

FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

March 8 and 9, 2016

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

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

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

One of the conditions that must be met for a compounded drug product to qualify for the exemptions in section 503A of the FD&C Act 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.

B. Difficult to Compound

Both sections 503A and 503B of the FD&C Act require compounded drug products to satisfy several requirements to qualify for the statutory exemptions from the FD&C Act. One of those requirements is that the compounded drug product is not one that the Agency has identified as being demonstrably difficult to compound. *See* sections 503A(b)(3)(A); 503B(a)(6).

Specifically, section 503A states that the compounded drug product may not be one that “presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.” *See* section 503A(b)(3).

Similarly, section 503B states that the compounded drug, or category of drugs, either is not one that “present[s] demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into the account the risks and benefits to patients,” or is compounded in accordance with “conditions that are necessary to prevent the drug or category of drugs from presenting [such] demonstrable difficulties.” *See* section 503B(a)(6).

FDA presented criteria to the advisory committee at its June 2015 meeting. These criteria included the following criteria which were described in more detail in the briefing materials for the meeting:

1. Complex Formulation
2. Complex Drug Delivery Mechanism
3. Complex Dosage Form
4. Bioavailability
5. Compounding Process Complexity
6. Physiocochemical or Analytical Testing Complexity

The committee provided the following recommendations which we have incorporated into the criteria for evaluation of whether drug products are demonstrably difficult to compound under sections 503A and 503B of the FD&C Act. Specifically, the committee recommended consideration of: (1) the compatibility and/or stability of the active pharmaceutical ingredients in the final dosage form (now incorporated under revised factor 1) and (2) the container closure system which may interact with the compounded drug (now incorporated into revised factor 3). In addition, the Agency has revised the document to clarify the description of each factor to more specifically track the statutory language. Attached at Tab 7 is a revised set of proposed criteria.

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

A. Quinacrine Hydrochloride (Tab 1)

1. Nominations (**Tab 1a**)
 - (a) Professional Compounding Centers of America
 - (b) National Community Pharmacists Association
 - (c) Fagron
2. FDA Reviews (**Tab 1b**)

B. Boswellia (Tab 2)

1. Nominations (**Tab 2a**)
 - (a) McGuff
 - (b) American Association of Naturopathic Physicians
 - (c) Alliance for Natural Health USA
 - (d) Integrative Medical Consortium
 - (e) American College for Advancement in Medicine
 - (f) Fagron
2. FDA Review (**Tab 2b**)

C. Aloe Vera 200:1 Freeze Dried (Tab 3)

1. Nominations (**Tab 3a**)
 - (a) International Academy of Compounding Pharmacists
 - (b) Fagron
2. FDA Review (**Tab 3b**)

D. D-Ribose (Tab 4)

1. Nominations (**Tab 4a**)
 - (a) Fagron
2. FDA Reviews (**Tab 4b**)

E. Chondroitin Sulfate (Tab 5)

1. Nominations (**Tab 5a**)
 - (a) National Community Pharmacists Association
 - (b) International Academy of Compounding Pharmacists
2. FDA Review (**Tab 5b**)

F. Acetyl-L-Carnitine (Tab6)

1. Nominations (**Tab 6a**)
 - (a) Alliance for Natural Health USA
 - (b) Integrative Medical Consortium
 - (c) McGuff
 - (d) American Association of Naturopathic Physicians
 - (e) American College for Advancement in Medicine
 - (f) National Community Pharmacists Association
 - (g) Professional Compounding Centers of America
 - (h) International Academy of Compounding Pharmacists
2. FDA Review (**Tab 6b**)

III. Drug Products That Present Demonstrable Difficulties for Compounding

The revised proposed criteria for determining whether a drug product or category of drug products is demonstrably difficult to compound are found within the document attached at **Tab 7**.

A. Metered Dose Inhalers (MDIs) (Tab 8)

1. Nominations (**Tab 8a**)
 - (a) GlaxoSmithKline
 - (b) Public Citizen's Health Research Group
2. FDA Review (**Tab 8b**)

B. Dry Powder Inhalers (DPIs) (Tab 9)

1. Nominations (**Tab 9a**)
 - (a) GlaxoSmithKline
 - (b) Public Citizen's Health Research Group
2. FDA Review (**Tab 9b**)

Tab 1

Quinacrine Hydrochloride

Tab 1a

Quinacrine Hydrochloride

Nominations



March 4, 2014

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

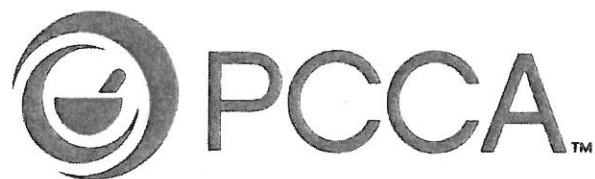
Sincerely,

A handwritten signature in black ink, appearing to read "A. Lopez", with a stylized flourish at the end.

Aaron R. Lopez, JD
Senior Director of Public Affairs
PCCA

A handwritten signature in black ink, appearing to read "John Voliva", with a stylized flourish at the end.

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



Quinacrine

Ingredient name	Quinacrine
Chemical name	Quinacrine
Common name(s)	Mepacrine, Atabrine
Chemical grade or description of the strength, quality, and purity of ingredients	Assay, Description, pH, Solubility; Example of PCCA Certificate of Analysis for this chemical is attached.
How the ingredient is supplied	Powder
Foreign Pharmacopeia recognition, including whether information has been submitted to USP for consideration of monograph development	None; not yet submitted to USP.
Bibliography of available safety & efficacy data	<p>Toubi E, et al. The reduction of serum B-lymphocyte activating factor levels following quinacrine add-on therapy in systemic lupus erythematosus. <i>Scand J Immunol.</i> 2006 Apr;63(4):299-303. [http://www.ncbi.nlm.nih.gov/pubmed/16623930]</p> <p>Canete R, et al. Randomized clinical study of five days apostrophe therapy with mebendazole compared to quinacrine in the treatment of symptomatic giardiasis in children. <i>World J Gastroenterol.</i> 2006 Oct 21;12(39):6366-70. [http://www.ncbi.nlm.nih.gov/pubmed/17072963]</p> <p>Collinge J, et al. Safety and efficacy of quinacrine in human prion disease (PRION-1 study): a patient-preference trial. <i>Lancet Neurol.</i> 2009 Apr;8(4):334-44 [http://www.ncbi.nlm.nih.gov/pubmed/19278902]</p>
Dosage form(s) into which the drug will be compounded	Capsules, Suppositories
Strength(s) of the compounded product(s)	Capsules: 25 – 200 mg Suppositories: 25 – 100 mg
Anticipated route(s) of administration	Oral, Rectal
Past & proposed use(s) of the compounded product(s)	Rheumatoid / Lupus, Antimalarial, Antiprotozoal
Available stability data for the compounded product(s)	Unless other studies performed / found: Capsule / Suppository: 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.



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

PCCA Canada
744 Third Street
London, ON N5V 5J2
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: QUINACRINE HYDROCHLORIDE
ITEM NUMBER: 30-2193
LOT NUMBER: C161238
MFG. DATE: 12/31/2013
EXPIRATION: 11/30/2018

CAS: 6151-30-0
MW: 508.9100000000
FORMULA: C₂₃H₃₀ClN₃O₂·2H₂O

TEST	SPECIFICATIONS	RESULTS
3chloro7methoxyacridone	pass	pass
Assay	>=99 %	99.60 %
Description	pass <i>BRIGHT YELLOW POWDER OR CRYSTALLINE POWDER; ODORLESS; BITTER TASTE.</i>	pass <i>Bright yellow powder</i>
Identification	pass	pass
pH	3-5	3.43
Solubility	pass <i>More soluble in hot water; slightly soluble in ethanol and methanol; insoluble in ether, benzene, acetone</i>	pass
Sulphated Ash	<0.1 % w/w	0.08 % w/w
Water	5-8 %	6.10 %

QC APPROVED
PRINT DATE: 3/3/2014
PAGE: 1 of 1

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.

PCCA Submission for Docket No. FDA-	
Ingredient Name	Quinacrine HCl
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	6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine dihydrochloride dihydrate
Common Name(s)	Mepacrine, Atabrine
UNII Code	G6242H2NAA
Chemical Grade	N/A
Strength, Quality, Stability, and Purity	Assay, Description, pH, Solubility; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmacopeias or registered in other countries	None; Used in India
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Capsules, Suppositories
Compounded Strengths	Capsules: 25 – 200 mg; Suppositories: 25 – 100 mg
Anticipated Routes of Administration	Oral, Rectal
Safety & Efficacy Data	<p>Toubi E, et al. The reduction of serum B-lymphocyte activating factor levels following quinacrine add-on therapy in systemic lupus erythematosus. Scand J Immunol. 2006 Apr;63(4):299-303. [http://www.ncbi.nlm.nih.gov/pubmed/16623930]</p> <p>Canete R, et al. Randomized clinical study of five days apostrophe therapy with mebendazole compared to quinacrine in the treatment of symptomatic giardiasis in children. World J Gastroenterol. 2006 Oct 21;12(39):6366-70. [http://www.ncbi.nlm.nih.gov/pubmed/17072963]</p> <p>Collinge J, et al. Safety and efficacy of quinacrine in human prion disease (PRION-1 study): a patient-preference trial. Lancet Neurol. 2009 Apr;8(4):334-44 [http://www.ncbi.nlm.nih.gov/pubmed/19278902]</p>

Used Previously to compound drug products	Rheumatoid / Lupus, Antimalarial, Antiprotozoal
Proposed use	Rheumatoid / Lupus, Antimalarial, Antiprotozoal
Reason for use over and FDA-approved product	Treatment failures and/or patient unable to take FDA approved product
Other relevant information - Stability information	Unless other studies performed / found: Capsule / Suppository: USP <795> recommendation of BUD for nonaqueous formulations – “no later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.



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Fax: 281.933.6627

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Fax: 519.455.0890

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CERTIFICATE OF ANALYSIS

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CAS: 6151-30-0
MW: 508.9100000000
FORMULA: C₂₃H₃₀ClN₃O₂·2H₂O

TEST	SPECIFICATIONS	RESULTS
3chloro7methoxyacridone	pass	pass
Assay	>=99 %	99.60 %
Description	pass	pass <i>Bright yellow powder</i>
Identification	pass	<i>BRIGHT YELLOW POWDER OR CRYSTALLINE POWDER; ODORLESS; BITTER TASTE.</i>
pH	3-5	3.43
Solubility	pass	pass <i>More soluble in hot water; slightly soluble in ethanol and methanol; insoluble in ether, benzene, acetone</i>
Sulphated Ash	<0.1 % w/w	0.08 % w/w
Water	5-8 %	6.10 %

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PRINT DATE: 3/3/20
PAGE: 1 of 1

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.

Submitted electronically via www.regulations.gov

March 4, 2014

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

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

Dear Sir or Madam:

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

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

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

In addition to the IACP spreadsheet of bulk drug substances referenced above, NCPA would also like to formally submit collectively for review and consideration of the FDA Pharmacy Compounding Advisory Committee the drugs and standards contained within the *British Pharmacopeia*, the *European Pharmacopeia* and the *Japanese Pharmacopeia*. NCPA respectfully requests that all drugs and standards contained within these three pharmacopeias for which no USP corresponding monograph exists be accepted and approved to be used for the preparation of compounded medications under section 503A of the *Federal Food, Drug and Cosmetic Act*.

NCPA is requesting the recognition of these pharmacopoeias as there are examples of situations when our members need access to these alternative compendia for monograph information. NCPA members may receive requests to compound medications that do not have a USP monograph, nor is the drug substance being used a component of an FDA approved drug product. When these situations arise, the *British Pharmacopeia*, the *European Pharmacopeia* and the *Japanese Pharmacopeia* are used in practice to ensure compounds are made with the highest assurance of quality.

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

Sincerely,

A handwritten signature in black ink, appearing to read "Steve Pfister", with a long horizontal flourish extending to the right.

Steve Pfister
Senior Vice President, Government Affairs

Attachment

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
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Quinacrine HCl	6-chloro-9-((4-(diethylamino)-1-methylbutyl)amino)-2-methoxyacridine dihydrochloride dihydrate	Mepacrine, Atabrine	G6242H2 NAA	From PCCA Database MSDS: Product is 100% by weight and stable.	powder	Not yet submitted to USP	Capsule, suppositories	Capsule: 25 - 200mg, Suppositories: 25 - 100mg	Oral, rectal	<p>Toubi E, et al. The reduction of serum B-lymphocyte activating factor levels following quinacrine add-on therapy in systemic lupus erythematosus. Scand J Immunol. 2006 Apr;63(4):299-303. [http://www.ncbi.nlm.nih.gov/pubmed/16623930]</p> <p>Canete R, et al. Randomized clinical study of five days of mebendazole compared to quinacrine in the treatment of symptomatic giardiasis in children. World J Gastroenterol. 2006 Oct 21;12(39):6366-70. [http://www.ncbi.nlm.nih.gov/pubmed/17072963]</p>	<p>antiprotozoal, antirheumatic</p> <p>It has a variety of actions and has been administered to millions of individuals. Its antirheumatic properties have been well documented but have not been exploited optimally for a variety of reasons. The drug is generally quite safe and could be used in low doses in lupus and rheumatoid arthritis patients as a steroid-sparing agent or synergistically with hydroxychloroquine.</p>
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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

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

Dear Sir or Madam,

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

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

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

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

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

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs



Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlsx file)

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

Fagron

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



What is the name of the nominated ingredient?

Quinacrine Hydrochloride

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

Yes, Quinacrine 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 Quinacrine pharmacological actions are provided Lerman, S J, and R A Walker. "Treatment of Giardiasis: Literature Review and Recommendations." Clin Pediatr (Phila) 21.7 (July, 1982): 409-14. Print. <http://www.ncbi.nlm.nih.gov/pubmed/7044642>

Canete, Roberto, Angel A Escobedo, Maria E Gonzalez, and Pedro Almirall. "Randomized Clinical Study of Five Days Apostrophe Therapy with Mebendazole Compared to Quinacrine in the Treatment of Symptomatic Giardiasis in Children." World J Gastroenterol 12.39 (October 21, 2006): 6366-70. Print. <http://www.ncbi.nlm.nih.gov/pubmed/17072963>

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-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine dihydrochloride

What is the common name of the substance?

Mepacrine Hydrochloride; Acrichinum ;Acrinamine; Antimalarinae Chlorhydras; Chinacrina; Hidrocloruro de atatabrina; Hidrocloruro de mepacrina; Hidrocloruro de quinacrina; Mepacrina, hidrocloruro de; Mépacrine, Chlorhydrate de ;Mepacrine Hydrochloridum; Mepakrin Hidroklorü

Does the substance have a UNII Code?

G6242H2NAA

What is the chemical grade of the substance?	BP grade
What is the strength, quality, stability, and purity of the ingredient?	Description: A yellow crystalline powder, odorless Solubility: Complies Identification A,B,C, & D: Complies Acidity: 3 - 5 3-Chloro 7-Methoxy Acridone: Complies Water: 5% - 8% Sulphated Ash: ≤ 0.1% Assay: ≥ 99%
How is the ingredient supplied?	Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	No foreign pharmacopeia monographs. Acrisuxin (Chemomedica, Austria) ,Acrisuxin (Geistlich, Switz.) ,Acrisuxin (Gewe, Ger.) ,Atabrine (Winthrop, Canad.) ,Collagenan (Beecham, Fr.) ,Maladin (Unicure, India) ,Quinacrine Soluble (May & Baker, UK)
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?	25-100mg
What are the anticipated route(s) of administration of the compounded drug product(s)?	Oral

<p>Are there safety and efficacy data on compounded drugs using the nominated substance?</p>	<p>Lerman, S J, and R A Walker. "Treatment of Giardiasis: Literature Review and Recommendations." Clin Pediatr (Phila) 21.7 (July, 1982): 409-14. Print. http://www.ncbi.nlm.nih.gov/pubmed/7044642</p> <p>Product Information: Atabrine(R). Sanofi Winthrop Pharmaceuticals, NY, NY, 1995 (discontinued), 1995.</p> <p>Canete, Roberto, Angel A Escobedo, Maria E Gonzalez, and Pedro Almirall. "Randomized Clinical Study of Five Days Apostrophe Therapy with Mebendazole Compared to Quinacrine in the Treatment of Symptomatic Giardiasis in Children." World J Gastroenterol 12.39 (October 21, 2006): 6366-70. Print. http://www.ncbi.nlm.nih.gov/pubmed/17072963</p>
<p>Has the bulk drug substance been used previously to compound drug product(s)?</p>	<p>Capsules</p>
<p>What is the proposed use for the drug product(s) to be compounded with the nominated substance?</p>	<p>Alternative treatment for Cestodiasis and Giardiasis</p>
<p>What is the reason for use of a compounded drug product rather than an FDA-approved product?</p>	<p>No FDA approved preparation for Quinacrine. Although Quinacrine is an FDA approved product it is currently unavailable on the market. It is very effective against giardia infection. It can be compounded to battle resistan strains of Giardia to Metronidazole or Tinidazole and be used as a first line treatment. (T. Gardner and D.Hill (2001) treatment of Giardiasis Clinical Microbiology Reviews Jan:114-128) Quinacrine is found to be 95% effective in 5-10days. It is a very effective option for this parasitic infection.</p>
<p>Is there any other relevant information?</p>	<p>All relevant information was expressed in the above questions</p>

Tab 1b

Quinacrine Hydrochloride

FDA Reviews



DATE: February 3, 2016

FROM: Shrimant Mishra, MD
Medical Officer, Division of Anti-Infective Products

Chunchun Zhang, PhD
Chemistry Reviewer, Office of New Drug Products
Office of Pharmaceutical Quality

Wendelyn Schmidt, PhD
Pharmacology/Toxicology Supervisor
Division of Anti-Infective Products

THROUGH: Edward Cox, MD MPH
Director, Office of Antimicrobial Products

Sumathi Nambiar, MD MPH
Director, Division of Anti-Infective Products

Dmitri Iarikov, MD PhD
Clinical Team Leader, Division of Anti-Infective Products

Ramesh Sood, PhD, Senior Scientific Advisor (acting),
Office of New Drug Products, Office of Pharmaceutical Quality

TO: Pharmacy Compounding Advisory Committee

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

I. INTRODUCTION

Quinacrine hydrochloride (HCl) 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 the treatment of rheumatoid arthritis, lupus, as an antimalarial and an antiprotozoal. This review is focused on the use of quinacrine HCl in infectious disease indications. The use of quinacrine HCl for other indications will be addressed separately.

We have reviewed available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this drug substance related to use as an antimalarial, an antiprotozoal, and an anti-tapeworm drug. For the reasons discussed below, we **do not recommend** that quinacrine HCl 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 for use in infectious diseases.

II. HISTORICAL BACKGROUND

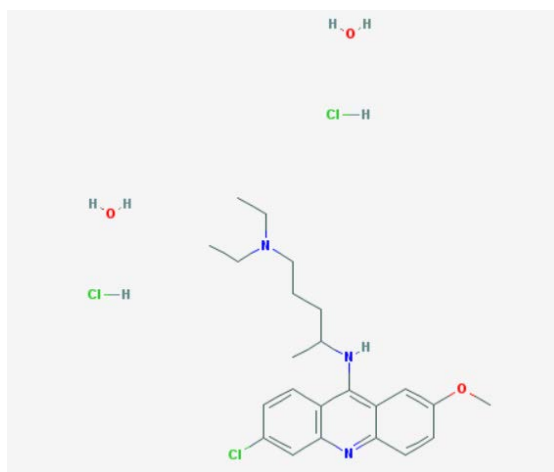
Quinacrine HCl is an antimalarial agent that was originally produced in the 1920's. In the 1940's, oral quinacrine HCl, marketed as Atabrine, became heavily used as a malaria treatment and prophylaxis agent, particularly for U.S. soldiers and Allies in World War II, due to the limited availability of quinine. By the end of World War II, its use in malaria had declined because of the development and efficacy of chloroquine. Atabrine marketing was discontinued in 1995. An injectable formulation of quinacrine HCl was approved in the United States in 1964 for treatment of ascites due to various cancers but marketing of this drug product was discontinued in 1977, and the NDA was withdrawn in 2003 (Health Hazard Evaluation, 1998; Federal Register 2003).

III. EVALUATION CRITERIA

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

This information was obtained via searches of the Micromedex database followed by cross-references with the Physician's Desk Reference.

Quinacrine HCl is 6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine dihydrochloride dihydrate; its structure differs only slightly from chloroquine (Wallace, 1989).



1. Stability of the API and likely dosage forms

Literature cited below indicates that quinacrine HCl, also known as quinacrine dihydrochloride dihydrate, is stable when protected from light. The PCCA Certificate of

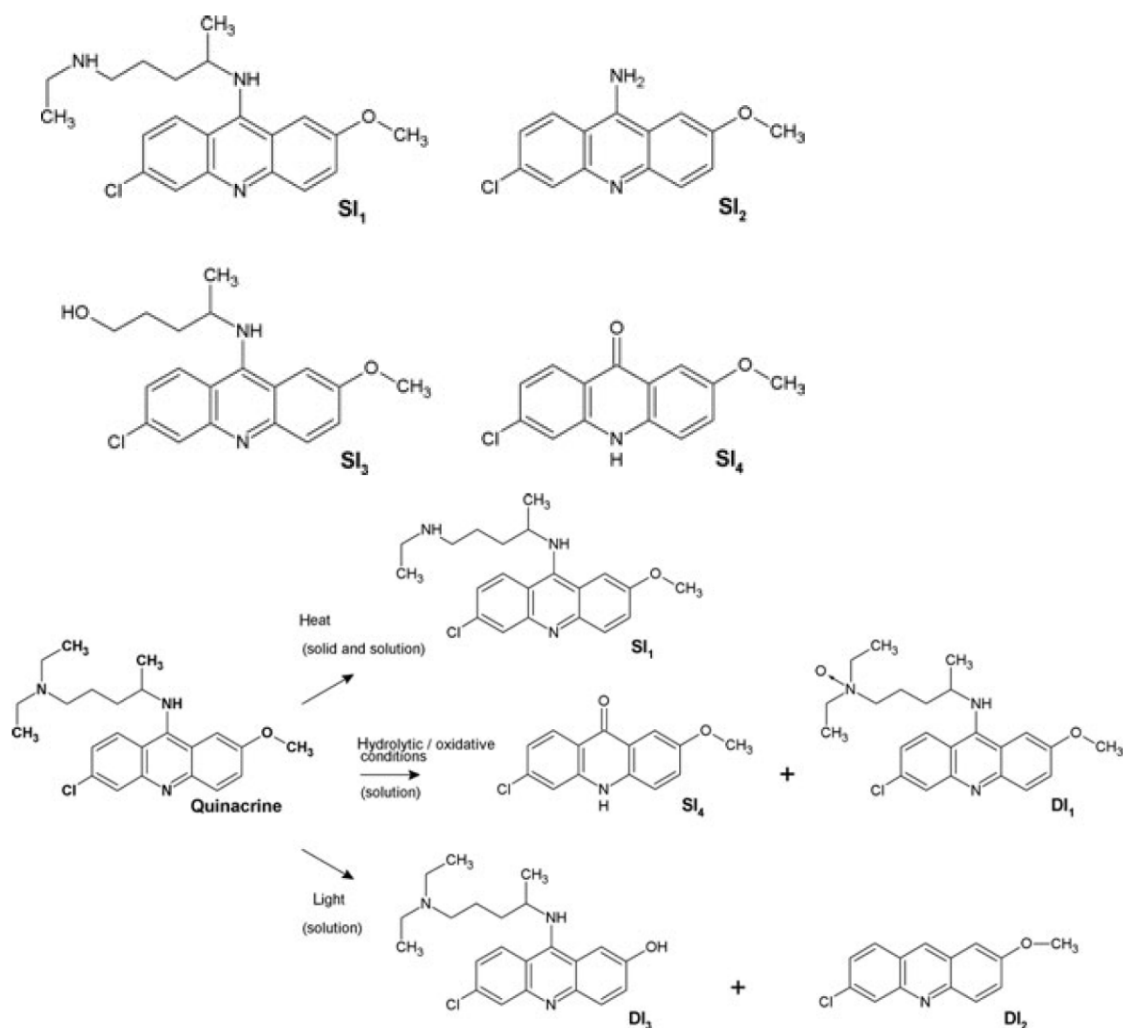
Analysis (CoA) provided with the nomination indicates that quinacrine dihydrochloride dihydrate is stable for five years (Rotival, 2011; Material Safety Data Sheet, 2006).

2. Probable routes of API synthesis

Quinacrine hydrochloride (also called quinacrine dihydrochloride dihydrate) is commercially available and patented. As described in the patents, the compound is prepared by condensing 1-diethylamino-4-aminopentane with 3,9-dichloro-7-methoxyacridine (Winthrop Chemical Company 1938; Abbot Laboratories, 1944).

3. Likely impurities

Quinacrine HCl appears to be available in a highly pure form. According to the PCCA CoA provided with the nomination, it can be obtained in a purity of 99.6%. We also identified another source of the substance available in a purity of 97%. Four impurities (SI1-SI4) are likely present in the drug substance under recommended storage conditions. The proposed degradation pathways of quinacrine HCl in solid state and aqueous solution are shown below (Rotival, 2011).



4. *Toxicity of those likely impurities*

Literature references indicate quinacrine HCl is mutagenic, as discussed further below, and clastogenic in vitro. The identified potential impurities are also possible genotoxins and mutagens (Rotival, 2011; Clarke et al., 2001).

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

Quinacrine HCl is a yellow powder with a melting point of 248-250 °C. The water solubility is 2.8 g/100 mL. The particle size distribution and polymorphism have not been reported.

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 other relevant information.

Conclusions: Quinacrine HCl (also called quinacrine dihydrochloride dihydrate) is well characterized, physically and chemically. It can be obtained in a highly pure form and is very stable when protected from light. As indicated above, quinacrine dihydrochloride dihydrate and related impurities are potentially mutagenic.

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

1. *Nonclinical Assessment*

The following information is summarized from the references listed below, which are the results of a search of Google, EMBASE, and Micromedex.

a. Pharmacology of the drug substance

Quinacrine HCl (marketed as Atabrine or Mepacrine) has been used in the treatment of giardiasis, malaria, lupus, rheumatoid arthritis, and cancer, as well as for female sterilization. Proposed mechanisms of action include DNA intercalation interference with RNA transcription and translation, inhibition of succinate oxidation interference with electron transport, inhibition of cholinesterase, and inhibitor of phospholipase A2.

b. Safety pharmacology

No safety pharmacology data are available for quinacrine HCl.

c. Acute toxicity

By the oral route, the median lethal dose (LD50) in the mouse was 1000 mg/kg while the LD50 in the rat was 900 mg/kg.

d. Repeat dose toxicity

Fischer 344 rats were fed a diet with 1000, 500, or 250 ppm quinacrine HCl for up to 2 years. The rats at 1000 and 500 ppm died with atrial thrombosis in combination with focal myocardial degeneration and congestion of lungs, liver and other organs. Hypertrophied myocardial cells with vacuoles and fibrosis were also noted. Necrosis of central liver parenchymal cells was also observed. Serum chemistries were not reported (Reuber, et.al., 1984).

e. Mutagenicity

Quinacrine HCl is a DNA intercalator. It was positive for mutagenicity in the AMES TA 1537, TA98 and WP2 strains (negative in TA100 and TA 1535). Quinacrine HCl was positive in the mouse lymphoma cell line and positive for chromosomal aberrations (but not polyploidy) in Chinese hamster ovary (CHO) cells. In vivo, the mouse micronucleus assay was negative (Clarke et al., 2001).

f. Developmental and reproductive toxicity

Quinacrine HCl was administered subcutaneously to rats at 120 mg/kg/day on gestation days 13 through 19. Increased fetal death, but no teratogenic changes were observed. Levels of quinacrine HCl in the liver were 549 mcg and 9 mcg in dams and fetii respectively (de RB, 1950). Blake et al. reported that intrauterine instillation of 0.4 to 4 mg of quinacrine HCl during pregnancy in the rat resulted in dose dependent increases in fetal mortality (In Zatuchni et al., 1983). Fetal death was also noted with intrauterine instillation in pregnant monkeys at 3 mg. Goodman and Gilman 1980 notes that quinacrine HCl should not be given to pregnant women as the drug readily crosses the placenta to the fetus (Goodman et al., 1980).

g. Carcinogenicity

A non-traditional carcinogenicity study is discussed in a separate consult, prepared by the Division of Bone, Reproductive, and Urologic Products.

h. Toxicokinetics

Quinacrine HCl by the oral route is rapidly absorbed in the rat. Distribution is primarily to the liver (concentration may be over 20,000 times higher than in plasma) and minimally to the cerebrospinal fluid (1-5% of plasma levels). Urinary excretion accounts for approximately 10% of the dose/day. Detectable levels may still be found in urine two months after cessation of therapy. The half-life is 5 to 14 days.

Conclusions: The nonclinical data for quinacrine HCl are scarce, particularly when limited to administration by the oral route using a tablet formulation. A rat study by Reuber et al., suggests that heart and liver are primary targets of toxicity, which correlates with liver accumulation (Reuber et al., 1984). Positive results were seen in mutagenic and clastogenic assays, but not in a mouse micronucleus assay. The Atabrine label and Goodman and Gilman note that the use of quinacrine is not recommended during pregnancy as the drug crosses the placenta. The evidence of mutagenicity, carcinogenicity, and developmental/ reproductive toxicity raise concerns about the safety of quinacrine HCl.

2. *Human Safety*

a. Reported adverse reactions

The safety profile of oral quinacrine HCl is well described in the various sources cited below. Safety of the use of quinacrine HCl is in part dependent on dose and duration.

i. Label of Discontinued Quinacrine HCl Product

As of the date of its discontinuation in 1995, the prescribing information for Atabrine included a boxed warning stating that “[p]hysicians should completely familiarize themselves with complete contents of this leaflet before prescribing Atabrine.”

The warnings section of the prescribing information indicated, among other adverse reaction, the following:

- Quinacrine may occasionally cause a transitory psychosis and should be used with special caution in patients over 60 years of age or in those with a history of psychosis.
- Use of quinacrine in patients with psoriasis may precipitate a severe attack of psoriasis.
- Quinacrine may exacerbate porphyria.

The warnings section concluded that the drug should not be used in patients with psoriasis and porphyria unless in the judgment of the physician, the benefit outweighs the possible hazard (Physician's Desk Reference, 1985).

The precautions section of the quinacrine HCl prescribing information stated that the drug should be used with caution in patients with hepatic disease of alcoholism or in conjunction with known hepatotoxic drugs. The Precautions section also indicated that quinacrine HCl should be administered with caution to patients with G-6-PD deficiency (Physician's Desk Reference, 1985). Quinacrine HCl was not recommended for use in pregnancy (Physician's Desk Reference, 1985).

ii. Adverse Reactions Described in Literature and the Atabrine Package Insert

Adverse reactions associated with quinacrine HCl use include the following:

Dermatologic effects

Yellowish discoloration of the skin, mucous membranes, and conjunctiva as well as a bluish- black discoloration of the nails has been observed. Discoloration generally occurs within 1 to 2 weeks after initiation of therapy and persists for 2 weeks to 4 months.

Quinacrine HCl can be associated with significant rashes, including eczematous and exfoliative rashes as well as worsening of psoriasis (Wallace, 1989; Physician's Desk Reference, 1985). Among 120,000 Australian soldiers who received quinacrine HCl, the incidence of lichen planus (a skin disease) was 1 in 2,000 in those receiving 100 mg/day (Wallace, 1989).

Gastrointestinal disorders

Nausea, diarrhea, vomiting, and abdominal cramps have been commonly associated with quinacrine HCl use (Physician's Desk Reference, 1985).

Hematologic effects

Aplastic anemia is one of the most serious adverse reactions associated with quinacrine HCl use. The incidence of quinacrine HCl -associated aplastic anemia was assessed based on the rates of aplastic anemia in soldiers who received quinacrine HCl for prophylaxis of malaria. There was almost a five-fold rise in the incidence of aplastic anemia within two years of introduction of quinacrine, from 0.66 to 2.84 cases per 100,000 soldiers (Wallace, 1989; Brio, 1965). One third of these cases were determined to be due to quinacrine HCl overdose or concomitant drugs known to be associated with aplastic anemia. Aplastic anemia developed after patients received quinacrine HCl at 100 mg daily for 3 months or longer and was often heralded by a lichen planus rash (Wallace, 1989; Physician's Desk Reference, 1985; Brio, 1965). Approximately 70% of the above cases were associated with patients presenting with lichenoid tissue reactions several months prior to the onset of aplastic anemia. When quinacrine HCl was used in patients with lupus with additional safety precautions, including monitoring of complete blood count (CBC), drug discontinuation after 8 weeks if no effect was seen or lichen planus developed or hemoglobin/reticulocyte count dropped, and in a daily dose not exceeding 100 mg, the incidence of aplastic anemia was assessed at 1: 500,000 patients (Wallace, 1989).

Hepatic effects

Elevated liver function tests and, rarely, hepatitis have occurred during long-term and short-term quinacrine HCl therapy (Physician's Desk Reference, 1985; Eshleman et al., 1970; Scoazec et al., 2003). Hepatitis was associated with therapeutic doses of quinacrine HCl and was considered an idiosyncratic unpredictable reaction similar to that caused by halothane (Gibb et al., 1985). Changes in liver tests were detected from 7 to 42 days after initiation of quinacrine HCl. Histological changes in the liver of patients who developed quinacrine HCl associated hepatitis included cytolysis, cholangitis characterized by marked duct wall fibrosis mimicking primary sclerosing cholangitis, and portal inflammatory infiltrates containing lymphocytes, plasma cells, and eosinophils(

Scoazec et al., 2003). In a comparative trial of quinacrine HCl in the treatment of Creutzfeldt-Jakob disease elevation in liver tests were noted at a higher rate in the quinacrine HCl arm (3/26 patients) as compared to the placebo arm (0/28 patients (Geschwind et al., 2013). In another trial in the treatment of Creutzfeldt-Jakob disease 16 out of 40 patients treated with quinacrine HCl discontinued the drug due to alanine aminotransferase elevation (Collinge et al., 2009). The rate of liver test abnormalities in the control arm in this trial was not reported.

Neurologic and Psychiatric effects

Quinacrine HCl can also have significant psychiatric effects including restlessness, insomnia, and psychosis (Physician's Desk Reference, 1985; Lally et al., 2012). One large study of 7,604 U.S. soldiers in the Second World War found an incidence of 0.4% for quinacrine HCl -induced psychosis (Wallace, 1989). Convulsions have occurred after administration of quinacrine HCl (Rockwell, 1968).

Ophthalmic effects

Reversible corneal edema or deposits, manifested by visual halos, difficulty focusing and blurred vision have been reported in patients taking quinacrine HCl long-term for malaria suppression (Physician's Desk Reference, 1985; Rockwell, 1968). Retinopathy has been reported in patients who received quinacrine HCl even for a short-term treatment of parasitic diseases. However, in comparison to chloroquine or hydroxychloroquine, quinacrine HCl -associated retinal toxicity appears to be less frequent (Zuehlke et al., 1981; Cox et al., 1994).

iii. Safety issues associated with non-oral use of quinacrine HCl.

As a female sterilizing agent, quinacrine HCl was originally studied using a slurry formulation that was instilled into the uterine cavity (Zipper et al., 1970). However, three deaths were reported (in the US and Bangladesh). It is unclear whether the deaths were due to erosion of the uterus and subsequent spillage of quinacrine HCl into the peritoneum or to effects of systemic exposure to quinacrine HCl. Quinacrine HCl pellets were subsequently used for female sterilization.

As regards the pellet formulation, on August 26, 1998, a safety assessment and Health Hazard Evaluation was conducted by FDA on a kit for uterine insertion of quinacrine HCl pellets for female sterilization [see Appendix 1]. In this evaluation, FDA raised concerns in three areas based on results from previously conducted toxicology studies on the oral formulation and the lack of adequate toxicology testing on the intrauterine pellet formulation:

- (1) possible carcinogenicity of quinacrine; specifically, quinacrine is a known mutagen and had tested positive in several genotoxicity tests, and the intrauterine administration of quinacrine pellets would result in significant tissue damage and the presence of known mutagen could result in development of cancer of the reproductive tract;

- (2) lack of sufficient pharmacokinetic data, specifically, concerns exist on the possible continuous exposure of the endometrium to the drug following intrauterine insertion; and
- (3) pharmacodynamic issues, specifically, that intrauterine instillation of the cytotoxic agent had been noted to be unsuccessful for complete destruction of the endometrium and had resulted in neoplastic transformation of residual endometrial cells.

The evaluation noted that drugs with positive mutagenicity and cytotoxicity profiles, such as quinacrine HCl, were of concern with regard to increased cancer risks in humans. FDA concluded that the potential and known risks may outweigh any proposed advantages this procedure may have over surgical sterilization in the United States.

On October 14, 1998, FDA issued a warning letter regarding unapproved quinacrine HCl pellets labeled for non-surgical female sterilization [see Appendix 2]. In this letter, FDA highlighted many of the same safety concerns identified in the August 1998 Health Hazard Evaluation summarized above and concluded that non-surgical female sterilization is an unsafe use of quinacrine HCl pellets. Citing safety concerns, FDA requested that the unapproved quinacrine HCl pellets for non-surgical female sterilization be immediately removed from the market. In October 2008, a WHO Panel recommended that “until the totality of safety, effectiveness and epidemiological data has been reviewed, quinacrine HCl should not be used for non-surgical sterilization of women in either clinical or research settings.” To date, this interim statement has not been updated or removed.

Oral formulations of quinacrine HCl have also been used for pleurodesis. When used for pleurodesis, quinacrine HCl has been associated with chest pain (Dikensoy et al., 2005).

b. Clinical trials assessing safety

Please refer to section B (2) (a) of this review. Given the amount of public information available, analyses of safety data are based on the cumulative analyses of literature rather than on particular clinical studies of quinacrine HCl.

c. Pharmacokinetic data

When administered orally, quinacrine HCl is rapidly absorbed from the GI tract, even in the presence of severe diarrhea. Plasma levels increase in 2 to 4 hours and reach a peak in 8 to 12 hours. Quinacrine HCl is distributed widely in tissues and can accumulate over time, particularly in the liver (Wallace, 1989; Physician’s Desk Reference, 1985). Due to accumulation in body tissues, quinacrine HCl is eliminated slowly from the body, primarily through urine with less than 11% of elimination daily. As noted above, quinacrine HCl can cross the placenta and reach the fetus (Wallace, 1989).

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

Safer first line alternative therapies are available for all infectious disease indications for which quinacrine HCl would be utilized.

While quinacrine HCl was once considered a first-line treatment for giardiasis, an intestinal protozoal infection presenting as diarrhea and abdominal discomfort, tinidazole and nitazoxanide have been approved and replaced quinacrine HCl for this indication. In addition, metronidazole is commonly used off-label for the treatment of giardiasis.

However, recently, there has been some increase in the use of quinacrine HCl for the treatment of cases nonresponsive to nitroimidazoles. These cases are commonly described as refractory giardiasis and present as recurrent episodes of diarrhea which may be associated with weight loss and malnutrition.

A recent case series supplemented by a literature review described 110 cases of giardiasis that failed treatment with nitroimidazoles (Meltzer et al., 2014). The cases were reported between 1962 and 2013. In 21 out of 110 cases, patients were retreated with quinacrine HCl monotherapy and 19 out of 21 were cured. In 2 cases, subjects were cured with quinacrine HCl after failure of several courses of nitroimidazoles, albendazole, and nitazoxanide. In 14 out of 110 cases, patients were retreated with a combination of quinacrine HCl and a nitroimidazole and all 14 patients were cured.

Another literature review reported successful treatment of refractory giardiasis with a quinacrine-nitroimidazole combination (Escobedo et al., 2014). The usual dosage of quinacrine HCl for the treatment of giardiasis was 300 mg a day in divided doses for 5-10 days. It should be noted that most of the quinacrine HCl use occurred outside of the United States.

In taeniasis (tapeworm infection), quinacrine HCl has been replaced by praziquantel and is no longer used in the United States to treat this condition.

Quinacrine HCl is no longer used as an anti-malarial drug because more effective and less toxic alternatives are available, such as chloroquine, mefloquine, atovaquone-proguanil, and artemether-lumefantrine.

As noted above, quinacrine HCl's effect on prion disease is being explored in two recently completed trials; they do not appear to show positive findings (Geschwind et al, 2013; Collinge et al., 2009).

Conclusions: The well-known safety profile of quinacrine HCl presents significant concerns about the use of this substance in compounded drug products, which do not carry the same labels and warnings as approved products. Quinacrine HCl is known to be mutagenic and is not recommended for use in pregnancy. Adverse effects related to the use of quinacrine HCl include aplastic anemia, hepatitis, severe dermatitis, and exacerbation of psoriasis and psychosis. Several FDA-approved drugs have demonstrated safety for use as anti-malarials and anti-protozoals.

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 indicated above, although the evidence is limited to analyses of case reports/series and no controlled trials of quinacrine HCl in treatment of refractory giardiasis were identified, quinacrine HCl has been successfully used in the treatment of giardiasis that was non-responsive to other anti-protozoal drugs (Zipper et al., 1970; Dikensoy et al., 2005).

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

No. Giardiasis and tapeworm infection would not be considered serious or life threatening. Quinacrine HCl is no longer used for the treatment of malaria.

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

Yes, there are more effective first-line alternatives for the majority of infectious diseases where quinacrine HCl may be potentially used. Please see comments to section B (2) (d).

Conclusions: There are more effective first-line alternative drugs for the majority of infectious diseases where quinacrine HCl may be potentially used. However, limited literature data suggest that quinacrine HCl might be effective in patients with giardiasis refractory to commonly used agents. Quinacrine HCl is not currently used for the other indications reviewed in this consult, including for no serious or life-threatening conditions.

D. Has the substance been used historically in compounding?

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

Given the recent unavailability of quinacrine HCl by traditional avenues since the discontinuation of atabrine in 1995, there has been moderate experience using this drug in its compounded form. However, it's unclear how much of that use occurs in the United States, particularly with regard to use in refractory giardiasis (most such cases appeared to occur in Europe). The use associated with compounding in the US is more likely to be associated with treatment of rheumatologic conditions, which are addressed in a separate consult.

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

At the time of its discontinuation in 1995, the oral quinacrine HCl product label included the following indication statement: "ATABRINE is indicated for the treatment of

giardiasis and cestodiasis” (Physician’s Desk Reference, 1985). Currently, quinacrine HCl is being used in a variety of ways worldwide for treatment of both infectious and noninfectious diseases. In terms of infectious disease uses, quinacrine HCl currently is used primarily as an agent to treat refractory or chronic giardiasis. It has also been used as an anti-tapeworm agent and is currently being explored as an agent to treat prion diseases (Geschwind et al., 2013; Collinge et al., 2009). In terms of noninfectious uses, quinacrine HCl has been used to treat lupus (particularly cutaneous lupus), rheumatoid arthritis, refractory pulmonary effusion and pneumothorax, induce female sterilization, and is being explored for use as an adjuvant treatment for particular tumors.

Quinacrine HCl’s noninfectious disease uses appear to outstrip its infectious disease uses in both diversity of usage and prevalence. Quinacrine HCl pellets were used in many developing countries in the 1980’s and early 1990’s as a nonsurgical contraceptive agent. The pellets were delivered through an IUD and found to induce scarring in the endometrial wall/fallopian tubes. Though the rate of current usage of this method is unclear because of safety concerns related to the medication, there is evidence of at least some relatively recent usage (Afzal, 2014; Jensen, 2014).

Quinacrine HCl has recently reemerged for use in cutaneous lupus erythematosus, particularly refractory cases in combination with the other antimalarials (Chang et al., 2011; Kuhn et al., 2011). Generally, the dose is around 100 mg a day (though higher doses can be given), and it is given for a prolonged period of potentially several months; its maximal effect takes 6-8 weeks (Kuhn et al., 2011). It can also be used instead of the other antimalarials in subjects with preexisting retinopathy. The supply appears to come from compounding pharmacies. Quinacrine HCl may also be useful in other rheumatologic illnesses such as dermatomyositis (Ochsendorf, 2010). Quinacrine HCl is being explored for use against several tumor types due to particular anti-neoplastic activities noted in vitro (Hede, 2011). Quinacrine HCl is also used for the treatment of pleurodesis though its use may be more targeted to non US regions (particularly Scandinavia)

3. *How widespread its use has been*

It is difficult to estimate how widespread the compounding of quinacrine HCl has been. In infectious diseases its use seems to be rather limited.

Though quinacrine HCl has been used to treat a wide variety of medical conditions, it is still unclear how frequently such usage occurs, particularly in the United States. Indeed, its use in Spain was noted to be minimal due to lack of availability and information on its use (Gonzalez-Sixto et al., 2010).

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

It appears that quinacrine HCl is still used in some countries for the treatment of giardiasis and tapeworm infections in a limited number of patients. Quinacrine HCl also has been used as a sterilization agent in females more recently. It is unclear, however,

whether quinacrine HCl in other countries is used in compounded or manufactured formulations.

Conclusions: We cannot estimate the use of quinacrine HCl through compounding and have not found evidence to indicate that for infectious diseases indications more than a limited amount of quinacrine HCl has been compounded in the United States.

III. RECOMMENDATION

Although quinacrine HCl was initially used as an antimalarial agent, its current usage in infectious diseases is limited to rare cases of refractory giardiasis, mostly outside the United States. Quinacrine HCl is now primarily used for noninfectious indications including systemic lupus erythematosus (SLE), nonsurgical female sterilization, pleurodesis, and exploratory treatment of prion diseases and various tumors. Much of this usage also occurs outside the United States.

We have evaluated quinacrine HCl, as an antimalarial and an anti-tapeworm agent, for use in compounding based on its physicochemical characteristics, safety, effectiveness, and evidence of historical use in compounding. It is well-characterized, physically and chemically, and there is some evidence of its historical use in compounding, at least since the marketed version of the drug was discontinued. Regarding safety, however, quinacrine HCl is a known mutagen and is associated with serious adverse reactions such as aplastic anemia, hepatitis, severe dermatitis, exacerbation of psoriasis, and psychosis. Furthermore, when quinacrine HCl was marketed, its use was not recommended during pregnancy, and the label warned that special caution should be exercised when it was used in patients over 60 years of age. All these safety concerns resulted in the inclusion of a boxed warning in the quinacrine HCl label. Regarding efficacy, there is some limited evidence related to its use for giardiasis but not for the treatment of malaria or tapeworms. There are FDA-approved products available for these indications that have demonstrated safety and effectiveness.

Therefore, the use of quinacrine HCl without providing complete prescribing information presenting directions for use, risks, and warnings, as would be the case if the drug is allowed for compounding, may be associated with increased risks to the patients. For infectious disease indications, these risks are not outweighed by the benefits of quinacrine HCl, given the limited evidence of efficacy and the availability of other alternative treatments for anti-malarial and anti-protozoal uses. Given all the above considerations, we do not recommend that quinacrine HCl be added to the list of drug substances that can be used for compounding for the treatment of infectious diseases. In a limited setting, whether for an individual patient or for research purposes, it would be more appropriate to obtain quinacrine HCl through the expanded access IND process, where the provision of safety information may be secured. However, the risk-benefit considerations for this substance might be weighed differently for other treatment areas.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: February 5, 2016

FROM: Keith M Hull, M.D., Ph.D.
Medical Officer, Division of Pulmonary, Allergy, and Rheumatology
Products

THROUGH: Nikolay P. Nikolov, M.D.
Clinical Team Leader, Division of Pulmonary, Allergy, and
Rheumatology Products

Sarah Yim, M.D.
Associate Director, Division of Pulmonary, Allergy, and Rheumatology
Products

Badrul Chowdhury, M.D., Ph.D.
Division Director, Division of Pulmonary, Allergy, and Rheumatology
Products

TO: Pharmacy Compounding Advisory Committee

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

INTRODUCTION

Quinacrine hydrochloride (HCl) has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The substance was nominated for use in the treatment of rheumatoid arthritis and lupus as an antimalarial and an antiprotozoal. This consult is limited to an assessment of the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) assessment of the appropriateness of including quinacrine HCl on the 503A bulk drug substances list as it pertains to the lupus and rheumatoid arthritis uses.

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 quinacrine HCl *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.

EVALUATION CRITERIA

Please see the review prepared by the Division of Anti-Infective Products (DAIP) and the Office of Pharmaceutical Quality for information on the physical and chemical characteristics and non-clinical safety of quinacrine HCl.

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

We have reviewed the following available relevant information specific to the use of quinacrine hydrochloride for rheumatoid arthritis or lupus:

- Reported adverse reactions
- Clinical trials assessing safety
- Pharmacokinetic data
- The availability of alternative approved therapies that may be as safe or safer, including approved products used off-label

This information is discussed in detail below.

Lupus

1. Background

Literature searches were conducted using the National Library of Medicine's PubMed database with the search terms *quinacrine and lupus* and *quinacrine and rheumatoid arthritis*. Searches identified a total of 170 and 31 publications, respectively. A general assessment of abstracts and electronically available publications were reviewed to evaluate for the general safety and efficacy of quinacrine HCl in patients with lupus or rheumatoid arthritis. The majority of the data assessing the safety of quinacrine HCl were derived from clinical studies conducted from the 1940s through the 1960s, and as a result, many of the individual publications were not readily available for review. Consequently, much of the safety data for this review was obtained from more recent review articles summarizing the overall safety of quinacrine HCl. However, when possible, more recent studies were reviewed and found to be consistent with the overall safety profile described in earlier studies.

The use of antimalarial drugs for the treatment of rheumatologic diseases began in 1894 when Payne (Payne 1894) reported that quinine was effective for treating cutaneous lupus. However, its widespread use was limited due to substantial toxicity at therapeutic doses. Synthetic antimalarial drugs were subsequently developed over the next five decades and determined to also be effective at treating the manifestations of cutaneous and systemic lupus erythematosus. These synthetic antimalarials included quinacrine (a.k.a. mepacrine), chloroquine, and hydroxychloroquine, all of which are the current antimalarials most commonly used for systemic and/or cutaneous lupus.

Quinacrine HCl was initially developed in the 1930s and used extensively for malaria prophylaxis and treatment. In 1951, the first report of its use for the treatment of lupus was published in *Lancet* (Page 1951) and was subsequently followed with over 30 additional reports over the next eight years further supporting its efficacy for lupus and rheumatoid arthritis (Wallace 1989). A 1959 issue of *The New England Journal of Medicine* (Tye et al., 1959) reported improvement in 44 of 45 lupus patients treated with *Triquin*, a combination product containing quinacrine HCl, chloroquine, and hydroxychloroquine. *Triquin* was later approved in 1955 by FDA for the treatment of lupus but was subsequently removed from the market in 1973 as detailed in the Review of Quinacrine for the Withdrawn or Removed List consult.

2. *Reported Adverse Reactions*

Because quinacrine HCl has a long history of clinical use, especially in the treatment of malaria, its safety profile is well understood (Wallace 2000; Canete et al., 2006; Ehsanian et al., 2011; Collinge et al., 2009). The most frequently reported adverse reactions associated with quinacrine HCl include diarrhea, nausea, vomiting, abdominal pain, headache, and yellowing of the skin and mucous membranes. Rare cases of transient lupus-associated quinacrine HCl-induced hepatitis and peritonitis have been reported (Gibb et al., 1985), although these were attributed to doses three-fold higher than the generally recommended dose of 100 mg daily (See et al., 1998). At higher doses, patients have reported restlessness, vertigo, insomnia, nightmares, hyperirritability, and convulsions. Several publications have reported quinacrine HCl-induced psychosis ranging from 0.1-0.4% of patients (Lidz et al., 1946; Gaskill et al., 1945). Although rare, the most serious potential toxicity associated with quinacrine HCl is aplastic anemia, which was observed at rate of between 0.66-2.84 cases/100,000 soldiers treated with quinacrine HCl during World War II (Gonzalez-Sixto et al., 2010; Custer 1946; Palmer et al., 1953; Paton et al., 1955). One third of these cases were determined to be due to quinacrine HCl overdose or concomitant drugs known to be associated with aplastic anemia. Approximately 70% of the remaining cases were associated with patients presenting with lichenoid tissue reactions several months prior to the onset of aplastic anemia. Therefore, the rate of aplastic anemia in patients treated with quinacrine HCl who did not present with a lichenoid reaction is approximately 1 case/500,000 patients (Wallace 1994).

Like quinacrine, hydroxychloroquine and chloroquine have been associated with serious side effects such as hematologic effects (e.g., reversible agranulocytosis and aplastic anemia) and neurologic effects (e.g., psychosis, seizures). Because quinacrine does not appear to cause retinopathy, which is dose-related and irreversible with hydroxychloroquine and chloroquine, it is not uncommon for rheumatologists to add quinacrine when a patient appears to require additional antimalarial therapy and increasing the dose of hydroxychloroquine or chloroquine is not desirable due to the concern for retinal toxicity.

3. *Pharmacokinetic Data*

Quinacrine HCl is most commonly administered orally, where it is rapidly absorbed from the gastrointestinal tract with plasma levels increasing 2 to 4 hours after administration and peaking in 8 to 12 hours (Campbell 1986; Joint Report 1946; Wallace 1989). Plasma concentrations increase rapidly during the first week of administration and plateau by the fourth week. In general, tissue concentrations of quinacrine HCl are many fold higher compared to plasma levels. The highest concentrations are found in the liver, spleen, lungs, integument, and adrenal glands while the lowest concentrations are found in the brain, heart, and skeletal muscle (Shannon et al., 1944; Goodman et al., 1954). The half-life of quinacrine HCl varies between 5 to 14 days depending on the therapeutic dosing regimen and is approximately 80-90% bound to plasma proteins (Looareesuawan et al., 1988; Bjorkman et al., 1989). The major route of elimination is via renal excretion (Gaskill et al., 1945; Palmer et al., 1953).

4. *Alternative Treatments*

Although there are numerous drugs available for treating lupus, the most relevant for this discussion is the antimalarial drug hydroxychloroquine, which is FDA approved for the treatment of lupus and rheumatoid arthritis. Hydroxychloroquine was approved by FDA in 1955 and soon replaced the use of quinacrine HCl. However, quinacrine HCl is still prescribed primarily for the treatment of refractory cutaneous lupus or in conjunction with hydroxychloroquine for systemic lupus erythematosus. The rheumatology community has continually recommended the use of quinacrine HCl for the treatment of lupus, and it is listed as a treatment alternative in the scientific literature, major rheumatology text books, and online medical reference sites.

Rheumatoid Arthritis

Although monotherapy and combination therapy with antimalarial drugs have been demonstrated to be effective in treating rheumatoid arthritis, no individual study specifically evaluating quinacrine HCl could be identified using the currently available databases. However, the safety profile of quinacrine HCl would not be expected to be different in patients with rheumatoid arthritis compared to lupus patients given the overall similar safety profiles of chloroquine and hydroxychloroquine in the two diseases.

There are multiple approved therapies for rheumatoid arthritis. Medications used to slow disease progression are referred to as *nonbiologic and biologic disease-modifying antirheumatic drugs* (DMARDs). Since 1998, FDA has approved the following drugs for rheumatoid arthritis: leflunomide, etanercept, infliximab, anakinra, adalimumab, abatacept, rituximab, certolizumab, golimumab, tocilizumab, tofacitinib, golimumab intravenous (IV), and methotrexate subcutaneous injection.

