Torsade de Pointes (TdP), cardiac arrest, and sudden death.

<u>QT prolongation and cardiac arrhythmia - Background</u>:
Some non-antiarrhythmic drugs have the undesirable effect of delaying cardiac repolarization that is manifested as prolongation of the QT interval on electrocardiograms. The QT interval depicts the time interval from onset of depolarization (Q-wave) to the end of repolarization (T-wave). Excessive prolongation of the QT interval and a delay in cardiac repolarization creates an electrophysiological environment that favors the development of cardiac arrhythmias, most clearly torsade de pointes (TdP), but possibly other ventricular tachyarrhythmias as well. TdP and other ventricular tachyarrhythmias can lead to ventricular fibrillation and sudden death. The QT interval shortens as the heart rate increases, and therefore, QT intervals are usually corrected (QTc) using a rate-correction formula to take into account changes in heart rate (ICH Harmonized Tripartite Guideline, 2005).

In 2005, the International Committee on Harmonization (ICH), a collaborative body among the regulatory agencies of the European Union, Japan, and the U.S., issued a harmonized tripartite Guideline titled "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs," also referred to as the "ICH-E14 Guideline" (ICH Harmonized Tripartite Guideline, 2005). This guideline contains recommendations on the design, conduct, analysis, and interpretation

of a clinical study intended to determine whether a drug has a threshold pharmacologic effect on cardiac repolarization, as measured by QT/QTc prolongation; such a study is known as a "thorough QT" study. This study is typically conducted in healthy volunteers, and if not precluded by safety or tolerability concerns, the drug should be tested at substantial supratherapeutic exposures such that the concentration-response relationship for QT prolongation can be adequately characterized. According to the ICH-E14 Guideline, the threshold level of regulatory concern is around 5 msec, as evidenced by an upper bound of the 95% one-sided confidence interval (CI) around the mean effect on QTc of 10 msec. A "negative" thorough QT study is one where the upper bound of the 95% CI for the largest time-matched, placebo-corrected mean effect of the drug on QTc interval is < 10 msec. For a "positive" study, additional evaluations are needed to better characterize this potential risk. It should be noted that a thorough QT study, in and of itself, does not definitely exclude or confirm a drug's pro-arrhythmic potential. Other sources of data, including nonclinical data and adverse outcomes from post-marketing surveillance, are also important in assessing a drug's pro-arrhythmic risk.

Documented cases of TdP are relatively rare, even for drugs known to prolong the QT/QTc. Often, cases are not reported until large populations of patients have been treated with the drug in post-marketing settings. It is in such settings that a drug's pro-arrhythmic potential could interact with real world risk factors to culminate in significant clinical events, such as ventricular tachyarrythmia. Some risk factors for QT interval prolongation are electrolyte abnormalities, congestive heart failure, impaired drug metabolizing capacity or clearance (due to renal/hepatic impairment, drug interactions), female gender, history of QT prolongation, and older age. Evidence of adverse events possibly related to QT interval prolongation includes sudden death, ventricular tachycardia, ventricular fibrillation, syncope, and seizures. A well-characterized episode of TdP has a high probability of being drug-related, whereas the other events reported more commonly would be of particular concern when they are seen in a population at low risk for them (for example, young healthy adults experiencing sudden death).

Evidence of a drug's risk of QT prolongation, TdP, and sudden death may have a significant regulatory impact, depending on other key considerations such as a drug's indication, target population, magnitude of benefit, and alternative treatments. For example, the approval of several drugs, including terfenadine, astemizole, cisapride, and grepafloxacin, have been revoked because healthy patients experienced QT prolongation and life-threatening cardiac arrhythmia, while taking these medications (CDER Regulatory Science in Action, accessed 2015; Obias-Manno et al., 2007).

<u>Domperidone - Regulatory Background:</u>

Domperidone has been approved in multiple jurisdictions outside the United States since 1978 for certain gastrointestinal (GI) conditions. Until 2014, the highest dose approved worldwide was 20 mg four times a day (total daily dose of 80 mg orally) with no specific limitation on duration of use (MOTILIUM tablets Prescribing Information, 2004). Although not approved for lactation enhancement in any country, domperidone has also been used to increase milk production in lactating mothers. Published studies and

abstracts (Wan et al., 2008; Knoppert et al., 2013; Livingstone et al., 2007) have reported use of domperidone in total daily doses of 30 to 80 mg, administered in divided doses, and anecdotally, higher doses have been reported.

Domperidone is not approved for human use in the U.S. The FDA has taken several regulatory actions to curb the use of domperidone. In June 2004, FDA issued a warning against the use of domperidone to enhance lactation (FDA, 2004). This warning was issued for two reasons. First, published case reports and case studies reported QT prolongation, cardiac arrhythmias, cardiac arrest, and sudden death in patients receiving an intravenous form of domperidone, leading to the withdrawal of this formulation from non-U.S. markets in 1985. Second, in countries where non-intravenous formulations (oral, rectal suppository) remain available, labels specifically warn against the unapproved use of domperidone by breastfeeding women because the drug is excreted in breast milk and could expose a breastfeeding infant to unknown risks. FDA recommended that breastfeeding women not use domperidone to increase milk production because the known, serious pro-arrhythmic risk of domperidone outweighs any potential drug benefit for lactation enhancement.

At the same time as the June 2004 warning, FDA also issued an Import Alert, updated in 2012, which remains in effect today (FDA Import Alert, 2012). The alert instructs FDA field personnel to look for attempts to import domperidone so that it can be detained and refused admission into the U.S. Since 2004, FDA has issued warning letters to pharmacies that compound human drug products containing domperidone and firms that supply domperidone for use in human drug compounding. The letters state that all human drug products containing domperidone violate the Food, Drug, and Cosmetic Act, because they are unapproved new drugs and misbranded drugs. FDA warned that domestic distribution or importation of domperidone-containing products for human use violates the law.[1]

Although there are restrictions on domperidone, FDA recognizes that there are patients with severe GI motility disorders refractory to standard treatment who might benefit from domperidone and in whom the benefits of the drug may outweigh its risks. Domperidone is currently available to these patients through FDA's Expanded Access to Investigational New Drug (IND) program (FDA, 2015). This Expanded Access IND program ensures that the appropriate safeguards are in place to protect patients treated with domperidone from the drug's serious adverse effects, including QT prolongation and cardiac arrhythmias. Key features of the standard protocol under the IND include the following:

- Dosing from 10-30 mg four times a day
- Including only patients ≥ 12 years of age
- A prokinetic effect is needed as per investigator's judgment for the relief of ***refractory*** gastroesophageal reflux disease (GERD) with upper gastrointestinal symptoms, gastroparesis, and chronic constipation.

[1] In 2010 domperidone was approved for animal use.