Although each drug has its own specific safety profile, all of these drugs are associated with an increased risk of infection. In addition, oral glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) are approved for the treatment of rheumatoid arthritis.

Similar to DMARDs, glucocorticoids are associated with an increased risk of infection. NSAIDs are associated with gastrointestinal, renal, and cardiovascular adverse effects.

Conclusions

Millions of people have been treated with multiple doses of quinacrine HCl since the 1940s. Consequently, the safety profile has been well described in the medical literature. The most common adverse reactions involve headache, gastrointestinal symptoms, and yellowing of the skin, which are all reversible by lowering the dosage or discontinuation of the drug. The more serious adverse reactions, which include hepatitis, psychosis, and aplastic anemia, occur rarely and are typically associated with higher doses than the 100 mg/d used to treat rheumatic diseases. Performing a complete blood count and thorough skin exam every three months in quinacrine HCl-treated patients is recommended in the medical literature to screen for potential cases of aplastic anemia. Given the potential benefits of therapy in patients with refractory cutaneous lupus, discussed further below, the safety profile of quinacrine hydrochloride is acceptable considering the relative safety of other lupus treatments.

B. Are there concerns about whether the substance is effective for a particular use? If there are no data regarding effectiveness available, is the substance used to treat a serious or life-threatening condition for which there are approved alternative therapies available?

In developing our response to this question, we have considered the following, to the extent available:

- Reports of trials demonstrating effectiveness of the bulk drug substance as it is used in drug products
- Any clinical evidence of effectiveness, or lack of effectiveness, of drug products with the bulk drug substance
- Any anecdotal reports of effectiveness, or lack of effectiveness, of drug products with the bulk drug substance
- Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease
- Whether there are any alternative approved therapies that may be as effective or more effective, including approved products used off-label

Lupus

The efficacy of quinacrine HCl in treating patients with lupus was first established in 1951 (Page 1951). However, as discussed above, since the late 1950s, it has largely been replaced by hydroxychloroquine, which FDA approved in 1955 with a better characterized efficacy and safety profile.

Several review articles report a large case series involving 771 patients with discoid lupus erythematosus who were enrolled from 1940 to 1961 and described improvement with quinacrine HCl in 73% to 85% of patients (Dubois 1978; Wallace 1989). More recent

data support the use of quinacrine HCl in combination with hydroxychloroquine in patients with cutaneous lupus erythematosus. Chang et., al (2011) conducted a prospective analysis in 128 patients with cutaneous lupus erythematosus and concluded that the addition of quinacrine HCl 100 mg/d with standard doses of hydroxychloroquine was associated with an improved clinical response in patients who failed hydroxychloroquine monotherapy. Similarly, Cavazzana et., al (2009) evaluated the efficacy of hydroxychloroquine and quinacrine HCl combination therapy in the treatment of lupus skin lesions in patients refractory to hydroxychloroquine monotherapy. Thirty-four patients were treated with hydroxychloroquine 5 mg/kg/d (n=34) and either quinacrine HCl 100 mg/d (n=29) or quinacrine HCl 50 mg/d (n=5). A total of 29 of the 34 (85%) of patients demonstrated a clinical improvement with a more rapid response seen in patients receiving quinacrine HCl 100 mg/d compared to the 50 mg/d group. The authors concluded that the combination of hydroxychloroquine and quinacrine HCl was an effective therapy in the treatment of lupus skin lesions unresponsive to hydroxychloroquine alone. Three additional studies supporting the use of quinacrine HCl in combination with chloroquine or hydroxychloroquine were referenced in review articles, but were not readily available for independent review (Chung et al., 1997; Feldmann et al., 1994; Von Schmiedeberg et al., 2000). In 1996, the American Academy of Dermatology included quinacrine hydrochloride (100 to 200mg/d) on a list of first-line system treatments for lupus (Guidelines of Care for Cutaneous Lupus Erythematosus, 1996). Most recently, McCune and Gonzalez-Rivera have proposed that the addition of quinacrine HCl to hydroxychloroquine therapy should be seriously considered as long-term maintenance therapy of remission in patients with systemic lupus to reduce ocular toxicity (McCune et al., 2015). Furthermore, the use of quinacrine HCl is recommended in the most-recent algorithm for treatment of systemic lupus erythematosus (Muangchan et al., 2015).

Lupus is a systemic autoimmune disease considered a serious condition with increased morbidity and mortality. It can affect virtually any organ system; the more commonly involved organ systems are mucocutaneous, musculoskeletal, renal, nervous, cardiovascular, pleura, and lungs. The mucocutaneous and musculoskeletal systems are involved in over three-fourths of lupus patients. The current standard of care for treatment of mild-to-moderate manifestations of lupus includes non-steroidal anti-inflammatory drugs (NSAIDs), antimalarial drugs like hydroxychloroquine, and corticosteroids like prednisone. Life-threatening manifestations of lupus, such as those involving the kidneys, central nervous system, or blood vessels are treated more aggressively with drugs like high dose corticosteroids, or immunosuppressive agents like cyclophosphamide, azathioprine, and mycophenolate mofetil. Of these drugs, only prednisone and hydroxychloroquine have FDA approved labeling for use in lupus. FDA approved belimumab, a B-lymphocyte stimulator (BLyS)-specific inhibitor in 2011 for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy (BENLYSTA Prescribing Information Highlights, accessed September 2015). Currently, there is no approved treatment of lupus that has been shown to prolong survival or reverse the course of the disease. Lupus remains a disease with unmet medical need, especially for patients with active and life-threatening manifestations.

Rheumatoid Arthritis

Although monotherapy and combination therapy with antimalarial drugs have been demonstrated to be effective in treating rheumatoid arthritis, no individual study specifically evaluating quinacrine HCl could be identified using the currently available databases. Reports from the 1950s regarding quinacrine HCl's efficacy in rheumatoid arthritis were noted in several review articles. However, independent verification of the studies was not possible for this review.

Rheumatoid arthritis can be a serious condition. Approved alternatives are discussed above. Although quinacrine has also been used historically for rheumatoid arthritis, the availability of many highly effective FDA-approved treatments for RA has made the use of quinacrine uncommon for RA today.

Conclusions

Despite its well-documented antirheumatic properties, quinacrine HCl has never been carefully evaluated in prospective, well-controlled, double-blinded studies with prespecified endpoints. Nevertheless, the overall evidence suggests that quinacrine HCl fulfills a therapeutic need and is currently prescribed, albeit to a limited extent, for the treatment of cutaneous lupus and as an add-on therapy to patients who are refractory to hydroxychloroquine monotherapy. In our view, there is a body of evidence in the scientific literature that supports its effectiveness, especially as related to cutaneous lupus and patients who are refractory to hydroxychloroquine monotherapy. Additionally, given its lower retinal toxicity as compared to the FDA-approved antimalarials, quinacrine HCl may be an option for patients with lupus who respond to antimalarial therapy but have retinal disease. Furthermore, the rheumatologic community has continually recommended the use of quinacrine HCl for the treatment of lupus, and it is listed as a treatment alternative in the scientific literature, major rheumatologic text books, and online medical reference sites.

There is insufficient evidence to support the use of quinacrine HCl for the treatment of rheumatoid arthritis, especially in the context of numerous therapies that have established efficacy and the risk of irreversible structural damage with ineffective therapies.

C. Has the substance been used historically in compounding?

In developing our response to this question, we have considered the following, to the extent available:

- Length of time the substance has been used in pharmacy compounding
- The medical condition(s) it has been used to treat
- How widespread its use has been
- Recognition of the substance in other countries or foreign pharmacopeias

Please see DAIP's review for information on the historical use of quinacrine HCl in compounding.

RECOMMENDATION

In light of the information set forth above and in DAIP's consult, we ***recommend that quinacrine HCl be placed*** on the list of bulk drug substances allowed for use in compounding under section 503A for oral administration. This recommendation is based on the data supporting its efficacy in the treatment of cutaneous and systemic lupus and its overall safety profile, which has important differences compared to the approved antimalarials typically used for SLE (especially hydroxychloroquine); this allows it to be used in conjunction with other antimalarials. The safety concerns with quinacrine are well known, and are monitored for by clinicians who choose to use quinacrine. The most concerning of these is aplastic anemia, which is a very rare idiosyncratic reaction, which may be reversible but also may be life-threatening and may require bone marrow transplant. For those patients who require additional anti-malarial therapy, but are at risk of irreversible retinopathy and blindness with an increased dose of an approved antimalarial, or who are at risk of life-threatening lupus flares if not adequately treated, adding 100 mg or less of quinacrine to lower doses of hydroxychloroquine or chloroquine has been a valuable therapeutic alternative.

As discussed in the DAIP consult, quinacrine HCl is well characterized physically and chemically and has been used since the 1940s as an antimalarial and antiprotozoal agent and for the treatment of patients with refractory cutaneous lupus erythematosus. Because quinacrine HCl has a long history of clinical use, especially in the treatment of malaria, its safety profile is well understood. Quinacrine HCl is used to treat lupus in a manner similar to chloroquine and hydroxychloroquine, FDA-approved products that are used in the treatment of lupus. In comparison with chloroquine or hydroxychloroquine, quinacrine HCl has lower retinal toxicity. In 1996, the American Academy of Dermatology included quinacrine HCl (100 to 200mg/day) on a list of first-line system treatments for lupus.

Of note, DPARP acknowledges DAIP's recommendation not to include quinacrine HCl on the 503A bulk drug substances list for anti-malarial and anti-protozoal uses and DBRUP's recommendation not to include quinacrine HCl on the 503A bulk drug substances list for use in intrauterine administration. However, this consult is limited to DPARP's assessment of the appropriateness of including quinacrine HCl on the 503A bulk drug substances list as it pertains only to lupus and rheumatoid arthritis indications.

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DATE: February 9, 2016

FROM: Lisa Soule, MD, Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products

THROUGH: Christine Nguyen, MD, Deputy Director for Safety
Division of Bone, Reproductive, and Urologic Products

Julie Beitz, MD, Director
Office of Drug Evaluation III

SUBJECT: Review of Quinacrine Hydrochloride for Intrauterine Administration

TO: Pharmacy Compounding Advisory Committee

I. INTRODUCTION

Quinacrine hydrochloride (quinacrine HCl) has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The substance was nominated for use in the treatment of rheumatoid arthritis, lupus, as an antimalarial and an antiprotozoal. FDA's Division of Anti-Infective Products (DAIP) evaluated quinacrine HCl for inclusion on the 503A list for the proposed antimalarial and antiprotozoal uses. The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) evaluated quinacrine HCl for the section 503A list for the proposed lupus and rheumatoid arthritis uses.

In addition to the nominated uses, the Agency is aware that an intrauterine form of quinacrine HCl has been used for non-surgical female sterilization. Safety concerns about this procedure have been identified in the literature and by public health organizations over the past 40 years. In light of this information, the Division of Bone, Reproductive, and Urologic Products (DBRUP) was asked to prepare a secondary review addressing the safety of the intrauterine use.

We have reviewed available data on the physicochemical characteristics, effectiveness, and historical use in compounding of this substance discussed in the DAIP and DPARP reviews, as well as the safety information set forth below. For the reasons discussed below, we **do not recommend** that quinacrine HCl 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

Please refer to the review prepared by DAIP on the physical and chemical characteristics, the non-clinical safety of quinacrine HCl and the historical use of quinacrine HCl in compounding.

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

Quinacrine HCl is a derivative of acridine, and belongs to a class of compounds that are well known to have mutagenic properties (Ferguson et al., 1991). Compounds of this class have a planar structure and can intercalate into DNA and cause various types of mutations (Nasim et al., 1979).

Quinacrine HCl was studied as a female sterilizing agent initially using a slurry formulation that was instilled into the uterine cavity (Zipper et al., 1970). However, three deaths were reported (in the United States and Bangladesh). It is unclear whether the deaths were due to erosion of the uterus and subsequent spillage of quinacrine HCl into the peritoneum or to effects of systemic exposure to quinacrine HCl. The slurry formulation was discontinued, and subsequently, a pellet formulation was developed in 1977 and studied initially by Dr. Jaime Zipper in Chile (Zipper et al., 1980). In this method, quinacrine HCl pellets are placed inside the uterine cavity with the aim of creating fibrosis and occlusion of the Fallopian tubes.

During the latter part of the 20th century, investigators and practitioners in a number of countries used intrauterine quinacrine HCl as a sterilizing agent. The World Health Organization (WHO) estimated that over 140,000 quinacrine sterilizations were performed in 34 countries over the period from 1977-2000. However, the procedure was banned in Vietnam in 1993, in Indonesia in 1994, and in India and Chile in 1998, following reports of women being sterilized without their consent and due to concerns about potential long-term safety (Hieu et al., 2003; Mudur, 1998; Meeting report: The quinacrine debate and beyond, 2001).

On June 17, 1997, an FDA Talk Paper was issued warning consumers not to purchase certain unapproved products that pose significant, possibly life-threatening health risks (See Appendix 1). One of the two products in question, which was offered for sale on the Internet, was a female self-sterilization kit, formerly marketed as Femestra kit. The kit, which used pellets of quinacrine HCl, was described in the FDA Talk Paper as “an unapproved drug, which can cause ectopic pregnancy, abnormal pregnancies, and permanent damage to a woman’s reproductive organs.”

On August 26, 1998, a safety assessment and Health Hazard Evaluation were conducted by FDA on the kit for uterine insertion of quinacrine HCl pellets for female sterilization (see Appendix 2). In the August 1998 Health Hazard Evaluation, FDA raised concerns in three areas based on results from previously conducted toxicology studies on the oral formulation and the lack of adequate toxicology testing on the intrauterine pellet formulation:

- 1) Possible carcinogenicity of quinacrine: specifically, quinacrine is a known mutagen and had tested positive in several genotoxicity tests, and the intrauterine administration of quinacrine HCl pellets would result in significant tissue damage and the presence of known mutagen could result in development of cancer of the reproductive tract;
- 2) Lack of sufficient pharmacokinetic data: specifically, concerns exist on the possible continuous exposure of the endometrium to the drug following intrauterine insertion; and

- 3) Pharmacodynamic issues: specifically, that intrauterine instillation of the cytotoxic agent had been noted to be unsuccessful for complete destruction of the endometrium and had resulted in neoplastic transformation of residual endometrial cells.

The August 1998 Health Hazard Evaluation noted that drugs such as quinacrine HCl with positive mutagenicity and cytotoxicity profiles were of concern with regard to increased cancer risks in humans. Several safety concerns were also identified, including uterine perforation during insertion, possible intraperitoneal leakage of dissolved drug product, formation of hematometra, increased risk for reproductive tract cancers, development of abnormal uterine lesions, and ectopic pregnancy. FDA concluded that the potential and known risks may outweigh any proposed advantages this procedure may have over surgical sterilization in the United States.

On October 14, 1998, FDA issued two warning letters regarding unapproved quinacrine HCl pellets labeled for non-surgical female sterilization (see Appendix 3, 4). In these letters, FDA highlighted many of the same safety concerns identified in the August 1998 Health Hazard Evaluation summarized above and concluded that non-surgical female sterilization is an unsafe use of quinacrine HCl pellets. Citing safety concerns, FDA requested that the unapproved quinacrine HCl pellets for non-surgical female sterilization be immediately removed from the market.

Due to the product's known mutagenicity, a rat carcinogenicity study was conducted in the 2000's by a U.S. research organization interested in developing quinacrine HCl as a sterilizing agent. Results of this study were published (Cancel et al., 2010). The stated conclusion of the authors was:

We conclude that two doses of quinacrine administered approximately 21 days apart into the uterus of young sexually mature rats at dose levels ≥ 70 mg/kg increased the lifetime risk of tumor development in the reproductive tract. The types of tumors that developed were mostly uncommon for this strain of rat. The incidence of these tumors was dose-related and was significantly increased at a local quinacrine dose that was a small multiple (8x based on a mg quinacrine/g uterus basis) of the human dose of quinacrine used for non-surgical female sterilization.

This U.S. research organization decided in late 2006 not to continue development of quinacrine HCl for female sterilization, explaining in a journal publication (Sokal et al., 2007) the findings of concern and its reason for discontinuing work on the product:

FHI's research plan included a "go/no-go" decision point when data became available from a rat carcinogenicity study, at which time results would be reviewed along with other data on quinacrine's safety and effectiveness. Preliminary results became available in November 2006, and FHI subsequently notified the FDA. We followed a consultative process within FHI and with outside experts, stakeholders and FHI's advisory committee, of women's health advocates regarding our decision and its dissemination.

FHI's 2-year rat carcinogenicity study showed a clear, dose-related increase in reproductive tract tumors following intrauterine administration of quinacrine. After

Careful review of these data with outside experts, and taking into account earlier test results indicating quinacrine is mutagenic *in vitro*, and lower-than-desired effectiveness, a “no-go” decision was made. We shared our decision with other researchers and stakeholders, prior to publication of the rat study. Most appreciated our notification, and the news of our decision did not result in alarmist or inappropriate publicity in the media.

In October 2008, the World Health Organization (WHO) convened a technical panel (WHO, Interim statement, accessed 2016) to discuss the safety of quinacrine sterilization. The panel of experts concluded the following:

- Currently available genetic toxicity data are sufficient to support the conclusion that quinacrine is genotoxic *in vitro*. No additional *in vivo* studies are recommended, “because negative results would not negate positive *in vitro* study results.”
- In the two-year rat carcinogenicity study, a dose-related increased incidence of both benign and malignant tumors of the vagina, cervix and uterus was observed in the quinacrine-exposed animals. However, changes such as inflammation, necrosis and cystic dilation of the uterus were also observed. As the panel report noted, “Thus, the findings did not allow the Panel to distinguish between a direct genotoxic effect of quinacrine, a secondary effect of inflammation and tissue regeneration, or a combination of the two, in the genesis of observed tumors in rats.”
- The available epidemiologic studies showed no excess risk of reproductive tract cancer but were limited in statistical power. Thus, the report noted that “the Panel could not exclude a modest increased risk in gynecologic cancers.”
- Safety outcomes other than cancer were not reviewed.

Overall, the WHO Panel recommended that “until the totality of safety, effectiveness and epidemiological data has been reviewed, quinacrine should not be used for non-surgical sterilization of women in either clinical or research settings.” To date, this interim statement has not been updated or removed.

Conclusions: In light of the risk of carcinogenicity and potentially life-threatening risks discussed above, we have significant concerns about the safety of quinacrine HCl for intrauterine use.

B. Are there concerns about whether the substance is effective for a particular use? If there are no data regarding effectiveness available, is the substance used to treat a serious or life-threatening condition for which there are approved alternative therapies available?

DBRUP has reviewed the literature on the effectiveness of intrauterine administration of quinacrine HCl for female sterilization. The majority of efficacy data are based on follow up of women in developing countries, and there are almost no randomized or controlled clinical trials. Where follow-up data on pregnancy are available, they are typically collected only on a subset of sterilized women; where reported, typically 10-20% of subjects have been lost to follow up.

Pregnancy data are not consistently based on serum or urine pregnancy. In addition, the available data do not rely upon a single standard method of sterilization, so the data may not be pooled or compared across studies.

Reported (Sokal et al., 2008) pregnancy rates range from:

- 0.3 to 3.3% in first year
- 1.1 to 10% over five years
- 4.3 to 12.1% over 10 years
-

These rates compare unfavorably with surgical sterilization or intrauterine devices, which provide long-term contraception.

III. RECOMMENDATION

As discussed in the DAIP review, quinacrine HCl is well characterized physically and chemically and there is some evidence of its historic use in compounding. However, quinacrine HCl is a known carcinogen, it is genotoxic and cytotoxic. Female sterilization, the main indication for intrauterine administration of quinacrine HCl, can be done surgically. We have considered the physical and chemical characteristics, and the historical use set forth in DAIP's and DPARP's reviews. Due to the serious safety concerns discussed above, and the lack of compelling evidence of efficacy that is at least comparable to currently available methods of female sterilization, we recommend that quinacrine HCl for intrauterine administration **not be included** on the list of drugs that can be used in compounding under section 503A of the FD&C Act. Furthermore, we recommend that quinacrine HCL for intrauterine administration be placed on the 503A List 2 – Bulk Drug Substances That Raise Safety Concerns, because of the serious risk of female reproductive tract cancer. Drugs on 503A List 2 may not be used in compounding under section 503A unless and until FDA publishes a final rule authorizing their use under section 503A.

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DATE: February 8, 2016

FROM: Charles J. Ganley, MD
Director, Office of Drug Evaluation (ODE) IV
Center for Drug Evaluation and Research

THROUGH: John Jenkins, MD
Director, Office of New Drugs
Center for Drug Evaluation and Research

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Office of New Drugs (OND) Recommendation that Quinacrine Hydrochloride Not Be Placed on the 503A Bulk Drug Substances List

I. Reviews Conducted by OND Review Divisions

Fagron, Professional Compounding Centers of America, and National Community Pharmacists Association nominated quinacrine hydrochloride (“quinacrine”) for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (section 503A bulks list). Reviews of the uses of quinacrine proposed in the nominations were completed by the Division of Anti-Infective Products (DAIP) and the Division of Pulmonary and Allergy Drug Products (DPARP).

In addition to the reviews conducted by DAIP and DPARP, the Division of Bone, Reproductive, and Urologic Drug Products (DBRUP) conducted a review to discuss the concerns that the FDA has with the intrauterine administration of quinacrine. DBRUP recommended that if quinacrine were to be added to the list of bulk drug substances that can be used in compounding under section 503A, it should not be permitted to be compounded for intrauterine administration.

DAIP recommended that quinacrine not be placed on the section 503A bulks list. DAIP found that the availability of quinacrine to treat refractory giardiasis, which may be associated with treatable weight loss and malnutrition but is not considered life threatening, is not advised under section 503A. For this indication, DAIP is concerned about the substantial safety issues associated with the use of quinacrine and the absence of approved labeling to inform the practitioner and patient community regarding those substantial safety issues.

DPARP recommended that quinacrine be placed on the list. This recommendation was based on the data supporting the efficacy of quinacrine in the treatment of cutaneous and

systemic lupus and its overall safety profile relative to alternative treatments, of which the most serious adverse reactions can be monitored and some are reversible following discontinuation of the drug.

Because of the disparate recommendations from DAIP, DBRUP, and DPARP as to whether quinacrine should be placed on the section 503A bulks list, the Director of OND ODE IV reviewed the information in each division memorandum and is making a recommendation that, with the concurrence of the Director of OND, will represent the position of OND on this issue.

II. Evaluation Criteria

Four criteria have been developed for evaluating whether a substance should be included on the section 503A bulks list:

- 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.

To reach an overall recommendation regarding whether quinacrine should be added to the section 503A bulks list, OND considered the information presented in the three reviews that accompany this document and each of the four criteria described above.

Physical and Chemical Characterization

The Office of Pharmaceutical Quality review of the chemical and physical properties of quinacrine identifies that quinacrine “can be obtained in a highly pure form and is stable when protected from light.” There are no chemistry or physical characterization issues that would preclude quinacrine from being compounded.

Nonclinical and Clinical Safety

DAIP surveyed the published literature and tertiary reference information regarding quinacrine and found that it is a DNA intercalator, with positive results in mutagenic and clastogenic assays. DNA intercalators perturb DNA structure and stability and by definition are mutagens, which can in turn influence DNA-processing by proteins. A clastogen is a mutagenic agent that results in breakages of chromosomes. Because mutations can lead to carcinogenicity, many mutagens are considered potentially tumorigenic. There were no safety pharmacology data available and a no observed effect level has not been established for quinacrine toxicity or tumorigenicity. In the rat, oral quinacrine is readily absorbed, concentrates in the liver, crosses the blood brain barrier to a limited extent (1 – 5% of plasma levels) and has a half-life of 5 – 14 days. Intrauterine

administration in pregnant rats and monkeys has been shown to lead to increased fetal death.

Adverse events in humans were described in prescription labeling or literature for the previously marketed injectable (trade name Atabrine) and oral forms of quinacrine and the oral combination of quinacrine, chloroquine phosphate, and hydroxychloroquine sulfate (NDA 11-234, trade name Triquin). The most serious adverse event described is aplastic anemia, estimated to occur in 1:500,000 lupus patients taking doses of 100 mg/day maximum, despite monitoring of hematologic parameters and visual inspection for the development of lichen planus, which has been known to manifest prior to aplastic anemia. Labeling of the approved product Atabrine (Atabrine [package insert], 1994) warned that the drug could cause transitory psychosis, precipitate an occurrence of psoriasis, or exacerbate porphyria. Precautions in the label stated the drug should not be used in patients with hepatic disease or those taking other hepatotoxic drugs, due to the potential for hepatotoxicity, in patients with G-6-PD deficiency, or in pregnancy. Adverse effects of the gastrointestinal and ophthalmic system events have also been described. It is noted that the U.S.-approved drug hydroxychloroquine sulfate (trade name Plaquenil) bears labeling that describes a safety profile similar to quinacrine's known safety concerns, including a boxed warning.

As DBRUP described in its review, quinacrine has been used as an unapproved female sterilization agent, in pellet form or as a solution for intrauterine instillation, to scar the endometrial wall and Fallopian tubes and prevent pregnancy. Female sterilization via this route has never been an approved indication for quinacrine in the United States, and multiple alternative methods of female contraception and sterilization are approved. In addition to quinacrine's positive mutagenic and clastogenic effects, the results of a non-traditional carcinogenicity study published in 2010 concluded that a dose related increase in lifetime risk of reproductive tract tumors was observed in rats following administration of two intrauterine quinacrine doses. Based on an August, 1998 Health Hazard Evaluation, FDA issued an October 1998 warning letter regarding the unapproved products, citing mutagenicity, cytotoxicity and possible carcinogenicity of quinacrine and lack of sufficient pharmacokinetic data with which to determine a safe and effective intrauterine dose.

Historical Use of the Substance

- Atabrine tablets were available during World War II for the treatment and prophylaxis of malaria in troops. Use declined with the development of chloroquine. Marketing was discontinued in 1995.
- Atabrine as an injectable was approved in 1964 for the treatment of ascites associated with several types of cancer. The NDA was withdrawn in 2003.
- Triquin (quinacrine hydrochloride, chloroquine, hydroxychloroquine) tablet was marketed in the United States until its approval was withdrawn in 1973.
- An unapproved pellet dosage form of quinacrine for transcervical delivery was marketed in the late 1990's for female sterilization. FDA issued warning letters to the firms in 1998 and marketing was discontinued.

- The DPARP review cites peer-reviewed medical literature that discusses the use of quinacrine to treat lupus dating as far back as 1940. However, the extent to which quinacrine is used in the treatment of cutaneous lupus erythematosus (CLE), discoid lupus erythematosus (DLE), or systemic lupus erythematosus (SLE) is unclear.
- As noted in the DAIP review, due to the recent unavailability of quinacrine by traditional avenues since the discontinuation of Atabrine in 1995, there has been experience using this drug in its compounded form.

Available Evidence of Effectiveness or Lack of Effectiveness

Areas of therapeutic use were evaluated consistent with the nomination. The published literature describes a number of cases of giardiasis refractory to nitroimidazoles (e.g., tinidazole) alone having been successfully treated with quinacrine monotherapy or a quinacrine-nitroimidazole combination therapy (Nash et al., 2001). DAIP's review states that the option to treat giardiasis with quinacrine continues to be reported in the literature, although no treatment algorithms were identified that define quinacrine's specific place in a sequence of treatment options. DAIP also notes that quinacrine is no longer used in clinical practice for malaria or taeniasis (tapeworm) infections because other more effective and less toxic drugs have been approved in the United States for these conditions.

DPARP was asked to consider quinacrine's nomination for uses in rheumatoid arthritis and lupus. While antimalarial drugs have been used to treat rheumatoid arthritis in the past, DPARP concludes that the numerous approved biologic and nonbiologic therapies for rheumatoid arthritis provide sufficient treatment options.

Current rheumatology and dermatology treatment algorithms recommend quinacrine to improve symptoms of CLE, particularly the severely disfiguring subtype DLE that is refractory to hydroxychloroquine monotherapy and other therapies (Kuhn et al., 2011; Okon et al., 2013). In addition, some literature identifies use of quinacrine with hydroxychloroquine in the treatment of SLE, particularly in cases with extensive skin manifestation. Quinacrine is also recommended for use in combination with hydroxychloroquine to allow for a reduction in the dose of hydroxychloroquine to lower the overall risk of retinal toxicity (Zuehlke et al., 1981). However, no controlled clinical trials evaluating the efficacy of quinacrine in CLE, DLE or SLE could be identified. As the DPARP review points out, prednisone, hydroxychloroquine, and belimumab are approved in the treatment of lupus. Neither the approved treatments nor quinacrine have been shown to prolong survival or reverse the course of the disease.

III. Weighing of the Four Criteria and OND Recommendation

Based on weighing the four criteria, OND recommends that quinacrine hydrochloride **not be added to the list of bulk drug substances that may be compounded under section 503A** of the FD&C Act.

Physical and Chemical Characterization

- There are no chemistry or physical characterization issues that would preclude quinacrine from being compounded.

Historical Use of the Substance

- Quinacrine has a long compounding history.

Effectiveness

- For CLE, SLE and DLE, there is a long history of use for these conditions and some evidence that it is an effective therapy.
- As an antimalarial, an anti-protozoan and an anti-tapeworm therapy, quinacrine is effective but there are newer more effective and less toxic therapies available.

Safety

- As noted in the DAIP review, quinacrine is associated with serious adverse events both acutely and with prolonged use.
- Quinacrine's adverse effect profile is similar to other antimalarial drugs (hydroxychloroquine, chloroquine) currently approved with the exception that it does not appear to be associated with retinal toxicity.
- Quinacrine has been associated with the development of aplastic anemia. This was first reported during World War II when the rate of aplastic anemia increased in the Pacific war theater. The incidence of aplastic anemia increased from 0.66 / 100,000 prior to the use of quinacrine to 2.84 / 100,000 cases after its introduction (Custer, 1946). The occurrence of lichen planus while on therapy may be a predictor of the development of aplastic anemia. Approximately one-half of the cases of aplastic anemia were preceded by a lichen planus rash.
 - If a patient develops a lichen planus rash, quinacrine should be stopped.
 - Patients should be monitored for hypoplastic anemia while on quinacrine.

The Office of New Drugs does **not recommend quinacrine for the 503A bulks list** because of the serious side effects associated with the use of quinacrine. The DPARP review notes that the safety concerns with quinacrine are known to the clinicians who treat lupus patients. OND is not aware of information to support this, but suspects many rheumatologists are familiar with quinacrine's serious adverse effects. Placing quinacrine on the section 503A bulks list, however, would allow any prescribers, not just rheumatologists, to prescribe it for any use, not just for lupus, and at any dose. Compounding pharmacies and websites could promote the use of quinacrine for many conditions without much FDA oversight. In addition, because of the possibility for developing serious side effects with quinacrine, an approved package insert should be available to inform both practitioner and patient of the serious side effects and provide recommendations for appropriate follow up. Such package inserts are not required for compounded drugs, and an approved package insert will not be available for a compounded drug containing quinacrine. Therefore, the FDA recommends that quinacrine **not be included on the 503A bulk list**.

FDA recognizes that in some circumstances, clinicians would choose to prescribe quinacrine for some patients who are either unresponsive to approved alternative

therapies or have discontinued approved alternative therapies because of adverse effects. For these situations, the best mechanism for availability is through an expanded access Investigational New Drug (IND) application. An expanded access IND application provides safeguards for patients because under an IND, an investigational brochure containing safety information is prepared, information on the safety of the drug is provided to the patient through informed consent, consistent follow up for patients is required, and a consistently manufactured product is provided to patients. As it would for any drug, FDA is willing to work with sponsors if they should choose to submit an IND application or develop the drug for marketing.

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Tab 2

Boswellia

Tab 2a

Boswellia
Nominations

September 30, 2014

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



Re: Docket FDA-2013-N-1525

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

To Whom It May Concern:

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

Request for Extension

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

This is an issue of great importance which will limit the number of available compounded drugs products available to physicians and, therefore, will limit the number of individualized treatments to patients. McGuff CPS and physician stakeholders have not had the time to collect, review, and collate all documentation necessary to submit the intended list of compounded drugs required to assure all patient therapies are represented in our submission. McGuff CPS respectfully seeks an additional 120 day period for the purpose of coordinating the various stakeholders and gathering the essential information necessary to provide the Agency with the most comprehensive information.

McGUFF
COMPOUNDING
PHARMACY
SERVICES

2921 W. MacArthur Blvd.
Suite 142
Santa Ana, CA 92704-6929

TOLL FREE: 877.444.1133
TEL: 714.438.0536
TOLL FREE FAX:
877.444.1155
FAX: 714.438.0520
EMAIL: answers@mcguff.com
WEBSITE: www.mcguff.com

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
Dichloroacetic 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,

A handwritten signature in black ink that reads "Jud Richland". The signature is written in a cursive, flowing style with a long horizontal stroke at the end.

Jud Richland, MPH
Chief Executive Officer



Alliance for Natural Health USA

6931 Arlington Road, Suite 304
Bethesda, MD 20814

email: office@anh-usa.org
tel: 800.230.2762
202.803.5119
fax: 202.315.5837
www.anh-usa.org

ANH-USA is a regional office of ANH-Intl

INTERNATIONAL
anhinternational.org

September 30, 2014

VIA ELECTRONIC SUBMISSION

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

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

Docket No. FDA-2013-N-1525

Dear Sir/Madam:

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

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

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

"Promoting sustainable health and freedom of healthcare choice through good science and good law"

As discussed in detail below, in the interest of compiling a comprehensive 503B List more time is needed to provide the required information. This will benefit both FDA, by reducing the subsequent number of petitions for amendments, and consumers, by allowing continued access to important substances.

Organizational Background of Commenter Alliance for Natural Health USA

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

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

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

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

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

For the initial request for nomination, it was estimated that compiling the necessary information for just one nominated ingredient would require five to ten hours. With the revised request requiring more information, the time to put together all of the data for a single nomination likely will be higher. Given that it is necessary to review all possible ingredients and provide the detailed support, or risk losing important therapeutic ingredients, this task requires more time than has been designated by the Agency. While ANH-USA recognizes there will be additional opportunities to comment and petition for amendments after the 503A List is published, the realities of substances not making the list initially makes this request for more time imperative. For example, if a nomination for a substance cannot be completed in full by the current September 30, 2014 deadline, doctors and patients will lose access to such clinically important substances and face the

administrative challenges in obtaining an ingredient listing once the work of the advisory committee is completed. There is no regulatory harm in providing additional time to compile a well-researched and comprehensive initial 503A List.

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

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

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 Sub sulfate; 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.

Comments, Integrative Medicine Consortium

Docket FDA-2013-N-1525

September 30, 2014

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

Page 6

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,

A handwritten signature in black ink, appearing to read "Michael J. Cronin N.D.", written in a cursive style.

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.



ACAM
American College for
Advancement in Medicine

380 Ice Center Lane, Suite A
Bozeman, Montana 59718
Toll-free 800-LEAD.OUT (532.3688)
F: 406-587-2451
www.acam.org

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.

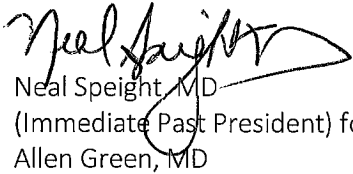


ACAM
American College for
Advancement in Medicine

380 Ice Center Lane, Suite A
Bozeman, Montana 59718
Toll-free 800-LEAD.OUT (532.3688)
F: 406-587-2451
www.acam.org

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

Nominations Submitted by: McGuff Compound Pharmacy Services, Inc., American Association of Naturopathic Physicians, Alliance for Natural health USA, Integrative Medical Consortium, and 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?	Boswellia
Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?	Yes. Multiple studies and research are available on Pubmed regarding the clinical use of Boswellia. Sample article: Gupta I, Gupta V, Parihar A, et al. Effects of Boswellia serrata gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. Eur J Med Res 1998;3:511-4. http://www.ncbi.nlm.nih.gov/pubmed/?term=Gupta+I%2C+Gupta+V%2C+Parihar+A%2C+et+al.+Effects+of+Boswellia+serrata+gum+resin+in+patients+with+bronchial+asthma%3A+results+of+a+double-blind%2C+placebo-controlled%2C+6-week+clinical+study.+Eur+J+Med+Res+1998%3B3%3A511-4.
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?	Dietary Supplement Monograph for Boswellia serrata and Boswellia serrata extract in USP.
What is the chemical name of the substance?	Boswellia Serrata Extract
What is the common name of the substance?	Boswellia , Indian Frankincense
Does the substance have a UNII Code?	4PW41QCO2M (for Boswellia serrata extract)
What is the chemical grade of the substance?	Herbal extract

What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Boswellia serrata is supplied as a resin extract powder, light yellow.
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?	USP Dietary Supplements for Boswellia serrata and Boswellia serrata 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?	Capsule strengths can range from 50 mg to 300 mg per capsule

<p>What are the anticipated route(s) of administration of the compounded drug product(s)?</p>	<p style="text-align: center;">Oral</p>
<p>Are there safety and efficacy data on compounded drugs using the nominated substance?</p>	<p>(Please see literature in Relevant Information section).</p> <p>SAFETY: LIKELY SAFE ...when used orally and appropriately. Indian frankincense has been safely used in several clinical trials lasting up to six months</p> <p>POSSIBLY SAFE ...when used topically. Indian frankincense cream 0.5% has been safely used for up to 30 days (21156,21157).</p> <p>PREGNANCY AND LACTATION: LIKELY SAFE ...when used orally in amounts commonly found in foods (4912). There is insufficient reliable information available about the safety of using Indian frankincense in medicinal amounts. Effectiveness:</p> <p>POSSIBLY EFFECTIVE Osteoarthritis. Some clinical research shows that taking specific Indian frankincense extracts can reduce symptoms of osteoarthritis. In two clinical trials, using a specific Indian frankincense extract (5-Loxin) 100 mg daily or 250 mg daily significantly improved pain and functionality scores in patients with osteoarthritis after 90 days of treatment. Pain scores were reduced by about 32% to 65%. Patients began to have significant improvement within 7 days of treatment. The extract used in this study was standardized and enriched to contain 30% of the boswellic acid AKBA (17948,17949).</p> <p>Another clinical trial evaluated another specific Indian frankincense extract (Aflapin) 100 mg daily. This extract significantly improved pain and functionality scores in patients with osteoarthritis after 90 days of treatment. Pain scores were reduced by about 47%. Patients began to have significant improvement within 7 days of treatment. The extract used in this study was standardized and enriched to contain 20% of the boswellic acid AKBA (17949). In another preliminary clinical trial, the same Indian frankincense extract (Aflapin) 50 mg twice daily for 30 days significantly decreased pain and stiffness scores compared to placebo in patients with osteoarthritis (21145).</p> <p>In a preliminary crossover trial, taking a different Indian frankincense extract 333 mg daily also significantly reduced symptoms of osteoarthritis, such as knee pain and swelling (12432). In another clinical trial, pain, stiffness, and functional ability were significantly improved compared to baseline in subjects taking Indian frankincense extract 333 mg three times daily or valdecoxib 10 mg daily for six months. The effects of Indian frankincense persisted for one month after stopping treatment. However, no between group comparisons were reported (21146).</p> <p>Taking two capsules of a specific combination product containing Indian frankincense 100 mg, ashwagandha 450 mg, turmeric 50 mg, and zinc complex 50 mg (Articulin-F) three times daily for three months significantly decreased pain and disability scores in patients with osteoarthritis (19276). However, the effect of Indian frankincense alone on osteoarthritis symptoms cannot be determined from this study.</p> <p>Ulcerative colitis. Two clinical trials show that taking Indian frankincense can improve some symptoms of ulcerative colitis and some pathological measures. In one study, taking Indian frankincense 350 mg three times daily significantly improved symptoms and disease markers in patients with ulcerative colitis. In this study, about 82% of patients taking Indian frankincense went into remission compared to 75% taking sulfasalazine (1709). In another preliminary clinical study, taking Indian frankincense 300 mg three times for 6 weeks improved symptoms and some measures of disease pathology in about 90% of patients. In this study 70% of patients taking Indian frankincense went into remission compared to 40% taking sulfasalazine 3 grams daily (12438).</p> <p>INSUFFICIENT RELIABLE EVIDENCE to RATE</p> <p>Asthma. There is some preliminary evidence that taking Indian frankincense extract orally might help asthma. It may improve force expiratory volume (FEV), reduce the number of asthma attacks, and decrease dyspnea and rhonchi (1708).</p> <p>Collagenous colitis. In one small clinical trial, Indian frankincense extract 400 mg three times daily for six weeks significantly increased clinical remission rate compared to placebo in patients diagnosed with collagenous colitis. Clinical remission was defined as having an average of three or fewer soft or solid stools daily during the last week of the study (21152).</p> <p>Crohn's disease. There is preliminary evidence that taking Indian frankincense extract orally might reduce some symptoms of inflammatory bowel disease. One clinical study found that it worked as well as mesalamine (Asacol, Pentasa) for Crohn's disease (12436); however, other clinical research shows that taking Indian frankincense 800 mg orally three times a day did not increase rates of remissions and quality of life any more than placebo in patients with Crohn's disease (17241).</p> <p>Rheumatoid arthritis (RA). There is conflicting research about the usefulness of Indian frankincense extract taken orally for rheumatoid arthritis (12433,12434). In one clinical trial, taking two capsules of a specific combination product containing Indian frankincense 100 mg, ashwagandha 450 mg, turmeric 50 mg, and zinc complex 50 mg (Articulin-F) three times daily for three months significantly improved pain, morning stiffness, grip strength and disability scores in patients with rheumatoid arthritis compared to placebo (21154). However, taking two tablets of a different combination product (RA-1) containing Indian frankincense, ashwagandha, ginger, and turmeric three times daily for 16 weeks did not significantly reduce most symptoms of rheumatoid arthritis compared to placebo (21155). The effect of Indian frankincense alone in rheumatoid arthritis is unknown.</p>

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?	Inflammatory bowel disease, rheumatoid arthritis, osteoarthritis and possibly asthma.
	<p>For Inflammatory bowel disease, traditional Tx's are: Aminosalicylates, steroids, NSAIDs. For Rheumatoid arthritis, traditional Tx's are: NSAIDs, Steroids, DMARDs like methotrexate, Immunosuppressants, TNF- alpha inhibitors. For Osteoarthritis, traditional Tx's are NSAIDs and narcotics. For Asthma, traditional Tx's are Beta agonists like albuterol, Long-Acting-Beta-Agonists, Corticosteroids, Leukotriene modifiers.</p> <p><u>NSAIDs worsen inflammatory bowel disease:</u> Inflamm Bowel Dis. 2014 Sep 16. [Epub ahead of print] Nonsteroidal Anti-inflammatory Drugs and Inflammatory Bowel Disease: Pathophysiology and Clinical Associations. Habib I1, Mazulis A, Roginsky G, Ehrenpreis ED.</p> <p><u>Due to the many side effects of NSAIDs, large meta-analysis continue to evaluate many aspect around the chronic use:</u> Health Technol Assess. 2006 Oct;10(38):iii-iv, xi-xiii, 1-183. A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatorydrug-induced gastrointestinal toxicity: a systematic review with economic modelling. Brown TJ1, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, Rostom A, Symmons D.</p> <p><u>Even after new practices were implemented to limit the side effects of NSAIDs, GI bleeding continues to be the biggest concern and cause of fatalities:</u> Arthritis Res Ther. 2013;15 Suppl 3:S3. doi: 10.1186/ar4175. Epub 2013 Jul 24. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Sostres C. Garqallo C.J. Lanás A.</p>

<p>What is the reason for use of a compounded drug product rather than an FDA-approved product?</p>	<p><u>Estimate patient population:</u> Thrity-five to fifty percent of patients with inflammatory bowel disease find that the available drugs do not help their symptoms.</p> <p>Ten to Twenty percent of osteoarthritis and rheumatoid arthritis patients prefer alternative options to FDA approved drugs either because of severe long term side effects, short term side effects or the lack of efficacy.</p> <p>Boswellia as an anti-inflammatory is safe and has no serious medical side effects even at very high doses (see literature below). <u>This review demonstrates Boswellia as a safe alternative to NSAIDs without the side effects of ulcers and cardiovascular events:</u> Clin Pharmacokinet. 2011 Jun;50(6):349-69. doi: 10.2165/11586800-000000000-00000. Boswellia serrata: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. Abdel-Tawab M1, Werz O, Schubert-Zsilavec M.</p> <p><u>This Cochrane review, the most respected among reviews, compiles the literature and shows promising benefit of Boswellia in osteoarthritis with low risk of adverse effects.</u> Cochrane Database Syst Rev. 2014 May 22;5:CD002947. doi: 10.1002/14651858.CD002947.pub2. Oral herbal therapies for treating osteoarthritis. Cameron M1, Chrubasik S.</p> <p><u>Promising treatment for colitis:</u> Phytother Res. 2014 Sep;28(9):1392-8. doi: 10.1002/ptr.5142. Epub 2014 Mar 12. Boswellia serrata has Beneficial Anti-Inflammatory and Antioxidant Properties in a Model of Experimental Colitis. Hartmann RM1, Fillmann HS, Morgan Martins MI, Meurer L, Marroni NP.</p> <p><u>Antioxidant, Kidney and Liver protection and anti-diabetic properties in Boswellia:</u> Jundishapur J Nat Pharm Prod. 2012 Fall;7(4):168-75. Epub 2012 Oct 7. The Antioxidant Capacity and Anti-diabetic Effect of Boswellia serrata Triana and Planch Aqueous</p>
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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

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

Dear Sir or Madam,

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

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

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

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

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

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs



Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlsx file)

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

Fagron

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



What is the name of the nominated ingredient?	Boswellia Serrata Extract
Is the ingredient an active ingredient that meets the definition of “bulk drug substance” in § 207.3(a)(4)?	Yes, Boswellia Serrata Extract 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 Boswellia Serrata Extract pharmacological actions are provided Siddiqui MZ. Boswellia serrata, a potential anti-inflammatory agent: an overview. Indian J Pharm Sci. 2011;73(3):255-61. doi:10.4103/0250-474X.93507. Ammon HP. Modulation of the immune system by Boswellia serrata extracts and boswellic acids. Phytomedicine. 2010;17(11):862-7. doi:10.1016/j.phymed.2010.03.003.
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?	N/A
What is the common name of the substance?	Indian frankincense
Does the substance have a UNII Code?	4PW41QCO2M
What is the chemical grade of the substance?	no grade

What is the strength, quality, stability, and purity of the ingredient?	<p>Appearance: White to cream crystalline powder with characteristic odor Identification: The IR Spectra of the sample should be concordant with that of the working standard . Loss on Drying: ≤ 5.0% pH: 4.0 – 6.0 Solubility Soluble in alcohol Residue on Ignition: ≤ 2.0% Loose Density: ≥ 0.3g/ml Tapped Density: ≥ 0.4g/ml Sieve Test (passes through) 40 Mesh: ≥ 95%; 60 Mesh: ≥ 60% Heavy Metals: ≤ 20ppm Lead: ≤ 1ppm Arsenic: ≤ 1ppm Total Plate Count: ≤ 3000cfu/g Yeast & Mold: ≤ 100cfu/g Escheria Coli: Should be absent Salmonella: Should be absent S. Aureus: Should be absent P. Aeruginosa: Should be absent Content Boswellic Acid by Titration: ≥ 65%</p>
How is the ingredient supplied?	<p>Powder</p>
Is the substance recognized in foreign pharmacopeias or registered in other countries?	<p>No foreign pharmacopeia monographs or registrations found.</p>
Has information been submitted about the substance to the USP for consideration of monograph development?	<p>No USP Monograph submission found.</p>
What dosage form(s) will be compounded using the bulk drug substance?	<p>Capsules</p>
What strength(s) will be compounded from the nominated substance?	<p>200-300mg</p>
What are the anticipated route(s) of administration of the compounded drug product(s)?	<p>Oral</p>

<p>Are there safety and efficacy data on compounded drugs using the nominated substance?</p>	<p>Ammon HP. Modulation of the immune system by <i>Boswellia serrata</i> extracts and boswellic acids. <i>Phytomedicine</i>. 2010;17(11):862-7. doi:10.1016/j.phymed.2010.03.003.</p> <p>Abdel-Tawab M, Werz O, and Schubert-Zsilavec M. <i>Boswellia serrata</i>: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. <i>Clin Pharmacokinet</i>. 2011;50(6):349-69. doi:10.2165/11586800-000000000-00000.</p> <p>Siddiqui MZ. <i>Boswellia serrata</i>, a potential anti-inflammatory agent: an overview. <i>Indian J Pharm Sci</i>. 2011;73(3):255-61. doi:10.4103/0250-474X.93507.</p> <p>Sterk V, Büchele B, and Simmet T. Effect of food intake on the bioavailability of boswellic acids from a herbal preparation in healthy volunteers. <i>Planta Med</i>. 2004;70(12):1155-60. doi:10.1055/s-2004-835844.</p>
<p>Has the bulk drug substance been used previously to compound drug product(s)?</p>	<p>Yes, cream</p>
<p>What is the proposed use for the drug product(s) to be compounded with the nominated substance?</p>	<p><i>Boswellia</i> is used for its anti-inflammatory properties. M. Abdel-Tawab O. Werz and M. Scubert-Zsilavec(2011) <i>Boswellia Serrata</i>: An overall Assessment of in vitro,Preclinical,Pharmacokinetic and Clinical Data <i>Clin Pharmacokinet Jun</i>;50(6):349-69</p>
<p>What is the reason for use of a compounded drug product rather than an FDA-approved product?</p>	<p>There are no FDA approved <i>Boswellia</i> preparations. There are a multitude of preparations used to treat inflammatory conditions. The most popular are NSAIDs and cox inhibitors. These FDA approved medications come with a host of side effects on gastrointestinal lining and black box warnings. There is a need for a preparation that involves less gastrointestinal and cardiovascular side effects. <i>Boswellia</i> has shown promise and better side effect profile than currently available FDA approved medications. (http://www.ncbi.nlm.nih.gov/pubmed/21553931) <i>Boswellia Serrata</i> can at the very least be beneficial alternative for those patients whom already have history of GI complaints.</p>
<p>Is there any other relevant information?</p>	<p>All relevant information was expressed in the above questions</p>

Appendix 1: Reference List Cited in the 503A Nominations for Boswellia

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Tab 2b

Boswellia
FDA Review



DATE: February 9, 2016

FROM: Janet Maynard, MD, Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products

Marcie Wood, PhD, Nonclinical Supervisor
Division of Pulmonary, Allergy, and Rheumatology Products

Luqi Pei, PhD, Nonclinical Reviewer
Division of Pulmonary, Allergy, and Rheumatology Products

Cassandra Taylor, PhD, Botanical Review Team
Office of Pharmaceutical Quality

Jinhui Dou, PhD, Botanical Review Team
Office of Pharmaceutical Quality

Charles Wu, PhD, Botanical Review Team
Office of Pharmaceutical Quality

Su-Lin Lee, PhD, Botanical Review Team
Office of Pharmaceutical Quality

THROUGH: Badrul Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy, and Rheumatology Products

Sau Lee, PhD
Associate Director for Science (Acting) and
Botanical Review Team Leader, Office of Pharmaceutical Quality

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Boswellia Serrata Extract for Inclusion on the 503A Bulk Drug
Substances List

I. INTRODUCTION

Boswellia serrata extract (BWSE) 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 inflammatory bowel disease, rheumatoid arthritis (RA), osteoarthritis (OA), asthma, and for anti-inflammatory properties generally. This review will focus on the RA and OA proposed uses.

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 BWSE 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. Background Information

Boswellia is a genus of trees in the Burseraceae family that includes various different species. *Boswellia* resin and extract are available on the U.S. market as dietary supplements in oral form and also have been traditionally used in topical formulations. *Boswellia* extract is a naturally derived complex mixture. *Boswellia* extracts are commonly derived from the resin of two main *Boswellia* species: *Boswellia serrata* Roxb. ex Colebr.¹ (also referred to as Indian Frankincense) and *Boswellia carterii* Birdw.² (also referred to as Frankincense or Olibanum) (Ammon, 2006). In this document, the terminology referring to the substance (i.e. *Boswellia*, extract, resin, etc.) is used from the data source. For example, the term *Boswellia* is used if this was the terminology utilized in the data source reviewed. The term *Boswellia* extract will be utilized if the species origin is unknown. Table 1 summarizes the compendial descriptions of *Boswellia* botanicals found in the United States, European and Chinese Pharmacopeias.

Table 1: Description of *Boswellia* botanicals from various pharmacopeias

Name of Botanical	Description	Pharmacopeia
<i>Boswellia serrata</i>	Oleogum resin obtained by incision or produced by spontaneous exudation from the stem and branches of <i>Boswellia serrata</i> Roxb.	United States, Dietary Supplements, Errata to Second Supplement to USP 37 – NF 32
<i>Boswellia serrata</i>	Extract prepared from pulverized <i>Boswellia serrata</i>	United States, Dietary Supplements, Errata to Second Supplement to USP 37 – NF 32
Indian Frankincense/ Olibanum indicum	Air-dried gum-resin exudate from stem or branches of <i>Boswellia serrata</i>	European, 8.0
Olibanum	Dried resin exuding from the bark of <i>Boswellia carterii</i> or <i>Boswellia bhawdajiana</i> ; drug is divided into Somalia olibanum and Ethiopia olibanum	Chinese, 2010 English Edition, p.301

The composition of *Boswellia* extracts varies widely. *Boswellia* extract from *Boswellia serrata* and *Boswellia carterii* contain several main classes of compounds including 22–

¹ Origin in India and the Punjab region extending to Pakistan.

² Origin in Oman, Yemen (Arabian Peninsula), Somalia and Nubia. The synonym of *Boswellia carterii* is *Boswellia sacra* Flück.

80% total boswellic acids, 5–15% volatile oils and 10–40% other compounds, as summarized in Table 2 (Ammon, 2006; Büchele et al., 2003; Sharma et al., 2009; Su et al., 2012; Fan et al., 2005; Siddiqui, 2011; Hamm et al., 2005).

Boswellia extracts may also contain tirucallic acids, other acids, and non-acid materials (Sharma et al., 2009). For example, BWSE used in the study of Sharma *et al.* consisted of approximately 60–65% boswellic acids, 15–20% tirucallic acids, and 13–18% other acids (Table 3). For comparison, the Boswellia dietary supplements marketed in the United States generally contain approximately 65% total boswellic acids (i.e., 650 mg/g (Google search, accessed 2015)

The most common boswellic acids are four structurally related compounds: boswellic acid (BA), acetyl boswellic acid (ABA), 11-keto-boswellic acid (KBA), and acetyl 11-ketoboswellic acid (AKBA) (Abdel-Tawab et al., 2011). Both BA and ABA have α and β isomers, while KBA and AKBA have β isomers only (Sharma et al., 2009; Abdel-Tawab et al., 2011; Singh et al., 2008). Table 4 presents general chemical structures and chemical properties of the four most common boswellic acids, as well as the varying percentages of KBA and AKBA amongst the two species, *Boswellia serrata* and *Boswellia carterii*.

Table 2. Major components of *Boswellia serrata* and *Boswellia carterii* extract

Studies	Büchele 2003		Sharma 2009	Su 2012	Fan 2005	Siddiqui 2011	Hamm 2005	Ammon 2006	
Species	<i>B.S.</i> ^a	<i>B.C.</i> ^b	<i>B.S.</i> ^a	<i>B.C.</i> ^b	<i>B.C.</i> ^b	<i>B.S.</i> ^a	<i>B.C.</i> ^b	<i>B.S.</i> ^a	<i>B.C.</i> ^b
Extraction solvent	Methanol, 3h	Methanol, 3h	Ethanol, RT	Water, reflux, 2h	70% aqueous acetone, RT	-	-	-	-
Total boswellic acid (% w/w)	62-75	74.4	60-65	22.1	40	30-60	65-85	55-57	66
Active ingredients in boswellic acid extracts (%)									
AKBA	10	24	-	-	-	-	-	-	-
KBA	14	5	-	-	-	-	-	-	-
BA	49	33	-	-	-	-	-	-	-
ABA	21	32	-	-	-	-	-	-	-
Volatile oil (% w/w)	-	-	5-9	-	-	5-10	5-9	7.5-15	5-9
Polysaccharides (% w/w)	-	-	25-30	-	-	20-30	10	-	-

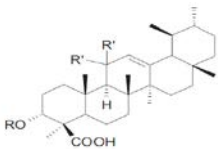
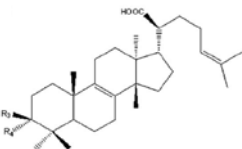
^a *B.S.* = *Boswellia serrata*

^b *B.C.* = *Boswellia carterii*

Literature suggests that boswellic acids are the major active components and can serve as chemical markers of Boswellia extracts (Sharma et al., 2009; Safayhi et al., 1992; Ammon et al., 1993; Lalithakumari et al., 2006; Roy et al., 2006). The USP Dietary Supplement Monographs for *Boswellia serrata* resin and extract include testing for the content of the keto derivatives of β -boswellic acid based on the sum of AKBA and KBA (*Boswellia serrata*, USP; *Boswellia serrata* Extract, USP; Indian Frankincense, EP). These four structurally related compounds can be quantified and characterized with current analytical techniques (Ammon, 2006; Sharma et al., 2009; Singh et al., 2008; *Boswellia serrata*, USP; *Boswellia serrata* Extract, USP; Indian Frankincense, EP; Olibanum, CP). According to Singh et al., (2008) the abundance of these acids in the

Boswellia serrata extract is in the following order: BA (~ 29.4%), ABA (~14.63%), AKBA (~7.35%) and KBA (~3.56%). However, it is important to note that the composition of *Boswellia* extracts, as well as the total and relative proportions of boswellic acid analogs, can differ depending on the botanical source (e.g., *Boswellia serrata* vs. *Boswellia carterii*) and manufacturing method (Ammon, 2006; Büchele et al., 2003; Sharma et al., 2009; Su et al., 2012; Fan et al., 2005; Siddiqui, 2011; Hamm et al., 2005; Abdel-Tawab et al., 2011; Singh et al., 2008). Despite the usefulness of BA, ABA, KBA and AKBA as chemical markers for *Boswellia* extract, their total content and relative proportions cannot be adequately controlled to ensure the quality of the bulk drug substance without proper controls of the botanical raw material (i.e., adopting good agricultural practices (GACP)) and the manufacturing process. Currently, the efforts to support reasonable management and sustainable production of *Boswellia* in its native habitat (i.e., India and Ethiopia) are limited (Lemenih et al., 2011).

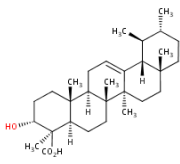
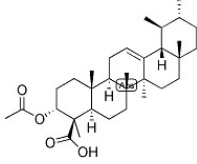
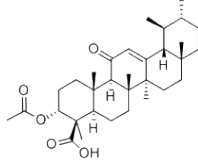
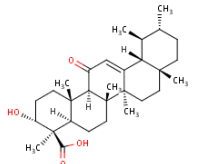
Table 3: Composition of *Boswellia serrata* extract

Class	Boswellic acids ^a	Tirucallic acids ^b	Other acids	Non-acid material
Structure			Not available	Not available
Concentration	60 – 65%	15 – 20%	13 – 18%	~ 7%

^a Boswellic acid (R= H, R' R' = H2), Acetyl, boswellic acid (R= OAc, R' R' = H2), 11-keto-boswellic acid (R=H, R' R' = O), and acetyl 11-keto-boswellic acid (R= OAc, R' R' = O)

^b Acetyl tirucallic acid (R₃ = OAc, R₄ = H) and 3-keto-tirucallic acid (R₃ + R₄ = O)

Table 4: Chemical properties of Boswellic acids analogs

CASRN	631-69-6	5968-70-7	67416-61-9	17019-92-0
Chemical name	Boswellic acid	3-O-acetyl boswellic acid	3-O-acetyl-11-keto boswellic acid	11-ketoboswellic acid
Abbreviation	BA	ABA	AKBA	KBA
Structure				
Mol. formula	C ₃₀ H ₄₈ O ₃	C ₃₂ H ₅₀ O ₃	C ₃₂ H ₄₈ O ₅	C ₃₀ H ₄₆ O ₄
Mol. weight	456.7	498.74	512.72	470.68
Isomer	α, β ^a	α, β ^a	β	β
Concentration ^b	29.41%	14.63%	7.35%	3.56%
Species				
<i>Boswellia carterii</i>			2.2-2.9	3-4.7
<i>Boswellia serrata</i>			3.3	0.5

^a Ratios of the α:β isomers are 37:63 and 22:78 for BA and ABA, respectively.

^b These concentrations are based on the total acid content of the *Boswellia serrata* gum resin.

In the past three decades, the boswellic acid analogs from boswellia extract have been studied as purified molecules, which by definition are not considered botanicals, and active components in partially purified extracts for their anti-inflammatory effect. Different Boswellia extracts with quantified levels of boswellic acid analogs (mainly AKBA) were studied for their toxicity as well as efficacy for various indications (Kimmatkar et al., 2003; Sengupta et al., 2008; Sengupta et al., 2010; Vishal et al., 2011; Pedretti et al., 2010). The levels of boswellic acid analogs used in these clinical studies are summarized in Table 5. AKBA and other boswellic acid analogs have been reported in commercial Boswellia dietary supplement extract products, 5-Loxin® and Aflapin® (Lalithakumari et al., 2006; Roy et al., 2006; Sengupta et al., 2008; Sengupta et al., 2010; Vishal et al., 2011; Pedretti et al., 2010), and were tested for the treatment of knee osteoarthritis and damaged skin. All of the products listed in Table 5 had some quality controls in place for the botanical raw material and manufacturing processes, as demonstrated by the reported quantifiable levels of at least one of the four boswellic acid markers in each product. The evaluation of the clinical and nonclinical data will be covered in the relevant sections below.

Table 5: Summary of clinical studies utilizing boswellic acid using mainly KBA and AKBA as marker compounds for Boswellia

Clinical Studies	BWSE extract dose (daily)	Product	Marker	Amount of marker (daily)	Indication
Kimmatkar et al., 2003	Oral 1 g, 8 weeks	Woknel™	AKBA: 2 % KBA: 6.44 % BA: 35.4 % ABA: 10.4 %	AKBA: 20 mg KBA: 64.4 mg BA: 354 mg ABA: 104 mg	Knee Osteoarthritis
Sengupta et al., 2008	Oral 100 mg and 250 mg, 90 days	5-Loxin®	AKBA: 30 %	AKBA: 30 mg and 75 mg	Knee Osteoarthritis
Sengupta et al., 2010	Oral 100 mg, 90 days	5-Loxin® Aflapin®	AKBA: > 30 % AKBA: > 20 %	AKBA: >30 mg AKBA: > 20 mg	Knee Osteoarthritis
Vishal et al., 2011	Oral 100 mg, 30 days	Aflapin®	AKBA: >20 %	AKBA: > 20 mg	Knee Osteoarthritis
Pedretti et al., 2010	Topical Once	5-Loxin®	AKBA: 30% BA+ABA+KBA: 20 %	-	Photo and age-damage skin

2. Probable routes of API synthesis

As stated above, Boswellia extract is a naturally derived mixture. Therefore, there is no synthetic pathway for this API.

Different manufacturing processes (including various solvent extractions) have been utilized to concentrate the boswellic acids from boswellia resins. In the world's production of Boswellia extract, there is a lack of universal standardization in

manufacturing (i.e., lack of process quality controls)(Siddiqui, 2011). Sabinsa Corporation is the major United States manufacturer of Boswellia products with standardized levels of boswellic acids (Dharmananda, 2003; Sabinsa Corporation, accessed 2015). The exact manufacturing process is not known due to confidentiality of industry methods. Most likely, based on the scientific literature, the resin is extracted with alcohol (e.g., methanol, ethanol) and purified to obtain the extract. There are also other extraction methods for Boswellia, for instance CO₂ extracted Frankincense for cosmetic usage and steam stillled Frankincense with low yield of essential oil for topical use in skin. As mentioned above, in addition to the botanical source, the manufacturing process can affect the total level and relative proportions of boswellic acid analogs, which in turn can affect the quality of the bulk drug substance due to the lack of quality controls.

3. *Likely impurities*

Both the United States and European Pharmacopeias (Table 6) include impurity testing in the Dietary Supplement monographs for Boswellia, and an API used in drug products might include similar impurities. Residual solvents used for extraction should also be considered as impurities and be tested according to USP.

Table 6: Compendial analytical methodologies for *Boswellia* impurities

Test	Cited Method and Threshold	Pharmacopeia
Heavy Metals (Inorganic Impurities)	Method II <231>: NMT 20 ppm	United States
Procedure: Articles of Botanical Origin (Organic Impurities)	<i>Method for Pesticide Residue Analysis</i> <561>: Meets the requirements	United States
Loss on Drying	<731>: Dry 1.0 g of Extract at 105°C for 2 h: is loses NMT 5.0% of its weight	United States
	(2.2.32): Maximum 8.0%, determined on 1.000 g of powdered herbal drug (355) (2.9.12) by drying in an oven at 105°C for 3 h	European
Total Ash	(2.4.16): maximum 10.0%	European
Microbial Enumeration	<2021>: Total aerobic bacterial count does not exceed 10 ⁴ cfu/g, and the total combined molds and yeast count does not exceed 10 ³ cfu/g	United States
Microbiological Procedures for Absence of Specified Microorganisms	<2022>: Meets the requirements of the tests for absence of <i>Salmonella</i> species and <i>Escherichia coli</i>	United States

4. *Toxicity of likely impurities*

While the BWSE impurities are unknown, the most likely potential impurities include those listed above in Table 6 and residual solvents.

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

The known characteristic chemical markers and potentially active components of BWSE are boswellic acids or boswellic acid analogs. It is unknown whether the physiochemical characteristics of BWSE and boswellic acid analogs such as particle size and polymorphism are pertinent issues in drug 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*

Boswellia resin (a botanical raw material) primarily has been collected from *Boswellia serrata* and *Boswellia carterii* for medicinal purposes for centuries. As the resin is formed by human intervention (i.e., by wounding the tree bark) from well-known species, false identification at the plant source is not likely if proper controls are in place. Properly trained experts can identify the resin by its morphology, unique taste and aroma. Comprehensive pharmacognosy methods including source plant identification, morphological and microscopic characterization, and chemical analyses of Boswellia resin, as well as physiochemical analyses of Boswellia extracts, are available in literature, including the USP dietary supplement monograph and pharmacopeias of other countries (e.g., European Pharmacopeia and Chinese Pharmacopeia) (*Boswellia serrata*, USP; *Boswellia serrata* Extract, USP; Indian Frankincense, EP; Olibanum, CP).

As mentioned above, Boswellia resin contains relatively well-characterized boswellic acid analogs, a group of unique chemical markers that are the presumed active molecules. The four major boswellic acid analogs (Table 4) can be quantified as marker compounds by following dietary supplement monograph methods in USP and other references (Ammon, 2006; Sharma et al., 2009; Singh et al., 2008; *Boswellia serrata*, USP; *Boswellia serrata* Extract, USP; Indian Frankincense, EP; Olibanum, CP). Those methods can potentially be used to identify and characterize the quantitative level of boswellic acid analogs (e.g., AKBA) in Boswellia extract. Although the total percentage of the polysaccharides as a group in the extract can be measured, the polysaccharide/carbohydrate portion of the extract is difficult to fully characterize at the molecular level. The same is true about the volatile oil fraction, which contains hundreds of small molecules, such as monoterpenes, sesquiterpenes, and other uncharacterized molecules. Quantification of each molecule is technically challenging, and the analytical information would be vital in determining the dose of Boswellia extract for a specific patient and indication (Paul, accessed 2015). In addition, despite the availability of these analytical methods, the quality of boswellia (i.e., consistency in composition including other components in addition to the four major boswellic acid analogs) cannot be assured without proper control of raw materials and manufacturing process.

Conclusions: As noted above, the composition of Boswellia extracts, including the total content and the relative proportions of the four major boswellic acid analogs (BA, ABA, KBA and AKBA), differs depending on the botanical source and extraction method. Therefore, although the four boswellic acid analogs, which are considered useful chemical markers for this mixture, can be characterized and quantified, their total content and relative proportions as well as the levels of other components (e.g., polysaccharide/carbohydrate portion and volatile oil fraction of the extract) cannot be adequately controlled to ensure the consistent quality of this substance

unless there are proper controls of the botanical raw material (including the adoption of good agricultural and collection practices (GACP)) and manufacturing processes. By considering this factor and recognizing there is no assurance that such raw material and manufacturing controls will be in place for the bulk drug substances used for pharmaceutical compounding, this factor weighs against recommending that BWSE be added to the 503A list.

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

1. Nonclinical Assessment

a. Pharmacology of the drug substance

The pharmacology of BWSE is not fully understood. Animal studies and pilot clinical trials indicate that BWSE has anti-inflammatory properties but the exact mechanism(s) of action is unknown. Anti-inflammatory effects have been attributed mostly to boswellic acids, but other components such as tirucallic acids may also contribute. Below is a summary of mechanisms of action for rheumatoid arthritis based on the review of Abdel-Tawab et al. (2011).

The mechanism by which BWSE exerts efficacy in arthritic disease is not known but may be associated with inhibition of CatG (the serine protease cathepsin G), mPGES-1 (microsomal prostaglandin E synthase-1), and with the inhibition of the formation of inflammatory mediators. CatG is released by macrophages during RA-associated inflammatory and angiogenic events. Increases in PGE2 and mPGES-1 levels were found in the synovial fluid of arthritic joints. Boswellic acids inhibited the activity of CatG, mPGES-1, and several known biochemical mediators of inflammation, including cytokines (e.g. TNF α , IL-1b) and pro-inflammatory enzymes (catG, 5-LO, p12LO, COX-1, CYP-2C8/2C9/3A4) in various in vitro tests. The IC₅₀ values ranged between 0.6 and 55 μ mol/L. The most pronounced inhibition was observed for the catG and mPGES-1 enzymes. The respective IC₅₀ for catG inhibition was 0.6, 0.8, and 1.2 μ mol/L for AKBA, BA, and β ABA, respectively. The IC₅₀ values for inhibiting mPGES-1 were 3, 5, and 10 μ mol/L for AKBA, β BA, and KBA, respectively. Boswellic acids also suppressed the transformation of PGH2 to PGE2 mediated by mPGES-1 in A549 cells in vitro.

A number of other mechanisms of action for boswellic acids have been proposed. Some potential mechanisms include, but are not limited to, leukotriene antagonist (Singh et al., 2008), human elastase inhibitor (Safayhi et al., 1992), 5-lipoxygenase inhibitor (Siddiqui, 2011), topoisomerase inhibitor (Syrovets et al., 2000), and antioxidant (Hartmann et al., 2014).

BWSE has been shown to possess anti-inflammatory activities in vivo in a number of animal models (Table 7). Briefly, topically applied BWSE reduced both arachidonic acid-induced and croton oil-induced ear edema in mice and carrageenan-induced ear edema in rats. In paw swelling models, after intravenous injection or topical application of BWSE, dose-related decreases in the severity of paw swelling induced by adjunct (dead *M. tuberculosis*) and carrageenan in rats were observed (Singh et al., 1996).

Pharmacologic activities of BWSE have traditionally focused on boswellic acids, but recent studies showed that tirucallic acid also inhibited mPEGS-1 at similar concentrations (0.4 – 3 μ M) (Verhoff et al., 2014).

Table 7: Effects of BWSE in Animal Models of Inflammation and Arthritis

Extract/dosage	In vivo model	Observed anti-inflammatory effects
Methanolic BWSE 50–200mg/kg PO od ^a	Carrageenan-induced edema in rats and mice Dextran-induced edema in rats Cotton pellet-induced granuloma test in rats Formaldehyde arthritis in rats	Inhibition of paw volume by 26–43% in rats and 20–34% in mice Inhibition of edema by 21–51% Weak inhibitory action Inhibition of paw volume by 23–44% Reduction of total leukocyte count by 16–42% in synovial fluid; moderate to marked improvement in gait
Drug treatment started on d14 and terminated on d28	Adjuvant-induced established arthritis in rats Adjuvant-induced developing arthritis in rats	32–50% inhibition on d14 with marked inhibition of secondary lesions 34–52% inhibition on d28
Methanolic BWSE 25–100mg/kg PO od	BSA-induced arthritis in rabbits	Reduction of leukocyte count by 18–48% in synovial fluid
Methanolic BWSE 50–200mg/kg PO od	Carrageenan-induced pleurisy in rats	Reduction of exudate volume by 19–25% and total leukocyte count by 36–44%
70% aqueous acetone extract of <i>Boswellia carterii</i> 0.45–0.9 g/kg/d PO (IG) for 7 d	Freund’s adjuvant-induced rat-paw edema	Significant reduction in paw edema vs control, in addition to lengthening paw withdrawal latency
Aqueous acetone extract of <i>B. carterii</i> 0.9 g/kg PO (IG) for 10 d	Adjuvant arthritis in Lewis rats	Significant reduction of arthritic scores, paw edema and local TNF α and IL-1 β vs control
Mixture of BAs 100mg/kg PO	Papaya latex-induced rat-paw inflammation	Inhibition of inflammation by 41% (3 h) vs control
Mixture of BAs 50–150mg/kg PO	Papaya latex-induced rat-paw inflammation	Inhibition of inflammation by 19.9% with 50mg/kg dose, 26.7% with 100mg/kg dose and 29.7% with 150mg/kg dose, vs control
BAs, lupeolic acids, tirucallane-type acids isolated from methanolic extract of <i>B. carterii</i>	TPA-induced ear inflammation in mice	ID50 of all tested compounds: 0.05–0.49mg/ear
Alcoholic BWSE 50–200mg/kg	Carrageenan-induced pleurisy in rats	Significant reduction of volume of pleural exudate vs control and inhibition of infiltration of PMNLs into the pleural cavity
Alcoholic BWSE 25–100mg/kg PO and local injection (5–20mg/knee)	BSA-injected knee of rat	Significant reduction of total leukocyte count at 50 and 100mg/kg oral doses and after local injection
Acetyl BA mixture (50% AbBA, 37% AKBA, 5% AaBA, 5% other terpinoids) 20mg/kg IP od for 21 d	Experimental autoimmune encephalomyelitis in guinea pigs	Reduction of experimental symptoms between d11 and d21
BSB108 400mg/10 kg PO od for 6 wk	Dogs with OA and degenerative conditions	Resolution of intermittent lameness, local pain, stiff gait

a. AaBA= acetyl-a-BA; AbBA= acetyl-b-BA; AKBA= acetyl-11-keto-b-BA; BA= boswellic acid; BSA= bovine serum albumin; dx = day x; ID50 = dose that produces 50% inhibition; IG = intragastrically; IL = interleukin; IP = intraperitoneally; OA= osteoarthritis; od = once daily; PMNL= polymorphonuclear leukocyte; PO= orally; TNF = tumor necrosis factor; TPA= 12-O-tetradecanoylphorbol-13-acetate.

b. Safety pharmacology

Evaluations of the safety pharmacology of BWSE have not been reported in the literature.

c. Acute toxicity

Evaluations of the acute toxicity of BWSE have not been reported in the literature, but the dietary supplement 5-Loxin[®] (i.e., AKBA-enriched BWSE) was tested for its acute toxicity in rats (Lalithakimari et. al., 2006). 5-Loxin[®] is BWSE enriched with 30% AKBA. The total Boswellic acid content in 5-Loxin[®] is approximately 85% (w/w). The minimal lethal dose of 5-Loxin[®] was greater than 5000 mg/kg in rats. Rats (SD, 5/sex) were dosed orally with 5000-mg/kg/day for 14 days. One rat died on day one. This rat showed duodenum blockade upon necropsy. No signs of toxicity were observed in any other rats throughout the dosing period. The mortality does not appear to be treatment-related.

d. Repeat dose toxicity

There are no well-designed and well-controlled, quality data to evaluate the toxicity of BWSE, but no significant toxicity was observed when rats (CD, n = 5/sex/dose) were dosed in a dietary study with 5-Loxin[®] at doses up to 1500 mg/day (i.e., concentration of 2.5% in diet) for 90 days (Lalithakumari et al., 2006).

e. Mutagenicity

Studies evaluating the mutagenicity of BWSE have not been conducted, but 5-Loxin[®] was not mutagenic in a modified bacterial gene mutation assay (Ames test, Lalithakimari et. al., 2006). Four strains of *Salmonella typhimurium* (TA 98, TA 100, TA 1535, and TA 1537) were used in the test. 5-Loxin[®] was tested at concentrations up to 3000 µg/plate. Also, BWSE did not induce chromosomal aberrations in an in vivo rat micronucleus assay, and it did not cause DNA damage in a Comet assay (Sherma et al. 2009). In the micronucleus assay, groups of male Wistar rats (5/dose) were dosed by oral gavage with 0, 125, 250, 500, or 1000-mg/kg/day BWSE, or 40-mg/kg/day cyclophosphamide (positive control) for 15 days. Rats were sacrificed 14 hours after the last dose. Micronuclei formation in the bone marrow erythrocytes was determined. DNA damage in bone marrow cells was also assessed using the Comet assay. No increases in micronuclei and DNA fragments were observed in BWSE treatment groups. The cyclophosphamide treated rats showed a typical, positive response.

f. Developmental and reproductive toxicity

Developmental and reproductive toxicity of BWSE in nonclinical laboratory animals have not been reported in the literature, but BWSE and similar products are not recommended for use in pregnant women, according to the Chinese Pharmacopeia (2010).

g. Carcinogenicity

Evaluations of the carcinogenic potential of BWSE have not been reported in the literature.

h. Toxicokinetics

Evaluations of toxicokinetics of BWSE have not been reported in the literature.

Conclusions: The available information is insufficient to conduct a sound nonclinical safety assessment of BWSE, a mixture of several compounds. BWSE has been shown to possess anti-inflammatory properties in vitro and in vivo, but the toxicological profile of BWSE ingredients, alone or in combination, is very limited. There is no evaluation of the general toxicity, carcinogenicity, or developmental toxicity of BWSE in animals. However, federal regulations allow closely related material, Olibanum (*Boswellia* spp), to be used as flavoring agent in food (21 CFR172.510).

2. *Human Safety*

a. Reported adverse reactions

In the literature, there are studies describing the safety of BWSE. In general, BWSE appeared well-tolerated. The most commonly reported adverse events with BWSE were gastrointestinal, including diarrhea, abdominal pain, and nausea (Abdel-Tawab et al., 2011).

However, traditional uses of *Boswellia serrata* include “menorrhoea, dysmenorrhoea, and emmenagogue” (Jadhav et al., 2005; Kamboj, 1988; Basch et al., 2004). Emmenagogues are products that stimulate blood flow in the pelvic area and uterus and can induce an abortion or prevent pregnancy. Sources suggest it should not be utilized in pregnancy due to these concerns (Basch et al., 2004; <http://www.wellness.com/reference/herb/boswellia-boswellia-serrata/dosing-and-safety> (accessed 1/21/16)). Safety of BWSE during pregnancy has not been systematically studied, and therefore cannot be recommended. This is a significant safety concern given the potential use of BSWE by women of child bearing potential.

Another notable safety concern is related to the potential increase in the anticoagulant effect of warfarin that could lead to adverse events related to bleeding. The literature describes cases where the international normalized ratio (INR) increased with concomitant intake of warfarin and *Boswellia serrata* (Paoletti et al., 2011).

The Office of Surveillance and Epidemiology (OSE) evaluated the FDA Adverse Event Reporting System (FAERS) for all adverse events reported with *Boswellia*, particularly anything related to *Boswellia* and pregnancy loss. The FAERS search retrieved seven foreign reports of adverse events with the use of *boswellia*, including one duplicate report. In all six cases, *boswellia* was administered concomitantly with other medications. Three cases were from one literature report describing drug interactions

between boswellia and warfarin that resulted in an over-anticoagulation effect. One case reported gastrointestinal bleeding and decreased hemoglobin with concomitant boswellia and ibuprofen use. One case reported pancytopenia and myelodysplastic syndrome with administration of methotrexate, boswellia, and other concomitant medications. One case was a “poison information center” report involving boswellia and multiple other medications. There were no reports of pregnancy loss associated with boswellia.

The Center for Food Safety and Applied Nutrition (CFSAN) was consulted and the Signals Management Branch provided adverse events for Boswellia Serrata Extract from the Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS). CAERS is a post-market surveillance system that collects reports about adverse events and product complaints potentially related to CFSAN-regulated products. These products include conventional food (and beverages), dietary supplements, infant formulas, and cosmetics. The adverse event reports about a product and the total number of adverse event reports for that product in CAERS only reflect information as reported and do not represent any conclusion by FDA about whether the product actually caused the adverse event. There were 208 cases in which the patient reported taking a product containing Boswellia. Limited details regarding the cases were provided. There was a spectrum of adverse event severity, including serious and life-threatening adverse events. Many adverse events required hospitalization and there were patient deaths. In all of the adverse events, patients were taking other medications or the product contained multiple components, including boswellia. In terms of the deaths, one death was a 76 year old woman who was hospitalized for low blood pressure, internal bleeding, a gastrointestinal infection, ruptured colon, and kidney failure. It was reported that the supplement containing multiple components, including Boswellia, reacted with the patient’s blood pressure and cholesterol medications. Another death was a 70 year old man who had a “massive stroke.” A third death was a 65 year old man taking warfarin who developed an elevated INR and had an infection in “his blood and his heart.” Given that the adverse events involved products with multiple ingredients, no definitive conclusions regarding the causality of the adverse events related to Boswellia exposure could be established. There were no reports of pregnancy loss associated with Boswellia.

b. Clinical trials assessing safety

The safety of BWSE has been assessed in randomized, controlled trials that were performed to assess efficacy and safety. In general, BWSE appeared to be well-tolerated, however the number of patients evaluated was fairly limited and it was frequently unclear if there were standardized safety assessments. There were no serious adverse events in patients who received BWSE. In studies of osteoarthritis, the primary adverse events were gastrointestinal. Specifically, studies describe “loose motions in one, epigastric pain and nausea in one, which responded to usual symptomatic treatment” (Kimmatkar et al., 2003); “diarrhea, nausea, abdominal pain, mild fever (up to 37.5°C [99.5°F]) and general weakness” (Sengupta et al., 2008); “acidity” (Sengupta et al., 2010); nausea and headache (Vishal et al., 2011); and diarrhea and abdominal cramps leading to study discontinuation in one patient (Sontakke et al., 2007). A Cochrane review (Cameron et al., 2014) assessed the safety data for BWSE in OA studies and

noted that it was uncertain if there was an increased risk of adverse events or withdrawals with BWSE due to variable reporting across studies.

The safety of BWSE has been assessed in randomized, controlled trials in rheumatoid arthritis. In general, BWSE appeared well-tolerated. Similar to studies in osteoarthritis, the primary adverse events were gastrointestinal. In a study published by Chopra et al., (2000) that utilized RA-1, a drug containing *Boswellia serrata* and other plant extracts, the adverse event that was more common with RA-1 than placebo was loss of body weight. Another study published by Etzel (1996) noted that side-effects were very mild.

c. Pharmacokinetic data

There are limited data available on the pharmacokinetic properties of BWSE. One published paper noted that “the sparse studies clearly indicate that the plasma concentration of boswellic acids vary markedly between subjects and depend on the pharmaceutical preparation and the conditions of intake” (Abdel-Tawab et al., 2011). The plasma concentrations obtained for boswellic acids in humans after oral administration are summarized in Table 8.

Table 8: Overview of the maximum plasma concentration (C_{max}) of boswellic acids (BAs) determined in different studies

Dosage	Condition	C_{max} of BAs determined in human plasma ($\mu\text{mol/L}$)					
		AKBA	KBA	β BA	A β BA	α BA	A α BA
BSE 1600 mg PO sd (n = 1) ^[21]		NA	1.9	NA	NA	NA	NA
BSE 4 \times 786 mg/day (containing α BA 137.8 mg/g, A α BA 33.7 mg/g, β BA 192.2 mg/g, A β BA 100.4 mg/g, KBA 66.6 mg/g and AKBA 38.1 mg/g) PO for 10 d (n = 1) ^[13]	Steady state	0.1	0.34	10.1	2.4	3.5	4.0
WokVel™ capsule (containing BSE 333 mg) PO sd after a meal (n = 12) ^{[22] a}		ND	2.72 \pm 0.18	NA	NA	NA	NA
Three BSE 800 mg capsules PO od for 4 wk (n = 3) ^{[23] a}	Steady state	0.04 \pm 0.01	0.33 \pm 0.1	6.35 \pm 1.0	4.9 \pm 0.5	NA	NA
Three BSE-018 dry extract 282 mg capsules (in total: α BA 103.71 mg, A α BA 26.25 mg, β BA 143.4 mg, A β BA 82.71 mg, KBA 48.12 mg, AKBA 28.71 mg) PO sd in the fasted state and after a high-fat meal (n = 12) ^{[16] b}	Fasted state	0.01	0.17	0.4	ND	ND	ND
	Fed state	[0.002–0.08]	[0.05–0.52]	[0.10–3.9]	2.5	0.69	0.24
		[0.03–0.52]	[0.21–0.9]	[0.91–4.7]	Only a few subjects had measurable plasma concentrations	[0.1–2.9]	[0.09–0.8]

a Values are expressed as mean \pm standard deviation.

b Values are expressed as mean [range].

α BA = α -boswellic acid; β BA = β -boswellic acid; A α BA = acetyl- α -boswellic acid; A β BA = acetyl- β -boswellic acid; AKBA = acetyl-11-keto- β -boswellic acid; BSE = *Boswellia serrata* gum resin extract; KBA = 11-keto- β -boswellic acid; NA = not analysed, ND = not detected; od = once daily; PO = orally; sd = single dose.

Source: Abdel-Tawab. Clin Pharmacokinet. 2011;50(6):349-69.

In a study published by Tausch et al. (2009), treatment with BWSE 800 mg three times daily for 4 weeks resulted in average steady-state plasma concentrations of boswellic acids in three patients as follows: β BA 6.35 $\mu\text{mol/L}$, A β BA 4.9 $\mu\text{mol/L}$, KBA 0.33 $\mu\text{mol/L}$, and AKBA 0.04 $\mu\text{mol/L}$. Sterk et al. (2004) studied the effect of food intake on the bioavailability of boswellic acids in healthy subjects following intake of 786 mg BWSE. There was a 3-fold increase in the maximum plasma concentration (C_{max}) of

KBA when BWSE was administered with a high fat meal. There was a 6-fold increase in C_{\max} of AKBA and β Ba when BWSE was administered with a high fat meal.

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

There are multiple approved therapies for osteoarthritis (OA). The treatment of OA is directed towards reduction of symptoms, such as pain and functional limitation. There are no pharmacological therapies that have been proven to prevent progression of joint damage due to OA. Multiple non-steroidal anti-inflammatory drugs (NSAIDs), including oral and topical NSAIDs, are FDA-approved for the treatment of OA. In addition, intra-articular hyaluronans and glucocorticoids are FDA-approved for the treatment of OA. Opioid analgesics are FDA-approved for the treatment of acute and chronic pain, and are used to manage pain associated with OA. Additional over-the-counter medications utilized for OA are acetaminophen, glucosamine, chondroitin, and capsaicin. Other treatments utilized for OA include joint replacement, physical therapy, and acupuncture.

There are multiple approved therapies for rheumatoid arthritis (RA). Medications utilized to slow down disease progression are referred to as nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs). Since 1998, FDA has approved the following drugs for RA: leflunomide, etanercept, infliximab, anakinra, adalimumab, abatacept, rituximab, certolizumab, golimumab, tocilizumab, tofacitinib, golimumab intravenous (IV), and methotrexate subcutaneous injection. While each drug has its own specific safety profile, all of these drugs are associated with an increased risk of infection. In addition, oral glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) are approved for the treatment of RA. Similar to DMARDs, glucocorticoids are associated with an increased risk of infection. NSAIDs are associated with gastrointestinal, renal, and cardiovascular adverse effects.

Conclusions: There are reports in the Indian literature that resin from boswellia may be an emmenagogue and induce abortion. Thus, BWSE should be avoided by women who are pregnant or may become pregnant. This is a significant safety concern given the potential use in women of child bearing potential. In clinical studies, BWSE has not been associated with other serious adverse events, but the quantity and quality of the available safety data are limited. It is associated with gastrointestinal adverse events, including diarrhea, abdominal pain, and nausea. There are reports of interactions with oral anticoagulants leading to an increase in the anticoagulant effect. There were post-market cases of adverse events, including serious adverse events, but limited conclusions were possible from the available data. There are multiple approved treatments for both osteoarthritis and rheumatoid arthritis with well-defined safety profiles. There are safety risks associated with the use of approved treatments for osteoarthritis and rheumatoid arthritis, however these risks are considered in the context of established efficacy. The potential for termination of pregnancy and potential interaction with oral anticoagulants are notable safety issues associated with the use of BWSE. Of note, there are limited high quality data available to support the overall safety of BWSE.

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*

Osteoarthritis (OA)

A Cochrane review (Cameron et al., 2014) assessed the efficacy data for BWSE in OA. The review included randomized controlled trials of orally administered herbal interventions compared with placebo or active controls in patients with osteoarthritis. The primary outcome measures were pain (visual analogue scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), including the pain, stiffness, and physical function subscales. Five studies of three different extracts from *Boswellia serrata* were included (Kimmatkar et al., 2003; Sengupta et al., 2008; Sengupta et al., 2010; Vishal et al., 2011; Sontakke et al., 2007). Additional details regarding these studies are included below.

The Cochrane review concluded that there is high-quality evidence from two studies (85 participants) that 90 days of treatment with 100 mg of enriched BWSE improved symptoms compared to placebo. Enriched BWSE reduced pain by a mean of 17 points (95% confidence interval (CI) 8 to 26). Similarly, enriched BWSE improved function by 8 points (95% CI 2 to 14). Possible benefits of other BWSE over placebo were noted in moderate quality evidence from two studies (97 participants) of BWSE (enriched) 100 mg plus non-volatile oil, and low quality evidence from a small single study of 999 mg daily dose of BWSE and 250 mg daily dose of enriched BWSE.

Five studies were included in the Cochrane review and are described in more detail below.

Kimmatkar et al. (2003) published a randomized, double-blind, placebo controlled, crossover study of 30 patients with knee OA. Patients were randomized to either 333 mg BWSE (Cap Wokvel™) (n=15) or placebo (n=15) three times daily for eight weeks. After eight weeks of therapy, patients crossed over to receive the opposite therapy for eight additional weeks. There was a 21-day washout period between the first and second interventions. Pain intensity, loss of function, and swelling were graded on a VAS from 0 to 3. There was a statistically significant difference in the severity of pain and swelling and improvement in loss of function in the BWSE treated patients compared to placebo treated patients (Table 9).

Table 9: Mean efficacy variables pre treatment and post treatment at first intervention in two groups

Parameter	Group 1 (BSE treated)		Difference	Group 2 (Placebo treated)		Difference	P value
	Pre- T/t	Post- T/t		Pre- T/t	Post- T/t		
Pain	2.7 ± 0.45	0.26 ± 0.45	2.4 ± 0.51	2.8 ± 0.41	2.5 ± 0.65	0.26 ± 0.59	P < 0.001
Loss of movement	2.8 ± 0.41	0.3 ± 0.48	2.4 ± 0.51	2.86 ± 0.35	2.46 ± 0.63	0.4 ± 0.63	P < 0.001
Swelling	1.1 ± 0.91	0	1.1 ± 0.91	1.1 ± 0.83	1.3 ± 1.11	-0.2 ± 1.01	P < 0.001

Pre- T/t – Prior to initiation of the assigned treatment;
 Post- T/t – After completion of eight weeks of assigned treatment;
 BSE – *Boswellia serrata* Extract.

Source: Kimmatkhar N. Phytomedicine. 2003;10:3-7.

Sengupta et al. (2008) published a double-blind, placebo-controlled clinical study of 75 patients with knee OA. Patients were randomized to three groups: placebo (n=25), 5-Loxin[®] 100 mg/day (n=25), and 5-Loxin[®] 250 mg/day (n=25). 5-Loxin[®] contains BWSE enriched to 30% 3-O-acetyl-11-keto-β-boswellic acid (AKBA). Patients received 90 days of therapy. There were statistically significant reductions in pain VAS, Lequesne's Functional Index (LFI), and WOMAC subscale scores for the low-dose (100 mg) versus the placebo and the high-dose (250 mg) versus placebo (Table 10). The numerical improvements were greater for the high-dose than the low-dose group.

Table 10: Student's t-test (paired) analysis for comparisons of the scores obtained from the low-dose and high-dose 5-Loxin groups at day 90

Student's t-test (paired) analyses for comparison of the scores obtained from the low-dose and high-dose 5-Loxin[®] groups at day 90

	n	Baseline		Day 90		95% CI (versus placebo)	P
		Mean	SD	Mean	SD		
Visual analogue scale score							
Placebo	23	56.88	12.04	41.76	15.98		<0.05
100 mg 5-Loxin [®]	24	57.05	8.71	21.37	7.13	-27.67, -13.11	<0.0001
250 mg 5-Loxin [®]	23	55.62	9.26	14.22	6.8	-34.94, -20.19	<0.0001
Lequesne's Functional Index							
Placebo	23	12.76	2.6	10.19	3.24		0.031
100 mg 5-Loxin [®]	24	12.1	2.76	7.78	4.61	-4.74, -0.07	<0.0001
250 mg 5-Loxin [®]	23	12.04	3.03	7	3.5	-5.19, -1.18	<0.0001
WOMAC pain subscale							
Placebo	23	38.04	2.03	31.74	2.58		0.1212
100 mg 5-Loxin [®]	24	42.08	2.93	19.17	3.55	-21.33, to -3.83	<0.0001
250 mg 5-Loxin [®]	23	37.17	2.88	15.22	2.50	-23.78 to -9.28	<0.0001
WOMAC stiffness subscale							
Placebo	23	33.15	2.73	24.45	2.37		0.2983
100 mg 5-Loxin [®]	24	31.77	3.61	14.06	3.71	-38.87, -6.85	<0.0001
250 mg 5-Loxin [®]	23	27.72	3.44	9.24	2.07	-43.35, -17.45	<0.0001
WOMAC function subscale							
Placebo	23	41.30	2.02	34.07	1.09		0.1048
100 mg 5-Loxin [®]	24	41.48	2.31	24.32	4.28	-18.64, -0.82	<0.0001
250 mg 5-Loxin [®]	23	38.56	2.32	17.267	1.98	-21.39, -12.23	<0.0001
MMP-3 (ng/ml)							
Placebo	15	902.1	275.6	928.5	216.02		0.4886
100 mg 5-Loxin [®]	16	893.6	270.1	637.2	224.5		<0.0001
250 mg 5-Loxin [®]	14	926.9	270.5	497.5	167.5		<0.0001

CI, confidence interval; MMP, matrix metalloproteinase; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Source: Sengupta K. Arthritis Res Ther. 2008;10:R85.

Sengupta et al. (2010) published a double-blind, randomized, placebo controlled study of 60 patients with knee OA. Patients were randomized to three groups: placebo (n=20), 5-Loxin[®] 100 mg/day (n=20), and Aflapin[®] 100 mg/day (n=20). As noted above, Loxin[®] contains BWSE enriched to 30% AKBA. Aflapin[®] contains BWSE enriched with AKBA and *Boswellia serrata* non-volatile oil. Patients received 90 days of therapy. Efficacy endpoints included pain VAS, LFI, and the WOMAC subscales. There were statistically significant reductions in pain VAS, LFI, and WOMAC subscale scores for 5-Loxin[®] versus placebo and Aflapin[®] versus placebo (Table 11).

Table 11: Student's t-test (paired) analyses for comparison of the scores obtained from the Aflapin and 5-Loxin groups at day 90

	n	Baseline		Day 90		95% CI (versus placebo)	p
		Mean	SD	Mean	SD		
Visual analogue scale score							
Placebo	19	47.7	6.5	38.3	9.0	34.0, 42.7	0.0013
5-Loxin 100 mg/day	19	48.2	6.1	26.2	16.5	18.2, 34.1	<0.0001
Aflapin 100 mg/day	19	47.7	7.3	20.2	12.3	14.2, 26.1	<0.0001
Lequesne's Functional Index							
Placebo	19	12.3	2.8	10.9	3.0	9.4, 12.3	0.0496
5-Loxin 100 mg/day	19	12.4	2.6	8.9	3.7	7.1, 10.7	<0.0001
Aflapin 100 mg/day	19	12.0	2.4	7.0	2.6	7.1, 9.6	<0.0001
WOMAC pain subscale							
Placebo	19	44.7	11.5	36.3	10.5	31.2, 41.4	0.0021
5-Loxin 100 mg/day	19	46.1	7.6	25.3	17.2	17.0, 33.6	<0.0001
Aflapin 100 mg/day	19	45.0	13.3	13.9	8.3	10.0, 17.9	<0.0001
WOMAC stiffness subscale							
Placebo	19	39.5	11.2	29.6	9.5	25.0, 34.2 p	0.0059
5-Loxin 100 mg/day	19	39.5	11.2	17.1	16.8	9.0, 25.2	0.0001
Aflapin 100 mg/day	19	39.5	13.3	11.8	12.8	5.7, 18.0	<0.0001

	n	Baseline		Day 90		95% CI (versus placebo)	p
		Mean	SD	Mean	SD		
WOMAC function subscale							
Placebo	19	42.0	10.3	32.0	10.8	26.8, 37.2	0.0025
5-Loxin 100 mg/day	19	43.1	7.8	25.2	15.0	17.9, 32.4	<0.0001
Aflapin 100 mg/day	19	42.0	8.4	16.2	8.1	12.3, 20.1	<0.0001

CI, confidence interval; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Source: Sengupta K. Int J Med Sci 2010;7:366-77.

Vishal et al. (2011) published a randomized, double-blind, placebo controlled cross-over study of 60 patients with knee OA. Patients were randomized to two groups: placebo (n=30) and Aflapin[®] 100 mg/day (n=30). Patients received 30 days of therapy. There were statistically significant reductions in pain VAS, LFI, and WOMAC subscale scores for Aflapin[®] versus placebo (Table 12).

Table 12: Normalized pain and function scores after 30 days of study treatment

Parameter and treatment	Baseline mean ± SD	Day-30 mean ± SD	p value (vs. baseline)	p value (vs. placebo)
Visual analogue scale score				
Placebo (n=29)	47.6 ± 9.7	39.3 ± 9.5	<0.0001	NA
Aflapin 100 mg/day (n=30)	48.0 ± 6.0	24.5 ± 11.9	<0.0001	<0.0001
Lequesne's Functional Index				
Placebo (n=29)	12.5 ± 3.4	12.4 ± 2.6	0.7646	NA
Aflapin 100 mg/day (n=30)	12.8 ± 3.7	8.4 ± 3.8	<0.0001	<0.0001
WOMAC pain subscale				
Placebo (n=29)	45.9 ± 10.5	40.3 ± 11.4	0.001	NA
Aflapin 100 mg/day (n=30)	47.8 ± 12.4	24.2 ± 12.0	<0.0001	<0.0001
WOMAC stiffness subscale				
Placebo (n=29)	37.5 ± 14.9	34.1 ± 15.6	0.2024	NA
Aflapin 100 mg/day (n=30)	38.8 ± 13.3	20.0 ± 15.6	<0.0001	0.0014
WOMAC function subscale				
Placebo (n=29)	40.6 ± 9.5	36.8 ± 11.5	0.0029	NA
Aflapin 100 mg/day (n=30)	41.1 ± 11.8	22.5 ± 11.1	<0.0001	<0.0001

NA, not applicable; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Source: Vishal AA. Int J Med Sci. 2011;8:615-22.

Sontakke et al. (2007) published a randomized, prospective, open-label, comparative trial of BWSE and valdecoxib in 66 patients with knee OA. Patients were randomized to either valdecoxib 10 mg daily (n=33) or BWSE (Cap Wokvel™) 333 mg three times daily (n=33). The drug intervention period was for a period of six months. Efficacy endpoints included WOMAC pain subscale, WOMAC stiffness subscale, and WOMAC function subscale. The results were compared at baseline and multiple time-points, up to 7 months. When comparing BWSE to valdecoxib, there were statistically significant reductions in the three WOMAC subscale scores for favoring valdecoxib at 1 month, and favoring BWSE at 7 months (one month off drug treatment) (Table 13).

Table 13: Comparison of WOMAC scores in the two treatment groups at different time intervals

Time	Pain		Stiffness		Difficulty in performing daily activities		
	<i>Boswellia serrata</i> extract	Valdecoxib	<i>Boswellia serrata</i> extract	Valdecoxib	<i>Boswellia serrata</i> extract	Valdecoxib	
Base-line	245.3±77.57	246.0±71.38	87.67±36.30	91.45±22.87	893.3±220.7	877.8±156.6	
After 1 month	225.5±85.94*	140.2±74.12 [#]	78.55±38.29*	47.76±27.79 [#]	824.7±269.6*	434.2±271.8 [#]	
After 2 months	159.5±96.58 [#]	152.2±193.4 [#]	57.91±34.24 [#]	39.55±23.18 [#]	582.7±296.2	348.7±207.5 [#]	
After 3 months	128.6±84.56 [#]	105.2±59.61 [#]	47.48±31.05 [#]	33.70±21.10 [#]	483.6±274.7	330.5±205.3 [#]	
After 4 months	107.8±79.57 [#]	101.9±71.04 [#]	41.06±29.10 [#]	34.58±24.15 [#]	408.7±262.1	335.9±229.7 [#]	
After 5 months	88.3±65.36*	82.12±63.39 [#]	33.73±23.58 [#]	27.61±22.05 [#]	348.7±219.7	269.6±212.3 [#]	
After 6 months	82.85±62.31 [#]	85.42±68.85 [#]	30.45±21.84 [#]	29.18±24.14 [#]	325.2±207.9	282.8±225.3 [#]	
After 7 months	81.67±63.29** [#]	197.7±111.3	29.82±21.55** [#]	81.15±41.49	322.6±207.8** [#]	775.5±392.4	
Repeated Measures ANOVA	F	26.62	3.850	68.02	11.42	111.7	10.07
	df	7,263	7,263	7,263	7,263	7,263	7,263

Repeated Measures ANOVA followed followed by Dunnett's multiple comparison test showed as *P<0.05 and **P<0.001 when BSE compared to Valdecoxib in each symptom group. [#]P<0.001 when compared to base-line

Source: Sontakke S. Indian Journal of Pharmacology. 2007;39:27-9.

Of note, in several of the publications, there was lack of clarity regarding the efficacy findings, analysis methods, or the comparisons being made. For example, it was frequently unclear if the publication was comparing the response rate within or between treatment groups. Thus, there are limitations to the analysis of BSWE efficacy in OA.

Rheumatoid arthritis (RA)

Sander et al. (1998) published a study of resinous extracts of *Boswellia serrata* (H15, indish incense) in patients with RA. The article is written in German, however the abstract is available in English. The study enrolled 37 patients with active RA who received 3600 mg of H15 or placebo daily. The primary efficacy measures were joint pain and swelling, ESR, CRP, pain scores, and NSAID doses at 6 and 12 weeks. There “was no subjective, clinical, or laboratory parameter showing a clinically relevant change from baseline or difference between both groups at any time point of observation.”

Chopra et al. (2000) published a 16-week, randomized, double-blind, placebo controlled parallel efficacy trial in 182 patients with active RA. Of the total study population, 89 patients received RA-1, containing purified plant extracts of *Withania somnifera* (ashwagandha), *Boswellia serrata* (gugulla), *Zingiberis officinale* (adrak or ginger), and *Ciruma longa* (haldi or circumin). Although improvement was numerically superior in the RA-1 group, it was not statistically significant for mean change in multiple clinical efficacy variables, such as joint count pain, joint count swelling, pain (VAS), health assessment questionnaire (HAQ), patient global assessment, and physician global assessment. The RA-1 group showed significant improvement with respect to increased proportion of patients who “ever” showed a 50% or greater reduction in swollen joint count and swollen joint score. However, the results are difficult to interpret as the drug included multiple components. The effect of RA-1 on inhibition of structural progression was not assessed.

Etzel (1996) published a review of more than 260 patients who were treated with H15, an extract of the gum resin of *Boswellia serrata*. The studies had different designs, included patients with different diagnoses (including RA, OA, and “juvenile chronic arthritis”), and limited information was available regarding the type of trial and the results. Only one study of 48 patients was described as placebo controlled and double blind. The author concluded that “[n]ot all studies yielded the same results under all criteria, but we found definite effects within the following parameters: H15 produced a significant reduction in swelling and pain compared to the placebo ($p < 0.05$); ESR was significantly reduced in one study ($p < 0.05$); Morning stiffness was often reduced; The patients often could considerably reduce their intake of NSAID during the course of treatment; The patients’ general health and well-being improved.” There was no discussion of the potential effect of BWSE on inhibition of structural damage.

Additional publications that reviewed drugs with multiple components, such as Kulkarni et al. (1992), were not reviewed as it would be difficult to determine which component or components were contributing to the potential efficacy of the product. Of note, Kulkarni et al. (1992) notes “radiological assessment did not show any significant change either due to drug or placebo therapy.”

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

The identified conditions, including OA and RA, can be serious conditions.

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

There are multiple approved therapies for OA (see above, Section II.B.2.(d)). These treatments include oral and topical NSAIDs and intra-articular hyaluronans and glucocorticoids. Opioid analgesics are FDA-approved for the treatment of acute and chronic pain, and are used to manage pain associated with OA. Approved therapies are used to treat the pain and functional limitations associated with OA. No therapies have been proven to prevent progression of joint damage due to OA.

There are multiple approved therapies for RA (see above, Section II.B.2.(d)). These medications are referred to as nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs). In addition, oral glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) are approved for the treatment of rheumatoid arthritis. Better outcomes are achieved in RA by early compared with delayed intervention with DMARDs (Lard et al., 2001). All approved therapies have clearly established efficacy in the treatment of RA. Use of potentially ineffective therapy could be associated with irreversible structural damage.

Conclusions: Although there are limitations to the available data, there appears to be some evidence that BWSE may improve symptoms in a proportion of patients with osteoarthritis. However, there are numerous approved therapies that have established efficacy for osteoarthritis and the quality and quantity of the data available for BSWE are limited. In RA, the studies do not provide convincing evidence for the use of BSWE for the treatment of RA. There is insufficient evidence that this substance should be used in compounding for the treatment of rheumatoid arthritis, especially in the context of numerous therapies that have established efficacy and the risk of irreversible structural damage with ineffective therapies.

D. Has the substance been used historically in compounding?

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

Historically, Boswellia has been used for millennia throughout the world for spiritual, religious and pharmacological uses (Paul, accessed 2015), particularly in Ayurvedic and traditional Chinese medicines. Usage dates back to ancient civilizations ca. 2500 BC (i.e.,

Egyptians, Greeks, and Romans) (Paul, accessed 2015) and *Boswellia* has been used for centuries in Ayurvedic medicine ca. 1st and 2nd centuries (as Indian frankincense) (Ammon, 2006) as well as traditional Chinese medicine ca. 500 AD (as olibanum) (Dharmananda, 2003). In Chinese medicine, *Boswellia* and myrrh are usually used together and often with other herbs for wound healing, pain, arthritis and other diseases. *Boswellia carterii* resin has been known as one of the oldest herbal medicines. It is still currently used in China at 3–10g resin/day for the treatment of pain, wounds and arthritis (Chinese Natural Herbs, accessed 2015). The oldest written document mentioning frankincense as a drug is on the papyrus Ebers, which was given to Moritz Fritz Ebers in 1873. It contained practical information for medical doctors with approximately 900 prescription formulae and was most likely written ca. 1500 BC at the time of Pharaoh Amenophis I (Ammon, 2006; Martinez, et al., 1989).

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

Boswellia serrata resin is known to have various therapeutic uses in Ayurvedic medicine, for example, as an anti-inflammatory, analgesic, diuretic, antiseptic, and many others (Ammon, 2006). In Chinese medicine, *Boswellia carterii* resin has been used from 3–10 g/day for the treatment of pain, arthritis, wounds and injuries (Chinese Natural Herbs, accessed 2015). Both oral and topical formulations, often with myrrh and other herbs, have been used.

3. *How widespread its use has been*

As one of the oldest herbal medicines, *Boswellia* resin has been used in Africa, Europe and Asia for thousands of years for treating symptoms of various diseases. Today, commercial products with boswellia extracts are marketed in the United States as herbal/dietary supplements and as a part of the integrative health or complementary and alternative medicine practice. It is one of the commonly used herbal medicines in China for treating pain and other arthritis related symptoms, often in combination with myrrh and several other herbs.

On October 21, 2002, orphan designation (EU/3/02/117) was granted by the European Commission to Pharmasan GmbH, Germany, for *Boswellia serrata* resin extract for the treatment of peritumoral edema derived from brain tumors. In November 2006, the product was withdrawn from the Community Register of designated Orphan Medicinal Products on the request of the sponsor.

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

Monographs for identification of *Boswellia* resin and *Boswellia serrata* extract are included in the United States, European and Chinese Pharmacopoeias as dietary supplements, herbal drugs, and Chinese medicines, respectively (Table 1). *Boswellia* is commonly used in Ayurvedic and Traditional Chinese Medicine. *Boswellia carterii* (i.e., olibanum) resin is one of the most commonly used herbal medicines in China for wound healing. We are unaware of any country that has approved drug products containing

Boswellia extracts that are analyzed and qualified at standards that are equivalent to the current FDA standards for a new drug. However, Boswellia extracts in other regions, such as China, Europe and Canada, are marketed as over-the-counter (OTC) products to treat various diseases, such as arthritis and pain.

Conclusions: BWSE has been used in the treatment of multiple inflammatory conditions for centuries. There are reports of global use of BWSE for a variety of inflammatory conditions and pain.

III. RECOMMENDATION

We have evaluated the physical and chemical characteristics, safety, effectiveness, and historical use of BWSE in compounding. Since it is a naturally-derived, botanical substance, BWSE's physical and chemical characteristics can vary according to the source and extraction method. Although the four major boswellic acid analogs (BA, ABA, KBA and AKBA) can be characterized and quantified, their total content and relative proportions as well as the levels of other components cannot adequately be controlled to ensure a consistent composition of this bulk drug substance unless there are proper controls of the botanical raw materials and manufacturing processes.

The limited safety data suggest BWSE appears to be generally well-tolerated. However, there are reports in the Indian literature that resin from Boswellia may be an emmenagogue and induce abortion, which is a significant safety concern, especially given that BWSE may be used by women of childbearing potential and compounded drug products are not required to have labeled warnings. It is also associated with gastrointestinal adverse events, including diarrhea, abdominal pain, and nausea. There are reports of interactions with oral anticoagulants leading to an increase in the anticoagulant effect. Of note, OA and RA are chronic conditions, and the carcinogenicity of BWSE has not been assessed. There are multiple approved treatments for both OA and RA with well-defined safety profiles.