- Excluding patients with cardiac rhythm abnormalities (such as clinically significant bradycardia, sinus node dysfunction, or heart block, and prolonged QTc (QTc> 450 milliseconds for males, QTc>470 milliseconds for females), history of ventricular tachycardia, ventricular fibrillation).
- Safety monitoring every 2 months (Year 1) and every 6 months (after Year 1) includes physical exam, EKG, CBC, liver panel, renal panel, and concomitant medication review. See table in Appendix A.
- Providing physicians a list of drugs that interact with domperidone that should be avoided. See list in Appendix B.
- Including in the Informed Consent information on increased prolactin levels, extrapyramidal side effects, breast changes, and cardiac arrhythmias (including QT prolongation and sudden death).

In jurisdictions outside of the U.S. where domperidone is approved for certain GI conditions, the use of domperidone has recently been significantly restricted because of cardiac safety concerns. In 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) re-evaluated the benefit-risk balance of domperidone for the approved indications because cases of QT prolongation, cardiac arrhythmias, and sudden death continued to be reported. Based on findings from pharmacovigilance, pharmacoepidemiologic studies, studies of drug-drug interactions, and other studies, in April 2014, the EMA concluded that there is an increased risk of serious cardiac adverse drug reactions, such as QT prolongation and sudden cardiac death (SCD), associated with domperidone use. The risks are increased in patients over 60 years of age, those who are using higher doses (> 30 mg/daily) and/or who are using concomitant QT-prolonging drugs or products that increase domperidone exposure (European Medicines Agency, 2014; European Medicines Agency PRAC Assessment Report, 2014).

The EMA PRAC recommended the following actions:

- Retain “relief of symptoms of nausea and vomiting” indication; revoke other indications (for example, epigastric sense of fullness, upper abdominal discomfort, bloating, heartburn with or without regurgitation of gastric contents in adults) due to limited efficacy data in light of known cardiac arrhythmia risks;
- Reduce maximum recommended dose and duration to 10 mg three times a day (tid) (total daily dose of 30 mg orally) for up to 7 days in adults/adolescents >35 kg (those < 35 kg, 0.25 mg/kg tid orally);
- Remove higher dose formulations not consistent with new dosage recommendations (oral formulations of 20 mg, and 10 mg and 60 mg rectal suppositories).
- Contraindicate in patients with risk factors for QT prolongation and with concomitant use of QT prolonging drugs or potent CYP3A4 inhibitors
- Consider that similar cardiac arrhythmia risks exist when using domperidone off-label

These recommendations were adopted in 2014 by the Coordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh), the regulatory body representing the European Union (EU) Member States. In 2014, the United Kingdom, Belgium, and the Netherlands removed domperidone's non-prescription status. (i.e., available in a pharmacy without prescription, under supervision of a pharmacist). Due to cardiac safety concerns, it was determined that domperidone should be available as a prescription-only medication; patients need to have medical assessment to determine whether domperidone is an appropriate treatment before receiving a prescription for domperidone. In January 2015, Health Canada issued a Recalls & Alert advisory warning healthcare providers and consumers of the increased risk of serious ventricular arrhythmias or SCD associated with domperidone (Health Canada, 2015). Health Canada also adopted the same recommendations as the EMA, and advised that the safety information applies to all patients using domperidone, whatever the condition being treated.

Safety review:

The following sections represent FDA's independent assessment of the available cardiac safety data for domperidone. Much of this data also supported the recent restrictive regulatory actions from the EMA, summarized in the 2014 EMA PRAC report, and Health Canada.

a. Reported adverse reactions--Spontaneous case reports

Shortly after its 1978 marketing approval in Europe, domperidone was associated with serious cardiac adverse reactions, including QT prolongation, TdP, cardiac arrest and sudden death, when large doses were rapidly infused intravenously for anti-emetic treatment during chemotherapy in cancer patients. In the early 1980s, Joss et. al. (Joss et. al., 1982), Giaccone et. al. (Giaccone et. al., 1984) and Bruera et. al. (Bruera et. al., 1986) reported on seven such patients. Due to these reports and an increasing number of such cases worldwide, the intravenous formulation was withdrawn from the European market for safety reasons in 1985. Subsequently, these serious cardiac reactions were also noted with other pharmaceutical forms of domperidone, specifically oral and rectal suppository formulations.

Reports of adverse cardiac drug reactions from Europe, the United Kingdom, the Netherlands, and other countries show many cases of QT prolongation, ventricular arrhythmias, torsade de pointes, cardiac arrest and sudden death associated with domperidone. In 2013, the PRAC was asked to evaluate the benefit-risk balance of domperidone for the approved GI indications. A cumulative review (European Medicines Agency PRAC Assessment Report, 2014) of the sponsor's safety database through January 31, 2012, yielded 342 cases of serious cardiac adverse events among all age groups, including children. Of those 342 cases, the most frequently reported events were cardiac arrest (n=50), myocardial infarction (n=41), electrocardiogram QT prolonged (n=39), tachycardia (n=27), cyanosis (n=23), arrhythmia (n=22), palpitations (n=20), cardiac failure congestive (n=20), cardiac failure (n=19), bradycardia (n=18),

torsade de pointes (n=16), ventricular tachycardia (n=11), angina pectoris (n=11), and ventricular fibrillation (n=9). Of the 87 fatal cases, 64% were in females and 41% were in those 65 or older. The total daily dose in the fatal cases was most frequently over 30 mg orally per day. When the analysis was focused on cardiac conduction events, 156 cases were noted. Among the 60 cases with time to onset, 20 occurred the same day as the first dose, and 44 cases occurred within the first week.

Examination of the EMA's pharmacovigilance database (Eudravigilance) through March 7, 2013, found 219 cases; many of these cases were also contained in the sponsor's safety database described above. The most frequently grouped reactions were ventricular arrhythmias and cardiac arrest (N=64), followed by rate and rhythm disorder (N=60). The median time to onset was two days (range 0-1,135 days) (European Medicines Agency, 2014; European Medicines Agency PRAC Assessment Report, 2014). The review of these pharmacovigilance databases shows the risks are increased in patients older than 60 years of age, who are using higher doses (> 30 mg orally daily) and/or who are using concomitant QT-prolonging drugs or products that increase domperidone exposure.

Between 1985 and 2006, Health Canada received nine reports of heart rate and rhythm disorders with domperidone: two prolongation of QT interval, four torsade de points, three of arrhythmia, atrial fibrillation, ventricular tachycardia, bradycardia, and palpitation (Djelouah et al., 2007).

As noted in the regulatory background for domperidone, FDA is concerned about the use of domperidone for lactation enhancement. FDA's Office of Surveillance and Epidemiology/Division of Pharmacovigilance II reviewed the FDA Adverse Event Reporting System (FAERS) from January 1, 1965 through April 16, 2015, for reports of cardiac adverse events of interest (e.g., QT prolongation, dTP, sudden death, cardiac arrhythmias) or associated symptoms (e.g., syncope, malaise, dizziness) in women of reproductive age who might be using domperidone for lactation, specifically in females less than or equal to 50 years of age. Twelve cases fit the defined search criteria.