Boswellia has been used historically in traditional Chinese medicine for wound care, treating pain, and arthritis. While there appears to be some evidence that this substance may improve the symptoms of osteoarthritis in a proportion of patients, the same is not true when it is used for the treatment of rheumatoid arthritis. BWSE has not been shown to be effective in inhibiting radiographic progression of RA. Approved products are available for the treatment of RA and there is a risk of irreversible structural damage with ineffective therapies.

Based on a balancing of the four evaluation criteria, we recommend that Boswellia not be added 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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Vishal, AA., Mishra, A., Raychaudhuri, SP. A double-blind, randomized, placebo controlled clinical study evaluates the early efficacy of aflapin in subjects with osteoarthritis of knee. *Int J Med Sci.* 2011, 8, 615-22.

Verhoff et al. Tetra- and pentacyclic triterpene acids from the ancient anti-inflammatory remedy frankincense as inhibitors of microsomal prostaglandin E(2) synthase-1. *J Nat Prod.* 2014, Jun 27; 77(6):1445-51.

Tab 3

Aloe Vera 200:1 Freeze Dried

Tab 3a

Aloe Vera 200:1 Freeze Dried
Nominations



September 30, 2014

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

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

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

Dear Sir or Madam:

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

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

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

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

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS

Corporate Offices: 4638 Riverstone Blvd. | Missouri City, Texas 77459 | 281.933.8400
Washington DC Offices: 1321 Duke Street, Suite 200 | Alexandria VA 22314 | 703.299.0796

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

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

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

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

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

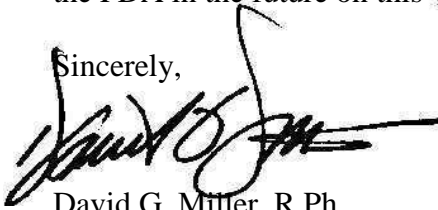
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

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

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

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

Sincerely,

A handwritten signature in black ink, appearing to read "David G. Miller", with a large, stylized flourish extending upwards and to the right.

David G. Miller, R.Ph.
Executive Vice President & CEO



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

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Aloe Vera Gel Extract
Chemical/Common Name	Aloe Vera Gel Extract
Identifying Codes	85507-69-3
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	Not Listed in USP/NF for this specific salt/form

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	

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	aloe vera [see aloe]
Chemical/Common Name	aloe vera [see aloe]
Identifying Codes	09TD8L5SQV
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	Not in USPNF, Food Codex Compendia or USPMC

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	gingivitis/plaque FDA. OTC Active Ingredients List. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf Accessed 2-10-2014, last updated April 7, 2010

Past and Proposed Use	The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.
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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	Aloe Vera
Chemical/Common Name	Aloe Vera
Identifying Codes	
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	Not Listed in USP/NF for this specific salt/form

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	

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	aloe ingredients (aloe, aloe extract, aloe flower extract)
Chemical/Common Name	aloe ingredients (aloe, aloe extract, aloe flower extract)
Identifying Codes	V5VD430YW9, ZY8
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	Not in USPNF, Food Codex Compendia or USPMC

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	laxative stimulant laxative FDA. OTC Active Ingredients List. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf Accessed 2-10-2014, last updated April 7, 2010

Past and Proposed Use	The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.
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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

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

Dear Sir or Madam,

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

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

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

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

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

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs



Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlsx file)

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

Fagron

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



What is the name of the

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

Aloe Vera 200:1 Freeze Dried

Yes, Aloe Vera 200:1 Freeze Dried 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 Aloe Vera Freeze Dried pharmacological actions are provided MJ, Hollyoak MA, Moaveni Z, Brown TL, Herndon DN, Hegggers JP. Retardation of wound healing by silver sulfadiazine is reversed by Aloe vera and nystatin. Burns. 2003 Dec;29(8):834-6. PubMed PMID: 14636760.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=14636760>

Rajar UD, Majeed R, Parveen N, Sheikh I, Sushel C. Efficacy of aloe vera gel in the treatment of vulval lichen planus. J Coll Physicians Surg Pak. 2008 Oct;18(10):612-4. doi: 10.2008/JCPSP.612614. PubMed PMID: 18940117.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=18940117>

Visuthikosol V, Chowchuen B, Sukwanarat Y, Sriurairatana S, Boonpucknavig V. Effect of aloe vera gel to healing of burn wound a clinical and histologic study. J Med Assoc Thai. 1995 Aug;78(8):403-9. PubMed PMID: 7561562.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=7561562>

Chithra P, Sajithlal GB, Chandrakasan G. Influence of aloe vera on the healing of dermal wounds in diabetic rats. J Ethnopharmacol. 1998 Jan;59(3):195-201. PubMed PMID: 9507904.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=9507904>

Ajmera N, Chatterjee A, Goyal V. Aloe vera: It's effect on gingivitis. J Indian Soc Periodontal. 2013 Jul;17(4):435-8. doi: 10.4103/0972-124X.118312.

PubMed PMID: 24174720; PubMed Central PMCID: PMC3800403.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=24174720>

Shahzad MN, Ahmed N. Effectiveness of Aloe Vera gel compared with 1% silver sulphadiazine cream as burn wound dressing in second degree burns. J Pak Med

Assoc. 2013 Feb;63(2):225-30. PubMed PMID: 23894900.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=23894900>

Silva MA, Trevisan G, Klafke JZ, Rossato MF, Walker CI, Oliveira SM, Silva CR, Boligon AA, Flores FC, de Bona Silva C, Athayde ML, Ferreira J. Antinociceptive

and anti-inflammatory effects of Aloe saponaria Haw on thermal injury in rats. J Ethnopharmacol. 2013 Mar

7;146(1):393-401. doi: 10.1016/j.jep.2012.12.055. Epub

2013 Jan 17. PubMed PMID: 23333747.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=23333747>

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

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

What is the common name of

Aloe; Aloe barbadensis

Does the substance have a

ZY81Z83H0X

What is the chemical grade

No grade

What is the strength, quality, stability, and purity of the ingredient?

Appearance: White to light beige powder

Polysaccharides: Naturally occurring within 200x

Specific Gravity: 0.99 – 1.01

How is the ingredient

Powder

Is the substance recognized in foreign pharmacopeias or registered in other countries?

Abanta (Columbia, Arg.) ,A-Bruzzzy (Hoe, Malaysia) ,A-Bruzzzy (Hoe, Singapore) ,Acnestal (Biomedica, India) ,Acniben Toallitas (Isdin, Chile) ,Ac-Sal (Isdin, Chile) ,Actine (Darrow, Braz.) ,Actine (Darrow, Braz.) ,Acuaderm (Bajer, Arg.) ,After Burn (Medimpex, Hung.) ,After Burn (Tender, Cz.) ,Aftersun (Isdin, Arg.) ,Agisten with Aloe Vera (Perrigo, Israel) ,Ale (Zee, India) ,Alkagin (Dermoteca, Port.) ,Alkagin (Ganassini, Fr.) ,Aloat NC (Shalaks, India) ,Aloax (Ativus, Braz.) ,Alockin (Zydus, India) ,Alo-E (Maneesh, India) ,Aloebeel (Fortbenton, Arg.) ,Aloedent (Odontofarma, Arg.) ,Aloe Grande (Gordon, USA) ,Aloekin (Zydus, India) ,Aloemagnolia (Nordin, Mex.) ,Aloe Vera Gel (GNLD, Austral.) ,Aloe Vera Plus (GNLD, Austral.) ,Alogard (Mars, India) ,Aloven (Vensat, India) ,Alovit (Micro, India) ,Alovit-AF (Micro, India) ,Alra (Medi-Test, Fr.) ,Alv (Laborate, India) ,Amenite Vera (Amenite, Arg.) ,Andantol Jalea (Zuoz, Venez.) ,Antiac (Salcura, UK) ,Antiacneicos Ac-Sal (Isdin, Port.) ,Apaisac (Biorga, Hong Kong) ,Aphtagone (Trima, Israel) ,Aptha-X (CTI, Israel) ,Aristaloe (Neo Dermos, Arg.) ,Aristaloe (Neo Dermos, Arg.) ,Atomo Ordenador (Imvi, Arg.) ,Aze (Tai Guk, Singapore) ,Barrocutina (Esme, Arg.) ,Biorevit Gel (DNR, Arg.) ,Bioskin (Biomedica, India) ,Biotene with Calcium (Laclede, USA) ,Blistex Aloe & Vitamin E (Key, Austral.) ,Bodi Kleen (Geritrex, USA) ,Bodi Oil (Geritrex, USA) ,Bon-Apetit (Norton, Ukr.) ,Boots Antenatal Massage Cream (Boots Healthcare, Malaysia) ,Boudreaux's All Natural Butt Paste (Fleet, USA) ,Brunavera (Euroderm, Arg.) ,Calosoft (Micro, India) ,Calvera (Psyco Remedies, India) ,Capso (Sinclair, Ital.) ,Capson (Pharmatrix, Arg.) ,Cellenergy (K2 Health & Wellness, Chile) ,Chap Stick (Wyeth Consumer, NZ) ,Cicatriline (HRA, Fr.) ,Cimfi (Aamorb, India) ,Control Acne (Pharmalab, Arg.) ,Coral (Biosciences Pharmakon, India) ,Cortaid with Aloe (Pharmacia, Singapore) ,Crema De Ordene (Nolt, Arg.) ,Curacao (Age D'or, Singapore) ,Cutidermin Crema Regeneradora (Szabo, Arg.) ,Cutidermin Spray Humectante (Szabo, Arg.) ,Derm'attive Solaire (Sidone, Braz.) ,Dermaide (Dermaide, USA) ,Dermaloe (Forder, Arg.) ,Dermamoist (Psychotropics, India) ,Dermtex HC with Aloe (Pfeiffer, USA) ,Dermvien (Hautel, Arg.) ,Desitin Creamy (Johnson & Johnson, Singapore) ,Dew Derm (Shalaks, India) ,Dewsoft (Torrent, India) ,Diabecon (Himalaya Herbal, India) ,Disoderme (Plough, Port.) ,Don't Bug Me (Relax, UK) ,Duraflex Comfort (Trimarc, USA) ,Eelovit (Ind-Swift, India) ,Ekotrofil (Ecobi, Ital.) ,Elovera (Glenmark, India) ,Elovera (Glenmark, India) ,Elovera (Glenmark, Malaysia) ,Elovera (Glenmark, Philipp.) ,Elovera (Glenmark, Rus.) ,Elovera-SPF (Glenmark, India) ,Enfacare (Biolink, Philipp.) ,Entertainer's Secret (KLI, USA) ,Epitaloe (Mediwhite, Ital.) ,Equilibrium Creme Anti-transpirante (SFD, Port.) ,Eurocolor Post Solar (Euroderm, Arg.) ,Europrotec Post Solar (Euroderm, Arg.) ,Evaren (Indoco, India) ,Eve Care (Himalaya, Ukr.) ,Evecare (Himalaya Herbal, India) ,Evecare (Himalaya Herbal, India) ,Faringel (CaDiGroup, Ital.) ,Flucirac (Natiris, Venez.) ,Forehead-C (Lina, UK) ,Fray Romano (Ximena Polanco, Chile) ,Galenic Restaurador Capilar (Neo Dermos, Arg.) ,Gamerol (Gache, Venez.) ,Gelconordin (Nordin, Mex.) ,Gelsem (Medinteg, Venez.) ,Geri-Lav Free (Geritrex, USA) ,Ginoxil Ecoschiuma (Sinclair, Ital.) ,Glicoisdin (Isdin, Chile) ,Gold Bond Medicated Triple Action Relief (Chattem USA) Hawaiian Tropic Cool Aloe with I.C.F. (Tanning Research USA)

,Lana Medicated Triple Action Relief (Cratam, USA) ,Lanolan Triple Action Cream with NOLAN (Fanning Research, USA) ,Hemorid For Women (Thompson, USA) ,Herbaccion Nutriderm (ISA, Arg.) ,Herr (RND, India) ,Hidrate (Unichem, India) ,Hipoglos Cremoso (Andromaco, Mex.) ,Hiruscar (Medinova, Philipp.) ,Hiruscar (Medinova, Singapore) ,Humidus (Curatio, India) ,Intima (Pascual, Philipp.) ,Ivan (Arlak, India) ,Jengimiel (Jengimiel, Venez.) ,Jengimiel Sabila (Jengimiel, Venez.) ,Jointfit (Combiphar, Indon.) ,Jula (Fem Care, India) ,Korisma (Cratus, India) ,KW (Lagos, Arg.) ,Lamisil Odor Eze (Novartis, NZ) ,Lipz Ointment (Hamilton, Austral.) ,Lorasil Feminine Hygiene (Vita Health, Malaysia) ,Malvaticin Natural Soft (Daudt, Braz.) ,Maprosol Gel (LDA, Arg.) ,Maternity Crema de Ordene (San Ceferino, Arg.) ,Maximum Strength Flexall 454 (Chattam, USA) ,Miaderm Radiation Relief (Aiden, USA) ,Micodual (K2 Health & Wellness, Chile) ,Moiste (Hetero, India) ,Moisturex-AF (Ranbaxy, India) ,Mucobase (Defuen, Arg.) ,Mucotrol (Edwards, USA) ,Multi-Mam Compressas (Farmalight, Port.) ,Nap (Roomi, Philipp.) ,Nasal-Ease (Health Care Products, USA) ,Nasoclear Aloegel (Zydus, India) ,Negacne (Wierhom, Arg.) ,Nenegloss (Maver, Chile) ,Neo-Healar (Arab, Malaysia) ,Ninfagin (RPF, Ital.) ,Ocusun (Apotex, Arg.) ,Odontobiotic (Higate, Arg.) ,Olamine (Pharmatrix, Arg.) ,Omicohol A (Omicron, Arg.) ,OraMagicRx (MPM, USA) ,Oramin-G (Molex Ayus, Indon.) ,Percutane (Genepharma, Austral.) ,Pervicol (Phoenix, Arg.) ,Pervicol Toallas (Phoenix, Arg.) ,Phytosyl Plus (Vita Health, Singapore) ,Postopyl (LED, Fr.) ,Post Solar Nort (Nolt, Arg.) ,PoxClin (Chefaro, Ger.) ,Pregnacare (Vitabiotics, Hong Kong) ,Probeks (Hebron, Braz.) ,Proctocella Complex (Peter, Ital.) ,Psor-Asist (Plunkett, Austral.) ,Puraloe (Eurolab, Arg.) ,Puraloe Nutritiva (Eurolab, Arg.) ,Puraloe Post Solar (Eurolab, Arg.) ,Pure Gardens (Awareness, Canad.) ,RadiaPlex Rx (MPM, USA) ,Rapaid Rash-Relief (McGloins, Austral.) ,Recover Whitening (Pharmatrix, Arg.) ,Refrane P (Neo Dermos, Arg.) ,Refrane Plus (Neo Dermos, Arg.) ,Repelente Zasu (Zasu, Arg.) ,Rhinodoron (Weleda, Fr.) ,Rhinodoron (Weleda, Ger.) ,Rinupret (Bionorica, Ger.) ,Rx Support Heartburn & Acid Reflux Plus Aloe (Mason, USA) ,Sadeltan F (Hautel, Arg.) ,Sclerovis H Plus (Amnol, Ital.) ,Sinose (Salcura, UK) ,Snella Vag (Investi, Arg.) ,Soapelle (Darrow, Braz.) ,Sofderm (Cipla, India) ,Solarcaine (Schering-Plough, UK) ,Solarcaine Aloe (Balmar, NZ) ,Solarcaine Aloe Extra Burn Relief (Schering-Plough, USA) ,Solarcaine Aloe Vera Gel (Schering-Plough, Chile) ,Solenil Post Solar (Fortbenton, Arg.) ,Solenil Post Solar Cool Gel (Fortbenton, Arg.) ,Stay Moist Lip Conditioner (Stanback, USA) ,T3 Acne (Hoe, Malaysia) ,Talowin (Costec, Arg.) ,TDF AHA Facial Wash for Oily/Acne Prone Skin (EIG, Malaysia) ,Triple Care Cleanser (Smith & Nephew, USA) ,Triple Care Cream (Smith & Nephew, Austral.) ,Triple Care Protective Cream (Smith & Nephew, USA) ,Ureadin Rx DB (Isdin, Chile) ,Ureadin Rx RD (Isdin, Chile) ,Velostin (Solas, Indon.) ,Vera Plus (Giscard, Arg.) ,Veraskin (Pharma 2000, Fr.) ,Vicks Baby Balsam (Procter & Gamble, Austral.) ,Vicks Baby Balsam (Procter & Gamble, Ital.) ,Vicks Baby Balsam (Procter & Gamble, NZ) ,Vitrum Beauty Elite (Unipharm, Ukr.) ,Vulnopur (Deverge, Ital.) ,Wick SinexAloe (Procter & Gamble, Austria) ,Xicanil Control NF Locion (Gramon, Arg.) ,Xyloprocto Toallas (AstraZeneca, Arg.) ,Yeast-Gard Advanced Sensitive Formula (Lake, USA) ,Zim's Max Freeze (Perfecta, USA)

Has information been submitted about the
What dosage form(s) will be compounded using the bulk

No USP Monograph submission found.

Creams, Gels

What strength(s) will be compounded from the	0.1-10%
What are the anticipated route(s) of administration of	Topical
Are there safety and efficacy data on compounded drugs	Muller MJ, Hollyoak MA, Moaveni Z, Brown TL, Herndon DN, Hegggers JP. Retardation of wound healing by silver sulfadiazine is reversed by Aloe vera and
Has the bulk drug substance been used previously to	Aloe Vera has been used in topical creams and gels for the treatment of burns, cuts, ulcers and diabetic wounds.
What is the proposed use for the drug product(s) to be	Aloe Vera may be used in topical creams and gels for the treatment of burns, cuts, ulcers and diabetic wounds.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	There are no FDA approved products containing Aloe Vera for the indication above in existence at this time. The amount of literature on the use of Aloe Vera in burns is astounding. Its use goes back as far as Ancient Chinese and Egyptian cultures. (http://www.ncbi.nlm.nih.gov/pubmed/23888738) Current FDA approved products for burns involve a genre of dressings including Integra, Adaptic gauze and Artiss. These help protect the wound or help adhere skin grafts. However they will not treat those moderate to sever burns that don't require skin grafting. Those patients are left with pain control and controlling infection. Silver sulfadiazine is a first line for this area of burn treatment. However, in recent study Aloe vera proved superior in under three weeks of treatment. (http://www.ncbi.nlm.nih.gov/pubmed/19562446)(http://www.ncbi.nlm.nih.gov/pubmed/20361881) Aloe vera has been shown to provide positive results in general wound care. After 100 decades of use Aloe Vera is still proving its worth in medical care.
Is there any other relevant information?	All relevant information was expressed in the above questions

Tab 3b

Aloe Vera 200:1 Freeze Dried
FDA Review



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: February 8, 2016

FROM: Cassandra Taylor, PhD
Chemistry Reviewer, Botanical Review Team
Office of Pharmaceutical Quality

Jinhui Dou, PhD
Pharmacologist, Botanical Review Team
Office of Pharmaceutical Quality

Jianyong (Jerry) Wang, PhD
Pharmacology Reviewer, Division of Dermatology and Dental Products

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

Milena Lolic, MD
Clinical Reviewer, Division of Dermatology and Dental Products

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

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

David Kettl, MD
Clinical Team Leader, Division of Dermatology and Dental Products

Sau (Larry) Lee, PhD
Team Leader, Botanicals Review Team
Office of Pharmaceutical Quality

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

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Aloe vera freeze-dried 200:1 for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

Aloe vera freeze-dried 200:1 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 “the treatment of burns, cuts, ulcers, and diabetic wounds.” The nomination states that the substance will be used to prepare topical creams and gels at concentrations of 0.1-10%.

The nomination does not provide a definition or description of “Aloe vera freeze-dried 200:1.” “Aloe vera freeze-dried 200:1” can be literally interpreted as any extract or dry powder derived from whole Aloe vera leaf or any part of *Aloe vera* (i.e., the botanical raw material) with a concentration ratio of 200 to 1 (i.e., 200 g of *Aloe vera* botanical raw material yields one gram of the freeze dried extract). On average, every 200 g of freeze-dried Aloe vera gel will produce 1 g dry powder (i.e., 200:1). Thus, we can assume that the nominated product (Aloe vera freeze-dried 200:1) is Aloe vera gel freeze-dried (200:1). Because there is ambiguity of what the nominated substance is, we will discuss the chemical profiles of Aloe vera leaf, latex, and gel in this consult, despite the fact that none of them is considered well characterized.

The nomination does not specify the basic characteristics of cuts, burns, and wounds for which Aloe vera freeze-dried 200:1 is intended (e.g., size, location, duration, and infection status), all of which are critical elements for efficacy and safety assessments of the proposed remedy.

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 Aloe vera freeze-dried 200:1 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.

Aloe vera freeze dried 200:1, the specific nominated product, is one type of marketed Aloe vera and is widely available as a dietary supplement. It can be purchased in health stores and is widely available on the internet including vendor sites such as Amazon.com.

The review team could find scant information regarding the specific nominated Aloe vera product. No literature in PubMed was identified for this specific product in the treatment of burns, cuts, and wounds. The literature in the nomination does not specifically address the 200:1 freeze dried nominated product.

As discussed below in Section B (2), the Office of Surveillance and Epidemiology review did not identify any cases that specifically identified Aloe vera 200:1 freeze dried in relevant database searches.

The discussion below provides information on general aspects of Aloe vera and its relevance to the treatment of burns, cuts, and wounds.

II. EVALUATION CRITERIA

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

(The term *Aloe vera* refers to a species of succulent plants, one of about 500 related species within the *Aloe* genus.) Most of the commercially available substances or products derived from *Aloe vera* are complex mixtures, which may contain various classes of chemical compounds, such as polysaccharides, organic acids, and anthraquinones. Generally speaking, the major components of *Aloe vera* (i.e., the polysaccharides) are poorly characterized. Available analytical techniques appear only adequate to quantify *Aloe vera* polysaccharides as a chemical class, while differentiation of *Aloe vera* polysaccharides from similar polysaccharides in other botanicals remains a technological challenge.

The leaf of the succulent plant *Aloe vera* (L.) Burm.f. (syn. *Aloe barbadensis* Mill.) is the most commonly used species in traditional medicine. *Aloe vera* leaf is the main portion of the plant *Aloe vera*, in particular the gel (i.e., gel from the inner portion of the *Aloe* leaf; see Figure 1) and is the botanical material for the nominated substance. However, the complicated taxonomy and broad nomenclature of *Aloe vera* and the other 500 related species of the *Aloe* genus presents a quality control issue, especially for compounders, prescribers and consumers. A manufacturer without proper raw material quality control, which requires techniques in botany/pharmacognosy, will also have great difficulty in determining whether the *Aloe* extract used in herbal medicines or dietary supplements is indeed from *Aloe vera* and/or is a freeze-dried standardized *Aloe vera* gel/extract (200:1). To date, over 1,400 recorded common and scientific names (including accepted names and synonyms) are used to generally describe *Aloe* plants (The Plant List, 2015) as well as some of the other 500 recognized species of the *Aloe* genus, which may also have been used in conjunction with *Aloe vera* for the same or similar purposes in different parts of the world. Previously, *Aloe* was assigned to the families Liliaceae, Aloeaceae and Asphodelaceae, and now *Aloe vera* and other *Aloe* species are listed under the family Xanthorrhoeaceae. Before being merged into the Xanthorrhoeaceae family, the older references may cite these previous assigned families in describing *Aloe*.

There are three major classes of substances/products from the plant *Aloe vera*: *Aloe vera* leaf (or whole *Aloe* leaf); *Aloe* latex (from the whole leaf or the outer layer of the *Aloe* leaf); and *Aloe* gel (from the inner succulent part of the *Aloe* leaf). It is not certain, but the name *Aloe vera freeze-dried 200:1* and the nominated topical applications suggest *Aloe vera* gel is the botanical raw material for the nominated product. Because most of the marketed *Aloe* products do not have detailed raw material and other quality information, the physicochemical and biological properties of *Aloe* leaf, latex, and gel are outlined below.

- **Whole *Aloe* leaf**

Two portions of the *Aloe* leaf (Figure 1) with varying chemical constituents and presumed pharmacological activities are used medicinally for different purposes. The sap found just below the epidermis (i.e., rind) is commonly known as *Aloe* latex and the jelly-like substance of the inner leaf is the *Aloe* gel.

Figure 1: Aloe plant portions (Aloe vera Garden, 2015 & Miracle of Aloe, 2015)



The Aloe plant is mostly composed of water, 99 – 99.5%, leaving approximately 0.5-1% of solid material. Over 75 different potentially active compounds have been identified within the solid material that include: vitamins (water- and fat-soluble), mineral, proteins (enzymes), polysaccharides (simple and complex), phenolic compounds and organic acids. The majority of the dry leaf weight is composed of nonstarch polysaccharides and lignins, at values of 62.3% and 57.6% of the combined dry weight of both rind and pulp (Radha et al., 2015). Detailed analytical data (e.g., nuclear magnetic resonance, mass spectrometry) to fully characterize these polysaccharides for meaningful quality control are not available in the public domain.

In terms of plant proportions, the outer leaf or rind is 20-30% while the gel is 70-80% of the whole leaf weight (i.e., wet weight). Once the outer leaf and gel are dried, the compositional dry weights of lipids have been reported as 2.7% and 4.2%, respectively while proteins have been reported as 6.3% and 7.3%, respectively, which only account for a small percentage of the total weight of the dry leaf (Femenia et al., 1999).

- **Aloe latex**

Aloe latex has historically been used as a laxative due to the presence of the anthraquinone glycosides aloin A (barbaloin) and aloin B (isobarbaloin), see Figure 2 (Tyler 1994). Aloe latex also contains emodin, resins, aloesin, and free anthraquinone (i.e., aglycones) like aloes-emodin, anthranol, and chrysophanic acid (Vogler et al., 1999). The dried latex can contain 10-30% anthraquinone derivatives, which may cause serious diarrhea and/or abdominal pain that have largely led to the abandonment of its use for this indication (Dewick 1997).

monograph standards. The compositional analysis of the polysaccharide of Aloe vera gel is not detailed in any of the monographs.

Discussion and Recommendation

Because many chemical components of various chemical classes have been found within the Aloe leaf, it is difficult to fully characterize and quantify them accurately. The polysaccharides contained in Aloe vera gel and the whole leaf are very complex and are not well characterized by available techniques, such as nuclear magnetic resonance (NMR), mass spectrometry, infrared, or UV spectroscopy. In addition, the botanical source and part(s), and related cultivation and other processes used to produce various Aloe vera substances/products are important factors that need to be adequately controlled.

1. Stability of the API and likely dosage forms

No detailed data are available for discussion of stability. In general, Aloe products used as dietary supplements (as powdered or capsulated formulations) usually have a shelf life of 2 years. There are no data on the stability of Aloe vera (gel) freeze-dried 200:1. Aloe vera in liquid formulations (e.g., beverages, fresh gel, and creams) may have different shelf lives and often require the presence of preservatives.

2. Probable routes of API synthesis

The nominated substance, Aloe vera (gel) freeze-dried 200:1, is a botanical-derived natural product, which is not synthesized.

3. Likely impurities

For botanical products, *impurities* are typically defined as “contaminants”(e.g., heavy metals, pesticides). Likely impurities in Aloe products include:

- Residual organic solvents used in the manufacturing and purification process
- Heavy metal impurities linked to the source of the starting material
- Bioburden (such as microbial content, yeast, or mold) and microbial metabolites (e.g., aflatoxins,)
- Inorganic impurities, including heavy metals (e.g., lead, arsenic, mercury)

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

(This information is not available given that Aloe vera is poorly characterized at the molecular level.)

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

Aloe vera gel/extract is a complex mixture. Various chemical classes of naturally occurring molecules (e.g., amino acids, peptides, proteins, fatty acids/lipids, polysaccharides, anthraquinones) have been found in Aloe vera.

Conclusions

Based on the complex physicochemical characteristics of Aloe vera with multiple classes of molecules, we conclude that Aloe vera gel/extract in general is poorly characterized and prone to contamination from other botanical sources (such as related Aloe species). The nominated substance, Aloe vera (gel) freeze-dried 200:1 is not well defined and could not be properly identified and characterized by available analytical technology due to lack of information on standardization. Without appropriate raw material and manufacturing process control, it is difficult to differentiate one Aloe product from another.

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

1. Nonclinical Assessment

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

- PubMed
- TOXNET
- Google/Google Scholar

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

Aloe vera [*Aloe barbadensis* (Miller)] contains over 75 different potentially active compounds including water- and fat-soluble vitamins, minerals, enzymes, simple and complex polysaccharides, phenolic compounds, and organic acids. Alleged pharmacological properties of Aloe vera include anti-inflammatory, antifungal, antimicrobial, antiviral, wound healing, hypoglycemic/hyperglycemic activity, stimulatory/inhibitory effects on cell proliferation, angiogenic, immunostimulation/immunosuppression, laxative, anti-oxidant/pro-oxidant, anti-hyperlipidemic, anti-tumor, anti-arthritic, anti-psoriasis and anti-rheumatoid effects. Some of the inconsistent/contradictory results might be due to differences in the test material, including variations in constituents, in plant extracts resulting from different extraction and processing methods, and in plants grown or harvested under various conditions (Vogler et al., 1999; Boudreau et al., 2006; CIREP, 2007; Radha et al., 2014).

Although Aloe vera has a long history of use as a wound healing agent, contradictory results were noted in animal studies with different study designs and/or wound models. In a second-degree burn wound model in guinea pigs, Aloe vera gel hindered wound healing compared with 1% silver sulfadiazine cream (Kaufman et al., 1988). In another guinea pig study Aloe vera gel accelerated healing of full-thickness burn wounds (Rodríguez-Bigas et al., 1988). Aloe vera gel did not show significant effect on re-

epithelialization or wound contraction of full-thickness excision wounds in a pig model (Watcher et al., 1989). In a full-thickness excision wound model in rats, adding Aloe vera gel reversed the retardation of wound healing caused by silver sulfadiazine (Muller et al., 2003). In a mouse wound model Aloe vera accelerated wound healing by both oral (100 mg/kg/day in drinking water) and topical (25% cream) treatment (Davis et al., 1989). In a diabetic rat model Aloe vera gel accelerated healing of full-thickness wounds (Chithra et al., 1998).

b. Safety pharmacology

In a rat study conducted by Saleem et al., (2001), IV administration of aloe-emodin, aloin A and elgonica dimer A (extracted from Aloe vera) had a hypotensive effect on SD rats. Aloe-emodin induced a decrease in the mean arterial blood pressure by 26%, 52%, and 79% at doses of 0.5, 1, and 3 mg/kg, respectively.

c. Acute toxicity

Single oral doses of Aloe vera extract (extracted with 95% ethanol) were administered orally to mice at 500, 1000, and 3000 mg/kg. No signs of toxicity were noted except a decrease in CNS activity noted at mid and high doses (Shah et al., 1989). An estimated oral LD50 for Aloe vera extract (extracted with methanol) was 121 mg/kg in mice (Lagarto et al., 2001). No significant toxicity was noted when single injection of acemannan (a major polysaccharide contained in Aloe vera) was administered at dosages of 80 mg/kg IV or 200 mg/kg IP in mice, 15 mg/kg IV or 50 mg/kg IP in rats, or 10 mg/kg IV or 50 mg/kg IP in dogs (Fogleman et al., 1992a).

d. Repeat dose toxicity

Aloe vera extract (extracted with 95% ethanol) was orally administered to mice (in drinking water) at 100 mg/kg/day for 3 months. A decrease in red blood cell (RBC) count and significant sperm damage (megacephali and flat head, swollen achrosome, rotated head) was noted (Shah et al., 1989). Acemannan was administered by IV or IP routes as a 1.0 mg/ml solution to mice, rats and dogs, for 8 doses at 4-day intervals. A few deaths occurred in mice and rats, possibly resulting from improper injection or sequelae of necrosis at the injection site. The no observed adverse effect levels (NOAELs) for acemannan determined from these repeated injection studies were 20 mg/kg IV or IP in mice, 4.0 mg/kg IV and 50 mg/kg IP in rats, and 1.0 mg/kg IV in dogs; 5.0 mg/kg IP in dogs was considered to be the lowest observed adverse effect level (LOAEL), based on emesis and abdominal discomfort (Fogleman et al., 1992a). Acemannan was administered orally to rats for 14 days at 5% of the diet and for 6 months at up to 2000 mg/kg/day, and to beagle dogs for 90 days at up to 1500 mg/kg/day without significant toxicity noted in either species (Fogleman et al., 1992b).

Aloe vera powders, produced by two different methods (Process A: homogenization followed by lyophilization; Process B: homogenate was charcoal filtered prior to lyophilization) were administered to rats through diet for up to 5.5 months. Ingestion of Process A product at concentrations greater than 1% of the diet (approximately 110

mg/kg/day) was associated with diarrhea and a decrease in weight gain. Ingestion of 1% Process A and both 1% and 10% Process B products had no adverse effect on body weight gain, food intake, gastrointestinal transit time or gross pathology. The rats ingesting 10% Process B product exhibited a slight, but significant increase in fluid intake. Plasma concentrations of parathyroid hormone (PTH) and calcitonin were lower in Aloe vera-treated rats (Herlihy et al., 1998a and 1998b).

The effects of life-long Aloe vera ingestion were investigated in rats. Four groups of animals were included: Group A (control), diet without Aloe vera; Group B, diet containing 1% freeze-dried Aloe vera filet; Group C, diet containing 1% charcoal-processed, freeze-dried Aloe vera filet; and Group D, control diet and whole leaf charcoal-processed Aloe vera (0.02%) contained in the drinking water. This study suggested that life-long Aloe vera ingestion produced neither harmful effects nor deleterious changes in rats (Ikeno et al., 2002).

e. Mutagenicity

Three types of Aloe vera formulations (Aloe vera gel, Aloe vera whole leaf extract, and Aloe vera charcoal filtered whole leaf extract) were tested for mutagenicity in the Ames test and the results were all negative (NTP TR577, 2013). However, some anthraquinones extracted from Aloe vera, such as emodin and aloe-emodin, exhibited genotoxicity in in-vitro genotoxicity assays (Brusick et al., 1997). Aloe-emodin was reported positive in the Ames test (with and without metabolic activation), an unscheduled DNA synthesis (UDS) test using rat hepatocytes and in a cell transformation assay using C3G/M2 mouse fibroblasts. It was reported weakly positive/equivocal in a mammalian cell mutation assay (HGPRT mutation assay) in V79 cells (Westendorf et al., 1990). Aloe-emodin was also reported positive in the L5178Y TK^{+/−} mouse lymphoma assay and induced micronuclei dose-dependently in the same cell line (Muller et al., 1996). Heidemann et al. (1996) reported that aloe-emodin was positive in the Ames test and an in vitro chromosome aberration assay in CHO cells although it was negative in the HGPRT mutation assay in V79 cells. Heidemann et al., also reported that aloe-emodin was negative in an in vivo micronucleus test when single oral doses of aloe-emodin up to 1500 mg/kg were administered to mice. It was also negative in an in vivo cytogenetic (chromosome aberration) assay when single oral doses of aloe-emodin up to 2000 mg/kg were administered to rats, a mouse spot test (single oral doses up to 2000 mg/kg), and an UDS assay using rat hepatocytes (single oral doses up to 1000 mg/kg).

f. Developmental and reproductive toxicity

Aloe vera has been used as a traditional abortifacient agent in India, and Nath et al., (1992) studied its embryofetal toxicity in rats. The Aloe vera extract (extracted with distilled water) was administered to 5 pregnant rats at 125 mg/kg/day from gestation day 0 to gestation day 9. Five control rats were given vehicle only (1% gum acacia). Abortifacient activity was calculated as 21.5%. A decrease of mean fetal body weight was noted (46%). A total of 51 fetuses were examined for macroscopic effects, 25 examined for visceral abnormalities, and 26 for skeletal abnormalities. No macroscopic,

visceral, or skeletal deformities were noted in control fetuses. Macroscopic effects in treatment fetuses included kinking of tail (5.9%), clubbing of right hind limb (11.8%), and left wrist drop (19.6%). No visceral abnormalities were observed. Skeletal abnormalities in the treatment fetuses included non-ossification of skull bones (15.4%), wavy ribs (15.4%), non-ossified ribs (15.4%), fused tarsal (15.4%), and intercostal space in ribs (11.5%).

Kosif and Aktas (2009) studied the effects of Aloe vera gel on rat ovaries. Oral (gavage) doses of 140 mg/kg/day *Aloe vera* gel were administered to female rats during pregnancy (from breeding to birth). In Aloe vera gel-treated animals, histological changes in ovaries included vascular increase, decrease in primary follicle numbers, increase in secondary follicle numbers, and reduction of secondary follicle diameters.

g. Carcinogenicity

The National Toxicology Program has conducted a 1-year photocarcinogenicity study of Aloe vera in hairless mice and two 2-year oral (drinking water) carcinogenicity studies of Aloe vera in mice and rats, respectively.

In the 1-year photocarcinogenicity study, groups of SKH-1 hairless mice received topical applications of control cream or creams containing 3% or 6% (w/w) Aloe gel, whole leaf, or decolorized whole leaf or 7.46 or 74.6 $\mu\text{g/g}$ aloe-emodin to the dorsal skin region each weekday morning. The mice were irradiated with simulated solar light (SSL) each weekday afternoon. The topical applications of creams and irradiance exposures were conducted 5 days per week for a period of 40 weeks. Additional groups of mice received no cream and were exposed to 0.00, 6.85, 13.70, or 20.55 $\text{mJ}\cdot\text{CIE}/\text{cm}^2$ SSL per day. Under the conditions of these studies, it was concluded that Aloe gel or aloe-emodin had a weak enhancing effect on the photocarcinogenic activity of SSL in female but not male hairless mice. It was also concluded that Aloe whole leaf extract and decolorized leaf extract had a weak enhancing effect on the photocarcinogenic activity of SSL in both male and female hairless mice (NTP TR533, 2010).

Goblet cell hyperplasia of the large intestine was noted in both F344/N rats and B6C3F1 mice when Aloe vera nondecolorized whole-leaf extract (1, 2, and 3%) was administered orally via drinking water for 13 weeks. Based on this observation, 2-year drinking water studies were conducted to assess the carcinogenic potential of the Aloe vera whole-leaf extract when administered to F344/N rats at 0.5, 1, and 1.5%, and B6C3F1 mice at 1, 2, and 3%. Compared with controls, survival was decreased in the 1.5% dose group of female rats. Treatment-related neoplasms and non-neoplastic lesions in both species were confined primarily to the large intestine. Incidences of adenomas and/or carcinomas of the ileo-cecal and cecal-colic junction, cecum, and ascending and transverse colon were significantly higher than controls in male and female rats in the 1 and 1.5% dose groups. There were no neoplasms of the large intestine in mice or in the 0 or 0.5% dose groups of rats. Increased incidences of mucosa hyperplasia of the large intestine were observed in rats, and increased incidences of goblet cell hyperplasia of the large intestine occurred in mice. These results indicate that Aloe vera whole-leaf extract

is an intestinal irritant in both F344/N rats and B6C3F1 mice and a carcinogen of the large intestine in F344/N rats (Boudreau et al., 2013; NTP TR577, 2013).

h. Toxicokinetics

No information found.

Conclusions

Aloe vera products have been reported to possess a wide range of pharmacological activities. However, most claims are not supported by robust data obtained from well-controlled studies. For some claims, including wound healing benefits, there are inconsistent or contradictory data, which might be partly due to the differences in test material and animal models used in these studies. Repeat dose oral toxicity studies showed that Aloe vera caused diarrhea, decrease in weight gain, reduction in RBC count, and sperm damage. Some anthraquinones extracted from Aloe vera exhibited genotoxicity in various in vitro genotoxicity assays. Aloe vera has abortifacient activity when taken orally and it induced skeletal malformations in an oral embryofetal toxicity study in rats. In oral (drinking water) carcinogenicity studies, Aloe vera whole-leaf extract is an intestinal irritant in rats and mice and a carcinogen of the large intestine in rats.

In view of the complexities of the chemical and biological properties of Aloe vera, the safety concerns associated with topical use of Aloe vera are not sufficiently addressed at the present time. For the proposed clinical use of the 200:1 freeze-dried Aloe vera product, there is a lack of nonclinical data to evaluate the chronic dermal toxicity and dermal carcinogenicity potential of Aloe vera, considering that the proposed clinical use includes chronic indications.

2. *Human Safety*

The following databases were consulted in the preparation of this review:

- PubMed
- Web of Science
- UptoDate
- Cochrane reviews
- Google.

Reports of previous human experience as a food, dietary supplement, and herbal medicine in the U.S. and other parts of the world, with data reported online in the Natural Medicines Comprehensive Database and other sources (e.g., USP, WHO monographs, PubMed), suggests that Aloe vera products are generally well tolerated. Moderate and infrequent oral consumption of Aloe vera gel preparations (containing no anthraquinone derivatives) as food/beverages appears reasonably safe based on the marketed use of various products.

However, the anthraquinone derivatives in Aloe latex are likely a safety concern (including the concern of potential carcinogenicity), especially when used repeatedly at high doses. Topical use of whole Aloe vera leaf extract (containing anthraquinone, organic acids, and other components) may cause irritation of the skin or allergic reactions in sensitive individuals. Thus, use of whole Aloe extract on open wounds should be avoided. Aloe vera gel freeze-dried appears well tolerated. However, without appropriate raw material and manufacturing quality controls, Aloe vera gel contaminated with other Aloe vera components (e.g., anthraquinones) remains as a potential safety concern for topical applications on open wounds.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for Aloe vera freeze-dried 200:1 and concluded that:

- There were 173 reports in the FAERS data base associated with Aloe vera terms. However, none of those reports on Aloe vera has detailed product information to allow a determination of whether the nominated substance (Aloe vera freeze-dried 200:1) was used, either alone or as part of a compounded product.

The Center for Food Safety and Nutrition was also consulted to search their adverse event data base, CAERS, for adverse events associated with use of cosmetic products that have Aloe vera ingredients. Results showed that:

- There were 34 reports of adverse events in the CAERS database. None of those reports mentioned Aloe vera freeze-dried 200:1 as an ingredient.

However, in addition to frequently reported application site dryness, itching and erythema, notable reactions following use of cosmetic products included:

- Possible anaphylactic reaction (case #154286) that required an emergency room visit
- Two cases (#152320 and #139195) of severe urticarial reaction that required hospitalization

a. Reported adverse reactions

Safety assessment for Aloe vera products entails a virtually endless list of *indications* and hundreds of systemic and topical products that use variable parts of the plant as the source of an *active ingredient*. Additionally, this *active ingredient* is commonly mixed with other, poorly specified substances in the final product, making the assessment of a drug–adverse event causative relationship challenging.

Notable safety information includes:

- Regarding oral use of Aloe vera extracts in laxatives, in 2002 FDA required that all OTC Aloe-containing laxative products be removed from the U.S. market or

reformulated because the companies that manufactured them did not provide the necessary safety data (mutagenicity, genotoxicity, and carcinogenicity) (<http://www.fda.gov/OHRMS/DOCKETS/98fr/78n-036L-nfr0004-vol1107.pdf>, accessed September 24, 2015).

- There is one case report of acute hepatitis in a 57-year-old woman who took over-the-counter herbal tablets containing Aloe vera extract (Rabe et al., 2005). Hepatitis resolved after discontinuing the medication.
- There are two case reports of Aloe-induced Henoch-Schonlein purpura, followed by development of renal failure (Kim et al., 2007; Cholongitas et al., 2005).

b. Clinical trials assessing safety

There is very limited safety information from clinical trials using topical Aloe vera.

Thamlikitkul et al. (1991) reported similar rates of irritation or itching in the Aloe vera group and in the control (sulfadiazine) group (40% vs. 44%) in a trial evaluating treatment of burns.

In a different study for the same indication, Visuthikosol et al. (1995), reported mild pain at the application site in 93% of patients in both the Aloe vera and control group.

In a 2013 publication by Reddy et al., contact dermatitis was associated with Aloe vera topical products.

c. Pharmacokinetic data

No human pharmacokinetic information for Aloe vera is reported in the literature.

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

In addition to surgical treatments (excision, suturing, debridement, skin grafting) most wounds require certain types of dressings. There are multiple wound dressings available that according to UptoDate fall into three major categories:

1. Hydrogels for the debridement stage
2. Foam and low-adherence dressings for the granulation stage
3. Hydrocolloid and low-adherence dressings for the epithelialization stage

There are no significant safety concerns with these products.

Additionally, two biological topical products are FDA approved for chronic wound care:

- Collagenase Santyl ointment for enzymatic debridement of chronic dermal ulcers and severe burns. No significant safety concerns are associated with its use.

- Becaplermin gel 0.01% (Regranex), for the treatment of lower extremity diabetic neuropathic ulcers. Safety information includes a Boxed Warning regarding an increased rate of mortality secondary to malignancy observed in patients treated with three or more tubes of Regranex gel based on observations from a postmarket retrospective cohort study.

Conclusions

Clinical data indicate that topically applied Aloe vera products for a short period of time can be used without causing serious toxicity. Although it is not clear whether any of the studied products are compounded products that specifically include the Aloe vera freeze dried 200:1 nominated product, adverse events reported are not greater than those seen with many other topical products.

However, long-term safety is not known, particularly in regard to carcinogenicity, which was the major reason for removal of oral Aloe vera laxatives from the U.S. market.

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

The duration of the dermatologic injury to be treated with the nominated substance was not specified in the nomination. Note that effectiveness of Aloe in acute wound treatment vs. chronic wound treatment may vary considerably.

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

Aloe vera has been used since antiquity, with writings suggesting that it was widely used in ancient Egyptian, Greek, and Indian cultures. There are thousands of publications related to Aloe vera and its use in a wide variety of conditions. The nomination included ten references, two of which addressed indications unrelated to wounds, cuts, and burns. An exhaustive review of all published literature was not undertaken for this consult.

While there are multiple anecdotal reports of Aloe vera products' efficacy, this review will focus primarily on the results reported in two comprehensive reviews of published literature.

The 2012 Cochrane Review on "Aloe vera for treating acute and chronic wounds" provides the most comprehensive review of Aloe vera efficacy evaluated in controlled clinical trials. The authors examined randomized clinical trials for "any one of the following: surgical wounds, burns, lacerations and other skin injuries resulting from trauma. We considered a chronic wound as any one of the following: skin ulcers, infected wounds, surgical wounds healing by secondary intention, pressure ulcers, arterial and venous ulcers."

The study outcomes included:

Primary outcomes

- *Time to complete wound healing.*
- *Proportion of participants to have a completely healed wound.*

Secondary outcomes

- *Change in wound size.*
- *Cosmetic appearance of wound healing.*
- *Incidence of adverse events.*
- *Incidence of infection.*
- *Financial cost of wound healing.*
- *Quality of life.*

Of “178 possibly relevant studies,” only 7 were randomized, controlled studies and therefore deemed adequate for review. The examined literature included various formulations of Aloe vera products, including gels, creams, dressing and mucilage. It is not clear that any were compounded products that specifically included the Aloe vera freeze dried 200:1 nominated product.

The authors concluded: “There is currently an absence of high quality clinical trial evidence to support the use of Aloe vera topical agents or Aloe vera dressings as treatments for acute and chronic wounds.” This conclusion was based on the review of the five trials in patients with acute wounds (including burns and skin biopsies) and two with chronic wounds (pressure ulcer and secondary surgical wound closure) that met the criteria of randomized, controlled trials. In most of the trials, the risk of bias was high due to either selection or blinding issues.

Regarding Aloe vera for burn wound healing, a systemic review by Maenthaisong et al. (2006) concludes that “due to the differences of products and outcome measures, there is paucity to draw a specific conclusion regarding the effect of Aloe vera for burn wound healing.” This conclusion was based on the review of the four controlled clinical trials with a total of 371 patients.

Two representative reviews are described in more detail below:

Khorasani et al., (2009) reported that the rate of re-epithelialization and healing of the partial thickness burns was significantly faster in the site treated with Aloe than in the site treated with silver sulfadiazine (15.9 ± 2 vs 18.73 ± 2.65 days, respectively; $P < 0.0001$). Thirty patients with similar types of second degree burns were randomly assigned to either treatment. The study was within-subject controlled and blinded.

Thomas et al., (1998) described the results of a multicenter trial in 41 patients with small pressure ulcers stage II, III, or IV treated with either Aloe dressing or saline dressing. The mean healing time was similar, i.e., 5.3 ± 2.3 v. 5.2 ± 2.4 weeks, respectively.

Schmidt et al., (1991) reported delayed wound healing with Aloe vera gel. The trial enrolled 21 patients with postoperative wounds. The wounds that were treated with standard management healed in 53 ± 24 days, and those treated with Aloe vera gel required 83 ± 28 days ($p = .003$). The study was not blinded.

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

Burns, cuts and wounds may potentially be life-threatening conditions if they occupy a large amount of the body surface or become the source of significant blood loss or systemic infection.

In the nomination of Aloe vera gel, the extent and morphology of “burns, cuts, and wounds” was not sufficiently defined. However, it does not appear that the proposed potential use of Aloe vera topical products is intended for severe cases.

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

Standard of care treatment for wounds and burns includes wound cleansing, excision, suturing, debridement, skin grafting, and dressings in conjunction with supportive measures (adequate blood supply, nutrition, infection control). Depending on the type of the wound, different components of standard of care are employed and/or emphasized and effective.

There are no FDA-approved drugs for “accelerated wound closure,” which remains the focus of drug development for chronic wounds. There are many devices, particularly wound dressings, used for the treatment of burns, cuts and wounds.

There are, however, two biological topical products that are FDA approved for chronic wound care:

- Collagenase Santyl ointment is indicated for enzymatic debridement of chronic dermal ulcers and severely burned areas (FDA approval 1965).
- Becaplermin gel 0.01% (Regranex), recombinant human platelet-derived growth factor that is produced through genetic engineering, was approved for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply, when used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief, and infection control (FDA approval 1997).

Conclusions:

There is insufficient and conflicting information from controlled clinical trials regarding efficacy of the Aloe vera topical products in the topical treatment of cuts, burns, and wounds.

Furthermore, it is not clear whether the products used in those trials contained 200:1 freeze dried Aloe vera.

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

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

According to the National Center for Complementary and Integrative Health, “Aloe vera’s use can be traced back 6,000 years to early Egypt, as the “plant of immortality,” and presented as a burial gift to deceased pharaohs”

(<https://nccih.nih.gov/health/aloevera>, accessed on September 14, 2015).

Herbal medicine use of Aloe has been reported throughout the world for centuries, as well as use as a general tonic or food (Radha et al., 2015; Bordreau et al., 2006; Robson et al., 1982; Heggors et al., 1985; Klein et al., 1988). The Ancient Greeks and Romans used to treat wounds with Aloe vera (Chinese Herbs Healing, 2015). Documented medicinal use of Aloe vera appears in the Ebers Papyrus from the 16th Century BC, the mid-first century AD writings of Dioscorides’ *De Materia Medica* and Pliny the Elder’s *Natural History* (Barcroft et al., 2003), and in the *Juliana Anicia Codex* from 512 AD (Reynolds, 2004). In Ayurvedic medicine, Aloe vera is known as komarika, and the leaves are used to treat abdominal pains, swellings, burns, skin diseases, urinary disorders, fevers, and gastritis (Ayurvedic Medicinal Plants of Sri Lanka, 2015). According to the Chinese Materia Medica, powdered Aloe vera latex has been used in traditional Chinese medicine for centuries at a recommended oral dosage of 0.6 to 1.5g per day to treat a variety of conditions, such as constipation, headache, bloodshot eyes, convulsions, hemorrhoids, and parasites causing abdominal pain (Chow et al., 2005).

Aloe utilized in commercial products can be reconstituted from powder or concentrated liquid, but it can also be a diluted product from an “Aloe extract” (Fox, 1990). These different Aloe products made from various Aloe raw materials and multiple processing techniques will have fluctuating compositions, which will lead to differences in safety and efficacy profiles. There is a lack of information in the literature on the specific use of 200:1 freeze dried Aloe products.

Multiple clinical trials and animal studies have been conducted using a wide range of Aloe products to test many different indications. The majority of the indications are focused on wound healing and the treatment of various degrees of burns, along with a few other uses, such as prevention of dental plaque and gingivitis. Some of the Aloe products utilized in these studies are commercially available, with varying compositions, as Aloe gels, powders or creams, and were purchased directly from manufacturers, while a few studies simply claim to use *Aloe vera* and do not provide additional botanical or manufacturing information. Products containing Aloe vera gel, including freeze dried, were studied in some of the clinical trials summarized in Table 1.

In these trials, dosages of Aloe were often not quantitatively reported (i.e., g or mL/dose) outside of the frequency of applications (i.e., 3 times daily), especially for topical treatments. The majority of the literature lacked information regarding how the Aloe was

processed prior to its use in manufacturing of the final Aloe products. There were no chemical characterization data provided for the Aloe products utilized in these trials except for a few studies reporting their in-house preparation, extraction and manufacturing processes (Chithra *et al.*, 1998, Silva *et al.*, 2013, Khorasani *et al.*, 2009, Panahi *et al.*, 2012). Some trials provided the composition of the commercial Aloe products that were available through the manufacturers (Rajar *et al.*, 2008, Shahzad *et al.*, 2013). The lack of characterization data for the range of Aloe products used in these trials makes it difficult to draw any meaningful conclusion regarding the relationship of safety and efficacy of *Aloe vera* with the quality attributes of Aloe vera products.

Table 1: Topical *Aloe* Products Tested in Clinical Trials

Product	Dosage	Route of Administration	Indication	Reference
Aloe vera gel: 100% Aloe vera gel, carbomer 940, triethanolamine, tocopheryl acetate, tetrasodium EDTA (Nature Bounty, USA imported by Sigma Pharma, Pakistan)	Twice daily; prohibited from emollient usage during study	Topical	Vulval Lichen Planus	Rajar <i>et al.</i> , 2008
Lyophilized <i>Aloe vera</i> powder (LAVP); Made from mature <i>Aloe vera</i> leaves with rinds removed, colorless parenchyma was ground in blender and centrifuged to remove fibers; supernatant was lyophilized and stored at room temp until use	30mg LAVP plus small amount of water to form gel; twice daily	Orally (with oral tube) OR Topically to wound surface	Healing of dermal wounds in diabetic rats	Chithra <i>et al.</i> , 1998
Aloe vera gel (AloeTone JeIR) consisting of the 98% of unrefined gel from inner leaf of plant	Aloe soaked gauzes; wound dressing was done twice/day until healing was complete	Topical	Healing of second degree burns	Shahzad <i>et al.</i> , 2013

<i>Aloe saponaria</i> cream (0.3%-30%); fresh leaves cut in small pieces and macerated with 70% ethanol (extraction) and concentrated to dryness; dry extract was incorporated into Lanette cream (manufactured by Pharmacy of the Federal University of Santa Maria) for topical treatment	Once a day for 2 or 6 days	Topical	Treat thermal injury in rats	Silva <i>et al.</i> , 2013
Cream containing 0.5% Aloe vera gel powder, made from pure spray-dried Aloe vera powder (Zarband Phytopharmaceutical, Tehran, Iran); 0.50g Aloe vera powder was added to a cream made by researchers	Cream applied twice daily until burns fully healed and epithelialized; dressing change accompanied each application	Topical	Treatment of second-degree burns	Khorasani <i>et al.</i> , 2009
<i>Aloe vera</i> cream (Kia Behdasht Pharmaceutical Co., Hashtgerd, Iran); contained <i>Aloe vera</i> gel and olive oil as active components, prepared in oil/water emulsion base; <i>Aloe vera</i> to olive oil ratio in cream was ~3:2	3 times a day after washing and drying diaper area; duration of 10 days	Topical	Treatment of diaper dermatitis	Panahi <i>et al.</i> , 2012

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

There is an extensive list of potential uses for the Aloe vera products: constipation, genital herpes, psoriasis, seborrheic dermatitis, cancer prevention, chemotherapy adjuvant, common cold, dental plaque, diabetes, dry mouth, gingivitis, high cholesterol, inflammatory bowel disease, lichen planus, mucositis, scabies, diaper rash, heart disease, HIV infection, liver disease and radiation dermatitis among others (Mayo Clinic summary <http://www.mayoclinic.org/drugs-supplements/Aloe/safety/hrb-20058665>, accessed on September 14, 2015).

Aloe vera, the botanical raw material, is widely used topically in herbal preparations for treatment of various skin conditions, most notably for wound healing (Tyler 1994). Aloe vera is said to assist in wound healing and is often used in cosmetics for its moisturizing and emollient properties (Dewick 1997). It is also a common ingredient in cosmetics

products like lotions, ointments, creams, and shampoos. The carboxypeptidase and salicylate of Aloe gel can inhibit bradykinin, a pain producing agent while magnesium lactate can inhibit histamine with the potential to reduce itching (Klein 1988). Although preliminary studies of fresh *Aloe vera* gel suggested that it may be an effective treatment of minor skin ailments, the effectiveness of Aloe preparations is still not confirmed because the Aloe preparations studied were not standardized, and well-controlled large clinical studies are still lacking (Tyler 1994; Muller et al., 2003).

Aloe latex has traditionally been used orally as a laxative to relieve constipation. The potent laxative effects are due to the cleaved tricyclic anthracene nucleus in the anthraquinones that form anthrones in the colon, which irritate mucous membranes, leading to increased mucous secretion and peristalsis (Gennaro, 1996). Fluid and electrolyte secretion into the lumen are increased and the cathartic effects occur within 10 hours of ingestion while water and electrolyte reabsorption are inhibited and the loss of potassium from cells paralyzes the intestinal muscles (Wichtl et al., 1994). Some preliminary data suggest anthraquinone may have mutagenic and carcinogenic effects, but the data are conflicting. Due to lack of data to resolve certain carcinogenicity concerns, in 2002, FDA issued a final ruling stating that the orally administered stimulant laxative ingredient Aloe, including Aloe extract and Aloe flower extract, in OTC drug products is not generally recognized as safe (GRAS) or is misbranded (FDA *Federal Register*, 2002).

3. *How widespread its use has been*

Aloe vera is not approved as a drug in the United States in any form, and the extent of applications in compounding pharmacy may be limited. *Aloe vera* and its extracts have also been used in foods (e.g., vegetables, beverages), cosmetics, and dietary supplement products in the United States. In addition, Aloe vera is one of the commonly used herbal medicines in many parts of the world, including the most populous countries like China and India.

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

WHO and compendial monographs (e.g., Chinese Pharmacopeia) are available with guidance on testing for quality and recommendations for herbal medicine applications of Aloe vera. The WHO and compendial monographs do not include the nominated substance, Aloe vera (gel) freeze-dried (200:1).

Conclusions

Aloe vera leaf and latex are among the commonly used herbal medicines in many parts of the world with popular dietary supplement and food use in the recent decades. In addition, numerous topical products containing Aloe vera gel have been used or tested in clinical trials for the treatment of wounds and burns. However, those Aloe vera products previously used or studied were poorly characterized with no sufficient quality information to draw meaningful connections with the nominated substance Aloe vera (gel) freeze-dried (200:1). In addition, no

specific human experience to directly support the potential use of the nominated substance, Aloe vera (gel) freeze-dried (200:1), as a topical treatment for burns and wounds is provided by the nominator or available in literature.

III. RECOMMENDATION

We have evaluated Aloe vera freeze-dried 200:1 as a candidate for the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act in light of its physicochemical characteristics, safety, effectiveness, and historical use in compounding. Although Aloe vera generally (not specific to the 200:1 freeze dried extract that was nominated) has been used for millennia, we recommend that it ***not be included*** on the list of bulk drug substances allowed for use in compounding based on the following:

1. Aloe vera *extract* is used as a general term, and no adequate product quality information was provided in literature (or by the nominator) to allow differentiation of Aloe vera freeze dried 200:1, the nominated substance, from other Aloe extracts. Aloe vera may contain various classes of molecules, and it is not well characterized in its physical and chemical properties (especially the major components, polysaccharides). Additionally, raw material collection, storage, and the manufacturing processes used may change the physiochemical properties of the Aloe extract (especially the polysaccharides), making characterization and adequate quality control to ensure safety and efficacy for drug use even more difficult to achieve.
2. There are potential safety concerns of the anthraquinones in Aloe latex. Although the oral use of Aloe vera gel (mostly polysaccharides without anthraquinones) as dietary supplement/food appears to be reasonably safe, topical use of Aloe extract (especially those containing anthraquinones) on open wounds should be avoided because of the inability to differentiate potential contaminants from other botanicals by routine chemical analysis.
3. There is insufficient and conflicting information from controlled clinical trials regarding efficacy of the Aloe vera topical products in the topical treatment of cuts, burns, and wounds. Furthermore, it is not clear whether the products used in those trials contained 200:1 freeze dried Aloe vera.
4. Although short-term application of small amounts of topical Aloe vera products may have an acceptable dermal safety profile, there is a lack of long-term dermal safety data and pharmacokinetic data, which are necessary for full safety evaluation of topical products. The safety profile of Aloe vera shows that the anthraquinone derivative in Aloe latex may be unsafe, especially when used at high doses for repeated use (e.g., concerns of potential carcinogenicity). Nonclinical data also raise concern, showing that Aloe vera has abortifacient activity when taken orally and it induced skeletal malformations in an oral embryofetal toxicity study in rats. There is no information on the safety of 200:1 freeze dried Aloe products for topical use.

For the reasons stated above, we ***do not recommend*** that 200:1 freeze dried Aloe vera be included on the list of bulks drug substances for use in compounding.

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Tab 4

D-Ribose

Tab 4a

D-Ribose
Nominations



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

Re: Docket FDA-2013-N-1525

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

Dear Sir or Madam,

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

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

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

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

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

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs



Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlsx file)

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

Fagron

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



What is the name of the nominated ingredient?

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

Ribose (D)

Yes, Ribose 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 Ribose pharmacological actions are provided Teitelbaum JE, Johnson C, and St Cyr J. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. *J Altern Complement Med.* 2006;12(9):857-62. doi:10.1089/acm.2006.12.857.

Pliml W, von Arnim T, Stäblein A, Hofmann H, Zimmer HG, and Erdmann E. Effects of ribose on exercise-induced ischaemia in stable coronary artery disease. *Lancet.* 1992;340(8818):507-10.

Pauly DF, and Pepine CJ. D-Ribose as a supplement for cardiac energy metabolism. *J Cardiovasc Pharmacol Ther.* 2000;5(4):249-58.

Pauly DF, Johnson C, and St Cyr JA. The benefits of ribose in cardiovascular disease. *Med Hypotheses.* 2003;60(2):149-51.

Vijay N, MacCarter D, Shecterle LM, and St Cyr JA. D-ribose benefits heart failure patients. *J Med Food.* 2008;11(1):199-200. doi:10.1089/jmf.2007.503.

Omran H, Illien S, MacCarter D, St Cyr J, and Lüderitz B. D-Ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study. *European journal of heart failure.* 2003;5(5):615-619.

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?	2S,3S,4S,5R)-5-(hydroxymethyl)oxolane-2,3,4-triol; Beta-D-ribofuranose
What is the common name of the substance?	D-ribosa; D-ribose; Ribosa
Does the substance have a UNII Code?	681HV46001
What is the chemical grade of the substance?	no grade
What is the strength, quality, stability, and purity of the ingredient?	<p>Description: White Crystalline Powder</p> <p>Identification: Positive</p> <p>Particle Size:</p> <p>-Bulk Density: 0.5 g/mL - 0.9 g/mL</p> <p>-Tapped Density: 0.6 g/mL - 1.0 g/mL</p> <p>Melting Range: 85.0°C - 92.0°C</p> <p>Heavy Metal: ≤ 5 ppm</p> <p>Arsenic: ≤ 1 ppm</p> <p>Cadmium: ≤ 1 ppm</p> <p>Lead: ≤ 0.1 ppm</p> <p>Mercury: ≤ 0.1 ppm</p> <p>Loss on Drying: ≤ 0.5%</p> <p>Residue on Ignition: ≤ 0.1%</p> <p>Assay (Dried): ≥ 99.0%</p> <p>Total Plate Count: ≤ 1,000 cfu/g</p> <p>Yeast & Mold: ≤ 100 cfu/g</p> <p>Coliforms: Negative</p> <p>E. Coli: Negative</p> <p>Staphylococcus Aureaus: Negative</p> <p>Salmonella: Negative</p>
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?	Capsules
What strength(s) will be compounded from the nominated substance?	500-750mg
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?

Teitelbaum JE, Johnson C, and St Cyr J. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. *J Altern Complement Med*. 2006;12(9):857-62. doi:10.1089/acm.2006.12.857.

Pliml W, von Arnim T, Stäblein A, Hofmann H, Zimmer HG, and Erdmann E. Effects of ribose on exercise-induced ischaemia in stable coronary artery disease. *Lancet*. 1992;340(8818):507-10.

Pauly DF, and Pepine CJ. D-Ribose as a supplement for cardiac energy metabolism. *J Cardiovasc Pharmacol Ther*. 2000;5(4):249-58.

Pauly DF, Johnson C, and St Cyr JA. The benefits of ribose in cardiovascular disease. *Med Hypotheses*. 2003;60(2):149-51.

Vijay N, MacCarter D, Shecterle LM, and St Cyr JA. D-ribose benefits heart failure patients. *J Med Food*. 2008;11(1):199-200. doi:10.1089/jmf.2007.503.

Omran H, Illien S, MacCarter D, St Cyr J, and Lüderitz B. D-Ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study. *European journal of heart failure*. 2003;5(5):615-619.

Pauly DF, and Pepine CJ. D-Ribose as a supplement for cardiac energy metabolism. *journal of Cardiovascular Pharmacology and Therapeutics*. 2000;5(4):249-258.

8. Sinatra ST, and Roberts JC. Enhancing cardiac energy with ribose. *Life Extension*. 2007;13(50):26-31.

Addis P, Shecterle LM, and St Cyr JA. Cellular protection during oxidative stress: a potential role for D-ribose and antioxidants. *J Diet Suppl*. 2012;9(3):178-82. doi:10.3109/19390211.2012.708715.

Caretti A, Bianciardi P, Marini M, Abruzzo PM, Bolotta A, Terruzzi C, Lucchina F, and Samaja M. Supplementation of creatine and ribose prevents apoptosis and right ventricle hypertrophy in hypoxic hearts. *Curr Pharm Des*. 2013;19(39):6873-9.

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

Capsules

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

Ribose has been shown to be a beneficial supplement in the treatment of heart disease and Chronic Fatigue Syndrome

What is the reason for use of a compounded drug product rather than an FDA-approved product?

No FDA approved preparation for D-Ribose. D-Ribose levels are maintained in muscle tissue to help maintain energy and produce Adenine Tri-phosphate (ATP). D-ribose levels can drop in Chronic Fatigue syndrome causing muscle aches and stiffness. A study done in chronic fatigue and fibromyalgia patients showed significant reduction in clinical symptoms. (J.E. Teitelbaum, C. Johnson, and J. St. Cyr (2006) The Use of D-Ribose in chronic fatigue syndrome and fibromyalgia: A Pilot Study J. Altern Complement Med Nov;12(9):857-62) There are no FDA approved medications for chronic fatigue syndrome. D-Ribose has been shown to increase both objective and subjective clinical improvements in patients with cardiovascular diseases. (L.M. Shecterle, K.R. Terry, and J.A. St Cyr (2010) The patented uses of D-Ribose in Cardiovascular Diseases Recent. Pat.Cardiovasc Drug Discov Jun;5(2):138-42)

Is there any other relevant information?

All relevant information was expressed in the above questions

Tab 4b

D-Ribose

FDA Reviews



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: February 8, 2016

FROM: Philip Gatti, PhD, Pharmacology Reviewer
Division of Cardiovascular and Renal Products

Raj Madabushi, PhD, Clinical Pharmacology Team Leader
Office of Clinical Pharmacology

Thomas Papoian, Pharmacology Team Leader
Division of Cardiovascular and Renal Products

Sreedharan Sabarinath, Ph.D., Clinical Pharmacology Reviewer
Office of Clinical Pharmacology

Mohan Sapru, PhD, Chemistry Lead for Cardiovascular and Renal
Products (Acting), Office of New Drug Products, Office of
Pharmaceutical Quality

Shari Targum, MD, Clinical Team Leader
Division of Cardiovascular and Renal Products

Nancy Xu, MD
Medical Officer
Division of Cardiovascular and Renal Products

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

Norman Stockbridge, MD, PhD, Director
Division of Cardiovascular and Renal Products

Ellis Unger, MD, Director
Office of Drug Evaluation I

TO: Pharmacy Compounding Advisory Committee

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

I. INTRODUCTION

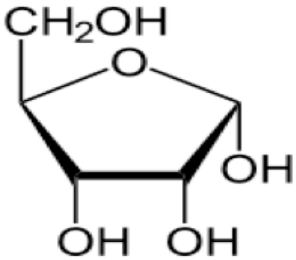
D-ribose has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for use in the treatment of heart disease and chronic fatigue syndrome.

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 D-ribose 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?

D-ribose is an aldopentose, a monosaccharide with an aldehyde ribose functional group at one end. It is a naturally occurring compound with the following features:

	<p>Common name: D-ribose Chemical name: A-D(-) ribofuranose Appearance: White crystalline powder with fruity sweet odor Empirical Formula: C₅H₁₀O₅ Molecular Weight: 150.13 CAS No.: 50-69-1 Melting Point: 95 °C Water Solubility : 0.1 g/mL (readily soluble in water)</p>
--	---

Ribose is a key backbone component in the cellular macromolecule ribonucleic acid (RNA). Typically, it exists in the cyclic form. It is important for the generation of adenosine triphosphate (ATP), the main energy source for the majority of cellular functions, including muscle contraction. D-ribose is commercially available, and some use it as a food additive or as a supplement, believing it to increase muscular energy, boost endurance, and promote recovery (Teitelbaum et al., 2006).

1. Stability of the API and likely dosage forms

D-ribose is stable at room temperature, though based on publically available information; some commercial manufacturers prefer temperature conditions of 2-8°C for its long-term storage. In solution, stability of D-ribose is significantly affected by pH and temperature. For example, the half-life for ribose decomposition is 73 min at 100°C and pH 7, and estimated at decades at 0°C and pH 7 (Larralde et al., 1995). D-ribose, as manufactured by Bioenergy Inc., a company that manufactures D-ribose for use as a dietary ingredient using *Bacillus subtilis* (*B. subtilis*), has been shown to be stable in poly bags at room temperature for 24 months (GRAS Notice, 2008).

D-ribose that is commercially available as dry powder is generally used for oral administration. However, there are also reports of its use for intravenous administration (Goodman et al., 1970).

2. *Probable routes of API synthesis*

Per the literature, several D-ribose synthesis methods are known, ranging from the chemical and enzymatic hydrolysis of yeast RNA to the chemical synthesis of D-ribose from D-arabinose, D-gluconic acid, D-glucose, L-glutamic acid, and D-xylose (De et al., 1997). A 1988 patent, US 4760139 A, details synthesis of D-ribose from D-xylose (Feniou et al., 1988). However, only D-ribose production with transketolase and/or D-ribu-lose-5-phosphate-3-epimerase-deficient Bacillus mutant has proved commercially feasible. The introduction of newer fermentation technologies have contributed to further improvements in bacterial D-ribose productivity, leading to D-ribose yields that exceed 90 g/L, starting from 200 g/L D-glucose (De et al., 1997). Moreover, the fermentation time and the concentration of undesirable by-products have significantly decreased. The amount of D-ribose produced worldwide by fermentation is estimated to be around 2000 tons per year.

The most likely route for API synthesis is fermentation-based synthesis of D-ribose using a transketolase deficient Bacillus mutant. The production of D-ribose is initiated by cultivating B. subtilis (with no or very low transketolase activity) in a nutrient-rich medium, followed by fermentation. During fermentation, glucose is converted to D-ribose, which accumulates in the culture broth. The culture broth is filtered to remove bacterial cells and undergoes extensive purification, followed by concentration through evaporation and crystallization with ethanol. The crystals are recovered by centrifugation, then dried and packaged. The final product obtained is generally $\geq 97\%$ ribose (De et al., 1997).

3. *Likely impurities*

The known inorganic impurities, i.e., heavy metal and arsenic, are present at acceptable levels of < 10 ppm and ≤ 2 ppm, respectively.

a) Quality Description of D-ribose as per the nomination document

Description: White Crystalline Powder Identification: Positive Particle Size: - Bulk Density: 0.5 g/mL - 0.9 g/mL - Tapped Density: 0.6 g/mL - 1.0 g/mL Melting Range: 85.0°C - 92.0°C Heavy Metal: ≤ 5 ppm Arsenic: ≤ 1 ppm Cadmium: ≤ 1 ppm	Lead: ≤ 0.1 ppm Mercury: ≤ 0.1 ppm Loss on Drying: $\leq 0.5\%$ Residue on Ignition: $\leq 0.1\%$ Assay (Dried): $\geq 99.0\%$ Total Plate Count: $\leq 1,000$ cfu/g Yeast & Mold: ≤ 100 cfu/g Coliforms: Negative E. Coli: Negative Staphylococcus Aureus: Negative Salmonella: Negative
--	--

Lead: ≤ 0.1 ppm Mercury: ≤ 0.1 ppm	
---	--

b) Sigma-Aldrich Specification for D-Ribose

TEST	Specification
Appearance (Color)	White to Off White
Appearance (Form)	Powder
Solubility (Color)	Colorless to Faint Yellow
Solubility (Turbidity)	Clear
100 mg/mL, H ₂ O	
Specific Rotation	-21.0 - -19.5 °
c = 4, H ₂ O, 20 deg C	
Heavy Metals (as Lead)	< = 10 ppm
Loss on Drying	< 0.5 %
Purity (GC)	> 99 %
Recommended Retest Period	-----
3 Years	

Specification: PRD.2.ZQ5.10000010957

c) Specification for D-Ribose by Parachem, Inc.

Specifications
Appearance : White crystalline powder
Specific Rotation : -19.0° to -21.0°
Heavy Metals : 20 ppm max
Arsenic : 2 ppm max
Loss on Drying : 0.5% max
Residue on Ignition : 0.2% max
Melting Point : 80.0°C - 90.0°C
Particle Size : 20 to 80 mesh
Assay : 97.0% to 102.0%
Total Calories : 4.5 - 5.0 Kcal/g
Total Carbohydrates : 99% min

Given that the nomination document does not specify any single synthetic pathway, it is likely that the impurities relate to the fermentation-based synthetic pathway involving the use of the transketolase deficient *Bacillus* mutant. Bioenergy, Inc. has established several specification parameters for manufactured D-ribose resulting from the fermentation-

based synthetic pathway involving the use of a transketolase deficient *Bacillus* mutant (see Table 1 below).

Table 1 Chemical and Physical Specifications for D-ribose

Table 1 Chemical and Physical Specifications for D-Ribose		
Specification Parameter	Specification	Method of Analysis
Appearance	Dry shape-holding characteristics with powdery texture that is white to slightly yellow in color.	Internal method (SOP-QC002-00)
Melting point	80 to 90°C	Internal method (derived from method I, CP2005 Appendix VI C)
Specific rotation	-19.0 to -21.0°	CP2005 Appendix VI E
D-ribose (purity)	97.0-103.0%	Internal method (SOP-QC002-00)
Loss on drying (moisture)	<2.0%	Internal method (derived from method I, CP2005 Appendix VIII L)
Ash	≤0.2%	CP2005 Appendix VIII N
Clarity of solution	≥95% transmittance	Bioenergy 30-014
Lead	≤0.1 ppm	AOAC 993.14
Arsenic	≤1 ppm	Method I, CP2005 Appendix VIII J
Total plate count	NMT 100 CFU/g	AOAC 990.12
Salmonella sp.	Negative/25g	AOAC 991.14
Coliforms	NMT 10 CFU/g	AOAC 992.21
Yeast and mold	NMT100 CFU/g	AOAC 992.11

Abbreviations: CFU, colony forming unit; NMT, not more than

Furthermore, Bioenergy, Inc. has claimed that no proteins, yeasts, molds, *Salmonella*, or *Escherichia coli* have been detected in the manufactured batches of D-ribose. According to Bioenergy, Inc., ethanol, other sugars and sugar alcohols produced in the fermentation process are largely removed during purification.

4. Toxicity of likely impurities

B. subtilis is generally regarded as non-toxicogenic and non-pathogenic. Antibiotic resistance is not expected as there are no known plasmids in *B. subtilis* that encode for antibiotic resistance. *B. subtilis* has traditionally been used in the commercial production of the Japanese delicacy *natto* by fermentation of soybeans, as well as in the commercial production of other compounds used in the food industry. Furthermore, *B. subtilis* is widely distributed in the environment and is naturally present in many foods that have been consumed by humans for decades with no evidence of food poisoning.

In the United States, carbohydrase (21 CFR 184.1148 [U.S. FDA, 2007b) and protease (21 CFR 184.1150 [U.S. FDA, 2007c) from *B. subtilis*, meeting food-grade specifications, are affirmed as GRAS for use in foods as enzymes at levels not exceeding current good manufacturing practice (U.S. FDA, 2007b,c). The affirmations are predicated on the use of nonpathogenic and nontoxicogenic strains of *B. subtilis* (U.S. FDA, 2007b,c).

D-ribose, as manufactured by Bioenergy, Inc. in accordance with current good manufacturing practices, meets appropriate food-grade specifications, and all raw materials and processing aids used in the manufacture of D-ribose, including water, activated carbon, sodium chloride, hydrochloric acid, ethanol, ion exchange resin, and defoaming agent, are permitted for use in food in the United States. D-ribose has been determined to be Generally Recognized as Safe for use as food additive (GRAS Notice, 2008).

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

D-ribose is water soluble, and there is no evidence of its physicochemical characteristics adversely affecting 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*

The API is neither poorly characterized nor difficult to characterize. Although D-ribose with its four chiral centers is stereochemically complex, it is quite well characterized.

Conclusions: The nominated substance, D-ribose, is well characterized, designated as a GRAS food additive, and is commercially available for use as a food additive, nutritional supplement, or investigational pharmacological agent. Based on the published research findings and publically available product information, D-ribose is well characterized, physically and chemically.

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

1. *Nonclinical Assessment*

Ribose exists as two enantiomers. D-ribose is the naturally occurring enantiomer, whereas L-ribose is not found in nature and needs to be synthesized chemically. D-ribose is present in all living cells and forms part of the backbone of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), where deoxyribose is synthesized from its precursor ribose. Phosphorylated ribose is a component of co-factors such as ATP and NADH that are involved in energy generation and carbohydrate metabolism. Riboflavin (vit. B12) helps aid in the endogenous production of D-ribose in the body. Ribose is not ingested in the diet in free form, except when included as a supplement, but it is produced and released in the body via breakdown of ingested compounds (such as vegetables and meats) that contain it (RNA, ATP, etc.). Bioavailability of orally administered D-ribose has been estimated to be 88% to 100%.

D-ribose has been shown to be involved in the glycation of proteins that can lead to protein aggregation, cell dysfunction, and cognitive impairments (Wei et al., 2012). Of the reducing sugars, D-ribose is much more reactive than is glucose in producing

advanced glycation end products (AGEs) that have been associated with many diseases, including cardiovascular disease and diabetes, and other age-related disorders, such as neurodegenerative diseases. In cell culture, AGEs have been shown to be toxic to various cell types, including neurons. However, other cell culture studies have shown the protective effects of D-ribose. The differences between toxic effects and protective effects have been attributed to different ribose concentrations used, duration of exposure, and state of the cell; protection is seen at lower concentrations for stressed cells, but toxicity is seen at higher concentrations for normal cells. When D-ribose was injected into mice, AGEs were detected in the brain at much higher levels than were seen with glucose at similar doses (Han et al., 2011). Also, presence of AGEs in the mouse brains was associated with impairment of spatial recognition (see below). The authors recommended monitoring of blood glycated products in patients receiving D-ribose.

a. Safety pharmacology

No studies were found.

b. Acute toxicity

No studies were found.

c. Repeat dose toxicity

Two repeat-dose toxicology studies in animals were published, one in rats (Griffiths et al., 2007) and one in rabbits (Ismail et al., 2010). The rat study evaluated the toxicity of sub-chronic administration of D-ribose to male and female Wistar rats. D-ribose was added to the diet of these rats for 13 days at concentrations of 0, 5, 10 and 20%. The highest dose was calculated to be 3.6 g/kg in females and 4.4 g/kg in males. Findings included dose-dependent decreases in body weights in all treated animals. The study did not evaluate the effects of ribose on plasma glucose concentrations.

Also, absolute and relative cecal weights were dose-dependently increased in all treated animals. No histopathological effects were observed. The no observed adverse effect level (NOAEL) was the highest concentration tested of 4.4 g/kg (= 26.4 mg/m²).

The rabbit study assessed the toxicity of D-ribose administered intravenously daily for 28 days. Three groups were tested: one control group received physiological saline (0.9%); the second group received a 4.2% ribose solution (420 mg/kg; 10 ml/kg) for the 28-day period and was euthanized immediately after the last dose. The third and final group received the same dose of ribose for 28 days, but the animals were sacrificed 15 days after the final dose. The only change observed in treated groups was a statistically significant increase in neutrophil percentage in male rabbits. This effect was also observed in the recovery group, but did not reach statistical significance. Plasma glucose levels decreased in males, but this effect did not reach statistical significance. No values for glucose were provided in the article. There were no other significant effects on organ weights or clinical chemistry parameters. The NOAEL was the only dose tested of 420 mg/kg (= 5.0 g/m²). Finally, mice administered D-ribose intraperitoneally at 0.2 and 2.0

g/kg/day for 30 days exhibited impairment of spatial learning and memory ability as tested in the Morris water maze (Han et al., 2011).

d. Mutagenicity

No studies were found.

e. Developmental and reproductive toxicity

No studies were found.

f. Carcinogenicity

No studies were found.

g. Toxicokinetics

Not performed in toxicity studies.

Conclusions: The two major, repeat dose toxicology studies that examined the effects of D-ribose were performed in the rabbit and the rat. No toxic effects were seen at the highest doses tested in the rabbit (420 mg/kg intravenously) and in the rat (4.4 g/kg orally). In male rabbits, a significant increase in neutrophil level was observed. A small but not statistically significant decrease in plasma glucose was observed, but no values were provided. No data were found on reproductive toxicity, genotoxicity or carcinogenicity. In the rat, an increase in cecal weight was observed. In conclusion, the available animal data do not raise significant concerns regarding the safety of D-ribose from a nonclinical perspective. However, there is insufficient nonclinical information available currently to evaluate the role of ribose-derived AGEs in the glycation of proteins, cell dysfunction, and possible cognitive impairments.

2. *Human Safety*

According to published medical literature, D-ribose has been used to treat a variety of disease conditions (ischemic heart disease, heart failure, cardiovascular disease, fibromyalgia, restless leg syndrome, myoadenylate deaminase deficiency (an inherited enzyme disorder of skeletal muscle), McArdle's disease (Glycogen Storage Disease type V), and adenylosuccinase deficiency) (Teitelbaum et al., 2006; Flanigan et al., 2010; Perez-Duenas et al., 2012; Perez-Duenas et al., 2014; Salerno et al., 1999; Shecterle et al., 2008; Shecterle et al., 2010; Zollner et al., 1986). WebMD states that ribose is "possibly effective for clogged heart arteries (coronary artery disease). Taking ribose by mouth seems to be effective for improving the heart's ability to manage low blood flow in people with coronary artery disease." Some of these conditions have FDA-approved alternative therapies. For example, the cardiovascular conditions (ischemic heart disease, heart failure, cardiovascular disease) have approved drug therapies. In the cardiovascular disease population, D-ribose has been studied as a dietary supplement or for use as a drug

as an adjunct *metabolic agent* (Kendler, 2006; Shecterle et al., 2011; Abozguia et al., 2007).

Furthermore, as discussed in section A, D-ribose is considered GRAS, under the conditions of its intended use as a food additive. This review, however, is focused on the use of D-ribose as a drug to treat disease conditions, not as a dietary supplement or food. Food products that contain D-ribose as a food additive at $\geq 1\%$ per volume or weight also contain other sources of carbohydrate (and thus glucose).

a. Reported adverse reactions

The most frequently reported adverse events are hypoglycemia, diarrhea/hyperperistalsis/loose stool (at higher doses), gastrointestinal discomfort, or nausea (Omran et al., 2003; Pliml et al, 1992; Sawada et al., 2009). Laboratory abnormalities include elevations in uric acid, aminotransferases, and gammaglutamyl transpeptidase activities (Seifert et al., 2009). For a summary of possible adverse reactions reported in healthy subjects and patients with cardiovascular disease, see Table 2 below.

b. Clinical trials assessing safety

According to published medical literature, D-ribose was studied in 4 placebo-controlled clinical trials (1 in healthy subjects and 3 in patients with cardiovascular diseases). Three of the trials had a cross-over design, which may limit the interpretation of adverse reactions attributable to D-ribose (Omran et al., 2003; Sawada et al., 2009; ; Seifert et al., 2008).

Trial design, dose, and the reported adverse events are summarized in Table 2 below (Omran et al., 2003; Pliml et al., 1992; Sawada et al., 2009).

Table 2 Placebo-Controlled Clinical Trials in Healthy Subjects and Patients with Cardiovascular Disease

Author Year	Population N total	Dose n on D-ribose Duration	Adverse Reactions
Healthy Subjects			
Seifert et al., * 2008	Healthy subjects (n = 19)	10 g/day po bid n = 19 14 days	“Asymptomatic mild hypoglycemia” Transient increase in uric acid at day 7
Cardiovascular Disease Population			
Sawada et al., *, ¹ 2008	Reduced EF, majority with MI, CAD, dobutamine stress test (n = 26)	180 mg/kg/h IV n = 26 4.5 hours	Not discussed.

Omran et al., *, ¹ 2002	Coronary artery disease and NYHA class II or III heart failure (n = 15)	5 g po tid n = 15 3 weeks	“no adverse effect”
Pliml et al., 1992	Ischemic Heart Disease, stable CAD (n = 20)	15 g po QID n = 10 3 days	Uric acid 7.4 – 8.4 mg/dL (3) Elevated transaminase/GGT (2) Unspecified

* cross-over design; ¹blinded

PO=oral administration, IV=intravenous, BID=twice daily, TID=three times daily, QID=four times daily, g/day=gram per day

NYHA class =New York Heart Association heart failure class

As shown in the table above, hypoglycemia and uric acid elevations were reported with D-ribose treatment in both healthy subjects and subjects with cardiovascular conditions. Furthermore, at doses of 60 g/day, elevations in liver enzymes and gastrointestinal symptoms also occurred with D-ribose use.

The clinical relevance of the D-ribose-induced hypoglycemia in patients with cardiovascular disease remains unclear. The 2008 GRAS submission suggests that humans can use D-ribose as an alternative energy source to glucose, and D-ribose, when used as a food additive, is generally regarded as safe, despite a detected laboratory abnormality (hypoglycemia). Furthermore, the clinical trials (shown in the table above) and other publications reported no serious or typical signs or symptoms (e.g., tachycardia, anxiety, sweating, hunger, seizure, or coma) of hypoglycemia attributable to D-ribose use (Quinlivan et al., 2014; Zollner et al., 1986; Ginsburg et al., 1997; Segal et al., 1957; Segal et al., 1958).

In patients with diabetes mellitus (who often have cardiovascular disease), we believe higher doses of D-ribose (e.g., when D-ribose constitutes a substantial fraction of total daily caloric intake) may complicate dosing of insulin or oral hypoglycemic agents. D-ribose levels likely do not register on a patient’s glucometer,¹ plasma glucose levels fall, creating the appearance of hypoglycemia, which can lead to inappropriate adjustment of a diabetic patient’s therapy. Therefore, we believe it is important to be able to instruct patients with diabetes mellitus how to monitor serum glucose level and adjust insulin when concomitant high pharmacologic doses of D-ribose are used. However, that would only be possible if patients’ glucometers reflected total metabolizable sugar.

The above mentioned trials are small and, for the most part, excluded diabetic patients; additional adverse events/reactions, such as clinically relevant hypoglycemia, could be possible, particularly for vulnerable disease populations. Two of the three cardiovascular

¹ We can find no direct comparison of responses to point-of-care glucometers to glucose and ribose, but saccharides are variably detected as glucose. Our strong suspicion is that ribose is generally not detected, because high exposure is reportedly associated with profound but asymptomatic hypoglycemia, and glucose dehydrogenase (the main basis for modern point-of-care glucometers) is not prominent in ribose metabolism.

trials excluded patients with diabetes mellitus/requiring insulin or oral hypoglycemic medications and did not appear to measure serum glucose levels (Omran et al., 2003; Sawada et al., 2009). The third trial (which did not report diabetes mellitus status or baseline glucose levels) instructed the patients not to take ribose while fasting (Pliml et al., 1992). Thus, published literature reports suggest that D-ribose can cause hypoglycemia, transaminase elevations, and uric acid elevations, but the data include few patients overall.

Similar to what is known with glucose, D-ribose has been reported to cause protein glycation. Theoretically, therefore, excess D-ribose could lead to microvascular and macrovascular complications, conditions known to be associated with elevated AGEs. This could be particularly problematic for patients with diabetes mellitus, who already suffer from complications of excess serum glucose and AGEs.

c. Pharmacokinetic data

Based on published studies (Thompson et al., 2013; Gross et al., 1989), orally administered D-ribose is rapidly and almost completely absorbed, with time to peak plasma concentration (t_{max}) ranging from 18-30 minutes in healthy subjects. The oral dose is limited by diarrhea occurring at doses higher than 200 mg/kg. More than proportional increase in D-ribose exposure is observed over the range of oral doses from 2.5 to 10 g, probably because of saturable metabolism.

Metabolism of D-ribose involves phosphorylation to D-ribose-5-phosphate, which undergoes further metabolism by pentose phosphate and glycolytic pathways. More than 80% of D-ribose in the systemic circulation is reported to be metabolized. The reported elimination half-life in healthy subjects is about 15-25 minutes. Excretion of D-ribose varied from 4-7% after oral dosing and up to 23% after intravenous administration. Food decreased bioavailability of D-ribose. A high-fat meal resulted in mean reductions in C_{max} and AUC of 43% and 41%, respectively, relative to fasting. A high-carbohydrate meal resulted in 69% and 65% reductions for C_{max} and AUC respectively.

A randomized, double-blind, cross-over study in healthy subjects showed that oral D-ribose can cause dose dependent reduction in blood glucose up to about 26 mg/dL on average (approximately 30% of baseline), occurring in 60 minutes post-dose (Sawada et al., 2009). The same study showed that the presence of food (high-fat or high-carbohydrate meal) did not influence the lowering of blood glucose compared to the fasting state. Blood glucose levels returned to baseline levels in about 2 hours.

C. The availability of alternative FDA-approved therapies that may be as safe or safer

D-ribose has not been proposed as an alternative to approved drugs, and its use would not likely interfere with patients receiving effective cardiovascular therapy. We note that many drug therapies have been approved for stable coronary artery disease, ischemic heart disease, and congestive heart failure. Approved drugs for chronic stable angina include beta-blockers, calcium channel-blockers, and nitrates. The approved drugs for

congestive heart failure include beta-blockers (e.g., carvedilol and metoprolol succinate), ACE inhibitors (e.g., enalapril), and angiotensin receptor blockers (e.g., valsartan, candesartan).

Conclusions: There is currently limited safety information on D-ribose use in patients with cardiovascular diseases, with or without diabetes mellitus. Hypoglycemia, detected with glucose monitoring, could complicate the titration of insulin in patients with diabetes, particularly when high pharmacologic doses of D-ribose and insulin are administered close in time.

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

In a number of small, short-term studies, D-ribose was studied as a metabolic agent, used as an adjunct to standard therapy, for improving cardiac function following stress or ischemia or for detecting viable myocardium following stress. This section focuses on the findings from the placebo-controlled trials, as described in Table 2, in patients with cardiac conditions (coronary artery disease, congestive heart failure).

A single-center, open-label study suggested that a 5-day oral course of D-ribose (60 g per day in four divided doses) appeared to improve endurance as assessed by treadmill exercise sessions in patients with stable coronary artery disease undergoing monitored exercise stress testing (Pliml et al., 1992). The mean treadmill walking time (in seconds) until 1 mm ST-segment depression was greater (276 vs. 223, $p=0.002$) on ribose than on placebo.

However, the treatment groups did not differ significantly in time to moderate angina (a specified symptom to stop the exercise test). Furthermore, the reading of the ECGs was not blinded; therefore, bias in reading the tracings cannot be ruled out. We believe that confirmation would be needed to establish whether D-ribose is effective for use as a drug for the treatment of coronary artery disease.

A single-center, feasibility study suggested that a 3-week course of D-ribose appeared to improve modestly some indices of diastolic dysfunction. However, the trial was exploratory, and did not specify a primary endpoint or control for multiplicity (Omran et al., 2003). Furthermore, although the quality of life (according to the SF-36 questionnaire) and physical function in New York Heart Association (NYHA) heart failure class II–III patients appeared to be improved by D-ribose, when compared to the baseline, similar effects were also observed in the placebo (dextrose) treatment group. A statistical analysis of the between-treatment group was apparently not performed, or was not reported. Therefore, clinically meaningful benefit of D-ribose as a drug product was not established.

Sawada and colleagues studied the ability of D-ribose to improve the contractile response of viable myocardium to dobutamine and to reduce stress-induced ischemia during dobutamine stress echocardiography (Sawada et al., 2009). The authors reported that D-ribose may improve the contractile response of segments with resting dysfunction to low dose dobutamine infusion; however, D-ribose did not significantly reduce the effects of

stress-induced ischemia. Pharmacokinetic data were not obtained. These findings are not sufficient to determine whether D-ribose can provide a clinical benefit.

Vijay and colleagues, citing their abstract in a 2008 letter to the editor published in the *Journal of Medicinal Food*, claimed that during submaximal cardiopulmonary exercise testing in patients with heart failure, D-ribose enhanced ventilatory efficiency, as evidenced by a 44% Weber functional class improvement (Vijay et al., 2008). This report is suggestive of a clinical benefit, but the results are inadequately reported.

Perkowski and colleagues, in another letter to the editor, reviewed the functional benefits of D-ribose in patients undergoing “off pump” coronary artery bypass procedures (Perkowski et al., 2007). Their cited primary studies/trials are either included in Table 2 and described above, or are only reported in abstract form, and thus provide limited information.

In summary, the reported studies of the utility of D-ribose for the treatment of cardiovascular disease provide no convincing evidence of a meaningful clinical benefit.

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

Ischemic heart disease and congestive heart failure are serious or life-threatening diseases/conditions.

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

The D-ribose nomination suggests the claim sought for D-ribose is a supplement to standard medical therapy. In the medical literature we reviewed, D-ribose is studied as a supplement to standard medical therapy for patients with congestive heart failure or stable coronary artery disease. Thus, D-ribose is not an *alternative* to any approved drug therapy.

Conclusions: The studies conducted are not sufficient to demonstrate D-ribose’s efficacy for any cardiovascular indications, based on both FDA’s review of the literature and from the data submitted in the nominations of D-ribose.

E. Has the substance been used historically in compounding?

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

It is not clear how many years D-ribose has been used in pharmacy compounding. According to searches of PubMed, EMBASE, and Web of Science databases, the earliest evidence of academic investigator sponsored studies of D-ribose in humans was 1946 (Wuest, et al., 1946). According to Pharmaprojects, in the 1990s, *ribose*² was studied in

² The terms ribose and D-ribose were used interchangeably prior to the 1990s.

an industry-sponsored clinical trial in the United States (Ribose, 2015). According to published literature, D-ribose has been in use as a dietary supplement, but it is difficult to determine when the use started. In addition to the aforementioned databases, searches of Westlaw, Ebscohost, Academic Search Complete databases suggest the earliest use of ribose as a dietary supplement was 1999 (R (Icon) Ribose Dietary Supplement, 1999; MN Bioenergy Ribose, 2009).

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

For the list of medical conditions D-ribose has been studied to treat, see section 2.2.2.3.

3. *How widespread its use has been*

It is difficult to assess from the medical literature the extent of D-ribose use in the United States or other countries for the treatment of medical conditions. According to articles identified by searching Westlaw and Natural Medicine databases, D-ribose is an ingredient in over 100 dietary supplement products (R (Icon) Ribose Dietary Supplement, 1999).

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

D-ribose is listed in the British pharmacopeia.

Conclusion: D-ribose appears to be widely used in dietary supplements. We have limited information about the extent of its use in compounded drug products.

III. RECOMMENDATION

We recommend that D-ribose *not* be included on the list of bulk drug substances allowed for use in compounding. D-ribose is well-characterized physically and chemically. Nevertheless, we based our recommendation on the lack of proven benefit associated with D-ribose as a drug product (separate from its use as an energy supplement/food additive), the potential safety concern of D-ribose use in the proposed target population, and the availability of safe and effective FDA-approved drug products which have undergone greater scientific scrutiny.

Although when used as a food ingredient, often in conjunction with additional carbohydrate consumption, D-ribose is generally recognized as safe, we believe that when used as a drug product, D-ribose may cause a false hypoglycemia if the dose constitutes a substantial fraction of total daily caloric intake. Because patients with diabetes mellitus often have concomitant coronary artery disease or ischemic cardiac myopathy/ischemic heart failure, the use of D-ribose as a drug product poses a potential safety concern in this population.

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DATE: February 9, 2016

FROM: Janet Maynard, MD, MHS
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products

THROUGH: Badrul Chowdhury, MD, PhD
Division Director
Division of Pulmonary, Allergy, and Rheumatology Products

TO: Pharmacy Compounding Advisory Committee

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

I. INTRODUCTION

D-ribose 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 heart disease and chronic fatigue syndrome. This consult will focus on the use of D-ribose for chronic fatigue syndrome. The term chronic fatigue syndrome will be used in this review because this is the term used in the nomination. Currently, FDA does not recognize a particular definition or name as appropriate for use in clinical trials of drug products for chronic fatigue syndrome (FDA Draft Guidance, 2014), which is also referred to as myalgic encephalomyelitis (ME) and systemic exertion intolerance disease (SEID).

We have reviewed available data on the safety and effectiveness of this substance for the proposed use for chronic fatigue syndrome. For the reasons discussed below, we **recommend** that D-ribose 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 for the proposed treatment of chronic fatigue syndrome.

II. EVALUATION CRITERIA

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

Conclusions: Please refer to the Division of Cardiovascular and Renal Products (DCRP) review. As noted in DCRP's consult, D-ribose is well-characterized physically and chemically.

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

1. *Nonclinical Assessment*

Conclusions: Please refer to the DCRP review.

2. *Human Safety*

- a. Human safety information, including reported adverse reactions, clinical trial assessing safety, or pharmacokinetic data.

Please refer to the DCRP review.

In the literature, there is one open-label uncontrolled study of D-ribose in 41 patients with fibromyalgia and/or chronic fatigue syndrome (Teitelbaum et al., 2006). No other studies of the safety or effectiveness of D-ribose were identified in the searched database (PubMed). In general, D-ribose appeared generally well-tolerated. Of the five patients that did not complete the study, three discontinued due to adverse events including “hyperanxious feeling (one patient), lightheadedness (one patient), and increased appetite (one patient).” Two patients decided not to begin the study. Of the remaining 36 patients who completed the study, one patient experienced transient nausea and another felt mild anxiety. Both of these reactions resolved by lowering the dose of D-ribose.

As discussed in its review, DCRP identified false hypoglycemia as a safety concern, especially in patients with diabetes mellitus who often have concomitant coronary artery disease or ischemic cardiomyopathy/ischemic heart failure. While patients with chronic fatigue syndrome may also have concomitant diabetes mellitus, risk/benefit considerations in chronic fatigue syndrome are influenced by the lack of currently approved therapies indicated for this serious disease. The Division of Metabolism and Endocrinology Products (DMEP) was consulted regarding the safety concerns related to administration of D-ribose and hypoglycemia. As discussed in DMEP’s review, it is unclear whether there is a maximum daily dose of D-ribose beyond which alterations in blood glucose are seen. In addition, there was insufficient information to make definitive conclusions with regard to risk for clinically relevant hypoglycemia and with regard to the potential for complicating management of patients with diabetes.

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

There are no approved therapies indicated for the treatment of chronic fatigue syndrome and there is significant unmet medical need for patients with chronic fatigue. Numerous therapies are used off-label for the treatment of chronic fatigue syndrome.

Conclusions: While false hypoglycemia could be a safety concern, there is insufficient information to determine the extent of the risk for clinically relevant hypoglycemia or the potential for complicating management of patients with diabetes.

C. Are there concerns about whether a substance is effective for chronic fatigue syndrome?

1. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance for chronic fatigue syndrome

As discussed above, an open-label uncontrolled pilot study was performed to evaluate the use of D-ribose in patients with fibromyalgia and chronic fatigue syndrome (FDA Draft Guidance, 2014). Forty-one adult patients, diagnosed by their physicians as having fibromyalgia (by American College of Rheumatology Criteria) and/or Chronic Fatigue Syndrome (by CDC criteria) were enrolled. Patients received 5 grams of D-ribose (CORvalen) three times per day mixed with food, water, or another beverage until the 280 gram container was empty. Outcome measures were assessed using discrete Visual Analogue Scale questions (DVAS) pre- and post-intervention. Measured parameters included energy levels, sleep disturbances, mental clarity, pain, and overall sense of well-being. Each parameter was assessed on a 1 to 10 scale, with 1 being the worst and 10 being the best. Of the 41 patients enrolled in the study, five patients were excluded from analyses because they were considered noncompliant. Of the 36 remaining patients, the average age was 48 years, 78% were female, 75% had fibromyalgia, and 58% had chronic fatigue syndrome. The average duration of D-ribose therapy was 28 days, with a range from 17 to 35 days. The authors reported significant improvements in energy levels, sleep patterns, mental clarity, pain threshold, and patient's state of well-being when comparing questionnaires at enrollment and at the completion of the study in all patients (Table 1). When evaluating the efficacy results by underlying diagnosis, the nine patients with chronic fatigue syndrome noted improvement on the measured parameters (Table 2). Of the 35 patients completing the assessment of overall subjective feelings, 23 (65.7%) experienced improvement during the course of the study (somewhat better to much better) while taking D-ribose.

Table 1: Pre- and Post-Ribose Assessments: All Patients

TABLE 2. PRE- AND POSTRIBOSE ASSESSMENTS: ALL PATIENTS

Category	N	Pre mean (std)	Post mean (std)	Difference (95% CI)	p-Value
Energy level	36	3.8 (1.1)	5.5 (1.5)	1.7 (1.1, 2.2)	<0.0001
Sleep	36	4.8 (1.6)	6.0 (1.9)	1.2 (0.6, 1.7)	0.0001
Mental clarity	36	4.9 (1.5)	5.7 (1.7)	0.8 (0.3, 1.3)	0.003
Pain	36	4.9 (2.3)	5.6 (2.2)	0.7 (0.1, 1.3)	0.026
Well-being	36	4.3 (1.3)	5.6 (1.5)	1.3 (0.8, 1.9)	<0.0001

CI, confidence interval.

Source: Teitelbaum et al., 2006.

Table 2: Pre- and Post-Ribose Assessments Per Diagnosis

TABLE 3. PRE- AND POSTRIBOSE ASSESSMENTS PER DIAGNOSIS

Category	FMS (N = 15)			CFS (N = 9)			Both FMS/CFS (N = 12)		
	Pre mean (std)	Post mean (std)	Improvement (%)	Pre mean (std)	Post mean (std)	Improvement (%)	Pre mean (std)	Post mean (std)	Improvement (%)
Energy	3.7 (1.0)	5.5 (1.5)	1.8 (48%)	4.2 (1.4)	6.1 (1.5)	1.9 (45%)	3.7 (1.2)	4.9 (1.4)	1.2 (32%)
Sleep	4.4 (1.2)	5.9 (1.6)	1.5 (34%)	5.6 (1.7)	7.2 (1.7)	1.6 (29%)	4.8 (1.9)	5.2 (2.2)	0.4 (8%)
Mental clarity	4.7 (1.0)	5.7 (1.8)	1.0 (21%)	5.2 (2.0)	6.6 (1.7)	1.4 (27%)	5.1 (1.7)	5.1 (1.3)	0
Pain	4.5 (2.3)	5.5 (2.0)	1.0 (22%)	6.7 (2.3)	7.8 (1.6)	1.1 (16%)	4.1 (1.6)	4.1 (1.2)	0
Well-being	4.1 (1.0)	5.7 (1.5)	1.6 (39%)	4.6 (1.7)	6.3 (1.2)	1.7 (37%)	4.3 (1.3)	5.0 (1.5)	0.7 (16%)

FMS, fibromyalgia; CFS, chronic fatigue syndrome.

Source: Teitelbaum et al., 2006.

Importantly, there was no control group, thus limited conclusions are possible from the data given the lack of comparator. Further, the number of patients with chronic fatigue syndrome was small and the clinical interpretation of the numerical changes is unclear.

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

Chronic fatigue syndrome is a serious condition.

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

There are no approved therapies indicated for the treatment of chronic fatigue syndrome.

Conclusions: There are limited data available from an open-label uncontrolled study of D-ribose in 41 adult patients with chronic fatigue syndrome and/or fibromyalgia. Given

the lack of control group, limited conclusions are possible from these data. Thus, the efficacy of D-ribose in chronic fatigue syndrome is unclear.

D. Has the substance been used historically in compounding?

Conclusions: Please refer to the DCRP review.

III. RECOMMENDATION

We **recommend** that D-ribose 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 for the proposed use for chronic fatigue syndrome. As noted in DCRP's review, D-ribose is well-characterized physically and chemically, and there is limited information available about its historical use in compounded drug products (as opposed to its use as a dietary supplement). When used as a food ingredient, D-ribose is generally recognized as safe. As noted in DCRP's review, false hypoglycemia could be a safety concern, especially in patients with diabetes mellitus who often have concomitant coronary artery disease or ischemic cardiomyopathy/ischemic heart failure. This safety concern was also reviewed by DMEP, which concluded that there is insufficient information to make definitive conclusions with regard to risk for clinically relevant hypoglycemia and with regard to the potential for complicating management of patients with diabetes. While patients with chronic fatigue syndrome may also have concomitant diabetes mellitus, risk/benefit considerations in chronic fatigue syndrome are influenced by the lack of currently approved therapies indicated for this serious disease. While the efficacy of D-ribose for chronic fatigue syndrome is unclear, it is used by some patients for treatment of the symptoms associated with chronic fatigue syndrome.

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Teitelbaum JE, Johnson C, St. Cyr J. The Use of D-Ribose in Chronic Fatigue Syndrome and Fibromyalgia: A Pilot Study. *J Altern Complement Med* 2006; 12:857-862.



DATE: February 5, 2016

FROM: William H. Chong, MD, Clinical Team Leader
Division of Metabolism and Endocrinology Products

THROUGH: Jean-Marc Guettier, MD, CM
Division Director, Division of Metabolism and Endocrinology Products

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Secondary Consult of D-ribose

I. INTRODUCTION

Ribose (D), also known as D-ribose, 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 heart disease and chronic fatigue syndrome. The substance has been evaluated by the Office of Pharmaceutical Quality, the Division of Cardiovascular and Renal Products (DCRP), and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP).

As part this evaluation, DCRP raised safety concerns about a possible association between administration of the substance and hypoglycemia. In particular, DCRP raised concerns that D-ribose might complicate the management of diabetes mellitus.

In light of the information in DCRP's and DPARP's reviews, the Division of Metabolism and Endocrinology Products (DMEP) was asked to consider and respond to the following:

1. What daily dose of D-ribose would complicate dosing of insulin or oral hypoglycemic agents?
2. What would the division recommend as the maximum daily dosage of D-ribose for patients with hypoglycemia?
3. What data are available to support a specified maximum daily dose of D-ribose?

II. DISCUSSION

D-ribose is a pentose sugar that has been nominated for use in compounding as an oral supplement in the treatment of heart disease and chronic fatigue syndrome. Decreases in blood glucose associated with administration of D-ribose were first reported in 1957 (Segal et al., 1957). This decrease may be dose-dependent (Gross et al., 1991). Despite this long-recognized association, the mechanism by which this occurs is unclear. Potential proposed mechanisms include slowing of glycogenolysis (either from inhibition of glycogen phosphorylase due to increases in adenosine triphosphate (ATP) or competition for phosphoglucomutase) or increases in insulin levels (Segal, 1958). In all of the reported studies, these findings have been asymptomatic (i.e., no symptoms of hypoglycemia were reported). A possible explanation for the absence of symptoms could be the use of ribose as an alternative substrate for metabolism, as ribose can be converted to glucose (Segal et al., 1958; Hiatt, 1958).

A. Studies Related to Risk of Hypoglycemia with Administration of D-ribose

1. 2008 GRAS Notice and Related Studies

D-ribose was the subject of a GRAS (Generally Recognized as Safe) determination for use as a food ingredient in 2008 (Bioenergy GRAS Exemption Claim, 2008; FDA Agency Response Letter GRAS Notice, 2008) at which time the FDA concluded that:

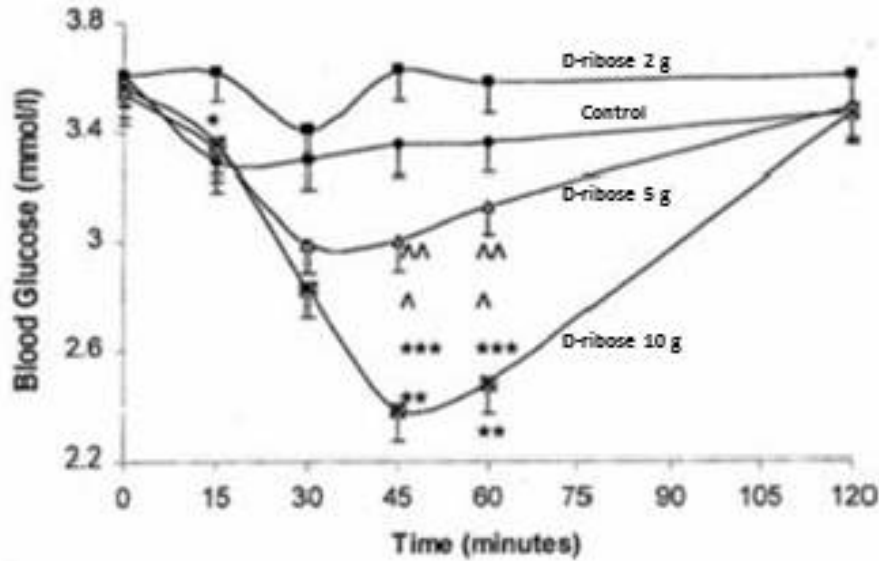
Based on the information provided by Bioenergy, as well as other information available to FDA, the agency has no questions at this time regarding Bioenergy's conclusion that D-ribose is GRAS under the intended conditions of use provided that D-ribose is used in conjunction with an additional carbohydrate energy source. The agency has not, however, made its own determination regarding the GRAS status of the subject use of D-ribose. As always, it is the continuing responsibility of Bioenergy to ensure that food ingredients your firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

The GRAS Notice submitted by Bioenergy states that the findings of decreased blood sugar with D-ribose administration were seen only ≥ 10 g/dose when administered orally and that these findings were typically transient (resolving within 2 hours of ingestion). At ≤ 5 g/dose, no statistically significant change in blood glucose was seen.¹ Furthermore, they state that in studies where D-ribose was administered in combination with a glucose source, no decrease in blood glucose was seen.²

¹ Though this is discussed in the GRAS Notice, this does not appear to be publicly available data and a publication of these findings could not be located.