Of the 12 cases identified, 5 involved patients in the U.S., and 3 of the twelve resulted in deaths, 1 of which occurred in the U.S. These 12 cases were also evaluated for a causal relationship and categorized as probable, possible, unlikely, or unassessable using a modified World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment[2] (WHO-UMC, 2015). Five cases were assessed as having *possible* causality, and three were assessed as having *probable* causality. Reported reasons for use in these eight cases included lactation enhancement (n=3) and gastroesophageal reflux disease (GERD) (n=2). Three cases did not report the reason for domperidone use. The

[2] A case was considered to be *probable* if the time of administration is related to the onset of the event, the event is unlikely to be attributed to disease or other drugs, *and* documentation of a positive dechallenge response is present. Rechallenge information is not required to categorize a case as *probable*. A case was considered to be *possible* if the time of administration is related to the onset of the event, the event may also be explained by disease or other drugs, *and* dechallenge information is unclear or not provided.

remaining 4 cases (of the initial 12 cases) were categorized as unlikely or unassessable and are not discussed further.

The three cases of *probable* causation are as follows:

- 2015: 32-year-old female was prescribed domperidone 20 mg orally three to four times daily (total daily dose of 60-80 mg) for lactation enhancement. The medication was compounded at a local pharmacy. Her medical history was significant for hypoglycemia ("rare occurrences"), epilepsy ("rare occurrences"), and asthma ("rare occurrences"). She reported no cardiac history. Her only concomitant medication was a prenatal vitamin. Domperidone was prescribed for lactation enhancement when the patient's infant was 3-months-old. Approximately 6 months after initiation of therapy, the patient developed palpitations, malaise and "syncope-like" feelings which prompted her to discontinue domperidone. Her symptoms resolved post-discontinuation.
- 2013: 46-year-old female with long-standing GERD was switched from metoclopramide and esomeprazole to domperidone 10 mg orally twice daily (total daily dose of 20 mg) and dexlansoprazole. Her medical history was significant for GERD, hypertension, esophageal strictures, a hiatal hernia, headaches, and depression. She had complaints of chest pain and palpitations before starting the new regimen; however, a stress test was not performed until day 4 of domperidone and dexlansoprazole use. She developed torsade de pointes during the stress test; cardioversion was initially successful; however, upon hospital transfer, she again developed torsade de pointes. Cardioversion was then unsuccessful, and she died.
- 2012: 34-year-old female was prescribed domperidone 30 mg orally four times daily (total daily dose of 120 mg) for lactation enhancement. Information regarding her medical history was not reported. After 4 days of domperidone, the patient had palpitations, shortness of breath, and difficulty getting out of bed. EKG showed QT prolongation which resolved after drug discontinuation.

The five cases of *possible* causation are as follows:

- 2015: 29-year-old female was prescribed an unspecified dose (one tablet three times daily) of domperidone orally for GERD. After approximately 3 weeks of domperidone, she experienced palpitations and possible arrhythmia. Medical history was significant for "IBS" (presumably, irritable bowel syndrome) and GERD. Concomitant medications included megestrol acetate, mirtazapine, three-day course of prednisone, multivitamin, B complex, vitamin D, vitamin C, psyllium, and "digestive enzymes." Domperidone was discontinued, but the patient's outcome after drug discontinuation was not provided. The concomitant medication mirtazapine is an additional potential etiology for the palpitations and possible arrhythmia.
- 2013: 34-year-old female had been prescribed numerous medications including domperidone 10 mg orally three times daily (total daily dose of 30 mg), subcutaneous sumatriptan, sertraline, pregabalin and ondansetron. The indication for domperidone use, duration of use, and information regarding her medical history was not reported. She was hospitalized after a collapse and was diagnosed

with drug-related complete heart block. The concomitant medications sumatriptan, sertraline, and ondansetron, in addition to domperidone, are additional potential etiologies for the drug-related heart block.

- 2012: 19-year-old female with no past medical history was prescribed unknown doses of domperidone, ciprofloxacin and metronidazole. The indication for domperidone use, duration of use, and route of administration was not reported. She developed QT prolongation and was found to have hypokalemia and borderline hypomagnesemia. The symptoms resolved when the medications were stopped and her electrolytes were repleted. The concomitant medication ciprofloxacin and the electrolyte abnormalities are additional potential etiologies for QT prolongation.
- 2012: 34-year-old female with a history of dilated cardiomyopathy was prescribed domperidone and furosemide. Indication for domperidone use, duration of use, and route of administration were not reported. She was found to have QT prolongation and torsade de pointes, hypokalemia, and borderline low magnesemia. QT interval normalized after stopping medications and repleting electrolytes. The electrolyte abnormalities are additional potential etiologies for QT prolongation and torsade de pointes.
- 2006: 35-year-old female with no past medical history was treated with an unspecified dose of domperidone orally for lactation enhancement. Duration of domperidone use was not specified. She developed QT prolongation and syncope two days after adding azithromycin to her medication regimen. No further outcomes are reported. The concomitant medication azithromycin is an additional potential etiology for the QT prolongation.

b. Reported adverse reactions—Pharmacoepidemiological studies

FDA's Office of Surveillance and Epidemiology/Division of Epidemiology II (DEPI II) conducted a systematic literature search and found 15 articles (including the two articles referenced in the previous two paragraphs) from 6 interpretable, non-experimental (clinical or non-clinical) studies of domperidone and QT interval prolongation, TdP, SVA, or SCD. A qualitative synthesis of the data found evidence for a 1.5- to 2.0-fold increased risk of SCD and/or SVA from current use of domperidone in the general population. The review noted that inferential error from residual confounding, exposure misclassification, and protopathic bias[3] in the studies are plausible, non-causal explanations for the association between SCD/SVA and current domperidone use. Of note, the studies included in the literature review were not designed to examine risk in women treated with domperidone for lactation insufficiency. Within the scope of its systematic review, DEPI II did not identify reliable information that could inform a lower, similar, or greater risk of harm in breastfeeding women. The EMA conducted a

[3] "A type of bias that can occur if the first symptoms of the outcome of interest are the reasons for using the treatment under study," from Porta, M, 2008, A Dictionary of Epidemiology, Oxford, Oxford University Press, page 198.

pharmacoepidemiologic review which included many of the same studies, and similarly concluded that domperidone exposure was associated with an increased risk ratio for SCD and/or SVA (European Medicines Agency, 2014; European Medicines Agency PRAC Assessment Report, 2014).

Details of two major studies reporting positive risk findings from the literature review are summarized below:

In 2010, Johannes et al. published a study that evaluated a cohort of domperidone users (n=83,212) using the electronic databases of Saskatchewan Health (Johannes et al., 2010). From the domperidone user cohort, 1,559 cases of SCD and 49 cases of serious ventricular arrhythmia (SVA) were identified, as well as 6,428 matched controls (non-cases), for the nested case-control study. The mean age of cases and controls was 79 years, and over half of the subjects were female. After adjusting for baseline risk factors for QT prolongation (for example, age, gender, use of anti-arrhythmic agents, concomitant use of QT prolonging drugs), the odds ratio (OR) for the composite endpoint of SCD/SVA associated with current domperidone use was 1.59 (95% CI 1.28-1.98). This suggests that current domperidone use was associated with a 59% increase in the risk for the composite endpoint of SVA/SCD.

Similarly, in 2010, Van Noord et. al. (Van Noord et. al., 2010) reported findings from a population-based, case-control study of the Integrated Primary Care Information database in the Netherlands. The study included 1,304 cases of SCD and 62 of SVA, compared with 14,114 matched controls. The study reported an unadjusted relative risk (as expressed by the OR in this study) for the composite endpoint of SCD/SVA with current domperidone use of 3.54 (95% CI 1.64-7.64) and 3.72 (95% CI 1.72-8.08) for the study endpoint SCD. After adjusting for baseline risk factors, the OR was 1.92 (95% CI 0.78-4.73) for the composite endpoint of SCD/SVA, and 1.99 (95% CI 0.80-4.96) for the study endpoint of SCD. These findings suggest that domperidone use was associated with an approximate 2-fold increase in the risks of SCD and SVA.

c. Clinical trials assessing safety

The following studies evaluated the effect of domperidone on QT interval:

1. Thorough QT study (European Medicines Agency PRAC Assessment Report, 2014): The sponsor conducted this study in 2012 at the request of the Belgium regulatory authority over concerns about continued reports of cases of QT prolongation, cardiac arrythmias, and sudden cardiac death. Conducted according to the ICH-E14 guideline (see section B.2), this trial was a randomized, double-blind, 4-way crossover, placebo and positive-controlled, single-center, single- and multiple-dose study to assess the effects of single and multiple doses of domperidone on the QTc interval in healthy adult subjects, at the approved domperidone doses of 10 mg orally four times daily (qid) and 20 mg orally qid. Forty-four healthy adult subjects between 18 and 45 years of age were enrolled and

received 4 treatments consisting of combinations of domperidone at both dose groups, placebo, and the positive control moxifloxacin (Biewenga et al., 2015).

Using study-specific corrected QT interval (QTcP), the largest difference between domperidone and placebo in LS means in the change from baseline was 2.0 msec (90% CI: 0.2-3.8 msec) for the domperidone 10 mg dose qid on Day 1, and 3.4 msec (90% CI: 1.0-5.9 msec) for the domperidone 20 mg qid dose on Day 4. In short, the results of the study showed no clinically relevant effect of domperidone on QTc interval when domperidone was administered to healthy subjects at 10 mg and 20 mg qid (i.e., up to a total daily dose of 80 mg domperidone), under the controlled conditions of the trial. A significant limitation of the study was the lack of multiples of the anticipated maximum therapeutic exposure needed to predict QT safety in real world settings, where patients take concomitant drugs and other products or have medical conditions that either contribute to QT prolongation or increase domperidone exposure to a threshold where QT prolongation is induced. The PRAC report, however, noted that "the inclusion of supratherapeutic doses (administered in healthy volunteers) was ethically questionable, because a potential relevant QTc prolongation was foreseen." (European Medicines Agency PRAC Assessment Report, 2014).

2. Drug-drug interaction studies: The EMA also reviewed drug-drug interaction studies with domperidone (European Medicines Agency PRAC Assessment Report, 2014).

Two studies evaluated the effect on QT when domperidone 10 mg taken 4 times a day is administered with a strong or moderate CYP3A4 inhibitor that also prolong QT interval (either ketoconazole or erythromycin, in these studies) in healthy subjects. The combination of domperidone and either drug resulted in a statistically significant increase in QTcF (a type of corrected QTc) at most timepoints during the 24-hour observation period: compared to placebo, a maximal increase of 13.6 to 15.3 msec. These findings exceeded the ICH-E14 guideline's regulatory threshold of concern for the QTc interval prolongation (a mean increase in QTc interval of > 5 msec with an upper bound of the 95% confidence interval of > 10 msec, compared to placebo). Of note, concomitant administration of ketoconazole or erythromycin resulted in a 2- to 3-fold increase in domperidone blood concentrations (Cmax). In the ketoconazole drug-drug interaction study, one male subject was withdrawn from the study because he developed ventricular tachycardia.

d. Pharmacokinetic data

Product labels outside the US, which are based on clinical trials of domperidone show that the drug domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. The absolute bioavailability of oral domperidone is approximately 15%, due to an extensive first-pass metabolism in the intestinal wall and liver. Domperidone undergoes rapid hepatic metabolism by hydroxylation and N-dealkylation. The 5-hydroxylated metabolite of domperidone appears to have some activity as well, and it is unknown if domperidone metabolites accumulate. The half-life

of domperidone is highly variable, ranging from 7 to 20 hours. Concomitant use of moderate or strong cytochrome P450 3A4 inhibitors (including prescription protease inhibitors, azole antifungals [such as ketoconazole], some macrolides [such as erythromycin and clarithromycin], verapamil, and diltiazem, herbal supplements, and grapefruit juice) can lead to increased concentrations of domperidone.

As noted below in section II (B)(2)(f) below, domperidone is transferred into human breast milk. The exposure of the infant to the drug and its metabolites is unknown.

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

***Lactation Enhancement*:** There are currently no approved pharmacotherapies for lactation enhancement. Women in the United States have the option to bottlefeed safely, although the benefits of breastfeeding are widely recognized.

Gastroparesis and Nausea/Vomiting: There is one FDA- approved pharmacotherapy for gastroparesis, metoclopramide. Metoclopramide is a dopamine antagonist, and has an indication for "the relief of symptoms associated with acute and recurrent diabetic gastric stasis". As per guidelines, metoclopramide administered in a liquid formulation is the first line of prokinetic therapy (Camilleri et al., 2013). Metoclopramide has a boxed warning for tardive dyskinesia, a serious movement disorder that is often irreversible. Erythromycin is used off-label for gastroparesis. As per guidelines, both IV and oral erythromycin are effective; these guidelines recommend consideration of IV erythromycin for hospitalized patients, and note that the long-term effectiveness of oral erythromycin is limited by tachyphylaxis (Camilleri et al., 2013). Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Erythromycin is a CYP3A4 substrate and inhibitor; co-administration of erythromycin and a CYP3A4 inhibitor may be associated with elevations in erythromycin exposures which may increase the prolongation of the QT interval. There are many approved pharmacotherapies for nausea and vomiting; these are summarized in Appendix C.

f. Other safety considerations - Pediatric population, Lactation, Pregnancy

Regarding QT risk in infants, several studies published between 2005 and 2013 reported QT prolongation in infants treated with domperidone for various gastrointestinal indications (Günlemez et al., 2012; Vieira et al., 2012; Djeddi et al., 2008). Doses reported in three of the studies ranged from 1.0 to 2.1 mg/kg/day in divided doses (Vieira et al., 2012; Rocha et al., 2005). One study showed the QT prolongation was not related to the dose of the drug (Djeddi et al., 2008). Another report was related to an accidental overdose given at home, 50 mg in 4 hours (Sanklecha et al., 2013).