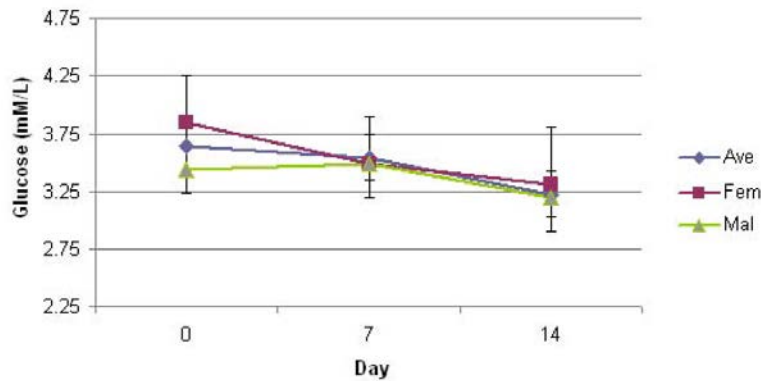
² Though it is discussed in the GRAS Notice, information on blood glucose does not appear in the publication that appears to be associated (Sawada S, et al. "Evaluation of the anti-ischemic effects of D-ribose during dobutamine stress echocardiography: a pilot study". *Cardiovascular Ultrasound*. 2009; 7:5).

As noted in the preceding paragraph, in the GRAS Notice, there is a statement that no statistically significant change in blood glucose was seen when D-ribose was administered at doses of ≤ 5 g/dose. This appears to be based on data presented at a conference. A publication that appears to be related (Fenstad et al., 2007) presents these findings concluding that there is no apparent difference compared to control with D-ribose at 2 g/dose and 5 g/dose (see below).



Source: Adapted from Figure 1 of Fenstad, et al., 2007

Another related publication (Seifert et al., 2008) reports the impact of oral D-ribose at doses of 10 g twice daily on fasting blood glucose at day 7 and 14 after starting treatment (see below). No statistically significant difference was seen at either time point compared to baseline, though there was a downward trend. This publication makes statements similar to those found in the GRAS Notice with regard to the transient effect on blood glucose and absence of effect at ≤ 5 g/dose, and it references the same abstract.



Source: Figure 1 of Seifert et al., 2008

2. Other Studies

Regarding the “no observed effect” level, in a study of healthy volunteers administered doses of 7 g D-ribose before and after exercise, no observed difference in glucose levels

was seen compared to placebo out to 85 minutes after the dose (see below) (Seifert et al., 2009). Whether this would remain true if subjects had been followed longer is unknown.

Arm, metabolite	Time (minutes)					
	0	8	16	24	55	85
Ribose						
UA (mg/dL)	4.23 ± 0.2	4.35 ± 0.2	4.58 ± 0.2	4.58 ± 0.2	4.65 ± 0.2	4.94 ± 0.2
Lactate (mM/L)	1.6 ± 0.4	6.6 ± 0.4	8.3 ± 0.4	8.9 ± 0.4	3.1 ± 0.4	2.3 ± 0.4
Glucose (mM/L)	3.6 ± 0.3	3.2 ± 0.3	3.6 ± 0.3	3.6 ± 0.3	4.1 ± 0.3	2.9 ± 0.3
Placebo						
UA (mg/dL)	4.37 ± 0.2	4.58 ± 0.2	4.69 ± 0.2	4.77 ± 0.2	4.83 ± 0.2	4.77 ± 0.2
Lactate (mM/L)	1.9 ± 0.4	6.8 ± 0.4	8.6 ± 0.4	9.2 ± 0.4	3.3 ± 0.4	2.1 ± 0.4
Glucose (mM/L)	3.1 ± 0.3	3.2 ± 0.3	3.6 ± 0.3	3.6 ± 0.3	4.1 ± 0.3	3.5 ± 0.3

Data are mean ± SD values.

Source: Table 1 of Seifert JG, et al. 2009

In considering these data, it is important to note that the majority of the study subjects in the published studies of D-ribose did not have diabetes mellitus. Given the already-present, impaired regulation of glucose seen in diabetes mellitus, it is possible that the observed effect may be different.

In the 1957 study originally describing the observed decrease in blood glucose with D-ribose (Segal et al., 1957), doses of 10-20 g of D-ribose were infused intravenously over 10-25 minutes. There were three patients with diabetes mellitus (presumably Type 1 Diabetes Mellitus (T1DM) as they were treated with insulin) in that paper, and the response of blood glucose to D-ribose infusion was similar (decreased blood glucose) though the percent decrease was much less (3-11% in patients with diabetes vs. 16-65% in healthy volunteers). The time of blood glucose nadir was much sooner in two of the patients with diabetes (< 20 minutes after ingestion) compared to a range of 30-90 minutes in the healthy volunteers and the third patient with diabetes. Of note, the patients with diabetes mellitus were off insulin therapy for 24 hours, thus the blood glucose values were markedly elevated (> 250 mg/dL). Also, though the percent change was attenuated in the patients with diabetes mellitus, the absolute change in blood glucose was of a similar magnitude in the two populations (range of 14-32 mg/dL in patients with diabetes vs. 11-41 mg/dL in healthy volunteers).

A separate study looked at the effect of D-ribose infusion on blood glucose in patients with diabetes (again, presumably T1DM) (Bierman et al., 1959). In this study, patients with diabetes mellitus received an infusion of 50 g D-ribose over 1 hour. The mean change in blood glucose was -21%, and the nadir was between 1 to 3 hours after the start of the infusion (see below). No symptoms of hypoglycemia were reported. The authors conclude that the changes were similar to that seen by Segal et al., (1958) and they conclude that the response is the same in patients with and without diabetes. It should be noted that the dose used in this study was substantially higher than that used by Segal et al. (1958). If the change in glucose is dose-dependent, then it is inappropriate to accept this conclusion.

Subject	Sex	Age	Weight (kg.)	Insulin dose (units/ day)	Initial value (mg. per cent)	GLUCOSE			
						Per cent change Hours			
						1	2	3	4
(A) Mild diabetic									
1	M	42	79	0	87	-1	-45	-46	-33
2	M	46	92	35	140	13	-11	-16	-1
3	M	47	96	15	149	0	-6	-13	-13
4	M	48	74	0	162	-9	-19	-17	-19
(B) Severe diabetic									
5	F	16	39	60	200	-15	-15	-14	-6
6	F	36	50	80	188	-20	-14	-5	-13
7	M	17	78	100	226	-9	-17	-12	-
8	M	30	80	60	129	+5	0	+9	+9

*Dose = 50 gm. in all cases except Subject No. 5, 40 gm.

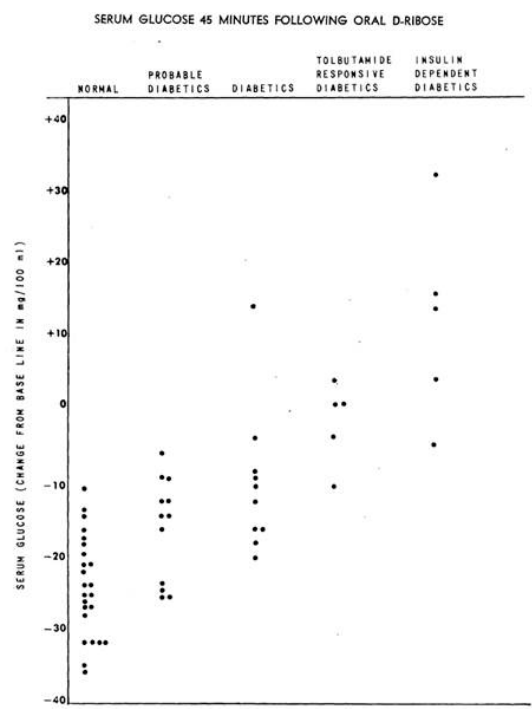
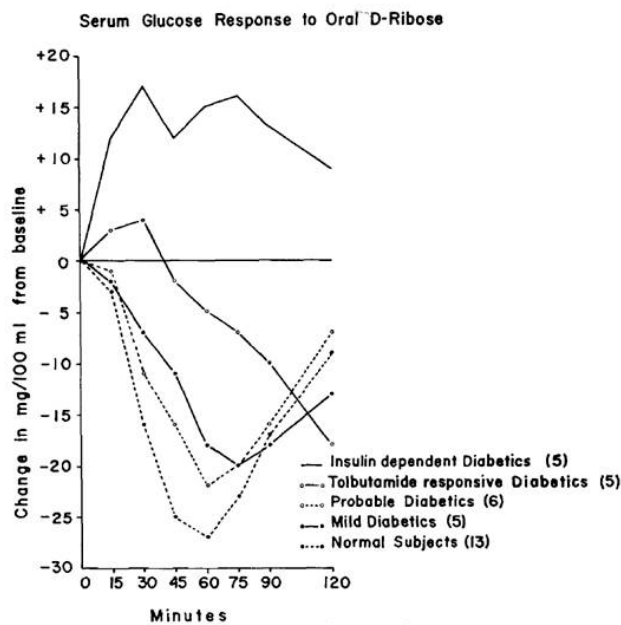
Source: Table 1 of Bierman et al., 1959

Oral administration of D-ribose in patients with diabetes has also been studied (Steinberg et al., 1970). In this study, 15 g of D-ribose was administered orally in study subjects divided into 5 categories:

1. Normals – based on peak blood glucose < 160 mg/dL and 2-hour blood glucose < 110 mg/dL on oral glucose tolerance test (OGTT)³
2. Probable diabetics – based on 1-hour blood glucose \geq 160 mg/dL 90-minute blood glucose \geq 135 mg/dL, and 2-hour blood glucose 110-120 mg/dL on OGTT
3. Mild diabetics – based on 1-hour blood glucose \geq 160 mg/dL and 2-hour blood glucose \geq 110 mg/dL on OGTT and not being treated
4. Patients with known diabetes responsive to tolbutamide (i.e., Type 2 Diabetes Mellitus (T2DM))
5. Insulin dependent diabetics (i.e., T1DM)

The authors noted that the decrease in blood glucose was not observed in subjects with insulin dependent diabetes (i.e., T1DM), altered in patients with diabetes treated with tolbutamide (i.e., T2DM), and attenuated in the probable and mild diabetics compared to the “normal” subjects (see below).

³ OGTT involved 300 g carbohydrate/day diet (plus other sources of calories) for \geq 3 days followed by administration of 7 ounces of Glucola (approximately 52.5 g glucose).



Serum glucose response to oral d-ribose at forty-five minutes

	Decrease at 45 min. in mg./100 ml.		Per cent decrease at 45 min.		p value
	Mean	S.E.M.	Mean	S.E.M.	
Normals	24	1.5	37	2.4	
Probable diabetics	16	2.1	25	3.2	0.005
Mild diabetics	11	2.5	18	3.2	0.001
Tolbutamide-responsive	2	2.1	2	2.0	0.001
Insulin-dependent	(+) 12	6.3	(+) 7	3.4	0.0001

Source: Adapted from Figure 1, Figure 2, and Table 1 of Steinberg et al., 1970

From this limited pool of data, it is unclear whether the blood glucose response to D-ribose would be expected to be the same in patients with diabetes versus those without diabetes. The data suggests that the responses may be different.

3. Conclusions Based on These Studies

Based on the reviewed literature, it is unclear whether the use of D-ribose would result in transient decreases in blood glucose in patients with diabetes. If the statements made in the GRAS Notice are accepted at face value, it appears that doses of ≤ 5 g/dose should not be associated with decreases in blood sugar, and that administration with food may also prevent any transient decreases in blood glucose. Results from a small study in healthy volunteers suggest that there would be no difference in blood glucose compared to placebo at doses of 7 g/dose. Due to the paucity of studies examining the effects of ribose administration in diabetic populations, it is unclear whether these observations can be directly translated to patients with diabetes.

Despite the consistent laboratory finding of decreased blood glucose after administration of D-ribose, it is important to note that the description of these events does not suggest

that they are clinically meaningful (i.e., they are asymptomatic). The clinical relevance of low blood glucose values in the absence of symptoms is unclear.

B. Risk of Ribosylation

The potential for changes in measured blood glucose is not the only factor to consider with regard to potential complication of diabetes management with D-ribose. As noted in the DCRP review, there is evidence to suggest that exposure to D-ribose can cause glycation of various proteins (i.e., ribosylation) (Wei et al., 2012). This is a concern for a few reasons. First, whether the presence of ribosylated proteins increases the risk for adverse clinical outcomes is unknown. However, as noted in the DCRP review, advanced glycation end products are generally associated with adverse effects. Second, it is unclear whether ribosylation of hemoglobin would occur and whether it complicates monitoring of glycemic control. This is important as management of diabetes mellitus relies upon measurements of HbA1c (a form of hemoglobin glycosylated by glucose [i.e., glycosylated]) to inform healthcare providers with regard to average blood glucose control for the preceding three months.

HbA1c is defined as the fraction of beta-chains of hemoglobin with a stable hexose (i.e., glucose) adducted to the N-terminal valine. It is typically expressed as a percentage of total hemoglobin. While the presence of ribosylated hemoglobin could in theory directly affect measurements of HbA1c, DMEP believes that this would be unlikely since current assays are fairly specific in identifying glycosylated hemoglobin. Notably, other glycosylated hemoglobins have been described (e.g., HbA1a1 [fructose 1, 6-diphosphate at N-terminal valine], HbA1a2 [glucose 6-phosphate at N-terminal valine], HbA1b [pyruvic acid at the N-terminal valine]) and glycation can occur at other sites of the beta-chain of hemoglobin, and current assays for HbA1c do not register these other forms (Sacks, 2012). We have no reason to believe that ribosylated hemoglobin would be different.

Conclusions: There is insufficient information to make definitive conclusions with regard to risk for clinically relevant hypoglycemia and with regard to the potential for complicating management of patients' diabetes.

III. DMEP RESPONSE TO QUESTIONS

1. What daily dose of D-ribose would complicate dosing of insulin or oral hypoglycemic agents?

There is insufficient information to determine whether the use of D-ribose would complicate dosing of insulin or other anti-diabetic drugs or what dose might complicate dosing. The available information suggests that administration D-ribose may acutely and transiently lower circulating glucose without causing symptoms in healthy volunteers and that chronic oral dosing of up to 20 g/day has no impact on circulating glucose in healthy adults. The effect of D-ribose in healthy volunteers appears dependent on dose. The influence of nutritional state (fasting/fed), disease state and co-administered drugs on the glucose lowering potential of D-ribose is either not addressed at all or inadequately addressed in the available literature.

The majority of the published studies were not performed in patients with diabetes mellitus. From the limited information in patients with diabetes, it appears that the glucose response may not be the same as in non-diabetics. However, these studies were performed in patients who were taken off therapy, and this may not be informative for what would be seen with concomitant therapy (whether insulin or other antidiabetic agents). Whether alterations in measured blood glucose would occur in patients with diabetes is unknown.

Whether the observed glucose lowering effects (if any) would result in inappropriate changes to a patient's antidiabetic regimen, would be dependent on the type of regimen and the frequency of self-monitored blood glucose (SMBG) readings, since it appears that these changes in blood sugar did not result in clinical signs or symptoms. In patients who are treated with basal-bolus insulin or insulin pump therapy and who routinely check blood glucose values multiple times a day, in theory, there may be errors in adjusting insulin dose. There is insufficient information to know whether this would be a problem for these patients. This would be dependent upon the timing between ingestion of D-ribose and SMBG, and whether ingestion of D-ribose has an effect on blood glucose in patients with diabetes. Assuming a response similar in observations seen in fasting, healthy volunteers, the concern is not one of hypoglycemia, but one of inadequate glycemic control. As HbA1c values should remain informative for guiding changes in therapy, this is not a significant concern. In patients with type 2 diabetes mellitus who may only be on oral antidiabetic agents and may not be performing daily or multiple daily SMBG readings, the observed effect on blood glucose may not impact dosing or adjustment of medications at all, as it appears to be seen predominantly in healthy adults subject to a fast, and appears transient and not associated with symptoms.

Though administration of D-ribose may impact blood glucose levels, we do not believe that it would impact measurements of HbA1c, which is used to guide treatment recommendations. For the majority of patients with diabetes (particularly patients with T2DM), HbA1c would be the primary guide for adjustment of therapy and transient changes in measured blood glucose would not be expected to play a major role in adjustments of therapy. Discrepancies between SMBG readings and measured HbA1c (if any) in the remaining patients should hopefully lead to further investigation by healthcare providers and identification of D-ribose as an issue.

2. What would the division recommend as the maximum daily dosage of D-ribose for patients with hypoglycemia?

It is unclear whether there is a maximum daily dose of D-ribose beyond which alterations in measured blood glucose are seen. The most conservative approach would be to use a daily maximum of 20 g/day (Seifert et al., 2008). Based on the available data (Seifert et al., 2009) it may also be reasonable to use a maximum of 7 g/dose, as doses of D-ribose below this do not appear to result in changes in blood glucose values. However, given the absence of symptoms, such a limit may be overly conservative. A more liberal approach would be to place no limit as none of the

changes in blood glucose appear to be clinically relevant. Alternatively, if the statements made in the 2008 GRAS Notice are accepted as true, then the available data suggest that concomitant administration with carbohydrates attenuates the observed effect on blood glucose. Recommending consumption with food may be an alternative option.

3. What data are available to support a specified maximum daily dose of D-ribose?

The support for the recommendation in our response to Question 2 comes from statements made by Bioenergy in the GRAS notice and small studies in healthy subjects. See the discussion under section II.A. above for details.

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DATE: February 5, 2016

FROM: Charles J. Ganley, M.D.
Director, Office of Drug Evaluation IV
Office of New Drugs
Center for Drug Evaluation and Research

THROUGH: John Jenkins, M.D.
Director, Office of New Drugs
Center for Drug Evaluation and Research

TO: Pharmacy Compounding Advisory Committee

SUBJECT: D-Ribose for 503A Bulk Drugs Compounding List

I. 503A Bulk Drug Substances List

The Office of New Drugs (OND) has evaluated reviews and recommendations from the Division of Cardio-Renal Products (DCRP), the Division of Pulmonary and Allergy Drug Products (DPARP), and the Division of Metabolic and Endocrine Products (DMEP) regarding the nomination of D-ribose for the list of bulk drug substances that can be used to compound under section 503A of the Federal Food, Drug, and Cosmetic Act (the 503A bulks list).

Fagron¹ submitted a nomination for oral D-ribose to be placed on the list of bulk drug substances that can be used to compound under the 503A bulks list. Their nomination identified oral capsules containing 500 - 750 mg of D-ribose as the anticipated compounded dosage forms for use in the treatment of “heart disease” and “chronic fatigue syndrome” (CFS).

II. Reviews Conducted by OND Review Divisions

DCRP evaluated D-ribose for use in heart disease and recommends that D-ribose not be placed on the list based on lack of evidence of clinical efficacy. In addition, they identified reports of the occurrence of asymptomatic hypoglycemia, as well as false hypoglycemia as a potential safety consideration for patients with heart disease and concomitant diabetes mellitus.

DPARP reviewed the use of D-ribose in the treatment of CFS and recommends that D-ribose be placed on the list based on several factors. The review finds that the reported

¹ Fagron is a St. Paul, Minnesota based firm that sells compounding supplies worldwide, including bulk drug substances and related equipment and materials.

efficacy of D-ribose in CFS is based on data from a single unblinded, uncontrolled study (Teitelbaum et al., 2006), a study design generally considered to limit the ability to adequately interpret the results. DPARP finds, however, that the lack of approved therapy for CFS, a serious condition, creates an unmet medical need for CFS therapy.

DMEP further evaluated the safety concerns identified by DCRP regarding the reported occurrence of asymptomatic hypoglycemia and the production of advanced glycation end-products (AGEs). DMEP concluded that there was insufficient information to make a definitive conclusion regarding the risk for clinically significant hypoglycemia or the likelihood of d-ribose related hypoglycemia impacting the management of patients with diabetes mellitus.

Because of the disparate recommendations of DCRP and DPARP on whether D-ribose should be placed on the list, the Director of OND ODEIV reviewed the information in the division reviews from DCRP, DPARP and DMEP and is making a recommendation that, with the concurrence of the Director of OND will represent the position of OND as to whether D-ribose should be included on the 503A bulks list.

III. Evaluation Criteria

Four criteria have been developed for evaluating whether a substance should be included on the 503A bulks list:

- 1) The physical and chemical characterization of the substance;
- 2) 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;
- 3) Any safety issues raised by the use of the substance in compounded drug products; and
- 4) The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists.

To reach an overall recommendation regarding whether D-ribose should be added to the list of bulk drug substances that may be used in compounding under section 503A, OND considered the information presented in the three reviews that accompany this document and each of the four criteria described above.

Physical and Chemical Characterization

The Office of Pharmaceutical Quality review has identified that there are no chemistry or physical characterization issues that would preclude D-ribose from being compounded.

Historical Use of the Substance

DCRP's review identified that there were academic investigator sponsored studies beginning the 1940s, but more widespread use of D-ribose as a dietary supplement began in the 1990s. While there are single ingredient and multiple ingredient dietary

supplement products containing D-ribose sold by compounding pharmacies, no evidence was found of the creation of drug products in pharmacies, based on a physician's prescription for the treatment of heart disease or chronic fatigue syndrome. Therefore, we conclude that there is not a history of this ingredient compounded as a drug.

Nonclinical and Clinical Safety

DCRP's review of nonclinical published literature did not identify many of the standard toxicology studies required for evaluation of drugs for FDA approval. However, the available animal data do not raise significant concerns. D-ribose is considered by FDA as Generally Recognized as Safe (GRAS) for use as a food additive, based on an assessment using a different process than the drug approval process.

DCRP's review identified that D-ribose has been studied in four short term controlled clinical trials, one that include healthy individuals (Seifert et al., 2008) and three that included patients with cardiovascular disease (Sawada et al., 2009; Omran, et al., 2003; Pliml et al., 1992). Among these trials, the most frequently reported adverse events were asymptomatic hypoglycemia, diarrhea/hyperperistalsis/loose stool, gastrointestinal discomfort or nausea. Laboratory abnormalities included elevations in uric acid, aminotranferases and gammaglutamyl transpeptidase. DPARP did not identify additional safety concerns specific to use of D-ribose in CFS.

DMEP's review of the occurrence of asymptomatic hypoglycemia concluded that there is insufficient information to make definitive conclusions regarding the risk for clinically significant hypoglycemia in healthy or diabetic patients. OND finds that in the absence of additional data to more thoroughly characterize this risk, we are unable to fully assess the relevance of this concern or to dismiss it. Additionally, the DCRP and DMEP reviews described the production of AGEs with D-ribose, which could lead to toxic effects with long term use. Further evaluation would be needed to assess the safety of D-ribose treatment of chronic diseases such as heart disease and CFS.

Overall, OND concludes that while the existing data do not demonstrate that substantial clinical safety considerations have been shown for D-ribose, there are insufficient data to fully assess the safety profile of D-ribose when used for treatment of a clinical disease or disorder.

Available Evidence of Effectiveness or Lack of Effectiveness

Areas of therapeutic use were evaluated consistent with the nomination, including heart disease and CFS. DCRP's review emphasized the placebo-controlled trials found in the literature (Sawada et al., 2009; Omran, et al., 2003; Pliml et al., 1992). It is noted that in the Sawada (2009) study, D-ribose was administered intravenously, while in the other studies D-ribose was given orally consistent with the 503A bulks list nomination. OND concurs that the design of these trials was inadequate (short term, unblinded, small numbers of subjects), per the DCRP review, to establish efficacy of D-ribose in the treatment of coronary artery disease, with or without congestive heart failure, or ischemic cardiomyopathy.

Regarding the efficacy of D-ribose in the treatment of CFS, DPARP reviewed the single study evaluating the use of D-ribose in CFS published in a peer-reviewed journal (Teitelbaum et al., 2006). DPARP considered the study supportive of the potential efficacy of D-ribose in the treatment of CFS. After assessing the details of the study's significant design and conduct limitations, OND finds that no scientific conclusions can be drawn from the study. The authors describe it as a "pilot study." It uses an open label design, so enrolled patients were aware that they were receiving D-ribose. The study did not employ a control (e.g., a placebo comparator), so changes in study endpoints values could not be assessed relative to another therapy or to no treatment. Of the 41 patients enrolled, 5 were considered noncompliant and excluded from the analyses. The 36 remaining patients self-reported having been previously diagnosed by their physician as having: CFS (n = 9) as assessed by CDC criteria (CDC's Chronic Fatigue Syndrome, accessed 2016); fibromyalgia (n = 15), or both CFS and fibromyalgia (n = 12). Visual analogue scales were used to assess scores for energy, sleep, mental clarity, pain and sense of well-being. There were no objective measures evaluated. Although statistically significant improvements in mean scores were reported among the group of 36, there were no statistically significant improvements in mean scores among the patients who were believed to have CFS, the indication for which D-ribose has been nominated. In general, this study's design cannot rule out evaluation bias, particularly in patients' self-rating of study endpoints including subjective symptoms such as "energy level" and "overall sense of well-being."

Overall, OND finds that this single, pilot study does not provide any evidence of effectiveness for treatment of CFS. Due to the trial's significant design limitations (uncontrolled, unblinded), inclusion of a small number of patients with CFS, and lack of comparator on which to base interpretation of changes in visual analogue scores, particularly those specific to CFS patients, OND finds that this study does not serve as a demonstration of the efficacy of D-ribose in the treatment of CFS and does not support the addition of D-ribose to the 503A bulks list.

IV. Weighing of the Four Criteria and OND Recommendation

Overall, OND recommends that D-ribose not be placed on the 503A bulks list.

- D-ribose has been found to be physically and chemically suitable for compounding;
- D-ribose has been marketed as a dietary supplement and food additive, but we are not aware of a history of it being compounded as a drug;
- Studies that have been conducted with D-ribose in heart disease and CFS have not provided sufficient evidence of efficacy to support its addition to the list; and
- While no clinically substantive safety concerns have been definitively identified or ruled out, additional information needs to be obtained to more fully characterize the safety of D-ribose, particularly related to asymptomatic hypoglycemia and the production of AGEs in the treatment of chronic disease.

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Tab 5

Chondroitin Sulfate

Tab 5a

Chondroitin Sulfate
Nominations

Submitted electronically via www.regulations.gov

March 4, 2014

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

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

Dear Sir or Madam:

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

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

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

In addition to the IACP spreadsheet of bulk drug substances referenced above, NCPA would also like to formally submit collectively for review and consideration of the FDA Pharmacy Compounding Advisory Committee the drugs and standards contained within the *British Pharmacopeia*, the *European Pharmacopeia* and the *Japanese Pharmacopeia*. NCPA respectfully requests that all drugs and standards contained within these three pharmacopeias for which no USP corresponding monograph exists be accepted and approved to be used for the preparation of compounded medications under section 503A of the *Federal Food, Drug and Cosmetic Act*.

NCPA is requesting the recognition of these pharmacopoeias as there are examples of situations when our members need access to these alternative compendia for monograph information. NCPA members may receive requests to compound medications that do not have a USP monograph, nor is the drug substance being used a component of an FDA approved drug product. When these situations arise, the *British Pharmacopeia*, the *European Pharmacopeia* and the *Japanese Pharmacopeia* are used in practice to ensure compounds are made with the highest assurance of quality.

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

Sincerely,

A handwritten signature in black ink, appearing to read "Steve Pfister", with a long horizontal flourish extending to the right.

Steve Pfister
Senior Vice President, Government Affairs

Attachment

National Community Pharmacists Association Chondroitin Sulfate 503A Nomination

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
Chondroitin sulfate	chondroitin sulfate	Chondroitin Sulfate	ZZAJ1K50XH	From PCCA MSDS: 100% by weight and stable.	Powder	Not USP; sold OTC in US as a dietary supplement.	Lotion Powder Scoop Gel	10%	2.5g	Topical (Vet)	Oral	<p>Bjordal JM, Klovning A, Ljunggren AE, et al. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. Eur J Pain 2007;11(2):125-138; Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2-23-2006;354(8):795-808; Cohen M, Wolfe R, Mai T, et al. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. J Rheumatol 2003;30(3):523-528; Mazieres B, Hucher M, Zaim M, et al. Effect of chondroitin sulphate in symptomatic knee osteoarthritis: a multicentre, randomised, double-blind, placebo-controlled study. Ann Rheum Dis 2007;66(5):639-645.</p>	<p>Indicated for the alleviation of joint pain in patients with osteoarthritis. Multiple controlled clinical trials since the 1980s have examined the use of oral chondroitin in patients with osteoarthritis of the knee and other locations (spine, hips, finger joints). Most of these studies have reported significant benefits in terms of symptoms (such as pain), function (such as mobility), and reduced medication requirements (such as anti-inflammatories). However, most studies have been brief (six month duration) with methodological weaknesses. Despite these weaknesses and potential for bias in the available results, the weight of scientific evidence points to a beneficial effect when chondroitin is used for 6-24 months. Longer-term effects are not clear. Early studies of chondroitin applied to the skin have also been conducted. Additionally several studies have shown promise for using chondroitin for interstitial cystitis, which is a chronic inflammation of the bladder. Chondroitin sulfate may also be helpful in patients with overactive bladder or unstable bladder control. Additional evidence is necessary before a firm conclusion can be drawn.</p>



September 30, 2014

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

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

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

Dear Sir or Madam:

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

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

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

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

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS

Corporate Offices: 4638 Riverstone Blvd. | Missouri City, Texas 77459 | 281.933.8400
Washington DC Offices: 1321 Duke Street, Suite 200 | Alexandria VA 22314 | 703.299.0796

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

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

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

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

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

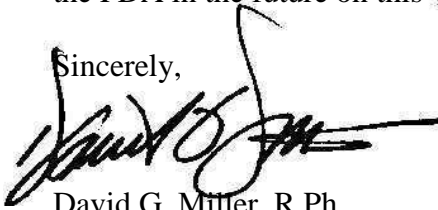
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

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

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

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

Sincerely,

A handwritten signature in black ink, appearing to read "David G. Miller", with a stylized flourish extending to the right.

David G. Miller, R.Ph.
Executive Vice President & CEO



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

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Chondroitin Sulfate
Chemical/Common Name	Chondroitin Sulfate
Identifying Codes	9007-28-7
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies <i>(including foreign recognition)</i>	Not Listed in USP/NF for this specific salt/form

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	

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

Tab 5b

Chondroitin Sulfate

FDA Review



DATE: February 10, 2016

FROM: Norman Schmuff, PhD
Chemistry Reviewer, Office of Pharmaceutical Quality

Belinda Hayes, PhD
Pharmacology Toxicology Reviewer, Division of Anesthesia, Analgesia,
and Addiction Products, Office of Drug Evaluation II

CDR Javier Muniz, MD
Medical Officer, Division of Anesthesia, Analgesia, and Addiction
Products, Office of Drug Evaluation II

John Feeney, MD
Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction
Products, Office of Drug Evaluation II

THROUGH: R. Daniel Mellon, PhD
Pharmacology/Toxicology Supervisor, Division of Anesthesia, Analgesia,
and Addiction Products, Office of Drug Evaluation II

Sharon Hertz, MD
Division Director, Division of Anesthesia, Analgesia, and Addiction
Products, Office of Drug Evaluation II

TO: Pharmacy Compounding Advisory Committee

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

I. INTRODUCTION

Chondroitin sulfate has been nominated for inclusion on the list of bulk drug substances for use in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for topical use in treatment of joint pain in patients with osteoarthritis and in treatment of interstitial cystitis and overactive bladder. This review will focus on the osteoarthritis use which is the only nominated use for which supporting references to scientific literature were submitted.

Although chondroitin was nominated for topical use to treat osteoarthritis, the scientific literature that was submitted in support of the nomination relates primarily to studies of oral administration for the treatment of osteoarthritis. Studies of oral administration could inform whether chondroitin has analgesic effects and describe a systemic safety

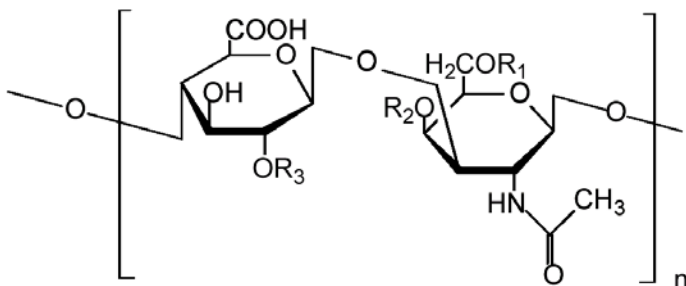
profile, however studies of topical administration would be required to demonstrate efficacy and local safety for that route of administration.

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

II. EVALUATION CRITERIA

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

The drug substance is a mixture of sulfated derivatives of chondroitin, a polymer composed of alternating N-acetylgalactosamine and glucuronic acid, with the following molecular structure:



Its structure is well characterized based on currently available techniques such as nuclear magnetic resonance (NMR), mass spectrometry, infrared spectroscopy (IR), UV, and elemental analysis.

This API is sold as a food dietary ingredient in dietary supplements in the form of powder, capsules (400 mg, 600 mg, and 750 mg) and tablets (600 and 750 mg). The commercially available chondroitin sulfate products are sold as unspecified mixtures, but reportedly have mainly two major components differing by the position of sulfation as shown above (Ji et al., 2009) : chondroitin sulfate A (chondroitin 4-sulfate, R₁ = H, R₂ = SO₃H and R₃ = H), and chondroitin sulfate C (chondroitin 6-sulfate, R₁ = SO₃H, R₂ = H and R₃ = H).

The following sources were consulted in the preparation of this review: PubMed, Chemical Abstracts Service -- SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia, and USP/NF. The databases were searched using the following term “chondroitin sulfate”

and the FDA Unique Ingredient Identifiers (UNII, e.g. 2ZAJ1K50XH, 7VZ9466BAB, V5E8ELO4W9, 6IC1M3OG5Z).

1. *Stability of the API and likely dosage forms*

Chondroitin sulfate solid is stable at ordinary storage conditions. The aqueous solution is stable under neutral conditions at low temperature (below 30 °C). Degradation and desulfation were observed at elevated temperature (60 °C), and the breakdown of polysaccharide linkages were observed under acidic and basic conditions (Volpi et al., 1999).

The substance has been nominated for topical use in lotions, powders, and scoop gels.

2. *Probable routes of API synthesis*

Currently, chondroitin sulfate is mainly produced from enzymatic digestion and extraction of bovine and marine animal tissues (Barnhill et al., 2006). Detailed information on the manufacturing process is not available in the literature.

3. *Likely impurities*

As an unspecified mixture, chondroitin sulfate obtained from current manufacturing procedures always contains two major derivatives: chondroitin 4-sulfate and chondroitin 6-sulfate. Depending on the source of animal tissue and purification techniques, the ratio between these two components may vary. Other impurities may include:

1. Other positional derivatives of chondroitin sulfate
2. The unsulfated chondroitin
3. Other peptides, proteins and biomolecules from the animal extracts
4. Other adventitious impurities from the source bovine and marine animal tissues.

4. *Toxicity of those likely impurities*

There are no data on the toxicity of the likely impurities in compounded chondroitin sulfate products. The toxicology profile of the chondroitin-related impurities are likely to be comparable to the toxicity of the parent molecule. Residual proteins and peptides from animal tissues may introduce allergens and other problems depending on the specific component and the amount of the impurity. Other aspects of toxicity studies can be found in Section B.

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

Chondroitin sulfate is usually a white powder, commercially available as its sodium salt, and the sodium salt is soluble in water (around 100 mg/mL). But chondroitin 6-sulfate, one of its major components, has a much lower solubility: 10 mg/mL. No reports were found in the literature about the impacts from the particle size and polymorphism of the compound on its bioavailability or bioactivity.

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

Chondroitin sulfate has been characterized as a mixture with proton nuclear magnetic resonance (^1H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), UV-Vis (ultraviolet – visual) spectroscopy, and MS (mass spectroscopy) spectrometry. As a polymer, chondroitin sulfate shows a distribution of molecular weight from 15,000 to 20,000 Daltons. The current commercially available chondroitin sulfate contains at least 8 – 9 % unsulfated chondroitin.

Conclusions: Chondroitin sulfate is an unspecified mixture, composed mainly of chondroitin 4-sulfate and chondroitin 6-sulfate in varying percentages. The compound is expected to be stable both as a solid and in neutral aqueous solutions. The nominated compound, as a mixture, has been characterized with various analytical techniques. The likely current manufacturing procedures are simple, but may lead to impurities with unknown structures.

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

1. Nonclinical Assessment

The nonclinical assessment included searches of the pharmacology and toxicology standard databases, including PubMed, ToxNet (HSDB, GeneTox, CCRIS), MicroMedix (ReproTox, ReproText, Shepards, TERIS) as well as general searches on the internet for any additional documentation.

a. Pharmacology of the drug substance

Chondroitin sulfate is the most abundant glycosaminoglycan (GAG) in the connective tissue including articular cartilage. Chondroitin sulfate is essential for the structural and functional integrity of cartilage since it is the majority constituents of GAG. It provides much of the cartilage tissue resistance to compression. Chondroitin sulfate is used as a dietary supplement to ameliorate pain due to osteoarthritis.

There are numerous published nonclinical studies examining the potential utility of chondroitin sulfate via various routes of administration in animal models of arthritis. We are not aware of any dermal animal efficacy studies. The

mechanism of action of chondroitin sulfate for the treatment of osteoarthritis has not been fully characterized. It is unlikely that significant amounts of intact chondroitin sulfate administered orally or dermally could gain access to the knee joint. A complete review of the existing published studies is beyond the scope of this consult. However, published studies have suggested that chondroitin sulfate may have anti-inflammatory properties which could reduce joint damage in osteoarthritis (OA) (e.g., Jomphe et al., 2008; Omata et al., 2000). Other reports suggest that chondroitin sulfate may promote epiphyseal growth plate proliferation and bone formation (e.g., Wolff, 2014). The potential mechanisms have been reviewed by Monfort et al. (2008).

b. Safety pharmacology

No formal central nervous system, cardiovascular, gastrointestinal, or respiratory safety pharmacology studies of chondroitin sulfate were identified in the published literature review through standard toxicology databases. However, Bali et al. (2001) summarized findings of cardiovascular, gastrointestinal, respiratory and renal studies conducted by Pierre (1967). There are limited details in the publication, but as per Bali, it summarized the gastrointestinal effects of chondroitin sulfate using the isolated intestinal loop model and in the mouse in vivo assay. In the intestinal loop model, chondroitin sulfate at concentrations of 1 to 3 mg/mL had no effects on the amplitude of intestinal contractions or in the tonicity of the intestine. Chondroitin sulfate administration (0.25 to 1 g/kg) had no effect on the rate of intestinal transit.

According to Bali, Pierre evaluated the potential cardiovascular effects of chondroitin sulfate at doses in the range of 25 to 100 mg/kg (perfusion rate 25/min, route not indicated). The species used was not mentioned. No effect on the electrocardiograms was reported. A slight and transitory decrease in arterial pressure was induced at 100 mg/kg.

Chondroitin sulfate had no effect on renal function. As per Bali, Pierre reported that subcutaneous administration of chondroitin sulfate (100 mg/kg) had no effects on volume or electrolyte concentration of urine.

Since the route of administration was not always indicated in these studies, the applicability of these data to the topical routes proposed is uncertain.

c. Acute toxicity

There were no acute nonclinical toxicity studies identified in the published literature based on the search described above. However, the potential acute toxicity of chondroitin sulfate in humans was estimated by determining the LD₅₀ values in rodents. The acute toxicity as defined by the LD₅₀ values for chondroitin sulfate, sodium salt was reported in a technical report prepared for NCI by Technical Resources International, Inc. to support the chemical nomination of chondroitin sulfate (Technical Resources International, 2002).

The source of the information listed, cited as being obtained from a Sigma Aldrich material safety data sheet (MSDS), was not specifically reported and cannot be independently verified. As indicated in the table below, excerpted from the referenced MSDS, LD₅₀ values have been assessed in rats and mouse following several routes of administration. Overall, the acute LD₅₀ doses for chondroitin sulfate in nonclinical species appear to be high. The oral LD₅₀ doses for chondroitin sulfate in both rodent species were greater than 10,000 mg/kg. These results suggested that toxicity of chondroitin sulfate following oral, subcutaneous, intraperitoneal, and intravenous administrations is low in rodents.

Table 1. LD₅₀ values for chondroitin sulfate in rodents

Species	Route of administration	LD₅₀ (mg/kg)
rat	Oral	>10,000
rat	intraperitoneal (IP)	2,900
rat	subcutaneous (SC)	3,700
rat	intravenous (IV)	>3,125
mouse	Oral	>10,000
mouse	IP	9,800
mouse	SC	>10,000
mouse	IV	4,980
Source: Sigma-Aldrich (2001) Material Safety Data Sheet as cited by Technical Resources International		

However, extrapolation from LD₅₀ values is not an adequate method to establish the safety of this compounded drug product for humans.

d. Repeat-dose toxicity

No repeat-dose nonclinical toxicity studies conducted with chondroitin sulfate were identified in the published literature via review of standard toxicology databases described above. One repeat-dose toxicology study of a patented preparation of hydrolyzed chicken sternal cartilage called BioCell Collagen II is available in the published literature (Schauss et. al., 2007). BioCell Collagen II (USA patents 6025.327; 6323319; 6780841 supplied by BioCell Technology, LLC in Anaheim CA, USA) is classified as a food grade nutraceutical powder minimally composed of 60% collagen type II, 20% chondroitin sulfate and 10% hyaluronic acid, and 1% other proteoglycans as well as 0.1% lipid, and 8% ash IBC Labs. The authors stated that this study was conducted in compliance with good laboratory practices and in accordance with OECD guidance. Covance Laboratories in Madison, Wisconsin conducted the study.

Sprague-Dawley rats (10/sex/group) were orally administered 0 (distilled water), 30, 300, or 1000 mg/kg of the test product once daily for 92 (males) or

93 (females) consecutive days. Animals were observed twice daily for mortality. Detailed observations, while handling the animal and when the animals were in an open field, were performed on Day 1 prior to the first dosing and weekly thereafter. Clinical signs were recorded, including any changes in skin, fur, eyes and mucous membranes, occurrences of secretions and excretions, and autonomic activity (e.g., lacrimation, piloerection, pupil size unusual respiratory pattern), changes in gait, posture, and response to handling, presence of clonic or tonic movements, stereotypies (e.g., excessive grooming, repetitive circling) or other bizarre behavior (e.g., self-mutilation, walking backwards, etc). Food consumption was measured weekly. Ophthalmologic evaluation was performed prior to the study and on Day 79. Clinical pathology samples from the orbital sinus were collected on Day 86. Organs weight was measured for the following organs: liver, kidney, adrenals, brain, heart, thymus, spleen, uterus, ovaries, testes, and epididymides. Gross necropsy was performed on all animals. The following organs and tissues were collected from all animals for future histological evaluation: all gross lesions, lungs, trachea, brain (sections of the medulla/pons, cerebellar cortex, and cerebral cortex), spinal cords (cervical, mid-thoracic and lumbar region), eyes, pituitary gland, thyroid/parathyroid, thymus, heart, aorta, sternum with bone marrow, liver, spleen, kidneys, pancreas, adrenals, ovaries, testes, uterus, vagina, epididymides, prostate, seminal vesicles, mammary gland, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, urinary bladder, mesenteric lymph node, mandibular lymph node, salivary glands, sciatic nerve, and skin. Histological examination was performed on the control and high group animals.

The test drug was reported as well tolerated at all four doses tested. No mortality, adverse effects, or clinical signs were observed. It was reported that on Day 38, one male in the mid-dose group was euthanized due to moribund condition. Postmortem examination showed a red discharge from the eyes and nose, nasal swelling, crooked or broken teeth, and minimal stomach content. It was concluded these symptoms were sustained from an injury and were not treatment-related. The reviewer concurs with this conclusion. No clear dose-dependent treatment-related effects on body weight were observed.

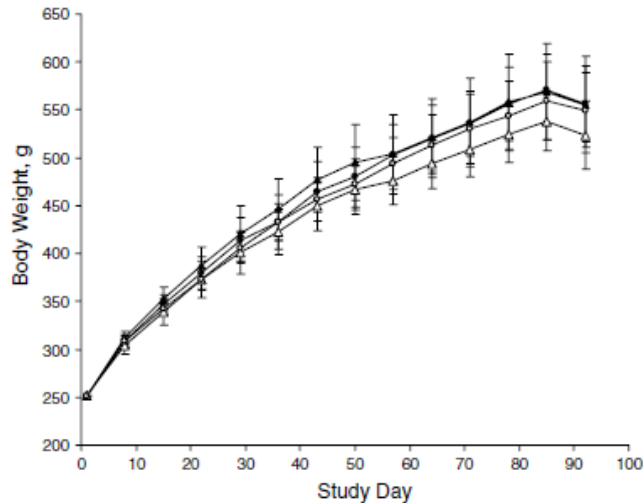


Fig. 1. Mean body weights of male rats in the control (closed triangles), low dose (30 mg BioCell Collagen II/kg/day, open triangles), intermediate dose (300 mg/kg/day, closed circles), and high dose (1000 mg/kg/day, open circles) groups of the subchronic oral toxicity study. No significant differences were found among the four groups.

The authors stated that food consumption, hematology and coagulation laboratory results of the treatment groups were comparable to the control group. As depicted in the authors' Table 1, a statistically significant ($p < 0.05$) decrease (82% of the control group) in alkaline phosphatase (ALP) level of the high-dose males was observed. A minimal but statistically ($p < 0.05$) significant increase in albumin (ALB) was observed in mid-dose males and globulin (GLOB) levels in high-dose females. The reviewer concurs with the authors conclusion that the observed changes in ALB and GLOB levels were “unrelated to treatment and non-adverse because there was no dose-relationship to the responses.”

Table 1
Selected clinical biochemistry values for male rats at Day 86 of the subchronic oral toxicity study^a

Dose	No.	AST (U/L)	ALT (U/L)	ALKP (U/L)	Tot Bil (mg/dL)	Creat (mg/dL)	Prot (g/dL)	ALB (g/dL)	GLOB (g/dL)	Na ⁺ (mmol/L)	Cl ⁻ (mmol/L)
0	9 ^b	109 ± 15	39 ± 5	114 ± 15	0.13 ± 0.02	0.33 ± 0.03	6.8 ± 0.2	3.5 ± 0.1	3.3 ± 0.1	144.1 ± 0.9	103.9 ± 1.5
30	9 ^b	120 ± 53	38 ± 8	111 ± 20	0.13 ± 0.01	0.33 ± 0.03	7.0 ± 0.4	3.6 ± 0.1	3.4 ± 0.3	144.2 ± 0.8	104.3 ± 1.7
300	9 ^c	96 ± 21	36 ± 5	103 ± 16	0.13 ± 0.02	0.32 ± 0.04	7.1 ± 0.3	3.7 ± 0.1 ^d	3.4 ± 0.3	144.4 ± 0.8	103.7 ± 0.8
1000	10	100 ± 18	33 ± 5	94 ± 13 ^d	0.12 ± 0.02	0.32 ± 0.03	6.9 ± 0.3	3.6 ± 0.1	3.3 ± 0.2	144.1 ± 1.1	103.5 ± 1.3

^a Values are mean ± standard deviation. Dose is in mg of BioCell Collagen II/kg/day. ALB indicates albumin; ALKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cl⁻, chloride ion; Creat, creatinine; Glob, globulin; Na⁺, sodium ion; Prot, total protein; and Tot Bil, total bilirubin.

^b Measurements were not performed for one animal in each of the control and low dose groups.

^c One animal was euthanized on Day 38 of the study.

^d Significantly different as compared with the control group, $p < .05$ by Dunnett/Tamhane-Dunnett test.

Organ weight evaluation showed statistically ($p < 0.05$) significant changes in mid- and low-dose males and females, respectively. Absolute brain weight of low-dose females was 7.5% higher than that of the control females. Spleen weight relative-to-brain weight was 15% lower in the mid-dose males than that of the control males. No histological changes in the high-dose animals were observed that could be correlated to these observed organ weight changes.

Gross examination did not reveal any significant treatment-related changes. The paper reports no treatment-related histological findings with the exception of a small increase in hepatocyte vacuolation in four males and one female from the high-dose group compared to two males and one of the females from the control group. Severity was rated as minimal. The authors conclude that the BioCell Collagen II product, by oral administration, at the recommended daily dose of 30 mg/kg, “would be well tolerated and safe in humans.” Assuming a no-observed-adverse-effect-level (NOAEL) of 1,000 mg/kg of this material, the product would deliver 200 mg/kg of chondroitin sulfate. This corresponds to a human equivalent dose of chondroitin sulfate of 1935 mg per 60 kg person. This study provides safety justification in a single species for a human intake of approximately 1,935 mg of chondroitin sulfate for up to 90 days.

No other repeat-dose toxicology studies were found in the published literature. Specifically, we have not been able to find any topical toxicology data. Chondroitin sulfate was apparently nominated to the National Toxicology Program (NTP) (Technical Resources International, 2002) for further chronic toxicology and carcinogenicity studies (Technical Resources International, 2002). A 13-week toxicology study testing the combination of glucosamine and chondroitin sulfate in rats appears to have been completed by NTP (2002). The study report is not available online.

e. Mutagenicity

There were no formal mutagenicity studies of chondroitin sulfate identified in the published literature. Ishidate et al. (1984) investigated the potential genotoxicity of sodium chondroitin sulfate, as part of a screening assay of food additives currently used in Japan, in an in vitro bacterial reverse mutation (Ames) and chromosomal aberrations assay in Chinese hamster fibroblast cell lines assay. The Ames assay tested sodium chondroitin sulfate at concentrations up to 42.5 mg/plate, with and without S9 in the following *Salmonella typhimurium* strains: TA92, TA94, TA98, TA100, TA1535, and TA1537. The in vitro chromosomal aberration assay, using a Chinese hamster fibroblast cell line, evaluated sodium chondroitin sulphate at concentrations up to 3 mg/mL. The concentrations of chondroitin sulfate evaluated in these assays and the positive controls used were not stated in the paper; thus the accuracy of these assays could not be confirmed. However, the results suggested that sodium chondroitin sulfate was not mutagenic in the in vitro bacterial reverse mutation and chromosomal aberration assays.

f. Developmental and reproductive toxicity

There were no reproductive and developmental toxicity studies of chondroitin sulfate identified in the published literature. However, the findings of a teratogenicity study conducted by Kamei (1961) were summarized in the technical report prepared for NCI (Technical Resources International, 2002).

The teratogenic potential of chondroitin sulfate was evaluated in pregnant mice administered 20 mg chondroitin sulfate subcutaneously on Days 9-11 of gestation. Results from this study suggested that chondroitin sulphate is a potential teratogen. It was reported that chondroitin sulfate produced non-statistically significant increases in malformations that consisted of cleft palate and flexed or curled tail, and significant growth inhibition in the fetuses. In contrast, no adverse effects were reported when 5,000 mg/kg chondroitin polysulfate was administered orally to rats and mice during the period of organogenesis (Hamada, 1972). However, the accuracy of either of these reports or the purity and chemical composition of the materials administered could not be confirmed as the citations were not able to be obtained.

g. Carcinogenicity

There were no 2-year carcinogenicity studies of chondroitin sulfate identified in the published literature. One study in the literature suggested that chondroitin sulfate had a synergistic anti-tumor effect when co-administered with mitomycin C in mice implanted sarcoma 180 ascites tumor (Mikami et al., 1980), doubling the 60-day survival in mice implanted with 1×10^6 tumor cells. Definitive studies would be required to confirm any anti-tumor potential of chondroitin sulfate. Although nominated to NTP for carcinogenicity testing, we can find no record that such studies were ever completed.

h. Toxicokinetics

Palmieri et al. (1990) investigated the metabolic fate of exogenous chondroitin sulfate following oral and intramuscular administration in rats and dogs. A dose of 16 mg/kg of [^3H]-chondroitin sulfate (mixture of 50% chondroitin-4-sulfate and 50% chondroitin-6-sulfate) was administered to Wistar rats by intramuscular (6/sex/time point) or oral route (10/sex/time point). The animals were fasted overnight and food was withheld for 4 hours after dosing. Rats were sacrificed at 24 and 72 hours postdosing and selected tissues were collected for radioactivity determinations. Fasted young beagle dogs (4/sex/time point) were orally administered 16 mg/kg of [^3H]-chondroitin sulfate (mixture of 50% chondroitin-4-sulfate and 50% chondroitin-6-sulfate). Blood, urine and fecal samples were collected from both rats and dogs at 24, 48, and 72 hours postdosing. In dogs, the synovial fluid was also collected after a carrageenan injection into the front limb joint. This dose of chondroitin sulfate in rats and dogs corresponds to a human equivalent dose of 154 mg/60 kg person and 533 mg/60 kg person, respectively, based on a body surface area comparison.

The authors reported that the single dose of chondroitin sulfate was well tolerated in both species by both routes and no treatment-related clinical signs and symptoms of local and general toxicity were observed. As depicted in the

author's figures below, the absorption of the radiolabel appears to rise rapidly in both species following oral administration and peaked at 14 and 28 hours postdosing in rats and dogs, respectively. In rats, a C_{max} for the radiolabel material of 7.1 mcg/mL was reached at 14 hours postdosing. At 150 min postdosing, plasma concentration was about 60% of the maximal plasma concentration. AUC_{0-tr} for the radiolabel was 463.6 mcg/mL. These studies only track the radiolabel and should not be interpreted to suggest absorption of intact chondroitin sulfate polymer.