Domperidone is transferred into human breast milk, and breastfed infants are expected to be exposed to domperidone via breastmilk. Studies thus far have shown that:

- A single maternal dose of 20 mg orally results in domperidone concentrations in breast milk of 0.24 ng/ml (at 2 hours after drug administration) and 1.1 ng/ml (at 4 hours after drug administration), while 10 mg three times daily resulted in a concentration of 2.6 ng/ml (Hofmeyr et al., 1985)
- Maternal doses of 10 mg and 20 mg orally three times daily results in average breast milk drug concentrations of 0.28 ng/mL and 0.49 ng/mL, respectively, at steady state (Wan et al., 2008)
- Maternal doses of 10 mg and 20 mg orally three times daily results in calculated infant doses of 0.03-0.07 mcg/kg/d and 0.05-0.11 mcg/kg/day, assuming a daily milk intake of 150 mL/kg (Wan et al., 2008)
- Another study showed maternal doses of 10 mg three times daily resulted in domperidone breast milk concentrations of 1.2 ng/mL. Assuming a daily milk intake of 150 mL/kg, this would result in a calculated dose of <0.2 mg/kg/day ingested by the infant (da Silva et al., 2001)

Because lactating mothers may use domperidone for weeks or months, breastfed infants could be exposed to domperidone for an extended period of time. Given these circumstances, combined with the QT risks seen with domperidone treatment of infants, there is a potential for QT prolongation in breastfed infants.

There is also the potential for use of domperidone by pregnant women for gastrointestinal indications. One published article described 120 women on oral domperidone during pregnancy for gastrointestinal problems. They were compared to 212 women with no exposure to the drug in pregnancy. Those exposed took a maximum dose of 30 mg orally daily from 3 weeks to 20 weeks' gestation. Three babies with malformations were born in each group (Choi et al., 2013). The sample size of the study was too small to draw any meaningful conclusion on the effect of domperidone on fetal outcomes.

Safety Conclusions:

There is ample evidence from pharmacovigilance reports, pharmacoepidemiologic studies, drug-drug interaction studies, and other published literature to conclude that:

- Domperidone, in various formulations, is associated with a serious risk of QT prolongation and its attendant consequences, including ventricular arrhythmias and sudden cardiac death. Cases often have associated cardiovascular risk factors, cardiovascular history, and/or concomitant medications associated with cardiac arrhythmias; however, serious adverse cardiac reactions have occurred in otherwise healthy young women with no apparent risk factors.
- . The dose- and exposure-response of domperidone in causing arrhythmias in humans are not well characterized. Cases of QT prolongation, cardiac arrhythmias, and sudden death have been reported with doses of domperidone that are approved in jurisdictions outside the US. In drug-drug interaction studies, QT prolongation was observed when domperidone was administered with drugs that also prolong QT and that increase domperidone exposures by 2- to 3-fold..

- The lack of assessment of supratherapeutic exposures in the 2012 thorough QT study limits the study's utility, because the study does not sufficiently inform the risk threshold of QT prolongation with real world use of domperidone. Despite the TQT study reporting that doses up to 20 mg qid do not prolong the QT interval, cases of QT prolongation, cardiac arrythmias, and sudden death have been reported with domperidone doses lower than 20 mg qid in postmarketing settings.
- Domperidone is secreted in human breast milk, which poses unknown risks to the exposed infant.

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

1. Lactation Enhancement

Domperidone is a peripheral dopamine antagonist which stimulates the release of prolactin from the pituitary, increases plasma levels of prolactin, and increases milk production. Prolactin is a peptide hormone secreted by the anterior pituitary gland. It is necessary for galactopoiesis, maintenance of the lactocyte, and maintenance of milk synthesis in the lactocyte. In most women, suckling induces a significant rise in maternal prolactin levels, with levels rising as much as 10-fold in some patients. Domperidone is known to be used as a galactagogue, with doses up to 40 mg orally four times daily; however, it has never been approved in any country for use in lactation. Whether domperidone is effective for lactation enhancement is unknown., as there are limited clinical trial data, discussed below.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

Limited data are available to support the use of domperidone for enhancement of lactation. A Cochrane review (Donovan et al., 2012) yielded two randomized placebo-controlled trials including a total of 59 mothers of preterm infants (Campbell-Yeo et al., 2008; da Silva et al., 2001). A meta-analysis of these 2 trials showed modest placebo-corrected increase in expressed breast milk of approximately 99 mL/day (95% CI: -2 to 201 mL) (~3.4 ounces) with domperidone 10 mg orally three times daily for 7 to 14 days in mothers of preterm (<37 weeks) infants. Neither trial showed significant improvements in longer-term outcomes of breastfeeding. No adverse effects were reported in the small number of subjects. The authors concluded that further trials should examine larger groups of mothers of preterm infants and consider breastfeeding outcomes over a longer period.

Other published clinical studies show that domperidone increases prolactin levels to 150%-600% of baseline, within 15-45 minutes, in nonpregnant and lactating women, and increases milk production by 1.5-2 times baseline in lactating women (Wan et al., 2008; Brouwers et al., 1980; Knoppert et al., 2013; Wagner et al., 2011; Camanni et al., 1980; Ingram et al., 2012). Doses in the studies were most commonly 30 mg orally daily, but

two studies included subjects on up to 60 mg orally administered daily. Neither of these studies showed a statistically significant difference in milk production with the increased dose. These studies were mostly observational, uncontrolled and had short duration of follow-up, which significantly limits the interpretation of the findings with regard to the efficacy of domperidone on lactation enhancement.

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

Although the benefits of breastfeeding are widely recognized, difficulty lactating is not a serious or life-threatening condition.

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

As noted above in Section II.B.2.e, there are currently no approved alternative therapies for enhancement of lactation. Women in the United States do have the option to bottlefeed safely, although the benefits of breastfeeding are widely recognized.

2. Gastroparesis and Nausea/Vomiting

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

Gastroparesis:

Gastroparesis is a disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction. Symptoms are chronic with episodic symptom exacerbation (Parkman et al., 2004). The core signs and symptoms of gastroparesis are nausea, vomiting, postprandial fullness, early satiety, and upper abdominal pain (Soykan et al., 1998; Hoogerwerf et al., Anaparthy et al., 2009).

An NDA for use of domperidone to treat gastroparesis was submitted in 1985. Data from 5 studies of 77 diabetic gastroparesis patients were reviewed and presented to an Advisory Committee (AC) in 1989. In two of these studies, the domperidone dose given was up to 30 mg orally qid. The AC voted unanimously not to recommend approval. The FDA statistical reviewers noted that the studies did not exhibit consistent, statistically significant differences in outcomes between domperidone and placebo (outcomes included gastric emptying, symptom scores, and global symptom assessments) (Stern, 1989).

Efficacy data for domperidone for the treatment of gastroparesis are available from the following trials:

- A randomized withdrawal placebo-controlled 4-week trial in 208 diabetic gastroparesis patients that showed a 54% lower total symptom score (TSS)

with domperidone 20 mg orally QID (n=105) vs. placebo (n=103) (p=0.025) (Camilleri et al., 2013; Silvers et al., 1998). TSS was the sum of investigator-assessed scores ranging from 0 to 3 for: nausea, abdominal distention/bloating, early satiety, vomiting, and abdominal pain (Silvers et al., 1998). A key limitation of this trial is the investigator assessment for the primary endpoint; currently, patient-reported outcome (PRO) measures are recommended (FDA Draft Guidance, "Gastroparesis: Clinical Evaluation of Drugs for Treatment," 2015).

- A randomized active-controlled 4-week trial in 95 diabetic gastroparesis patients showed similar reduction in TSS from baseline after domperidone 20 mg PO QID (41%) (n=48) vs. metoclopramide 10 mg PO QID (39%) (n=47) (Patterson et al., 1999). TSS was the sum of investigator-assessed scores ranging from 0 to 3 for: nausea, vomiting, early satiety, and bloating/distension (Patterson et al., 1999). Although reductions appeared to be similar (they did not reach statistical significance), the trial was not designed as a non-inferiority (NI) trial (which specifically aims to demonstrate that a novel treatment is not clinically worse than an active treatment based on a specific NI margin). As noted for the previous trial, a key limitation of this trial is the investigator-assessment for the primary endpoint instead of PRO measures as currently recommended (FDA Draft Guidance, "Gastroparesis: Clinical Evaluation of Drugs for Treatment," 2015).

- A randomized active-controlled 8-week trial in 28 pediatric diabetic gastroparesis patients (5 to 17 years of age) showed lower TSS with domperidone 0.9 mg/kg daily (median 3.1) (n=14) vs. cisapride 0.8 mg/kg daily (median 7.4) (n=14) ($p<0.01$) (Franzese et al., 2002). TSS was the sum of investigator-assessed scores ranging from 0 to 6 for: abdominal (epigastric and mesogastric) pain, early satiety or anorexia, feeling of abdominal fullness (or bloating) and regurgitation (or vomiting or heartburn) (Franzese et al., 2002). Again, as noted for the previous two trials, a key limitation of this trial is the investigator-assessment for the primary endpoint instead of PRO measures as currently recommended (FDA Draft Guidance, "Gastroparesis: Clinical Evaluation of Drugs for Treatment," 2015).

Nausea and Vomiting:

The product is currently approved in Europe for treatment of nausea and vomiting at a dose of 10 mg orally up to TID (European Medicines Agency PRAC Assessment Report, 2014). The efficacy data supporting this indication in Europe come mainly from three

studies (De Loose, 1980; Englert et al., 1979; Von Matushka, 1979) that together enrolled 251 and 249 patients receiving domperidone and placebo, respectively (European Medicines Agency PRAC Assessment Report, 2014). The PRAC Report concluded that these data "…support the use of domperidone 10 mg tid in the suppression of nausea and vomiting symptoms at week 2 and/or week 4 of treatment" and that "[c]linically relevant improvement in nausea and/or vomiting scores were reported in these studies following domperidone treatment compared to placebo" (European Medicines Agency PRAC Assessment Report, 2014).

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

Gastroparesis: Gastroparesis can be considered a serious or life-threatening condition.

Nausea and Vomiting: Nausea and vomiting can be considered serious or life-threatening condition.

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

Gastroparesis: There is one FDA-approved therapy, metoclopramide, which has been demonstrated to be effective in treating gastroparesis. Metoclopramide has a boxed warning for tardive dyskinesia, a serious movement disorder that is often irreversible.

Nausea and Vomiting: There are multiple FDA-approved therapies that have been demonstrated to be effective in treating nausea and vomiting (see Appendix C).

Efficacy Conclusions:

Lactation enhancement: Domperidone is known to be used for lactation enhancement, despite not having this indication approved in any country. However, there are very little reliable clinical data to support the drug's effectiveness or dosing recommendations for this indication. There are no approved pharmacotherapies for lactation enhancement.

Gastroparesis and Nausea/Vomiting: Domperidone is used for gastroparesis and for nausea/vomiting, and is approved in Europe for the latter use. There are data from randomized controlled trials to suggest efficacy for nausea/vomiting. There are also data from randomized clinical trials that suggest efficacy of domperidone to treat gastroparesis; however, these studies are either small or suffer from significant design flaws. There is one FDA-approved therapy for gastroparesis and numerous FDA approved therapies for nausea/vomiting.

D. Has the substance been used historically in compounding?

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

It is unknown exactly how long domperidone has been used in pharmacy compounding. Based on the fact that FDA placed an Import Alert on domperidone in 2004 and issued warning letters as recently as 2015 to pharmacies that compound domperidone, it can be concluded that domperidone has been imported into the US and has been used in pharmacy compounding for at least 10 years. We are aware of the marketing of domperidone in foreign jurisdictions since the 1970s.

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

As noted above, domperidone has been used for lactation enhancement, gastroparesis, and nausea/vomiting.

3. How widespread its use has been

A drug utilization review by the Office of Surveillance and Epidemiology using proprietary databases available to the Agency was conducted to characterize utilization of domperidone. Analyses of data from a database that provides national estimates of prescriptions dispensed from retail, mail-order and long-term care pharmacies shows that between 7,500 and 11,600 domperidone prescriptions were dispensed per year in the US between June 2009 through May 2015. These domperidone prescriptions were predominately dispensed in the outpatient retail setting. The prescriptions were mostly dispensed to women (77% of prescriptions), of which twenty percent of the prescriptions were to women aged 20-39 years and 26% of prescriptions were to women aged 40-59 years in the 12-month period ending in May 2015. Gastroenterologists accounted for the majority of the prescriptions dispensed (60% of prescriptions), although 6% of domperidone prescriptions were written by Obstetrician/Gynecologists (OB/GYNs). (IMS Health, National Prescription Audit, 2015)

Office based physician survey data from another proprietary database available to the Agency indicates that the most commonly reported indication associated with domperidone use was to treat gastroparesis and all intended outcomes of therapy were to treat or relieve gastric illnesses and symptoms. However, given the low use of domperidone in the US, its use for lactation enhancement may not have been captured in the office-based physician survey database, which is based on a sample of approximately 3,200 U.S. office-based physicians. Additionally, clinicians may be reluctant to report that they are using domperidone for lactation enhancement or any other purpose given that it is not approved for human use in the U.S. (Encuity Research, LLC, TreatmentAnswers, 2015)

Although the review did not find definitive evidence to support that domperidone is being used to enhance lactation in the US, prescriptions were written for women of

reproductive age and a portion of prescriptions were written by OB/GYNs. There is concern that domperidone is being used for lactation enhancement in the U.S.