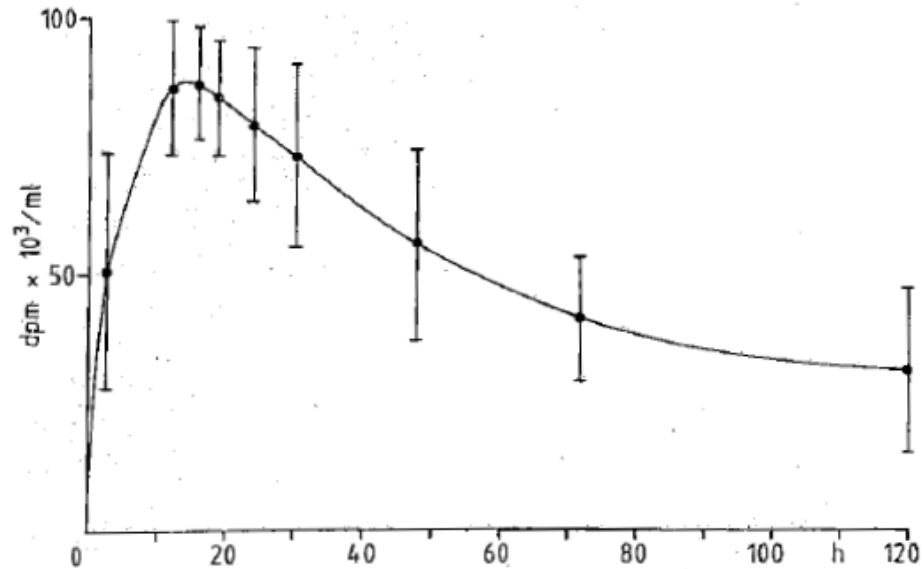


Fig. 1: Plasma levels of radioactivity in the rat after oral administration of tritiated CS.

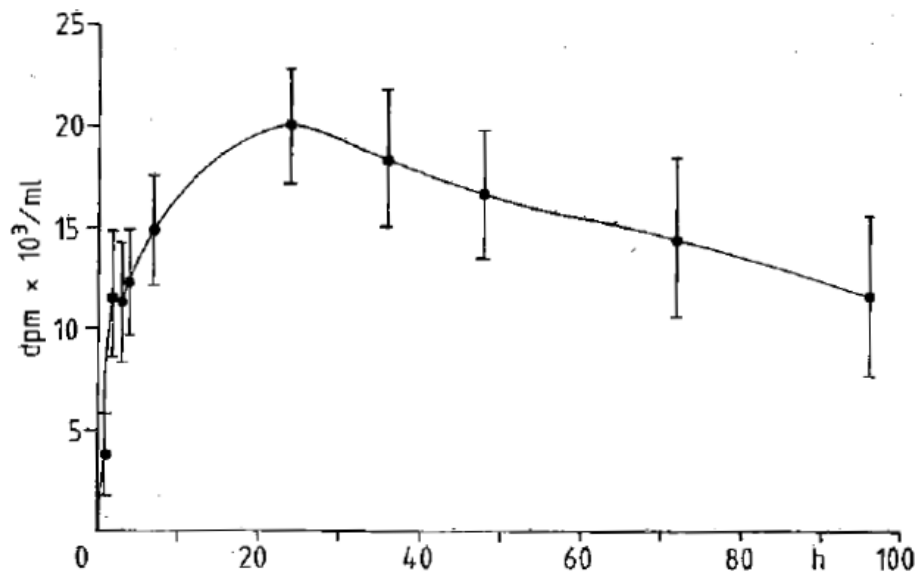


Fig. 3: Plasma levels of radioactivity in the dog after oral administration of tritiated CS.

As depicted in the authors' tables below, [³H]-chondroitin sulfate-derived radioactivity was measured in both feces and urine up to 72 hours after dosing in both species following oral and/or intramuscular administration. Following intramuscular administration, urine elimination was the primary route of elimination of [³H]-chondroitin sulfate-derived radioactivity in rats. Fecal elimination was the primary route of excretion in both rats and dogs following oral administration. Following oral administration, [³H]-chondroitin sulfate-derived radioactivity rapidly increased in both rats and dogs; but peak value was reached after 14 h in rats and 28 h in dogs.

Table 1: Distribution of radioactivity after oral administration of ³H-CS to the rat.

% of the administered radioactivity	Hours after administration		
	24	48	72
Urine	12.8 ± 3.8	17.8 ± 3.6	21.6 ± 2.4
Feces	23.8 ± 3.0	26.4 ± 1.0	26.6 ± 2.6
Tissues	54.3 ± 3.0	48.8 ± 2.8	41.4 ± 2.4

Data are mean ± S.D. of 10 animals.

Table 2: Distribution of radioactivity after intramuscular administration of ³H-CS to the rat.

% of the administered radioactivity	Hours after administration		
	24	48	72
Urine	49.8 ± 3.5	56.1 ± 4.0	58.9 ± 5.1
Feces	1.4 ± 0.4	2.7 ± 0.7	3.2 ± 0.6
Tissues	45.6 ± 5.6	38.7 ± 6.4	31.6 ± 5.9

Data are mean ± S.D. of 6 animals.

Table 3: Distribution of radioactivity after oral administration of ³H-CS to the dog.

% of the administered radioactivity	Hours after administration		
	24	48	72
Urine	7.0 ± 1.9	9.9 ± 1.5	11.2 ± 1.6
Feces	6.2 ± 1.4	14.0 ± 2.1	14.8 ± 1.3

Data are mean ± S.D. of 4 animals.

[³H]-chondroitin sulfate-derived radioactivity was detected in all organs 72 hours following oral administration (author's table below). The highest levels of [³H]-chondroitin sulfate-derived radioactivity were found in the small

intestine, liver, muscle, trachea, and joint cartilage 24 h after oral administration. [³H]-chondroitin sulfate-derived radioactivity was the highest in joint cartilage 72 h postdosing. [³H]-Chondroitin sulfate-derived radioactivity was measured in the synovial fluid of dogs. Specifically, [³H]-chondroitin sulfate-derived radioactivity was 66.5% higher in synovial fluid than in the plasma, as noted in the tables below.

Table 6: CS concentration calculated from radioactivity in dog plasma and synovial fluid from front limb joint.

	µg/ml
Plasma	6.0 ± 0.9
Synovial fluid	10.1 ± 2.2

Data are mean ± S.D. of 3 animals.

Table 5: Distribution of radioactivity in some tissues after oral and intramuscular administration of ³H-CS to the rat.

Tissues	24 h		72 h	
	Oral administration	Intramuscular administration	Oral administration	Intramuscular administration
	dpm/g tissue			
Small intestine	166 400	—	81 000	—
Liver	162 700	318 400	73 900	43 300
Kidney	143 900	897 000	86 800	65 800
Lung	99 700	79 700	69 700	43 600
Brain	31 000	39 200	39 400	40 600
Muscle	110 600	85 100	83 200	51 200
Eye	92 900	75 800	111 900	81 300
Trachea	104 100	91 000	100 700	84 800
Joint cartilage	103 000	94 400	127 800	92 000
Adipose tissue	27 100	25 800	40 100	32 400

This report concludes that about 70% of the radiolabel was absorbed after oral administration and most was excreted in the urine. Molecular weight analysis of the absorbed radiolabel indicated that the radiolabeled material appears to be a mixture of chondroitin sulfate, oligo and polysaccharides, monomers, water, and other newly synthesized compounds derived from metabolism of the radiolabeled chondroitin sulfate. It is not possible to state that intact chondroitin sulfate reaches the joint. Rather, the orally administered material appears to be metabolized and largely excreted via the kidney. Metabolic products do appear to be distributed throughout tissue, including the joint tissues.

No tissue distribution studies were identified following topical administration. The large molecular weight and hydrophilic nature of the molecule would suggest minimal, if any, absorption following topical application (Hadgraft et al., 1998).

Conclusions: From a nonclinical pharmacology toxicology perspective, the safety profile of chondroitin sulfate has not been adequately characterized by standard pharmacology and toxicology studies. The limited nonclinical toxicology studies that exist in the published literature have not identified any specific safety concerns for orally administered chondroitin sulfate. However, the amount of data available does not

constitute a complete evaluation of the substance. There is no nonclinical information available for the topical route of administration.

2. *Human Safety*

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

- Sources cited in the 503A nomination for chondroitin.
- An independent systematic literature search was also performed to identify the literature relevant to the human safety experience regardless of indication or route of administration. The Medline computer database search was limited to the last 20 years. The search yielded 269 publications.

Medline was searched by using the following strategy:

("chondroitin sulfate" OR "chondroitin sulphate" OR "chondroitin sulfates" OR "chondroitin sulphates")

AND

("adverse event" OR "adverse events" OR "adverse reaction" OR "adverse reactions" OR "side effect" OR "side effects" OR "toxicity" OR "safety")

Additionally, the Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for chondroitin through March 19, 2015. The Center for Food Safety and Applied Nutrition (CFSAN) collects reports of adverse events for dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was also conducted.

a. Reported adverse reactions

Bovine cartilage can be a source for the manufacture of chondroitin-containing products. Therefore, there is the possibility of transmission of bovine spongiform encephalopathy (BSE). There are both domestic (United States) suppliers and importers of chondroitin. Importers are required by an import alert (FDA Import Alert 17-04). Published 03/18/2011. Detention Without Physical Examination Bulk Shipments of High-Risk Bovine Tissue from BSE-Countries—Bovine Spongiform encephalopathy) to obtain their ingredients only from non-BSE countries, with appropriate documentation of the health of the animals as well as the country of origin. Chondroitin is not sourced from the bovine tissues that present the highest risk, neurological and glandular tissue.

In 2008, FDA became aware of an increase in the number of serious allergic-type hypersensitivity reactions, some of them fatal, in association with the use of intravenous bolus doses of heparin sodium. Oversulfated chondroitin sulfate (OSCS), a substance that mimics the biological activity of heparin, was identified as a contaminant in the heparin products associated with these adverse events. The health hazards related to OSCS in heparin products are not directly related to the compounding considerations discussed here for two reasons. OSCS is thought

to represent an intentional addition to heparin (to reduce production costs) and is not expected to occur naturally in chondroitin products. Also, the risk associated with OSCS in heparin products is greater because heparin is administered intravenously, while topical chondroitin is discussed here.

A search of the FAERS database for reports of adverse events associated with chondroitin products was conducted on April 8, 2015. The FAERS search covered the time period between January 1969 and April 2015 and retrieved 295 reports. Additionally, because chondroitin is marketed as a dietary supplement, CFSAN conducted a search for reported adverse events between January 2004 and June 2015 and retrieved 239 reports. The interpretation of the reported adverse events is limited by the presence of underlying diseases and/or concomitant medications in addition to the presence of little to no specific medical information in the majority of cases.

Overall, no significant safety signal was identified in the FAERS and CFSAN searches. There were no deaths that could be clearly attributed to chondroitin. Most reported adverse events were not serious and were non-specific (e.g., nausea, headaches, and diarrhea). However, there were various reports of events associated with allergic reactions (e.g., anaphylaxis, urticaria, rash, pruritus, asthma, swelling, hypersensitivity, lip/facial/eye swelling or edema, dyspnea) and with choking (e.g., dysphagia, choking and sensation of choking, foreign body trauma, removal of foreign body from throat). Some articles in the literature suggest that there is little risk for patients with seafood allergies using shellfish-derived chondroitin because the allergy-inducing compounds are contained within the flesh of the animal and not in the cartilage, the source of chondroitin. It should be noted that glucosamine-containing chondroitin combination products accounted for 23 out of the 24 hypersensitivity adverse events identified in the CFSAN search, and the predominant source of glucosamine is shellfish. In contrast, the predominant source of chondroitin is currently bovine cartilage. The large size of some oral chondroitin products, particularly when combined with methylsulfonylmethane (MSM), glucosamine, and/or hyaluronic acid, may partly explain the choking events reported.

Other significant adverse events found in the FAERS and CFSAN searches were three cases of seizures (two in patients with reported decreased phenytoin levels after starting chondroitin supplements; the third was confounded by concomitant medications) and four cases of Steven's Johnson Syndrome (two reported confounding concomitant medications; one described symptoms consistent with a drug reaction with eosinophilia and systemic symptoms).

Drug interaction was the most commonly reported adverse event in the FAERS search. For example, there are six cases of International Normalized Ratio (INR) elevation or bleeding while on concomitant warfarin therapy, one case of QTc prolongation in a patient taking dofetilide for atrial fibrillation (suspected drug-drug interaction resulting in elevated levels of dofetilide), and a case of

hypotension after starting chondroitin in a patient who was being treated with amlodipine and enalapril (with resolution upon discontinuation of chondroitin).

There are various reports of abnormal liver function (e.g., liver function abnormal, alanine aminotransferase increased, aspartate aminotransferase increased, and hepatitis) from the FAERS and the CFSAN searches. Of particular interest is FAERS case 8286152, a 47-year-old female with no reported contributory medical history, who experienced elevated liver enzymes and appendicitis while on chondroitin. After an appendectomy followed by normalization of her liver enzymes, she restarted the chondroitin supplement only to have her liver enzymes elevate again. Although critical information is missing (e.g., concomitant medications, laboratory values, time relationship between the supplement and the observed adverse reaction), this case is significant because it provides a positive challenge, positive de-challenge, and a positive re-challenge to chondroitin.

b. Clinical trials assessing safety

Although there are numerous published well-conducted, placebo-controlled clinical trials evaluating chondroitin, the published reports of these studies are almost exclusively focused on the efficacy-related primary and secondary endpoints. Safety assessments are given much less consideration in these reports. There is a large amount of variability in study design, number of subjects enrolled, and clinical monitoring. Large (over 150 patients), well-designed studies with reasonable clinical monitoring (i.e., clinical evaluations, hematology/chemistry assessments, etc.) utilizing at least 1,200 mg of chondroitin sulfate per day were uncommon in the literature search. Another relative limitation in the available literature is that most studies assess safety for no longer than 6 months. For the purpose of this review, we will focus on three of these well-designed, large studies providing long-term safety data at sufficiently high doses.

The NIH-sponsored, multicenter, double-blind, placebo- and celecoxib-controlled Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) evaluated the efficacy and safety of chondroitin, alone and in combination with glucosamine, as a treatment for knee pain from osteoarthritis. (Barnhill et al., 2006) The 2-year extension of GAIT, described below, provides some of the most informative safety data for chondroitin to date.

In the original GAIT study, patients were randomized with the use of a double-dummy design to one of 5 groups: placebo, celecoxib 200 mg daily, glucosamine 500 mg every 8 hours, chondroitin sulfate 400 mg every 8 hours, and glucosamine 500 mg plus chondroitin sulfate 400 mg every 8 hours. Safety monitoring included complete blood counts; measurement of serum aspartate aminotransferase, alanine aminotransferase, glucose, creatinine, and partial thromboplastin time; and urinalysis at each study visit. Specific cardiovascular monitoring for adverse events was not done. In this study, 1,583 patients were randomized and 318 were assigned to chondroitin-only and 317 patients were

randomized to chondroitin/glucosamine. Seventy-seven serious adverse events (SAEs) were reported in 61 patients across all groups although no specific breakdown of these SAEs or their relationship to a specific treatment arm was given in the publication. Only three SAEs were judged by the investigators to be related to study treatment and none of them occurred in patients randomized to chondroitin monotherapy. The number of patients who withdrew because of adverse events was similar across the groups. Common adverse events were generally mild and evenly distributed across the groups. Patients who received chondroitin sulfate had the highest incidence of “musculoskeletal and connective-tissue” (e.g., muscle cramp, pain in extremity) events and the lowest incidence of vomiting. A specific breakdown of the commonly-observed adverse events was not provided in the published GAIT study.

A 2-year extension to the GAIT study was published in 2010 (Jackson et al., 2010). In this study, there were 84 SAEs reported in 64 patients. Only five of the SAEs were considered possibly related to the study medications and none occurred in the chondroitin sulfate-only arm. Of the 79 SAEs not considered related to treatment by the investigators, only 9 SAEs were discussed in relation to the treatment arm although none of them occurred in the chondroitin-only subjects. In the glucosamine/chondroitin or combination arm, there was one case each of the following AEs: myocardial infarction, hypertension, palpitations, and transient ischemic attack. A specific break-down of commonly-observed AEs was not discussed in the published study.

The long-term safety of chondroitin is also addressed by a study published in 2002 by Verbruggen et al. This was a 3-year, randomized, double-blind, placebo-controlled study with a double-dummy design. Patients were randomized to four possible treatment groups and chondroitin sulfate 400 mg every 8 hours and its matching oral placebo were two of these. Forty-four subjects were randomized to the chondroitin-only arm and 34 completed the study. Only one subject withdrew from this study from the chondroitin-only arm due to an adverse experience of serious gastritis. Although relatively small in size, this study provides long-term safety data relevant to the chronic use of chondroitin sulfate.

The Summary of Product Characteristics (SPC) for Droglican (accessed June 2015) (a chondroitin product approved in Spain) lists the following under the Undesirable Effects section: gastrointestinal disorders, nausea (rare); hypersensitivity (very rare); edema, fluid retention (very rare). The SPC also notes under the Special Warnings and Precautions that patients with impaired glucose tolerance should be monitored and that “in very rare occasions (< 1/10.000) in such patients...cases of edema and/or water retention [have been reported].”

c. Pharmacokinetic data

From the Summary of Product Characteristics for Droglican (accessed June 2015) (Spain):

“Several studies demonstrate that the bioavailability of chondroitin sulphate ranges from 15 to 24% of the orally administered dose. Of the absorbed portion of chondroitin sulphate, 10% is in the form of chondroitin sulphate and 90% in the form of depolymerised derivatives of lower molecular weight, consistent with the hepatic first-pass effect. After oral administration, the maximum concentration of chondroitin sulphate in the blood is reached in about 4 hours. In blood, 85% of chondroitin sulphate and its depolymerised derivatives are bound to several plasma proteins. The volume of distribution of chondroitin sulphate is relatively low (around 0.3 L/kg)... At least 90% of the administered dose of chondroitin sulphate is firstly metabolised by lysosomal sulphatases, to be depolymerised laterly by hyaluronidases, -glucurininidases and -N-acetylhexosaminidases. Liver, kidneys and other organs intervene in the depolymerisation process of chondroitin sulphate. Metabolism interactions with other drugs have not been described. Chondroitin sulphate is not metabolized by cytochrome P450 enzymes. The systemic clearance of chondroitin sulphate is 30.5 mL/min or 0.43 mL/min/kg. The half-life ranges from 5 to 15 hours, depending on the experimental protocol. Chondroitin sulphate and its depolymerised derivatives are mainly eliminated by the kidneys. Chondroitin sulphate shows first-order kinetics after single dose of 3000 mg. Multiple doses of 800 mg in patients with osteoarthritis do not alter the kinetics of chondroitin sulphate.”

In contrast to the above, Jackson et al. (2010) found “...that a single CS [chondroitin sulfate, 400 mg] dose resulted in no detectable change in either the hydrodynamic size or disaccharide composition of the plasma CS.” Using the same formulation that was used in the NIH-sponsored GAIT trial (Bioiberica was the source of the chondroitin raw material), the authors concluded, “We have been unable to detect any of the dietary CS in the circulation under any dosing condition used; these conditions involved both long-term (3 months) and acute dosing, both alone and in combination with GlcN [glucosamine].”

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 (gastrointestinal, cardiovascular, renal, and hepatic toxicities, abuse and addiction), especially with long-term administration. The safety profile of chondroitin that emerges from a review of the literature and an examination of the FAERS and CAERS databases appears reasonably benign in comparison. There are cases of possible drug-drug interaction with anticoagulants such as warfarin reported in the literature and in the FAERS database, which may present a risk for bleeding, even with relatively short-term exposure. All six FAERS

cases of interactions with warfarin were related to oral administration of chondroitin. Overall, only two FAERS cases were related to topical administration of chondroitin: one case of rash and one case of renal failure.

Conclusions: Based on limited information, there have been no significant safety signals associated with the use of topical chondroitin. Some significant safety issues have been reported with oral chondroitin. It is possible that oral chondroitin sulfate, or possibly shellfish-derived contaminants present in some chondroitin products, was responsible for reports of allergic reactions (e.g., anaphylaxis, urticaria, rash, pruritus, asthma, swelling, hypersensitivity, lip/facial/eye swelling or edema, dyspnea). The majority of the allergic reactions were reported with glucosamine-containing combination products and the source of glucosamine is shellfish. In contrast, the predominant source of chondroitin is currently bovine cartilage. There may be an interaction with warfarin and a risk for bleeding associated with the oral use of chondroitin, based on cases of drug-drug interaction in both FAERS and the literature. However, none of the reported warfarin interaction cases were specifically linked to topical use of chondroitin.