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

Domperidone is approved and marketed for certain GI conditions in over 40 countries. Recently, however, significant restrictions have been placed on the approved use of domperidone, including removal of certain GI indications, over-the-counter status, and higher dose formulations, due to cardiac safety concerns (see section B.2 –domperidone-regulatory history).

Conclusions:

It is unknown exactly how long domperidone has been compounded in the U.S., although one can conclude that it has been compounded for at least a decade. FDA's analysis of drug utilization data indicates that approximately 7,500 to 11,600 domperidone prescriptions are dispensed annually. FDA has placed an Import Alert on domperidone since 2004. Domperidone (oral and rectal suppository formulations) is approved outside the US, although the EMA has recently restricted the drug's indications, dose and duration of treatment, and tightened safety warnings in labeling due to concerns over domperidone's serious pro-arrhythmic and cardiac risks.

III. RECOMMENDATION

We have evaluated domperidone for use in compounding based on its physicochemical characteristics, safety, effectiveness, and evidence of historical use in compounding. Based on those factors, we do not recommend that domperidone, at any dose, be included on the 503A compounding list.

Regarding its historical use, domperidone has been compounded in the U.S. for at least a decade and has been used in other jurisdictions since at least the 1970s. As stated above, its use in other jurisdictions has been increasingly restricted because of the pro-arrhythmic and cardiac risks. From a physicochemical perspective, domperidone is well-defined and acceptable for compounding.

However, both clinical and non-clinical data raise serious concerns about the safety of domperidone. At therapeutic doses approved outside the U.S., domperidone carries a serious risk of life-threatening cardiac arrhythmias and sudden cardiac death in all populations, including healthy lactating women and, potentially, their infants. Domperidone has known risks of QT interval prolongation and the dose and exposure at which domperidone can cause serious cardiac arrhythmias are not well characterized in patients. Therefore, there is potential for significant harm to the public if domperidone is prescribed and used without the important safeguards to ensure patient protection, which do not occur in the compounding setting permitted under section 503A of the FD&C Act. These safeguards include assessment of risk factors and concomitant medications that

could increase the risk of QT prolongation, appropriate dose and dose regimen selection, proper patient selection, and patient monitoring.

Moreover, the efficacy and the appropriate dosing regimen for domperidone as a galactagogue are uncertain. There is some evidence suggesting that domperidone may be beneficial for nausea/vomiting and gastroparesis, although the evidence is not robust.

Given the known, serious pro-arrhythmic risks and the unknown efficacy of domperidone for lactation, the use of domperidone for this indication is unacceptable. Similarly, given this level of uncertainty in benefits and the known risks of QT prolongation and the availability of FDA-approved products to treat these conditions, the use of domperidone for GI conditions in the compounding setting is also unacceptable.

In the U.S., domperidone is available for the treatment of certain GI conditions under an Expanded Access IND program that protects patients by assuring adequate safety monitoring, informed consent, a specified dose range, appropriate patient selection, and exclusion of factors that increase the risk of QT interval prolongation.

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APPENDIX A

The table of assessment and monitoring requirements for Domperidone INDs is taken from the "Domperidone Packet" available to physicians (FDA: Domperidone – How to Obtain, 2015).

Assessment and Monitoring Requirements for Domperidone INDs:

	Screening Visit	Every 2-Month Visit[1] (the first year)	Every 6-Month Visit[1] Thereafter
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Medical History	X	X	X
Physical Exam	X	X	X
12-Lead EKG	**See footnote #2: EKG Monitoring**		
Assessment of labs (CBC, liver panel, renal panel)	X[3]	X	X
Vital signs	X	X	X
(Re)Assessment of domperidone use (Benefit/Risk)		X	X
Review concomitant medication	X	X	X
Adverse events		X	X

1. **Required Additional Visits:**
   - ***If an increase in domperidone dose is being considered***, schedule an ***additional patient visit*** to perform each of the evaluations shown ***prior to increasing the domperidone dose***. In all patients whose domperidone dose was increased, perform each of the evaluations shown at an ***every 2-month visit for the first year after the domperidone dose was increased***, and then at an ***every 6-month visit thereafter***.
   - ***If considering starting any concomitant medication that may interact with domperidone***, schedule an ***additional patient visit*** to perform each of the evaluations shown ***prior to starting the concomitant medication*** (see list below in the section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone"). In all patients who have started any concomitant medication that may interact with domperidone, perform each of the evaluations shown at an ***every 2-month visit for the first year after the concomitant medication was started***, and then at an ***every 6-month visit thereafter***.
2. **EKG Monitoring:**
   - Screening Visit:
     - A ***new 12-Lead EKG*** will be obtained at the Screening Visit.

- Assessment Immediately After Initiation of Domperidone:
  - ***In all patients***, a 12-Lead EKG will be obtained ***3 to 7 days after domperidone is started.***
  - Timing of the EKG will be ***1 hour after the first domperidone dose of the day*** in which the EKG is done.
  - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
- Routine EKG Monitoring on a Stable Dose of Domperidone:
  - ***In all patients***, obtain an EKG at an ***every 2-month visit for the first year***, and then at an ***every 6-month visit thereafter***.
  - Timing of the EKG will be ***1 hour after the first domperidone dose of the day*** in which the EKG is done.
  - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
- Additional EKG Requirements if a Domperidone Dose Increase is Being Considered:
  - ***In all patients***, a 12-Lead EKG will be obtained ***at the additional visit prior to increasing the domperidone dose***, and ***3 to 7 days after the domperidone dose is increased***.
  - Timing of the EKG will be ***1 hour after the first domperidone dose of the day*** in which the EKG is done.
  - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
  - ***In all patients whose domperidone dose was increased***, obtain an EKG at an ***every 2-month visit for the first year after the domperidone dose was increased***, and then at an ***every 6- month visit thereafter***.
- Additional EKG Requirements if Starting Any Concomitant Medication that May Interact With Domperidone:
  - ***In all patients,*** a 12-Lead EKG will be obtained ***prior to starting the concomitant medication*** and ***3 to 7 days after the concomitant medication is started*** (see list below in the section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone").
  - Timing of the EKG will be ***1 hour after the first domperidone or domperidone/concomitant medication dose of the day*** in which the EKG is done.
  - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
  - ***In all patients who have started concomitant medications*** (see list below in the section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone"), obtain an EKG at an ***every 2-month visit for the first year after the concomitant medication was started***, and then at an ***every 6-month visit thereafter***.

3. **Assessment of Labs**:
   - Screening Visit:
     - For the initial screening, ***lab values from the prior 3 months*** may be assessed.

APPENDIX B

The "Domperidone Packet" available to physicians includes a listing of drugs that interact with domperidone and should be avoided for Domperidone INDs. That list is as follows:

1. Antidepressants: doxepin (Adapin®, Sinequan®, Zonalon®), clomipramire (Anafril®), amoxapine (Asendin®), trazodone (Desyrel®), venlafaxine (Effexor®), nefazodone (Serzone®), fluvoxamine (Luvox®), paroxetine (Paxil®), fluoxetine (Prozac®, Sarafem®), , sertraline (Zoloft®), amitriptyline (Elavil®, Endep®, Etrafon®, Limbitrol®, Triavil®), maprotiline (Ludiomil®), desipramine (Norpramin®), nortriptyline (Pamelor®), trimipramine (Surmontil®), imipramine (Tofranil®), protriptyline (Vivactil®),
2. Anti-psychotics: haloperidol (Haldol®), chlorpromazine (Thorazine®, Ormazine®), chlorpromazine pimozide (Orap®), sertindole (Serlect®), quetiapine (Seroquel®), mesoridazine (Serentil®), perphenazine (Triavil®), fluphenazine (Apo-Fluphenazine®, Modecate Concentrate®, Moditen®, Permitil®, PMS-Fluphenazine®, Prolixin®, Rho-Fluphenazine®), promazine (Sparine®), trifluoperazine (Stelazine®)
3. Anti-Emetics: prochlorperazine (Compazine®), thioridazine (Mellaril®), promethazine (Phenergan®), mesoridazine (Serentil®), thiethylperazine, (Torecan®), perphazine (Trilafon®), dolasetron (Anzemet®), dronabinol (Marinol®), droperidol (Inapsine®)
4. Anti-infective agents: erythromycin (such as E.E.S.®, E-Mycin®, Ilotycin® , Pediazole®, Aknemycin®), clarithromycin (Biaxin®), troleandomycin (TAO®), norfloxacin (Chibroxin®, Noroxin®), quinine sulfate, quinupristin and dalfopristin (Synercid®), pentamidine (Nebupent®, Pentacarinat®, Pentam®), sparfloxacin (Zagam®), grepafloxacin (Raxar®), azithromycin (Zithromax®), ofloxacin (Floxin®) levofloxacin (Levaquin®)
5. Anti-Fungal Agents: fluconazole (Diflucan®), itraconazole (Sporanox®), ketoconazole (Nizoral®), miconazole (Micatin®, Monistat®), terconazole (Terazol®), ticonazole (Vagistat®), butaconazole (Femstat 3®)
6. Antivirals: foscarnet (Foscavir®)
7. Protease Inhibitors: indinavir (Crixivan®), amprenavir (Agenerase®), ritonavir (Norvir®), nelfinavir (Viracept®), saquinavir (Invirase®, Fortovase®),
8. Anti-Hypertensives: nicardipine (Cardene®), isradipine (Dynacrirc®), moexipril/ HCTZ (Uniretic®)
9. Calcium Channel Blockers: verapamil (Calan®), diltiazam (Cardizem®), diltiazem/enalapril (Teczem®), verapamil/trandolapril (Tarka®), tocainide (Tonocard®), bepridil (Vascor®)
10. Anti-Arrhythmics: disopyramide (Norpace®, Norpace CR®), quinidine (such as Quinidex®, Cardioquin®,
    Quinaglute®, Duraquin®), procainamide (Procanbid® , Procan®, Pronestyl®,), flecainide (Tambocor®), sotalol (Betapace®), bretylium (Bretylol®), amiodarone (Cordarone®), ibutilide (Corvert®), moricizine (Ethmozine®)
11. Diueretics: bumetanide (Bumex®), furosemide (Lasix®), torsemide (Demadex®), etharcrynic Acid
    (Edecrin®), chlorothiazide (Diuril®), Indapamide (Lozol®)
12. Antilipemics: Bepridil (Vascor®), mibefradil (Posicor®),
13. Hematological Agents: cilostazol (Pletal®)
14. Respiratory Agents: zafirlukast (Accolate®), salmetrol (Serevent®)
15. Gastrointestinal Agents: cimetidine (Tagamet®), cisapride (Propulsid®)
16. Antidiarrheal: octreotide (Sandostatin®)
17. Antihistamines: azelastine (Astelin®), clemastine (Tavist®)
18. Migraine treatment: naratriptan (Amerge®), sumatriptan (Imitrex®), zolmitriptan (Zomig®)

19. Antimalarial: halofantrine
20. Muscle relaxants: tizanidine (Zanaflex®)
21. Miscellaneous: tamoxifen (Nolvadex®), warfarin (Coumadin®), phenytoin (Dilantin®), ziprasidone (Geodon®), risperidone (Risperdal®), formoterol fumarate (Foradil Aerolizer®), sildenafil (Viagra®)

APPENDIX C

The table below summarizes approved pharmacotherapies for nausea and vomiting.

Table 1. Summary of Pharmacotherapies Approved for Nausea and Vomiting

Drug	Dosage Form	Indications					
		PONV		CINV		Other NV	
		Prev-ention	Treat-ment	Prevention		Prev-ention	Treat-ment
				HEC	MEC		
5-HT3 Receptor Antagonists							
Zofran (ondansetron)	IV	√		√*	√*		
	Oral	√		√	√*	Radio-therapy	
Anzemet (dolasetron)	IV	√	√				
	Oral				√*		
Kytril (granisetron)	IV‡	√	√	√*	√*		
	Oral‡	√	√	√*	√*		
Sancuso (granisetron)	Trans-dermal			√	√		
Aloxi (palonosetron)	IV			√*,†	√*,#		
	Oral‡				√*,#		
NK1 Receptor Antagonists							
Emend (aprepitant)	Oral	√		√*,#	√*		
Emend (fosaprepitant)	IV			√*,#	√*		
Varubi (rolapitant)	Oral			√*,§	√*,§		
5-HT3 and NK-1 Antagonist							
Akynzeo (palonosetron and netupitant)	Oral			√*,#	√*,#		
Other							
Antivert (meclizine)	Oral					Motion Sickness	Motion Sickness
Compazine (prochlorperazine)	Oral‡						"severe"
	Rectal‡						"severe"
Inapsine (droperidol)	IV	√					
Marinol (dronabinol)	Oral			(√£)	(√£)		
Phenergan (promethazine)	Oral	√	√			Motion Sickness	Motion Sickness
	Rectal	√	√			Motion Sickness	Motion Sickness
Tigan (trimethobenzamide HCl)	IM		√				Gastro-enteritis
	Oral		√				Gastro-enteritis
Transderm Scop (scopolamine)	Trans-dermal	√				Motion Sickness	

CINV: Chemotherapy-Induced Nausea and Vomiting; PONV: Post-operative Nausea and Vomiting; NV: Nausea and Vomiting; HEC: Highly Emetogenic Chemotherapy: MEC: Moderately Emetogenic Chemotherapy
*initial and repeat courses; #acute and delayed; †acute; §delayed; £"nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments." (HEC or MEC indication not specified in Marinol label.)
‡The following drugs/dosage forms are discontinued: Kytril (IV and Oral), Aloxi (Oral), Compazine (Oral and Rectal)
Source: Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) and DailyMed (http://dailymed.nlm.nih.gov/dailymed/index.cfm)