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

Identification and selection of the literature

Medline was searched by using the following strategy:

```
("chondroitin sulfate" OR "chondroitin sulfates" OR "chondroitin sulfates"
[mesh] OR "chondroitin" [mesh] OR chondroitin)
AND
("randomized controlled trial"[Publication Type] OR "randomized controlled
trials as topic"[MeSH Terms] OR "randomized controlled trial"[TW] OR
"randomised controlled trial"[TW] OR "randomized controlled trials"[TW]
OR "randomised controlled trials"[TW] OR "random allocation"[MeSH
Terms] OR "random allocation"[TW] OR "random assignment"[TW] OR
"control groups"[MeSH Terms] OR "control groups"[TW] OR "control
group"[TW] OR "placebos"[MeSH Terms] OR "placebos"[TW] OR
"placebo"[TW] OR "single-blind method"[MeSH Terms] OR "single-
blind"[TW] OR "double-blind method"[MeSH Terms] OR "double-
blind"[TW] OR single-blinded[TW] OR "double-blinded"[TW] OR "Clinical
Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "clinical
trial" [tw] OR "clinical trials" [tw])
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The search with the above terms returned 302 articles.

Articles selected for review of the efficacy of chondroitin met the following inclusion criteria:

- Randomized controlled trial, and
- Conducted in patients with osteoarthritis (n=43)

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

Topical Chondroitin for Joint Pain Associated with Osteoarthritis

One trial conducted with a topical cream formulation of chondroitin that met the criteria for review was identified. No chondroitin cream is approved for marketing in the U.S.

The study reported positive effects of a combination cream in reducing OA knee pain. Cohen et al. (2003) randomized 63 patients and treated them over two months with a cream containing chondroitin, glucosamine, camphor, and peppermint oil. A combination product was used in this study and the study was not designed to investigate the efficacy of the individual components. Patients were instructed to apply the creams generously to painful joints and repeat as necessary. The average number of applications was about 3 per day and the authors estimate that only about 200 to 300 mg of chondroitin were delivered systemically per day (assuming 20-40% systemic absorption). A statistically significant difference in pain was observed at Week 8 in their study, with the groups appearing to separate at four weeks as well. However, they comment that "...there may have been some slight differences in the texture of the placebo and active creams." The latter raises concerns about adequate blinding of the study.

Oral Chondroitin for Joint Pain Associated with Osteoarthritis

Osteoarthritis (OA) is a chronic joint degenerative disease with a high prevalence in the elderly. The prevalence of symptomatic knee OA in patients less than 55 years of age is low, while about 40% of the population 65 years and older has symptomatic OA of the knee or hip. Pain and functional disability of the affected joints are the main clinical manifestations of OA. The correct diagnosis includes both clinical and radiological criteria. Treatment includes non-pharmacological therapies such as weight control, exercise, and physical therapy, as well as pharmacological intervention. An acute flare of OA is usually treated with analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs), or an intra-articular injection with corticosteroids. Topical NSAIDs are also used for knee OA.

For discussion, the controlled trials reviewed can be divided as follows:

- Trials published in 2005 or earlier
- The GAIT trial published in 2006, along with GAIT-related publications
- Trials published 2006-present

1995-2005

From the literature prior to 1995, a single abstract of a French-language report was reviewed and suggests favorable results with chondroitin in a controlled trial, n=120, in which patients were treated for three months and then followed for 2 months post-treatment (Mazières et al., 1992). There were 24 publications from 1995 to 2005 that

met the criteria for review. Many of the trials described in these publications suffered from design deficiencies: overly-short treatment periods (with or without crossover designs), open-label treatment, and lack of a clinical outcome measures. Some were small, active-controlled trials that showed no difference between treatments. Some only studied chondroitin in combination with other products, including glucosamine. Notable studies from this time period are discussed below.

A 1998 industry-sponsored supplement to the journal *Osteoarthritis and Cartilage* highlighted a number of positive studies of single-agent chondroitin for joint pain associated with OA of the knee. One of those articles (Bourgeois et al., 1998) stated, “Chondroitin sulfate... administered at a dosage of 1200 mg divided into three doses per day has now become a part of the therapeutic armoury of the French rheumatologist.” Bourgeois reported a 3-arm study (n=127) that was designed to investigate whether 1200 mg once per day would be as effective as 400 mg three times per day. As with some other studies in the supplement (Bucsi et al., 1998 ; Uebelhart et al., 1998, the Bourgeois study showed significant improvement in pain and reduction following NSAID use with chondroitin. The two dosing regimens of chondroitin in the Bourgeois et al. 1998 study performed similarly. The treatment periods in the three studies varied from 3 to 12 months and sample sizes ranged from 46 to 127 patients. In all three studies, between-group differences in pain scores emerged after several weeks of treatment.

Das et al. (2000) conducted a study, n=72, comparing a chondroitin and glucosamine combination product to placebo over 6 months and found a statistically-significant clinical improvement based on the Lesquene index of severity of OA. However, in a similar smaller study conducted by the same investigators in 21 patients with radiographic-severe OA, no between-group difference was observed. This is worth noting only because an often-referenced positive subgroup analysis of the GAIT trial³ (Clegg et al., 2006; see below) includes only those with moderate-severe OA pain.

Uebelhart et al. (2004) performed a study of oral chondroitin in patients with OA of the knee. The authors randomized 120 patients to chondroitin or placebo and followed them for a year. During the year, patients received their assigned treatment for two 3-month periods, each followed by a 3-month no-treatment period. Outcomes were measured after a year. The dose of chondroitin was 800 mg once daily. They reported statistically significant between-group differences on clinical outcomes (Lequesne’s algofunctional index and a visual analog scale) at Months 9 (end of the second treatment cycle) and 12 (3 months after the last treatment cycle). The authors believed the results supported a prolonged effect for chondroitin, even after treatment has ended.

Note that across all publications, different formulations of chondroitin may have been used. Also, where combinations of chondroitin with other agents were used, the relative contribution of the different agents to the overall results cannot be determined. Only factorial-design studies, such as the GAIT trial below, are capable of addressing this issue. In longer-term studies (6 to 12 months), with higher dropout rates, the handling of dropouts in the reported analyses may not have influenced the study outcomes.

GAIT, 2006

The Glucosamin/Chondroitin Arthritis Intervention Trial (GAIT) was a large, randomized, placebo-controlled and active-controlled (celecoxib) trial investigating the efficacy of glucosamine and chondroitin sulfate, when used individually and in combination for the treatment of pain associated with OA of the knee. The study had a full factorial design. A total of 1,583 patients with symptomatic OA of the knee were randomized equally to one of the following treatment groups:

- 1,200 mg of chondroitin sulfate daily
- 1,500 mg of glucosamine hydrochloride daily
- Both chondroitin and glucosamine
- 200 mg of celecoxib daily
- Placebo

The randomization was stratified by severity of knee pain, mild versus moderate to severe. There were just over 300 patients per treatment group. Patients were treated for 24 weeks.

The primary outcome measure in the GAIT trial was the WOMAC pain scale. The primary analysis was a comparison between the number of patients achieving a 20% reduction in pain in each of the three investigation groups (chondroitin, glucosamine, or the combination) and the number achieving a 20% reduction in the placebo group. Correcting for multiplicity with a Bonferroni correction, a p-value of 0.017 was considered significant for each of the three comparisons: chondroitin versus placebo, glucosamine versus placebo, and chondroitin/glucosamine versus placebo. The stated level of significance for the celecoxib-placebo comparison was also p=0.017. Last-observation-carried-forward was the method pre-specified in the analysis plan for handling dropouts for the primary analysis.

The results of the trials were as follows:

	Chondroitin	Glucosamine	Combination	Placebo	Celecoxib
Number of Responders (percent)	208/318 (65)	203/317 (64)	211/317 (67)	188/313 (60)	223/318 (70)
p-value	0.17	0.30	0.09		0.008

These results show that there is a large placebo response and that celecoxib is more effective than placebo in treating the pain of osteoarthritis. Chondroitin, alone or in combination with glucosamine, was not effective in increasing the responder rate in this trial. The relevance of these results to the topical use of chondroitin is uncertain.

Because there was an interaction between baseline pain severity and outcome in the primary analysis, a sub-group analysis was performed including only patients with baseline pain severity of 301 or greater on the WOMAC pain scale (scores range from 0 to 500). The results for this post hoc analysis were as follows:

	Chondroitin	Glucosamine	Combination	Placebo	Celecoxib
Number of Responders (percent)	43/70 (61)	46/70 (66)	57/72 (79)	38/70 (54)	50/72 (69)
p-value	0.39	0.17	0.002		0.06

These post hoc sub-group results are often referenced in support of the efficacy of the combination for the treatment of moderate to severe pain of OA. However, the comparison represents a post hoc analysis, potentially one of many conducted with the data. Interestingly, the results for this subgroup failed to demonstrate efficacy for the patients treated with celecoxib. While the results of the combination treatment group are interesting, there is no evidence from this study that chondroitin sulfate alone provides symptomatic relief from the pain of osteoarthritis, regardless of severity of the pain.

These results for chondroitin were unexpected, given the findings from previous, smaller controlled trials of chondroitin and subsequent meta-analyses of those same earlier trials.

2006-Present

Between 2006 and June 2015, there were 18 publications that met the criteria for review. Many of the trials suffered from the same design deficiencies as earlier studies: overly-short treatment periods (with or without crossover designs), open-label treatment, and lack of a clinical outcome measure. Some were small, active-controlled trials that showed no difference between treatments. Some only studied chondroitin in combination with other products, including glucosamine. Notable studies from this time period are discussed below.

Despite large enrollments, of 307 and 622 subjects, two large multi-center studies (Mazières et al., 2007; Kahan, et al., 2009) were unable to demonstrate a symptomatic benefit for chondroitin-treated patients with OA of the knee. A smaller study of 129 subjects conducted in Barcelona (Möller et al., 2010) did demonstrate a significant effect on reduction in knee pain at 3 months. Also, a single-center study in Geneva (Gabay, et al., 2011) with 162 subjects demonstrated a significant effect on pain reduction in OA of the hand at 6 months.

Zegels et al. (2013) performed a study similar to the Bourgeois et al., (1998) study already discussed. The Zegels et al. study enrolled 353 subjects and compared chondroitin 1200 mg once-daily, chondroitin 400 mg three times per day, and placebo. The investigators found that both chondroitin regimens performed similarly and better than placebo after 3 months.

Between 2011 and 2013, Bioiberica (Spain) sponsored the Multicenter Osteoarthritis Intervention Trial with SYSADOA (MOVES) to test whether the combination of chondroitin sulfate plus glucosamine was comparable to celecoxib in treating moderate to severe pain in patients with osteoarthritis after 6 months of treatment. This large study of 606 subjects demonstrated non-inferiority of the combination to celecoxib based on the

mean decrease in pain from baseline to 6 months using a standard pain scale. Because active-controlled trials showing no between-group differences can result if neither treatment is effective within the study, and it is already known that there can be a very large placebo effect in these studies, the results of the MOVES trial are inconclusive. A placebo treatment arm in the MOVES trial would have provided the assay sensitivity needed to determine whether there was actually a treatment effect for the two active arms. Further, without a glucosamine-only arm in the study, any effect of the chondroitin/glucosamine combination could possibly be attributed to the glucosamine alone.

A recent systematic review by Singh et al. (2015) concluded, “More high-quality studies are needed to explore the role of chondroitin in the treatment of osteoarthritis.”

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

Joint pain associated with osteoarthritis is considered a serious condition, as it interferes with the quality of life. Under-treated pain is associated with morbidity and mortality.

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. Due to differences in study designs, cross-study comparisons do not provide insight into comparative efficacy of chondroitin with approved treatments. The recently-completed MOVES study was an active-controlled trial that showed no difference between the chondroitin/glucosamine group and the celecoxib group. However, active-control trials showing no between-group differences can result if neither treatment is effective within the study. A third treatment arm in the MOVES study, a placebo arm, would have aided interpretation of the study results.

Conclusions: Based on the results of the GAIT trial, oral chondroitin, whether alone or in combination with glucosamine, appears to be ineffective for the treatment of pain associated with OA of the knee. There are several smaller clinical trials that reported favorable results, but these were generally smaller and of shorter duration than the GAIT study raising the possibility that any effect, if present, may only be transient. The relevance of these results to the topical use of chondroitin is uncertain.

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 chondroitin in pharmacy compounding. It has been discussed in medical literature dating back to the 1980s, but not specifically related to compounding.

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

Chondroitin has been used by multiple routes of administration and for the treatment of joint pain associated with OA, interstitial cystitis, and overactive bladder. There are two English-language reports of randomized controlled trials of intravesical chondroitin for interstitial cystitis. Neither trial reports a statistically-significant result in favor of chondroitin, but a favorable trend is discussed for at least one of the trials. Chondroitin is also used in some products for the treatment of dry eyes and cornea inflammation and for cataract surgical procedures.

3. *How widespread its use has been*

Chondroitin is used throughout the world.

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

Chondroitin is sold as a single agent or in combination products for oral use throughout the world. There is wide variability in the use of chondroitin-containing products and in how they are classified. They may be classified as prescription drugs or as health food supplements or both in any given country. It appears from the literature that chondroitin as a prescription drug has been approved in at least some European countries since the late 1990s. Chondroitin is also approved in Canada and a number of European countries (marketed as Uracyst/Uropol) for intravesical administration for interstitial cystitis. In the UK, it appears that it is approved for this latter use under the medical device regulations. It is also available in ophthalmological products in many countries.

One current producer of chondroitin is Bioiberica (Spain). According to a 2015 press release posted on the company website¹, their chondroitin product was recently approved in Austria, Hungary, the Czech Republic, Italy, and Poland through a mutual recognition procedure from Finland. Marketing authorization for a single-agent chondroitin product was granted in Finland in 2009. According to the company, their product is now approved as a medicinal product in 13 European countries. Statements in the literature suggest that Bioiberica may also be the provider of chondroitin used in the manufacture of several dietary supplements marketed in the United States. A combination product with glucosamine (Droglican, accessed June 2015) has also been approved for marketing in Spain as well as other countries.

In many European countries where chondroitin is approved, it is approved for non-acute treatment and it has been classified as a symptomatic slow-acting drug for OA (SYSADOA). The SYSADOA in use throughout Europe include glucosamine, chondroitin sulfate, and diacerein. Some nutraceuticals are also included in this group. There does not appear to be consensus on the role of

¹ <https://www.bioiberica.com/bioiberica-3/news-and-update/-bioiberica-obtains-approval-for-its-chondroitin-sulfate-as-an-ethical-drug-in-osteoarthritis-in-five-more-european-countries/>

SYSADOA in the pharmacological treatment of OA in Europe, but in general they are considered supplementary to analgesics and anti-inflammatory drugs.

In the United States, chondroitin is marketed as a dietary supplement by multiple different manufacturers for both oral and topical use. It is the subject of a current USP dietary supplement monograph.

Conclusions: The use of chondroitin is reported in many countries and its use appears widespread. It has been used for the indications of joint pain associated with osteoarthritis, interstitial cystitis, and overactive bladder. It is also used in some products for the treatment of dry eyes and cornea inflammation and for cataract surgical procedures. Information regarding the history and use of chondroitin in compounding was not found.

III. RECOMMENDATION

We have reviewed the physicochemical characteristics, safety, effectiveness, and historical use of chondroitin, and based on those factors, do not recommend inclusion of chondroitin on the 503A bulks list. The majority of information reviewed was for oral use. Studies of topical application of chondroitin would be necessary to establish efficacy and local safety for that route of administration.

Chondroitin sulfate is well characterized chemically and physically but the relative amounts of chondroitin sulfate A and chondroitin sulfate C in the mixture are not well defined and can vary. Although it has been used extensively worldwide, there are no data to confirm a finding of efficacy for osteoarthritis via the topical route, as discussed further below.

Regarding safety, while there are limited data supporting the safety of chondroitin, the absence of adequate nonclinical toxicology data, the lack of a systematic collection and reporting of safety data from clinical trials, and the lack of important information concerning the risk for drug-drug interactions preclude a finding that there is no risk. Although the limited nonclinical data do not identify safety concerns, the nonclinical safety profile of chondroitin has not been adequately characterized by standard pharmacology and toxicology studies. The single report of nonstatistically significant increase in cleft palate and flexed or curled tail and significant growth inhibition of the fetus following subcutaneous injection of chondroitin sulfate should be followed up if chondroitin were to be recommended for inclusion on the list. However, the clinical relevance to a topical application seems limited.

The clinical safety of chondroitin as described in the literature consists mostly of non-serious adverse events, with the most common side effects being nausea and diarrhea. However, there have been adverse events of concern reported in the literature that include increased effectiveness of anticoagulants and elevated liver function tests. A search of the FAERS database showed six reports of either bleeding or increased INR with

concomitant warfarin. Limitations of literature reports as well as the FAERS and CAERS databases severely limit the ability to determine causality of the adverse events, or the true number of events, but reports of a possible interaction with anticoagulants such as warfarin both in the literature and in FAERS cases provide at least some corroboration for the finding. There are a number of approved alternative treatments for OA-related pain that have been demonstrated to be effective, but all have associated risks.

Regarding effectiveness, the results of the NIH-sponsored GAIT, a large and well-controlled trial, suggest that chondroitin, whether alone or in combination with glucosamine, appears to be ineffective for the treatment of pain associated with OA of the knee. The positive results from some smaller, shorter trials conducted both before and after the GAIT trial suggest that, at best, any effect may be transient. As noted above, there are a number of approved alternative treatments for OA-related pain that have been demonstrated to be effective.

The recently-completed MOVES study is inconclusive by virtue of the study design chosen. While it was designed to address efficacy in patients with more severe symptoms (a subgroup of interest based on the GAIT trial results), it did not include a placebo arm. Designed as an active-control, non-inferiority trial, MOVES showed no difference between the chondroitin/ glucosamine group and the celecoxib group. However, active-control trials showing no between-group differences can result if neither treatment is effective within the study, and it has been demonstrated that this population can exhibit a very large placebo effect. A placebo treatment arm in the MOVES study would have provided the assay sensitivity to determine whether the study results reflect a finding of efficacy.

No dose-finding studies were found in the above review of the literature. Based on a balancing of the four evaluation criteria, we **do not recommend** that chondroitin sulfate be included on the list of bulk drug substances that may be compounded under 503A of the FD&C Act.

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Tab 6

Acetyl-L-Carnitine

Tab 6a

Acetyl-L-Carnitine
Nominations



Alliance for Natural Health USA

6931 Arlington Road, Suite 304
Bethesda, MD 20814

email: office@anh-usa.org
tel: 800.230.2762
202.803.5119
fax: 202.315.5837
www.anh-usa.org

ANH-USA is a regional office of ANH-Intl

INTERNATIONAL
anhinternational.org

September 30, 2014

VIA ELECTRONIC SUBMISSION

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

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

Docket No. FDA-2013-N-1525

Dear Sir/Madam:

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

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

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

"Promoting sustainable health and freedom of healthcare choice through good science and good law"

As discussed in detail below, in the interest of compiling a comprehensive 503B List more time is needed to provide the required information. This will benefit both FDA, by reducing the subsequent number of petitions for amendments, and consumers, by allowing continued access to important substances.

Organizational Background of Commenter Alliance for Natural Health USA

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

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

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

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

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

For the initial request for nomination, it was estimated that compiling the necessary information for just one nominated ingredient would require five to ten hours. With the revised request requiring more information, the time to put together all of the data for a single nomination likely will be higher. Given that it is necessary to review all possible ingredients and provide the detailed support, or risk losing important therapeutic ingredients, this task requires more time than has been designated by the Agency. While ANH-USA recognizes there will be additional opportunities to comment and petition for amendments after the 503A List is published, the realities of substances not making the list initially makes this request for more time imperative. For example, if a nomination for a substance cannot be completed in full by the current September 30, 2014 deadline, doctors and patients will lose access to such clinically important substances and face the

administrative challenges in obtaining an ingredient listing once the work of the advisory committee is completed. There is no regulatory harm in providing additional time to compile a well-researched and comprehensive initial 503A List.

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

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

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 Sub sulfate; 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.

Comments, Integrative Medicine Consortium

Docket FDA-2013-N-1525

September 30, 2014

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

Page 6

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,

A handwritten signature in black ink, appearing to read "Michael J. Cronin N.D.", written in a cursive style.

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:

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.

McGUFF
COMPOUNDING
PHARMACY
SERVICES

2921 W. MacArthur Blvd.
Suite 142
Santa Ana, CA 92704-6929

TOLL FREE: 877.444.1133
TEL: 714.438.0536
TOLL FREE FAX:
877.444.1155
FAX: 714.438.0520
EMAIL: answers@mcguff.com
WEBSITE: www.mcguff.com

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
Dichloroacetic 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,

A handwritten signature in black ink that reads "Jud Richland". The signature is written in a cursive, flowing style with a long horizontal stroke at the end.

Jud Richland, MPH
Chief Executive Officer



ACAM
American College for
Advancement in Medicine

380 Ice Center Lane, Suite A
Bozeman, Montana 59718
Toll-free 800-LEAD.OUT (532.3688)
F: 406-587-2451
www.acam.org

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.



ACAM
American College for
Advancement in Medicine

380 Ice Center Lane, Suite A
Bozeman, Montana 59718
Toll-free 800-LEAD.OUT (532.3688)
F: 406-587-2451
www.acam.org

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

Nominations Submitted by: Alliance for Natural Health USA, Integrated Medical Consortium, McGuff Compound Pharmacy Services, American Association of Naturopathic Physicians, and 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?	Acetyl-L-Carnitine Hydrochloride
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 acetyl-L-carnitine on PubMed. Key word: acetyl-L-carnitine. Or: see section "safety and efficacy data" below.
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?	No
What is the chemical name of the substance?	R-(-)-2-Acetyloxy-3-carboxy-N,N,N-trimethyl-1-propanaminium
What is the common name of the substance?	Acetyl-L-Carnitine Hydrochloride
Does the substance have a UNII Code?	NDW10MX58T
What is the chemical grade of the substance?	Acetyl-L-carnitine hydrochloride is not graded
What is the strength, quality, stability, and purity of the ingredient?	A valid Certificate of Analysis accompanies each lot of raw material. Raw material can be supplied by a 510-FDA registered manufacturer.
How is the ingredient supplied?	Acetyl-L-carnitine hydrochloride is a white crystalline powder.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	No EP, BP, JP monograph available China: Listed on National Inventory
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?	Acetyl-L-carnitine HCL 200 mg/mL preservative free
What are the anticipated route(s) of administration of the compounded drug product(s)?	Slow intravenous

<p>Are there safety and efficacy data on compounded drugs using the nominated substance?</p>	<ol style="list-style-type: none"> 1. Parnetti L, Gaiti A, Mecocci P, et al. Pharmacokinetics of IV and oral acetyl-L-carnitine in a multiple dose regimen in patients with senile dementia of Alzheimer type. <i>Eur J Clin Pharmacol</i> 1992;42:89-93. 2. Marcus R, Coulston AM. Water-soluble vitamins. In: Hardman JG, Limbird LE, eds. <i>The Pharmacological Basis of Therapeutics</i>, 9th ed. New York: McGraw-Hill; 1996. 3. Purpura DP, Girado M, Smith TG, et al. Structure activity determinants of pharmacological effects of amino acids and related compounds on central synapses. <i>J Neurochem</i> 1959;3:238. 4. Hayashi K. Action of carnitine on excitable tissues of vertebrates. In: Peeters H, ed. <i>Protides of the Biological Fluids</i>. Amsterdam: Elsevier; 1960:371-381. 5. Capecchi PL, Laghi Pasini F, Quartarolo E, Di Perri T. Carnitines increase plasma levels of adenosine and ATP in humans. <i>Vasc Med</i> 1997;2:77-81. 6. Perez Polo JR, Werrbach-Perez K, Ramacci MT, et al. Role of nerve growth factors in neurological disease. In: Agnoli A, Cahn J, Lassen N, et al. eds. <i>Senile dementias</i>, 2nd International Symposium. Paris: Libby; 1988:15-25. 7. Rai G, Wright G, Scott L, et al. Double-blind, placebo controlled study of acetyl-L-carnitine in patients with Alzheimer's dementia. <i>Curr Med Res Opin</i> 1990;11:638-647. 8. Bonavita E. Study of the efficacy and tolerability of L-acetylcarnitine therapy in the senile brain. <i>Int J Clin Pharm Ther Toxicol</i> 1986;24:511-516. 9. Sano M, Bell K, Cote L, et al. Double-blind parallel design pilot study of acetyl levocarnitine in patients with Alzheimer's disease. <i>Arch Neurol</i> 1992;49:1137-1141. 10. Spagnoli A, Lucca U, Menasce G, et al. Long-term acetyl-L-carnitine treatment in Alzheimer's disease. <i>Neurology</i> 1991;41:1726-1732. 11. Gecele M, Francesetti G, Meluzzi A. Acetyl-L-carnitine in aged subjects with major depression: clinical efficacy and effects on the circadian rhythm of cortisol. <i>Dementia</i> 1991;2:333-337. 12. Angelucci L, Ramacci MT. Hypothalamo-pituitary-adrenocortical functioning in aging: effects of acetyl-L-carnitine. In: DeSimone C, Martelli EA, eds. <i>Stress, Immunity and Aging, A Role for Acetyl-L-Carnitine</i>. Amsterdam: Elsevier; 1989. 13. Tempesta E, Casella L, Pirrongelli C, et al. L-acetylcarnitine in depressed elderly subjects. A cross-over study vs placebo. <i>Drugs Exp Clin Res</i> 1987;13:417-423. 14. Garzya G, Corallo D, Fiore A, et al. Evaluation of the effects of L-acetylcarnitine on senile patients suffering from depression. <i>Drugs Exp Clin Res</i> 1990;16:101-106. 15. Di Marzio L, Moretti S, D'Alo S, et al. Acetyl-L-carnitine administration increases insulin-like growth factor 1 levels in asymptomatic HIV-1-infected subjects: correlation with its suppressive effect on lymphocyte apoptosis and ceramide generation. <i>Clin Immunol</i> 1999;92:103-110. 16. Fedele D, Giugliano D. Peripheral diabetic neuropathy. Current recommendations and future prospects for its prevention and management. <i>Drugs</i> 1997;54:414-421. 17. Ido Y, McHowat J, Chang KC, et al. Neural dysfunction and metabolic imbalances in diabetic rats. Prevention by acetyl-L-carnitine. <i>Diabetes</i> 1994;43:1469-1477. 18. Onofrij M, Fulgente T, Melchionda D, et al. L-acetylcarnitine as a new therapeutic approach for peripheral neuropathies with pain. <i>Int J Clin Pharm Res</i> 1995;15:9-15. 19. Lowitt S, Malone JI, Salem AF, et al. Acetyl-L-carnitine corrects the altered peripheral nerve function of experimental diabetes. <i>Metabolism</i> 1995;44:677-680. 20. Swamy-Mruthinti S, Carter AL. Acetyl-L-carnitine decreases glycation of lens proteins: in vitro studies. <i>Exp Eye Res</i> 1999;69:109-115. 21. Calvani M, Arrigoni-Martelli E. Attenuation by acetyl-L-carnitine of neurological damage and biochemical derangement following brain ischemia and reperfusion. <i>Int J Tissue React</i> 1999;21:1-6. 22. Rosenthal RE, Williams R, Bogaert YE, et al. Prevention of postischemic canine neurological injury through potentiation of brain energy metabolism by acetyl-L-carnitine. <i>Stroke</i> 1992;23:1317-1318. 23. Aureli T, Micheli A, Di Cecco MF, et al. Effect of acetyl-L-carnitine on recovery of brain phosphorus
<p>Has the bulk drug substance been used previously to compound drug product(s)?</p>	<p>Yes.</p>
<p>What is the proposed use for the drug product(s) to be compounded with the nominated substance?</p>	<p>Acetyl-L-Carnitine is important for its role in fat metabolism, mitochondrial transfer across the membrane and provides energy to muscles including the heart. The supposed therapeutic attributes of acetyl-L-carnitine include: possible deficiency in vegans, Duchenne-type muscular dystrophy, and patients receiving dialysis, heart disease such as cardiomyopathy, arrhythmias, congestive heart failure, mitral valve prolapse, and angina pectoris, chemotherapy-induced peripheral neuropathy, cirrhosis of the liver, diabetes mellitus, trauma, intermittent claudication, infertility, Alzheimer's, AIDS, COPD, and may enhance athletic performance.</p>

** See Appendix 1 for Complete List of References

What is the reason for use of a compounded drug product rather than an FDA-approved product?	<p>There is no FDA-approved drug product containing acetyl-L-carnitine HCl. Acetyl-L-Carnitine is an acetylated form of L-carnitine and shows to be superior in bioavailability to L-Carnitine (Rebouche CJ. Kinetics, pharmacokinetics, and regulation of L-carnitine and acetyl-L-carnitine metabolism. Ann N Y Acad Sci 2004 Nov; 1033: 30-41). Acetyl-L-Carnitine has the capacity to cross the blood brain barrier and is structurally similar to neurotransmitter acetylcholine. It acts as an agonist when binding to acetylcholine receptors thus providing a supportive effect on the enzyme responsible for acetylcholine synthesis, choline acetyltransferase. The hydrochloride form, as seen in acetyl-L-carnitine HCl is used to convert insoluble amines into water-soluble compounds. In addition to providing L-carnitine, it provides acetyl groups that can be used for the formation of acetylcholine. Acetyl-L-carnitine has a variety of other neural effects that may be relevant to its potential as a nootropic compound. It can increase Protein Kinase C activity and reverse age-related decline in the number of NMDA receptors on the neuronal membrane.</p>
Is there any other relevant information?	Acetyl-L-carnitine is a derivative of levocarnitine.

Submitted electronically via www.regulations.gov

March 4, 2014

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

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

Dear Sir or Madam:

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

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

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

In addition to the IACP spreadsheet of bulk drug substances referenced above, NCPA would also like to formally submit collectively for review and consideration of the FDA Pharmacy Compounding Advisory Committee the drugs and standards contained within the *British Pharmacopeia*, the *European Pharmacopeia* and the *Japanese Pharmacopeia*. NCPA respectfully requests that all drugs and standards contained within these three pharmacopeias for which no USP corresponding monograph exists be accepted and approved to be used for the preparation of compounded medications under section 503A of the *Federal Food, Drug and Cosmetic Act*.

NCPA is requesting the recognition of these pharmacopoeias as there are examples of situations when our members need access to these alternative compendia for monograph information. NCPA members may receive requests to compound medications that do not have a USP monograph, nor is the drug substance being used a component of an FDA approved drug product. When these situations arise, the *British Pharmacopeia*, the *European Pharmacopeia* and the *Japanese Pharmacopeia* are used in practice to ensure compounds are made with the highest assurance of quality.

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

Sincerely,

A handwritten signature in black ink, appearing to read "Steve Pfister", with a long horizontal flourish extending to the right.

Steve Pfister
Senior Vice President, Government Affairs

Attachment

National Community Pharmacists Association -- 503A nomination for Acetyl L Carnitine Hydrochloride

Ingredient Name	Acetyl-L-carnitine hydrochloride
Chemical Name	2-(acetyloxy)-3-carboxy-N,N,N-trimethyl-, chloride, R-1-propanaminium
Common Name	Acetyl-L-carnitine (ALCAR)
UNII Code	6DH1W9VH8Q
Description of strength, quality, stability and purity	From PCCA Database MSDS: Product is 100% by weight and stable; should be protected from strong oxidizing agents and moisture.
Ingredient Format(s)	Powder
Recognition in Pharmacopeias	Not USP; sold OTC in US as a dietary supplement.
Final Compounded Formulation Dosage Form(s)	Capsules, oral solution
Final Compounded Formulation Strength	Capsules: 100-500mg, Oral Solution: 1-10%
Final Compounded Formulation Route(s) of Administration	Oral
Bibliographies on Safety and Efficacy Data	<p>Campone M, et al. A double-blind, randomized phase II study to evaluate the safety and efficacy of acetyl-L-carnitine in the prevention of sagopilone-induced peripheral neuropathy. <i>Oncologist</i>. 2013;18(11):1190-1. [http://www.ncbi.nlm.nih.gov/pubmed/24105751?dopt=Abstract]</p> <p>Muralidharan A, et al. Deciphering the potential efficacy of acetyl-L-carnitine (ALCAR) in maintaining connexin-mediated lenticular homeostasis. <i>Mol Vis</i>. 2012; 18: 2076–2086. [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3413440/]</p>

Final Compounded Formulation Clinical Rationale and History of Past Use	<p>The main function of L-carnitine is to transfer long-chain fatty acids in the form of their acyl-carnitine esters across the inner mitochondrial membrane before beta-oxidation. In humans, it is synthesized in the liver, kidney, and brain and actively transported to other areas of the body. For example, 98% of the total body L-carnitine is confined to the skeletal and cardiac muscle at concentrations approximately 70 times higher than in the blood serum. Supplementation may be necessary in rare cases of primary carnitine deficiency, which may be caused by a defect in carnitine biosynthesis, a defect in carnitine active transport into tissue, or a defect in renal (kidney) conservation of carnitine. Known conditions of secondary deficiency of carnitine (insufficiency), in which L-carnitine is effective, include chronic stable angina and intermittent claudication characterized by distinct tissue hypoxia (low oxygen levels). Another condition that may benefit from carnitine supplementation is decreased sperm motility. Although use in preterm infants suggests carnitine supplementation may aid in maintaining or increasing plasma carnitine levels and possibly weight gain, carnitine is not routinely added to preterm total parenteral nutrition (TPN). However, soy-based infant formulas are fortified with carnitine to levels found in breast milk. In 1986, the U.S. Food and Drug Administration (FDA) approved L-carnitine for use in primary carnitine deficiency. D-carnitine or DL-carnitine may cause secondary L-carnitine deficiency and should not be used. Used as a Supplement for Cognitive impairment, neuropathy, peyronie's disease; male infertility, age-related testosterone deficiency, Alzheimer's disease, antioxidant.</p>
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March 4, 2014

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

Sincerely,

A handwritten signature in black ink, appearing to read "A. Lopez".

Aaron R. Lopez, JD
Senior Director of Public Affairs
PCCA

A handwritten signature in black ink, appearing to read "John Voliva".

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	Acetyl-L-Carnitine
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	(3-Carboxy-2-hydroxypropyl)trimethylammonium acetate (ester) chloride
Common Name(s)	Acetylcarnitine; ALCAR
UNII Code	NDW10MX58T
Chemical Grade	N/A
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmacopeias or registered in other countries	OTC in US as a dietary supplement
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Capsules; Oral Solution
Compounded Strengths	100-500 mg Capsules; 1-10% Oral Solution
Anticipated Routes of Administration	Oral

Safety & Efficacy Data	Campone M, et al. A double-blind, randomized phase II study to evaluate the safety and efficacy of acetyl-L-carnitine in the prevention of sagopilone-induced peripheral neuropathy. <i>Oncologist</i> . 2013;18(11):1190-1. [http://www.ncbi.nlm.nih.gov/pubmed/24105751?dopt=Abstract]
	Muralidharan A, et al. Deciphering the potential efficacy of acetyl-L-carnitine (ALCAR) in maintaining connexin-mediated lenticular homeostasis. <i>Mol Vis</i> . 2012; 18: 2076–2086. [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3413440/]
Used Previously to compound drug products	Cognitive impairment, neuropathy, peyronie’s disease; male infertility, age related testosterone deficiency, Alzheimer’s disease, antioxidant
Proposed use	Cognitive impairment, neuropathy, peyronie’s disease; male infertility, age related testosterone deficiency, Alzheimer’s disease, antioxidant
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: 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; Oral Solution: USP <795> recommendation of BUD for “water-containing oral formulations” – “not later than 14 days when stored at controlled cold temperatures.”



PCCA USA
8901 South Wilcrest Drive
Houston, TX 77099
Tel: 281.933.6948
Fax: 281.933.6627

PCCA Canada
744 Third Street
London, ON N5V 5J2
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: ACETYL-L-CARNITINE HYDROCHLORIDE (N)
ITEM NUMBER: 30-2611 CAS: 5080-50-2
LOT NUMBER: C161485 MW: 239.7000000000
MFG. DATE: 08/18/2012 FORMULA: C9H17NO4.HCl
EXPIRATION: 08/31/2017

TEST	SPECIFICATIONS	RESULTS
Assay.	97-103 %	99.3 %
Description	pass <i>WHITE CRYSTALLINE POWDER; HYGROSCOPIC; CHARACTERISTIC ODOR AND TASTE.</i>	pass
Heavy Metals (as Pb)	<=20 ppm	10 ppm
Identification	pass	pass
Loss on Drying.	<=1.0 %	0.35 %
Melting point	pass <i>About 187</i>	pass 187.6C
Solubility	pass <i>VERY SOLUBLE IN WATER; SOLUBLE IN ALCOHOL</i>	pass
Spec. Rotation	-29.0--28.0	-28.1

QC APPROVED
PRINT DATE: 3/2/2014
PAGE: 1 of 1

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.

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS

Corporate Offices: 4638 Riverstone Blvd. | Missouri City, Texas 77459 | 281.933.8400
Washington DC Offices: 1321 Duke Street, Suite 200 | Alexandria VA 22314 | 703.299.0796

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

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

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

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

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

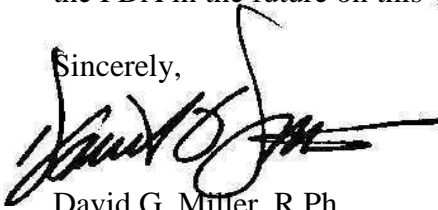
In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

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

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

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

Sincerely,

A handwritten signature in black ink, appearing to read "David G. Miller", with a stylized flourish extending to the right.

David G. Miller, R.Ph.
Executive Vice President & CEO



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

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Acetyl-L-Carnitine Hydrochloride
Chemical/Common Name Acetyl-L-Carnitine	2-(acetyloxy)-3-carboxy-N,N,N-trimethyl-, chloride, ®-1-propanaminium;
Identifying Codes	5080-50-2
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 <i>(including foreign recognition)</i>	Not Listed in USP/NF for this specific salt/form

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography <i>(where available)</i>	

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.

Appendix 1: Reference list in 503A Nominations for Acetyl-L-carnitine/Acetyl-L-carnitine hydrochloride

References cited by Alliance for Natural Health USA, Integrated Medical Consortium, McGuff Compound Pharmacy Services, American Association of Naturopathic Physicians, and the American College for the Advancement of Medicine

- Parnetti L, Gaiti A, Mecocci P, et al. Pharmacokinetics of IV and oral acetyl-L-carnitine in a multiple dose regimen in patients with senile dementia of Alzheimer type. *Eur J Clin Pharmacol* 1992;42:89-93.
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Tab 6b

Acetyl-L-Carnitine

FDA Review



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: January 27, 2016

FROM: Ben Zhang, PhD
Chemistry Reviewer, Office of Pharmaceutical Quality

David Carbone, PhD
Pharmacology/Toxicology Reviewer, Division of Neurology Products

Kenneth Bergmann, MD
Medical Officer, Division of Neurology Products

Gerald D. Podskalny, DO, MSPH
Clinical Team Leader, Division of Neurology Products

THROUGH: Ramesh Sood, PhD
Senior Scientific Advisor (acting), Office of New Drug Products, Office of
Pharmaceutical Quality

Lois Freed, PhD
Supervisory Pharmacologist, Division of Neurology Products

Eric Bastings, MD
Deputy Director, Division of Neurology Products

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Acetyl-L-Carnitine for Inclusion on the 503A Bulk Drug Substances
List

I. INTRODUCTION

Acetyl-L-carnitine 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 treatment of Alzheimer's disease, chemotherapy-induced peripheral neuropathy, hepatic encephalopathy in patients with cirrhosis of the liver, and for other uses (possible carnitine deficiency in vegans, patients receiving dialysis, antioxidant, enhanced athletic performance, trauma, infertility, cognitive impairment, diabetes mellitus, AIDS, heart diseases such as cardiomyopathy, arrhythmias, congestive heart failure, mitral valve prolapse, angina pectoris, Duchenne-type muscular dystrophy, chronic obstructive pulmonary disease, age-related testosterone deficiency, intermittent claudication, and Peyronie's disease). This review will focus

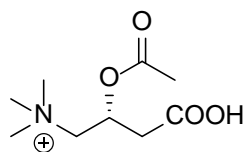
on the chemotherapy-induced peripheral neuropathy, hepatic encephalopathy, and Alzheimer's disease indications.

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 acetyl-L-carnitine 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?

Yes. The drug substance is an acetylated form of L-carnitine with the following molecular structure:

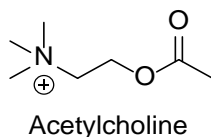


Acetyl-L-carnitine is found in adequate amounts in healthy humans. This compound is currently marketed as a dietary supplement as capsules (250 mg, 400 mg, 500 mg, 750 mg, and 1000 mg) and tablets (500 mg, 750 mg, and 1000 mg).

The following sources were consulted in the preparation of this review: PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia, USP/NF.

1. *Stability of the API and likely dosage forms*

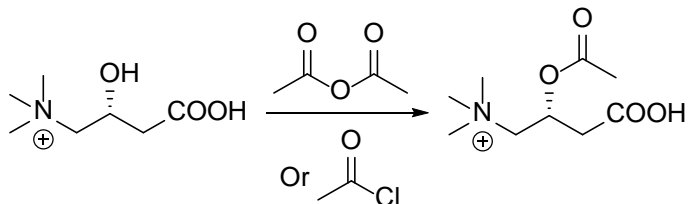
Acetyl-L-carnitine is likely to be stable as a solid. No report on the stability of this compound has been found in the literature. However, its aqueous solution is unlikely to be as stable as its solid form. Hydrolysis may occur on the ester group in aqueous solutions over time. This issue has been reported for acetylcholine (structure shown below), which is structurally similar to acetyl-L-carnitine. In aqueous solutions, modest degradation of acetylcholine was observed after 28 days at room temperature, and significant degradation happened at 50° C (Sletten et al., 2005). Given the similarities with acetylcholine, under ordinary storage conditions, acetyl-L-carnitine is likely to be stable when formulated as capsules, but not likely to be as stable when formulated as oral or injectable solutions.



The intended dosage forms proposed in the nomination are capsules, IV injection solutions, and oral solutions.

2. Probable routes of API synthesis

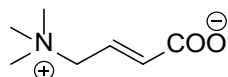
Acetyl-L-carnitine is most often synthesized by the acetylation of L-carnitine (Voeffray et al., 1987; Zhu et al., 2003; Chen et al., 2014). The conditions for the acetylation reaction may vary, but acetic anhydride and acetyl chloride are the most commonly used acetylation reagents.



3. Likely impurities

Likely impurities may include:

- 1) Residual reagents from reactions or purification processes, such as acetic acid;
- 2) Trace amount of the starting material, L-carnitine.
- 3) Byproduct from the elimination reaction, crotonobetaine (structure shown below).



4. Toxicity of those likely impurities

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

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

Acetyl-L-carnitine is a white crystalline powder, highly soluble in water and alcohol. No further information on the influence of particle size and polymorphism on bioavailability were found in the literature.

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

Acetyl-L-carnitine has been characterized with proton nuclear magnetic resonance (^1H NMR) spectroscopy, carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and mass spectrometry (MS).

Conclusions: Acetyl-L-carnitine is a well-characterized small molecule. The compound is likely to be stable as a solid under ordinary storage conditions when kept away from moisture and heat, but may have stability issues when formulated as an aqueous solution. The nominated compound is easily characterized with various analytical techniques and the synthesis of this compound has been well developed.

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

1. Nonclinical Assessment

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

Literature searches were performed in PubMed using the terms *acetyl l carnitine* and *carnitine* alone or in combination with the following terms: cognition, neuropathy, Alzheimer, Duchenne, mice, rats, dogs, cynomolgus, open field, heart rate, cardiac, blood pressure, ecg, respiration, respiratory rate, tidal volume, cancer, reproduction, fertility, mutagen, or impurity. Searches were performed in TOXNET using the terms *acetyl l carnitine* and *carnitine*. Standard searches for *acetyl l carnitine* alone or with the term *impurity* were performed using Google. The date range was not restricted in any search.

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

Acetyl-L-carnitine (ALC) is synthesized in human brain, liver, and kidney by acetylation of carnitine and is involved in the control of mitochondrial acyl-coenzyme A (acylCoA)/CoA balance and energy homeostasis, and in phospholipid and acetylcholine synthesis. ALC is available in the United States as a dietary supplement. No information was identified regarding potential impurities other than that discussed above.

b. Safety pharmacology

Administration of up to 1 mg/kg ALC in Sprague Dawley rats by intraperitoneal injection increased ambulation and rearing behavior in an open field tests (Drago et al., 1986). Information on cardiac or respiratory toxicity was not found.

c. Acute toxicity

Acute intravenous administration of ALC in mice resulted in clonic convulsions, cyanosis, and death (Fanelli, 1978); the LD_{50} was 1420 mg/kg. Intraperitoneal injection of 300 mg/kg ALC was not associated with acute toxicity in rats 5 to 28 months of age (Paradies et al., 1999).

d. Repeat dose toxicity

In mice, oral administration of ALC (406 mg/kg) for 4 weeks had no adverse effects (Morand et al., 2013). In rats, no adverse effects were reported following oral administration of 300 mg/kg ALC for 2 weeks or following intraperitoneal injection of 250 mg/kg ALC for 5 days. In dogs, oral dosing with 27.5 mg/kg ALC for 133 days resulted in no significant toxicity (Christie et al., 2009). No adverse effects were reported in juvenile male or female cynomolgus monkeys administered 50 mg/kg ALC by intramuscular injection for 2 weeks (Bodis-Wollner et al., 1991). Toxicity studies of longer duration were not found.

e. Mutagenicity

No information was available.

f. Developmental and reproductive toxicity

There was no effect of the ALC hydrolysis product L-carnitine on fertility, litter size, or offspring weight over 3 reproductive cycles when administered in the diet (1g ALC/kg chow) to female rats (Brandsch et al., 2003). No other information was available.

g. Carcinogenicity

No information was available.

h. Toxicokinetics

No information was available.

Conclusions: Although the information available on the toxicity of ALC was minimal, a literature search did not reveal any significant toxicity associated with ALC administration in animals.

2. *Human Safety*

This discussion of safety in humans considers the close pharmacological relationship between acetyl-L-carnitine (ALC) and L-carnitine. L-carnitine (also known as levocarnitine) is FDA-approved for “the treatment of primary systemic carnitine deficiency, acute and chronic treatment of patients with an inborn error of metabolism, which results in a secondary carnitine deficiency.” Secondary carnitine deficiency is associated with glutaric aciduria II, methyl malonic aciduria, propionic acidemia, and medium chain fatty acylCoA dehydrogenase deficiency, among others.

In mammals, the carnitine pool consists of nonesterified L-carnitine and many acylcarnitine esters, including ALC. Carnitine homeostasis is maintained by absorption from diet, a modest rate of synthesis, and efficient renal reabsorption. Dietary L-carnitine is absorbed by active and

passive transfer across cell membranes in the gastrointestinal system (Rebouche, 2004). Acetyl-L-carnitine is synthesized in human brain, liver, and kidney by acetylation of carnitine in cellular mitochondria. However, its metabolic relationship to L-carnitine is complex and not fully elucidated. If ingested, ALC can also act as a pro-drug of L-carnitine (Rebouche, 2004; Marzo et al., 1989). As such, it would be difficult to distinguish differences in the safety of one from the other.

Carnitine is naturally occurring in many dietary sources, but is in highest concentration in red meat. L-carnitine and ALC are also available as food supplements. The NIH Dietary Supplement Label Database (<http://dsld.nlm.nih.gov/dsld/index.jsp>) lists ALC as a nutritional supplement or dietary ingredient in 34 products. It is most commonly available as 500 or 750 mg capsules and is widely available to consumers.

For this review, we sought out published results, studies available in the public domain, and authoritative reviews. PubMed and ClinicalTrials.gov were consulted in the preparation of this review. There is considerable activity for both these drugs.

PubMed Search: January 1995 - October 2015					ClinicalTrials.gov	
Search Qualifiers	Citations, all categories	All Clinical Trial Publications	Phase 2 Clinical Trials	Phase 3 Clinical Trials	Completed or Ongoing	Open and Recruiting
Acetyl-L-Carnitine	995	109	5	0	34	6
L-Carnitine	8853	594	15	9	138	28

Of the 39 citations submitted by petitioners, we considered only the few that reported clinically derived information of efficacy and/or safety in humans collected in a methodologically sound manner (e.g., randomized, blinded, placebo-controlled trials). Special emphasis was placed on reviews such as Cochrane Collaboration meta-analyses that have surveyed some of the proposed uses. These reviews emphasize the evaluation of clinical efficacy and only comment on safety when there is sufficient information present. Because clinical trials published in medical journals generally do not include detailed safety information and often de-emphasize adverse events, these reports carry little information on risks related to ALC, which is often broadly characterized as “well tolerated.”

a. Reported adverse reactions

In light of the close chemical and metabolic relationship of ALC and L-carnitine, this safety review also refers to clinical information from the labels of FDA-approved L-carnitine products. L-carnitine is marketed in three formulations. L-carnitine injection, oral tablets, and oral solution are marketed under separate new drug applications (NDA). Several generic versions of these products are marketed under abbreviated new drug applications (ANDA).

FDA approved products containing L-carnitine:

L-carnitine NDAs held by Sigma Tau:

NDA 018948 (Carnitor, 1985) Oral tablet 330 mg

NDA 019257 (Carnitor and Carnitor SF [sugar free], 1986) Oral solution 1 g/10 ml

NDA 020182 (Carnitor, 1992) Injectable solution 200 mg/ml

L-carnitine ANDAs:

075567 (Eurohlth Intl Sarl, 2001) Injectable solution 200 mg/ml

075861 (Luitpold, 2001) Injectable solution 200 mg/ml

076851 (Lyne, 2004) Oral solution 1 g/10 ml

076858 (Core Pharma, 2004) Oral tablet 330 mg

077399 (Hi Tech Pharma) Oral solution 1 g/10 ml

L-carnitine is labeled for oral dosing beginning at 1 gram daily to a maximum of 3 grams a day. Intravenous solution is given as 50 mg/kg/day in divided doses (every 3 to 4 h) after an initial loading dose.

The last approved label (revised May 29, 2015,

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018948s026,019257s012,020182s013lbl.pdf) contains the following:

- There are no known contraindications or warnings.
- There are no reports of L-carnitine overdose.
- The safety and efficacy of oral levocarnitine has not been evaluated in patients with renal insufficiency. Chronic administration of high doses of oral levocarnitine in patients with severely compromised renal function or in end stage renal disease (ESRD) patients on dialysis may result in accumulation of the potentially toxic metabolites (trimethylamine and trimethylamine-N-oxide).
- Drug interaction: reports of international normalized ratio (INR) increase with the use of warfarin have been observed.
- The effect on human pregnancy and unborn fetus are not known. Studies in dairy cows indicate it would likely be excreted in human milk.
- Transient nausea and vomiting have been observed. Less frequent adverse reactions are body odor, nausea, and gastritis. An incidence for these reactions is difficult to estimate due to the confounding effects of the underlying pathology.
- Seizures have been reported to occur in patients, with or without pre-existing seizure activity, receiving either oral or intravenous levocarnitine. In patients with pre-existing seizure activity, an increase in seizure frequency and/or severity has been reported.

Of interest is the ALC dose-related body odor commonly described as “peculiar.” While not injurious, it is important to note that drug-related body odors can be quite noticeable and put the blinding in trials at risk, leading to biased assessments.

The table below lists the adverse events that have been reported in two L-carnitine double-blind, placebo-controlled trials in patients on chronic hemodialysis after intravenous injection. Events occurring at $\geq 5\%$ are reported without regard to causality. (Doses listed in milligrams reflect mg/kg/day total daily dose.) These tables contain safety information collected in well-controlled clinical trials and have been subject to FDA review. Patients with renal failure in these trials could be considered more susceptible to adverse events from L-carnitine exposure, but the breadth of adverse events appear to be no different from those seen in other patient populations receiving this drug.

Adverse Events with a Frequency $\geq 5\%$ Regardless of Causality by Body System

	Placebo (n=63)	Levocarnitine 10 mg (n=34)	Levocarnitine 20 mg (n=62)	Levocarnitine 40 mg (n=34)	Levocarnitine 10, 20 & 40 mg (n=130)
Body as Whole					
Abdominal pain	17	21	5	6	9
Accidental injury	10	12	8	12	10
Allergic reaction	5	6			2
Asthenia	8	9	8	12	9
Back pain	10	9	8	6	8
Chest pain	14	6	15	12	12
Fever	5	6	5	12	7
Flu syndrome	40	15	27	29	25
Headache	16	12	37	3	22
Infection	17	15	10	24	15
Injection site reaction	59	38	27	38	33
Pain	49	21	32	35	30
Cardiovascular					
Arrhythmia	5	3		3	2
Atrial fibrillation			2	6	2
Cardiovascular disorder	6	3	5	6	5
Electrocardiogram abnormal		3		6	2
Hemorrhage	6	9	2	3	4
Hypertension	14	18	21	21	20
Hypotension	19	15	19	3	14
Palpitations		3	8		5
Tachycardia	5	6	5	9	6
Vascular disorder	2		2	6	2
Digestive					
Anorexia	3	3	5	6	5
Constipation	6	3	3	3	3
Diarrhea	19	9	10	35	16
Dyspepsia	10	9	6		5
Gastrointestinal disorder	2	3		6	2
Melena	3	6			2
Nausea	10	9	5	12	8
Stomach atony	5				
Vomiting	16	9	16	21	15
Endocrine System					
Parathyroid disorder	2	6	2	6	4
Hemic/Lymphatic					
Anemia	3	3	5	12	6
Metabolic/Nutritional					
Hypercalcemia	3	15	8	6	9
Hyperkalemia	6	6	6	6	6
Hypervolemia	17	3	3	12	5

Peripheral edema	3	6	5	3	5
Weight decrease	3	3	8	3	5
Weight increase	2	3		6	2
Musculo-Skeletal					
Leg cramps	13		8		4
Myalgia	6				
Nervous					
Anxiety	5		2		1
Depression	3	6	5	6	5
Dizziness	11	18	10	15	13
Drug dependence	2	6			2
Hypertonia	5	3			1
Insomnia	6	3	6		4
Paresthesia	3	3	3	12	5
Vertigo		6			2
Respiratory					
Bronchitis			5	3	3
Cough increase	16		10	18	9
Dyspnea	19	3	11	3	7
Pharyngitis	33	24	27	15	23
Respiratory disorder	5				
Rhinitis	10	6	11	6	9
Sinusitis	5		2	3	2
Skin And Appendages					
Pruritus	13		8	3	5
Rash	3		5	3	3
Special Senses					
Amblyopia	2		6		3
Eye disorder	3	6	3		3
Taste perversion			2	9	3
Urogenital					
Urinary tract infect	6	3	3		2
Kidney failure	5	6	6	6	6

Adverse Events Reported to FDA

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events with a serious outcome associated with the use of ALC for the years 2000 to 2015.

As defined by CFR 314.80, *serious* includes death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. It is important to note that, because ALC is not an FDA-approved product, FAERS contains reports of ALC only when it is reported as a co-suspect product. FAERS contained 21 such reports, but following OSE review, a case series of 13 remained (reasons for exclusion included duplicate cases, erroneous drug coding, event preceding exposure, and so forth). Of these 13 cases, the attribution of ALC to the reported adverse events could not be determined, or it was unlikely given the limited case details or the presence of a more likely alternative etiology. All cases reported at least one additional suspect product. Treatment of peripheral neuropathy was the reason for use in five cases; the rationale for use was not reported in the others.

The Center for Food Safety and Nutrition was also consulted to search their adverse event database, CAERS, for adverse events associated with ALC. Queries using broad search terms were used to find events associated with products containing any form of carnitine.

Reports of 611 events were found, of which ALC was the product ingredient in just 68 of these. Of these 68 reports, ALC was the solitary ingredient in products associated with only eight events. The products involved in the other reports contained ALC formulated with a variety of vitamins, minerals, trace metals, and unidentifiable proprietary named ingredients. These reports included scant information about the effected individual's baseline medical condition, how much drug was taken, the seriousness of the event, and whether recovery occurred. Among the 68 reports, two sudden (presumed cardiac) deaths occurred. Other important unrelated health problems co-occurred in 31 patients at the time of the report. Of interest, five consumers reported convulsions, seven reported gastrointestinal distress, and allergic complaints occurred in seven (e.g., rash, swelling of face, hypersensitivity, etc.).

b. Clinical trials assessing safety

In the course of reviewing the three uses considered for compounding (see below), the individual studies and meta-analyses were scrutinized for useful adverse reaction information. No new or previously undescribed adverse drug related reactions were described when compared to L-carnitine. The most common adverse drug reactions collected in a non-systematic fashion from the many case reports and small trials are: gastrointestinal distress, hypertension, headache, dizziness, fever, vomiting, paresthesia, cough, tachycardia, palpitation, peripheral edema, vertigo, rash, bronchitis, and gastritis.

The meta-analysis reviewing ALC as a treatment for hepatic encephalopathy reports that "ALC was well tolerated and adverse events were reported infrequently and were minor" (Jiang et al., 2013). The individual citations for the placebo-controlled trials that were reviewed offered no more comment than that (Cecere et al., 2002; Malaguarnera et al., 2003, 2005, 2008, 2011a, 2011b, and 2011c).

The meta-analysis reviewing ALC as a treatment for dementia states that various adverse events were reported, but there were no statistically significant differences between treated and placebo groups (Hudson et al., 2003). Those reviewers note that there were large numbers of adverse events in the treated group as compared to the placebo controlled group in one unpublished Sigma Tau study of 60 patients treated with 2 g/d for 26 weeks. No further details were given. Thal et al., (1996) reported on a large multicenter trial in Alzheimer's disease (AD) supported by Sigma Tau. 431 patients who had AD for an average of 4 years entered the study, and 83% completed. Their mean age was 72 years, and 55 % were women. During the trial, 7 patients died, 3 of whom were taking ALC. The deaths were not thought to be related to the test drug. According to the authors, there were no "clinically significant" drug side effects. Three adverse events were considerably more common in the treatment group: body odor, increased appetite, and rash.

The placebo-controlled trials conducted with ALC for the prevention or treatment of peripheral neuropathy (see below) did not contribute any new information about drug related side effects. It should be noted that most of these studies were performed in

persons with cancer, who were often receiving chemotherapy and were therefore quite ill at baseline.

Where commented upon, clinical laboratory studies were not affected in all studies reviewed.

c. Pharmacokinetic data

The bioavailability of dietary L-carnitine is 54-87% and is dependent on the amount of L-carnitine in the meal. Absorption of L-carnitine dietary supplements is primarily passive; bioavailability is 14-18% of dose. Unabsorbed L-carnitine is mostly degraded by microorganisms in the large intestine. After single-dose intravenous administration (0.5 g), acetyl-L-carnitine is rapidly, but not completely, hydrolyzed, and acetyl-L-carnitine and L-carnitine concentrations return to baseline within 12 hours. As circulating L-carnitine concentration increases (as after high-dose intravenous or oral administration of L-carnitine), efficiency of reabsorption decreases, and clearance increases, resulting in rapid decline of circulating L-carnitine concentration to baseline. Elimination kinetics for acetyl-L-carnitine are similar to those for L-carnitine. There is evidence for renal tubular secretion of both L-carnitine and acetyl-L-carnitine (Rebouche, 2004).

Intravenous administration has been studied in a small number of both healthy volunteers (Marzo et al., 1989) and patients with dementia (Parnetti et al., 1992). After single injection, plasma ALC levels peaked quickly and returned to baseline within 12 hours. Plasma concentration of L-carnitine, in this case a metabolite of ALC, peaked at 30 to 60 minutes and declined to baseline by 24 hours. Both are actively cleared by the kidney. In the dementia population, measurement of ALC and L-carnitine after chronic administration of ALC (60 days) reveals that with chronic administration, active renal excretion, which increases to meet the rise in serum concentration of ALC and L-carnitine, compensates to lower serum concentrations of both ALC and L-carnitine (in the table below from Parnetti et al., 1992, T8 through T60 refers to the day of sampling in this two month study).

Table 6. Mean (SD) plasma concentration (nmol · ml⁻¹) of L-carnitine (LC), total acid soluble L-carnitine (TC), acetyl-L-carnitine (ALC) and short chain L-carnitine esters (SCCE) during multiple dose therapy. (T8–T10 i.v.; T11–T60 oral route)

	Period C			Period D			
	T8	T9	T10	T11	T12	T35	T60
LC	178 (83.3)	132 (45.9)	166 (50.7)	58.0 (12.0)	55.7 (10.7)	46.3 (8.82)	43.9 (10.5)
TC	928 (509)	612 (219)	965 (452)	71.9 (13.1)	66.4 (11.1)	57.4 (9.04)	55.5 (10.9)
ALC	722 (425)	445 (154)	737 (360)	12.4 (3.57)	9.77 (2.24)	9.72 (2.94)	10.3 (3.72)
SCCE	750 (430)	480 (176)	799 (409)	13.9 (4.26)	10.7 (2.38)	10.9 (3.14)	11.6 (3.74)

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

L-carnitine is approved for use as noted above. Acetyl-L-carnitine is also widely available as a nutritional supplement, although such supplements are not drugs that can

be used to treat disease states. There are FDA-approved treatments for the conditions proposed for treatment (see Section C.3 below).

Conclusions: Acetyl-L-carnitine has been studied in large multicenter clinical trials for a variety of indications. To the extent elaborated upon in these study reports from the publically available scientific literature, it appears to be generally non-toxic if considered for chronic use. However, there are approved alternative treatments for the conditions proposed here. The effect on blood clotting and the risk for seizures identified in the labeling of FDA-approved L-carnitine products suggest that patients with these conditions should avoid ALC.

ALC is closely chemically related to L-carnitine, a drug approved in the United States. The adverse event profile appears to be very similar to that drug. If compounded, it would likely be safe when taken orally up to 3 g /d. Chronic administration of ALC does not require intravenous or oral loading. There are no nominations for urgent medical uses of ALC for which a loading dose may be useful.

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

The uses proposed in the nominations for ALC include a wide variety of syndromes and conditions. Some of the proposed uses are not considered in this review because they were unevaluable. Some nominations cited support from studies performed with other members of the L-carnitine family of compounds. For example, L-carnitine and propionyl-L-carnitine, but not ALC, have been studied in intermittent claudication (Delaney et al., 2013). Some conditions were included in the nomination supported only by non-clinical laboratory work with no evidence from studies in humans.

In general, there are few efficacy trials of ALC that were performed in a randomized, blinded, and methodologically sound fashion. Relevant publications in this regard are summarized below. Outside of these proposed areas of use, the remaining conditions lack evaluable data supporting efficacy. Special emphasis was placed on reviews such as Cochrane Collaboration meta-analyses that have surveyed some of the proposed uses below. These reviews encompass the studies submitted in support of the nomination.

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

Chemotherapy-induced peripheral neuropathy

The disease process causing peripheral neuron damage puts a greater requirement for cellular energy on the affected tissue. (Fedele et al., 1997). Because of the putative *neurotrophic* properties of ALC suggested by non-clinical studies, it was hypothesized that ALC would benefit peripheral neuropathy by augmenting neuronal metabolic processes.

Peripheral neuropathy can result from a variety of diseases and toxic exposures (e.g., HIV, cancer chemotherapy, and diabetes mellitus). A PubMed search reveals that studies have been performed with ALC in each of these therapeutic areas. Of the 13 trials identified, the small

single-center studies have found positive effects of ALC with a variety of efficacy measures, including clinical pain scales and nerve conduction studies. However, these small single-center studies all suffer from methodological shortcomings. For example, it is not clear to what extent a modest reduction in pain or a small improvement in nerve conduction velocity is clinically significant.

Bianchi et al., (2005) measured the function of peripheral nerves using the speed of conduction of their nerve signals as the efficacy outcome in an open trial of 25 patients taking 3 g/d for 8 weeks. The nerve conduction tests were thought to be *objective* and no placebo control was employed. However, closer examination reveals the conduction velocity to still be markedly abnormal and that the improvement was quite small. If the study had had a measure of the clinical meaningfulness of this positive result, it would likely have revealed that, although significant statistically, it had no clinical import. In addition, it was not substantiated by other measures of nerve function (amplitude of the nerve signal). Conduction velocity was significantly increased and touted as such. In addition, limb temperature can significantly alter nerve conduction velocity. There is no agreement on the method or the duration that warmth that needs to be applied to adequately warm limbs to eliminate the effects of temperature change on the measurement of nerve conduction velocity (Cherniack et al., 2008). Temperature induced changes in nerve conduction velocity appear to be more pronounced in patients with polyneuropathy (Franssen et al., 1999). The study also analyzes the same data using multiple different methods and this increases the chances of having a false positive result. Secondary measures included patient-reported outcomes of neuropathy severity, and all patients perceived themselves as better. Without adequate blinding, randomization, and controls, it is impossible to know what to attribute to placebo effect.

DeGrandis and Minardi (2002) performed a blinded, randomized, placebo-controlled, pharmaceutical-sponsored trial of 333 patients with diabetic neuropathy treated with 2 g/d for 1 year. This trial also showed a modest increase in nerve conduction velocity. The authors themselves put this finding into perspective: “It should be noted that, overall, the absolute magnitude of the treatment-related changes in [nerve conduction velocity] parameters recorded in our study was relatively small.”

The multicenter trials performed with well-defined methodologies and rigorous controls for antiretroviral toxic neuropathy in patients with HIV infection (Youle et al., 2007), prevention of sagopilone-induced peripheral neuropathy (Campane et al., 2013), prevention of chemotherapy-induced peripheral neuropathy in patients with multiple myeloma (Callander et al., 2014), and prevention of taxane-induced neuropathy in adjuvant breast cancer therapy (Hershman et al., 2013) have been non-confirmatory.

Cirrhosis of the liver

ALC has not been used to treat cirrhosis of the liver, but has been studied as a treatment for the generalized brain dysfunction (hepatic encephalopathy) that results from cirrhosis. Hepatic encephalopathy (HE) is a common and potentially devastating complication of both acute liver failure and of chronic liver disease. It may be mild with clinically undetectable dysfunction of cognition, but severe HE can result in coma and death.

When the liver dysfunctions, a variety of physiological processes are impaired, but a key pathogenic feature is the inability to eliminate ammonia from the body. Ammonia is a metabolic by-product of nitrogen-containing compounds (e.g., proteins). It is metabolized by the liver to urea, which is excreted by the kidneys, although the brain and muscle are also important repositories for ammonia. In liver disease, the hepatic urea cycle is overloaded or bypassed (portosystemic shunting), and excess ammonia enters the systemic circulation (McPhail et al., 2010). Diagnosis of HE is made by measuring arterial ammonia, with supportive evidence from electroencephalography and psychometric testing. Current treatments of HE are thought to improve the syndrome through additional pathways beyond the lowering arterial ammonia.

Jiang et al., (2013) systematically reviewed the therapeutic efficacy of ALC in patients with hepatic encephalopathy. Out of 33 reviewed, the authors found seven reports (table below) that fit their criteria for randomized clinical trials of sufficient quality to be considered for review (Cecere et al., 2002; Malaguarnera et al., 2003, 2005, 2008, 2011a, 2011b, and 2011c). These studies share a common primary efficacy outcome, a reduction of serum ammonia levels. Secondary outcomes include liver function tests, some general cognitive measures, and electroencephalography (EEG).

The general conclusion of the analysis is that ALC was effective in reducing serum ammonia levels. However, there were no outcomes that suggested the clinical meaningfulness of a mean reduction of serum ammonia by 26 mg/dl. No conclusions were drawn regarding the consistency of secondary outcomes.

Mar Malaguarnera ⁹	2011	Italy	SHE	67 (33/34)	T: ALC 2g, bid C: placebo	90d	ALT, AST, γ -GT, ALB, ALP, PT, serum ammonia, psychometric tests, EEG, HRQL, etc.
Mic Malaguarnera ¹⁰	2011	Italy	HE 3	60 (30/30)	T: ALC 2g, bid C: placebo	90d	Psychometric tests, EEG, ALT, AST, PT, serum ammonia, etc.
Angelo Cecere ¹¹	2002	Italy	SHE	27 (16/11)	T: LC 6g/day C: no treatment	4weeks	Psychometric test, serum ammonia, neurological function test, etc.
Mic Malaguarnera ^{12a}	2011	Italy	HE 1 and HE 2	121 (61/60)	T: ALC 2g, bid C: placebo	90d	Mental fatigue score, serum ammonia, etc.
Mar Malaguarnera ¹³	2008	Italy	SHE	125 (65/60)	T: ALC 2g, bid C: placebo	90d	Liver Function Assessment, EEG, ALT, AST, serum ammonia, etc.
Mar Malaguarnera ¹⁴	2005	Italy	SHE	150 (75/75)	T: ALC 2g, bid C: placebo	90d	Liver Function Assessment, serum ammonia, etc.
Mar Malaguarnera ¹⁵	2003	Italy	HE 1 and HE 2	120 (60/60)	T: ALC 2g, bid C: placebo	60d	Serum ammonia, etc.

The seven studies in the meta-analysis appear to encompass some 660 participants, but six of the seven studies are authored by the same principal investigator and the seventh studied L-carnitine, not ALC. Review of the studies reveals that most of the patient data was collected from 2002 to 2005, and it appears that individual patients were described in more than one report. In the 2008 and 2011 papers, the studies appear to reflect the exact same population with different analyses performed. For example, where the EEG outcome was not different between treatment arms in 2008, a responder analysis was performed with a statistically significant result in the 2011 paper.

Methodologically speaking, it also appears that the analyses were performed on the completer or per protocol population and did not use intent-to-treat methodology. This will tend to magnify the potency of the treatment effect over what one might see in a general population of persons affected by HE. Finally, the authors conducted multiple statistical comparisons without adjusting

the critical alpha for repeated testing of the same population (multiplicity). Because of these caveats, the interpretation of the meta-analysis and the results found in the individual citations should be considered exploratory and in need of confirmation.

Alzheimer's disease

One proposed mechanism for the potential efficacy of ALC in dementia is that it provides an acetyl group for use by cellular metabolism to produce acetylcholine, among other cellular chemicals. Increasing cholinergic tone has been shown to improve the cognitive deficit of AD. A Cochrane Collaboration review performed by Hudson et al., (2003) looked at a wide range of studies of varied dosing and duration of treatment in patients with dementia defined by a variety of criteria. Over the decades during which these studies were conducted, the defining criteria for AD have been refined, as have the efficacy outcome measures used in clinical trials. This has made it difficult for meta-analyses to be performed in a meaningful fashion.

Out of 33 randomized, placebo-controlled trials, the Cochrane Collaboration reviewed 16 trial reports assessed as appropriately designed and that provided sufficient data for evaluation in patients with mild to moderate dementia. Five of the studies were performed by Sigma Tau Pharma (the NDA holder for L-carnitine) and unpublished data were obtained from the sponsor. All trials assessed the potential cognitive effect of ALC, and in addition most considered the severity of dementia, functional ability and clinical global impression. Of these, 6 were multicenter trials and the rest performed in a single center. The test dose of ALC ranged from 2 to 3 gm daily and was administered for 12 to 52 weeks to more than 1,400 patients. All of the trials, except those of Thal and colleagues presented a complete analysis, introducing bias that would have the potential to show improvement in a given disease population.

Thal and colleagues performed two, large, blinded, randomized, placebo-controlled parallel multicenter trials in both usual and early-onset AD (Thal et al., 1996 and 2000). These trials treated patients with mild to moderate AD as defined by well-accepted (National Institute of Neurological and Communicative Disorders and Stroke; Alzheimer's Disease and Related Disorders Association) research diagnostic criteria with 3 g/d for one year. Four hundred thirty-one patients with AD and 257 patients with early-onset AD were entered into the trials with a completion rate over 80%. Efficacy was based on the AD Assessment Scale cognitive component (ADAS-Cog) and the Clinical Dementia Rating Scale. In neither trial did ALC demonstrate improvement in cognition or slow the rate of cognitive decline. It is of interest to note that the early-onset AD trial was prompted by a post-hoc subgroup analysis of the 1996 study that suggested a beneficial effect in the early-onset subgroup. This was not borne out in the subsequent pivotal trial.

The Cochrane Collaboration review concludes:

There is evidence for benefit of ALC on clinical global impression as a categorical measure and on the [Mini Mental State Exam] at 24 weeks, but there is no evidence using objective assessments in any other area of outcome. Given the large number of comparisons made, the statistically significant results may be due to chance. At present there is no evidence to recommend its routine use in clinical practice. Many of the trials used rather vague descriptions of dementia

and trials using more strictly defined groups may be informative... However, the evidence does not suggest that ALC is likely to prove an important therapeutic agent (Hudson et al., 2003).

Similarly, following a request from the European Commission, the European Food Safety Authority reviewed the health claims related to ALC and found that “a cause and effect relationship has not been established between the consumption of acetyl-L-carnitine and contribution to normal cognitive function” (EFSA Panel, 2011).

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

Yes. Peripheral neuropathy, Alzheimer’s disease, and hepatic encephalopathy are serious conditions. There are FDA-approved treatments with proven efficacy and an appropriate risk-benefit ratio already on the market.

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

As described here, there are approved therapies in use for some of the conditions considered. (The use of L-carnitine has not been approved by the FDA for the treatment of these syndromes.)

- Peripheral neuropathy

There are currently no approved treatments for the prevention of peripheral neuropathy from chemotherapy or in diabetes mellitus. There are several FDA-approved medications for the treatment of the pain associated with peripheral neuropathy (Cymbalta (duloxetine), Lyrica, (pregabalin) and Nucynta ER (tapentadol)).

- Cirrhosis of the liver

The current treatment of hepatic encephalopathy focuses on reducing the associated hyperammonemia by targeting production, absorption from foods, and aid in elimination from sensitive organs. Lactulose and rifaximin (Xifaxan, Salix Pharma, NDA 021361) have been found to be effective and are the mainstays of current therapy (Hadjihambi et al., 2014).

- Alzheimer’s disease

Aricept (donepezil), Exelon (rivastigmine), Namenda (memantine), and Razadyne (galantamine) are FDA-approved for the treatment of dementia caused by AD.

Conclusions:

Although ALC is likely safe for use up to 3 gm/d (except in persons with a clotting disorder or seizures), there is no evidence to show that patients clearly benefit when it was evaluated in trials of the size, design, and sample size needed to substantiate the efficacy of ALC in any condition. L-carnitine, both a prodrug and metabolic product of ALC is already FDA-approved for the

treatment of metabolic disorders of carnitine in the United States. Illnesses and conditions for which ALC has been nominated for bulk compounding have other FDA-approved treatments available for use. There is no evidence from methodologically sound clinical studies showing the efficacy of ALC for the treatment of disease.

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

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

The extent of ALC use in pharmacy compounding is unknown. ALC has been available since at least 1964. It has been widely available as a dietary ingredient in dietary supplements for at least three decades. By 1983, it was understood as being a naturally occurring endogenous chemical substance in people as a result of L-carnitine metabolism (Albertazzi et al., 1983), and a preliminary report of its use in dementia was published (Acierno, 1983). L-carnitine itself was approved for use in the United States in 1985.

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

The list of conditions to which this nomination addresses itself (see above) represents the general scope of clinical investigation as found in searches in databases such as PubMed.

3. *How widespread its use has been*

ALC is widely available as a dietary ingredient in dietary supplements. It is not clear how widespread use of ALC is, but a simple Google search using the term *acetyl L carnitine* online found 33 pages of links to suppliers of supplements in the United States and abroad (including Europe and Asia). Internet websites selling ALC direct to consumers emphasize its use for increasing muscle strength, for its “anti-oxidant” and “metabolic enhancement” properties in addition to cognitive enhancement.

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

L-carnitine and ALC do not appear on the European Medicines Agency (EMA) website and do not appear to have undergone regulatory review.

As mentioned above, a request from the European Commission, the European Food Safety Authority reviewed the health claims related to ALC and found that “a cause and effect relationship has not been established between the consumption of acetyl-L-carnitine and contribution to normal cognitive function” (EFSA Panel, 2011).

A Google search using the term *worldwide availability of acetyl-L-carnitine* shows suppliers in Italy, India, South Korea, China, and Japan.

Conclusions: There is insufficient evidence to evaluate the extent to which ALC has been used in pharmacy compounding in the US and abroad. ALC is widely available as a dietary ingredient in supplements in this country and abroad. It does not appear to have received regulatory approval for use as a medicinal drug.

III. RECOMMENDATION

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

1. ALC is well characterized in its physical and chemical properties.
2. The safety profile of ALC suggests that it is well tolerated when given orally up to 3 g daily. There is insufficient knowledge with regard to its metabolic conversion to L-carnitine and other acyl-carnitine esters. It must be used with caution in anyone using anticoagulant drugs affecting the INR (e.g., warfarin), persons suffering from seizures, and in persons with renal insufficiency, a major route of elimination. There appears to be no medical need or justification for intravenous administration and the safety of administration by that route is unknown.
3. Extensive investigation of ALC in large randomized, blinded, and placebo-controlled trials fails to support its efficacy for any of the proposed uses. The disorders included in the nomination are serious medical conditions for which safe and effective treatments are available in the United States.
4. The extent of ALC use by compounding is unknown. It has been widely available as a dietary ingredient in dietary supplements for at least three decades.

Based on a balancing of the four evaluation criteria, we recommend that ALC not be added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act. Available data indicate do not demonstrate that ALC is effective for the conditions discussed.

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Tab 7

Drug Products That Present Demonstrable Difficulties for Compounding



Drug Products That Present Demonstrable Difficulties for Compounding: Background and Proposed Evaluation Criteria

I. Background

Section 503A of the Food, Drug, and Cosmetic Act (21 U.S.C. 353a) (FD&C Act or the Act) generally governs the application of federal law to pharmacy compounding. Under section 503A of the Act, compounded drug products are exempt, under certain conditions, from three key provisions of the Act: (1) the adulteration provision of section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements); (2) the misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications).

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

Both sections 503A and 503B require compounded drug products to satisfy several requirements to qualify for the statutory exemptions from the FD&C Act. One of those requirements is that the compounded drug product is not one that the Agency has identified as being demonstrably difficult to compound. *See* sections 503A(b)(3)(A); 503B(a)(6).

Specifically, section 503A states that the compounded drug product may not be one that “presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.” *See* section 503A(b)(3)(A).

Similarly, section 503B states that the compounded drug, or category of drugs, either is not one that “present[s] demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into the account the risks and benefits to patients,” or is compounded in

accordance with “conditions that are necessary to prevent the drug or category of drugs from presenting [such] demonstrable difficulties.” *See* section 503B(a)(6).

FDA solicited nominations for drug products or categories of drug products that are considered difficult to compound in the Federal Register of December 4, 2013 (FDA-2013-N-1523-0001). Approximately 71 unique drug products or categories of drug products were nominated. (*See* attached list.) In addition, based on its experience reviewing new and abbreviated new drug applications, FDA is also identifying drug products or categories of drug products that are known to be difficult to manufacture, and, therefore, would also be considered difficult to compound. If an FDA-approved drug product is particularly difficult to manufacture, for example, because of the need for highly specialized equipment or processes, a comparable drug product would also be difficult to compound.

This document presents the criteria FDA proposes to consider in evaluating whether drug products or categories of drug products are demonstrably difficult to compound under sections 503A and 503B.

II. Proposed Criteria for Evaluating Candidates

FDA has identified six criteria it proposes to use to evaluate whether drug products or categories of drug products are difficult to compound under sections 503A and 503B of the FD&C Act. The categories are not mutually exclusive. A drug product or category of drug products may meet one or more of these criteria that indicate it is a difficult to compound drug product or category of drug products. We propose to consider these criteria individually and collectively in deciding whether a drug product or category of drug products is difficult to compound under sections 503A and 503B of the FD&C Act.

FDA is proposing the following criteria for evaluating whether drug products or categories of drug products are difficult to compound under sections 503A and 503B of the FD&C Act:

1. Complex Formulation

Complex formulation refers to a formulation in which the ingredients (active pharmaceutical ingredients (APIs) or excipients) are required to have certain physicochemical characteristics or properties that are necessary to achieve or maintain the proper performance of the drug product. For example, crystalline (including polymorphs) or amorphous forms, or chirality or particle size of an API might be critical in some formulations to the safety and efficacy of the drug product. The compatibility and/or stability (physical and chemical) of the API(s) and/or excipients in the final dosage unit may also be evaluated to determine if the compounded drug product has a complex formulation. A complex formulation may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

2. Complex Drug Delivery Mechanism

Complex drug delivery mechanism refers to the way in which the drug is released from the dosage form or targeted for delivery in the body to achieve the desired therapeutic effect, such as passing through the stomach without dissolution and absorption or achieving permeation through the skin at a specific rate. Complex drug delivery mechanisms may include, for example, coated beads, polymeric matrices, or liposomes. A complex drug delivery mechanism may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

3. Complex Dosage Form

Complex dosage form refers to physical dosage units with characteristics that are difficult to consistently achieve or maintain. Complex dosage form also refers to container closure systems that may interact with the compounded drug and affect its intended use, either through physical (inconsistent dose administration) or chemical interactions between the compounded drug and the container closure system. Drug products may have very simple formulations, such as a single API, and a simple delivery mechanism, such as an injection, but the compounded drug product may be complex because the physical properties of the dosage form are difficult to achieve or maintain. Complex dosage forms may include, for example, propellant based aerosolized products or dry powder inhalers. A complex dosage form may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

4. Bioavailability

Bioavailability refers to the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. Drug products may be considered difficult to compound if bioavailability is challenging to achieve because of the characteristics of the API or compounded formulation such as low permeability and/or low solubility. Bioavailability may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

5. Compounding Process Complexity

Compounding process complexity refers to whether compounding the drug requires multiple, complicated, or interrelated steps and/or specialized facilities and/or equipment to achieve the appropriate drug product. An example of a complex compounding process would include the multi-step and highly inter-related process of creating multi-particulate dosage forms of solid oral beads that require wet granulation, extrusion, spheronization, fluid bed drying, coating or curing before they are processed into the final dosage form. Compounding process complexity may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

6. Physicochemical or Analytical Testing Complexity

Physicochemical or analytical testing complexity refers to the challenges presented with confirming the drug product will perform as expected with regard to certain characteristics. Drug products may demonstrate testing complexity when specialized analytical instruments and/or special training is necessary to show that the drug product will perform as expected. Performing cell-based assays for performance characterization (potency or permeability), and/or identifying constituents of complex mixtures by nuclear magnetic resonance, mass spectrometry, and/or X-ray powder diffraction (XRPD) could be considered examples of complex physicochemical or analytical testing. Physicochemical or analytical testing complexity may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.

Tab 8

Metered Dose Inhalers (MDIs)

Tab 8a

Metered Dose Inhalers (MDIs)

Nominations



4 March 2014

Food and Drug Administration
Division of Dockets Management (HFA-301)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Comments [Docket No. FDA-2013-N-1523]

Dear Sir or Madam:

Reference is made to the notice published by the Food and Drug Administration (FDA) in the Federal Register on 4 December 2013 (78 Fed. Reg. 72840), encouraging interested parties to nominate specific drug products or categories of drug products for inclusion in the Agency's list of products that present demonstrable difficulties for compounding (the difficult-to-compound list). The purpose of this submission is to note several drug products and categories of drug products that GlaxoSmithKline (GSK) believes warrant inclusion in the difficult-to-compound list.

GSK is a research-based pharmaceutical and biotechnology company. Our company is dedicated to the discovery, development, manufacture, and distribution of medicines and vaccines that enable people to live longer, healthier, more productive lives. GSK appreciates the opportunity to provide comments on this important topic. While GSK recognizes the importance of preserving access to compounded drugs when patients cannot be treated with FDA-approved products, inappropriate compounding activities can present significant risks. The timely issuance, and rigorous enforcement, of FDA's difficult-to-compound list is critically important to protect patients from these risks.

As described in the Federal Register notice, for a drug product to be compounded under either Section 503A or Section 503B of the Food, Drug, and Cosmetic Act (FDCA), it must (among other things) not be a drug product identified by the Secretary as one that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that product, taking into account the risks and benefits to patients. After evaluating the responses to its request for nominations, and after consulting with the Pharmacy Compounding Advisory Committee, FDA has stated that it plans to develop and publish a single list for compounding under both Sections 503A and 503B, using notice-and-comment rulemaking procedures.

In its request for nominations, the Agency lists a number of factors that may be relevant in assessing whether a certain drug product or category of products should be included in the difficult-to-compound list, including factors that may impact the potency, purity, or quality of a drug product, and thereby affect its safety or effectiveness. The factors listed by FDA include those related to: the drug delivery system; drug formulation and consistency; bioavailability; the complexity of compounding; facilities and equipment; training; and testing and quality assurance. Below, we list a number of drug products and categories of products that we believe should be included in the list, based on our assessment of these and other factors. GSK reserves the right to expand upon these comments or nominate additional drug products or categories of products in the future.

I. Respiratory Drug Products

Respiratory products often incorporate sophisticated drug delivery systems, such as dry powder or metered dose inhalers, which are precisely engineered and tightly controlled to deliver their active ingredients to local sites of action within the body. In addition to their device components, the formulations of respiratory medicines are often complex, using active and inactive ingredients with defined particle size profiles and other qualities that are intended to interact with those components in specific ways. The manufacturing of respiratory products thus requires sophisticated facilities and equipment, and highly trained personnel, beyond the capabilities of drug compounding operations. Post-manufacture, ensuring the quality and performance of such drug/device combination products requires difficult-to-perform testing, such as aerodynamic particle size distribution and emitted dose assessments.

Failure in any of these numerous elements – from device design and formulation work, to manufacturing, to quality assurance – would threaten the safety and effectiveness of the drug product. Moreover, these medicines generally cannot be compounded into more common dosage forms, such as tablets or capsules, because of concerns with dosing accuracy and bioavailability at the local sites of action. For these reasons, GSK believes that respiratory drug products, including the following GSK products, should be included in FDA's difficult-to-compound list:

- Advair Diskus® (fluticasone propionate and salmeterol) Inhalation Powder
- Advair HFA® (fluticasone propionate and salmeterol) Inhalation Aerosol
- Anoro™ Ellipta™ (umeclidinium and vilanterol) Inhalation Powder
- Beconase AQ® (beclomethasone dipropionate, monohydrate) Nasal Spray
- Breo® Ellipta™ (fluticasone furoate and vilanterol) Inhalation Powder
- Flonase® (fluticasone propionate) Nasal Spray
- Flovent Diskus® (fluticasone propionate) Inhalation Powder
- Flovent HFA® (fluticasone propionate) Inhalation Aerosol
- Relenza® (zanamivir) Inhalation Powder
- Serevent Diskus® (salmeterol xinafoate) Inhalation Powder
- Ventolin HFA® (albuterol sulfate) Inhalation Aerosol
- Veramyst® (fluticasone furoate) Nasal Spray

II. Modified Release Drug Products

Modified release products, including delayed, sustained, and extended release tablets and capsules, are generally manufactured using complex, often patent-protected, technologies. The failure of a drug compounding operation to understand, have access to, and utilize these technologies appropriately could result in products with poor dosing accuracy, bioavailability, or product-to-product uniformity – any of which may affect safety or effectiveness. The failure of a release mechanism, for example, may present a safety issue, if it leads to dose dumping, or an effectiveness issue, if the drug is not released into the circulation in a timely manner. For these reasons, GSK believes that modified release drug products, including the following GSK products, should be included in FDA's difficult-to-compound list:

- Coreg CR® (carvedilol phosphate) Extended-Release Capsules
- Requip XL® (ropinirole) Extended Release Tablets
- Rythmol SR® (propafenone hydrochloride) Extended-Release Capsules
- Wellbutrin SR® (bupropion hydrochloride) Sustained-Release Tablets
- Zyban® (bupropion hydrochloride) Sustained-Release Tablets
- Lamictal® XR (lamotrigine) Extended-Release Tablets

III. Drug Products Presenting Increased Risks

Certain drugs and drug products, including but not limited to those subject to Risk Evaluation and Mitigation Strategies (REMS), present increased risks. Adequate mitigation of these risks requires careful and consistent manufacturing, enhanced labeling and risk communications, and even restricted distribution. Compounded products containing drugs associated with teratogenicity, mutagenicity, or carcinogenicity may also present increased occupational risks to those performing the manufacturing operations themselves, through respiratory or skin exposure. These products therefore require sophisticated facilities and equipment, and highly trained personnel, to ensure not only the potency, purity, and quality of the drug products, but also the safety of those working with them. For these reasons, GSK believes that certain increased risk drug products, including the following GSK products, should be included in FDA's difficult-to-compound list:¹

A. Drug Products with Approved REMS²

- Potiga[®] (ezogabine) Tablets [Controlled Substance – Schedule V]
- Promacta[®] (eltromopag olamine) Tablets
- Zyban[®] (bupropion hydrochloride) Sustained-Release Tablets
- Avandamet[®] (rosiglitazone maleate and metformin hydrochloride) Tablets
- Avandaryl[®] (rosiglitazone maleate and glimepiride) Tablets
- Avandia[®] (rosiglitazone maleate) Tablets

B. Drug Products Presenting Occupational Risks

- Avodart[®] (dutasteride) Capsules
- Jayln[®] (dutasteride and tamsulosin hydrochloride) Capsules
- Tafenlar[®] (dabrafenib) Capsules
- Votrient[®] (pazopanib) Tablets
- Soriatane[®] (acitretin) Capsules
- Veltin[®] (clindamycin phosphate and tretinoin) Gel

IV. Anti-Epileptic Drug Products

Certain drugs are characterized by narrow margins between their effective and toxic doses. Others require careful dose selection and titration, because even small differences in dose or bioavailability can have clinical consequences for patients. Anti-epileptic drugs (AEDs) are perhaps the most well-known such products. Consistency of manufacturing, dosing uniformity, and reliable bioavailability are critical for these drug products. Any potential compounding of such products is highly complex, with significant potential for

¹ GSK understands that biological products, licensed under the Public Health Service Act, are not covered by the new drug application exemption provisions of Sections 503A and 503B of the FDCA. For this reason, biological products may not be compounded or distributed without an approved biologics license application. If FDA interprets Sections 503A and 503B to apply to biological products, however, such products – including the GSK products Benlysta[®] (belimumab) Injection, Arzerra[®] (ofatumumab) Injection, and raxibacumab injection – should be included in the do-not-compound list. Biological products are uniquely challenging to manufacture, handle, and distribute, and the inappropriate compounding of biological products would present significant risks to patients.

² Section 503B(a)(7) of the FDCA prohibits the compounding by outsourcing facilities of certain drugs subject to REMS (those approved with elements to assure safe use), unless the facilities demonstrate prior to beginning compounding that they will utilize controls comparable to the controls applicable under the relevant REMS. This does not address, however, compounding under Section 503A of the FDCA, or the compounding of other drugs presenting increased risks.

GSK Comment
Docket No. FDA-2013-N-1523
4 March 2014

errors that may affect the safety or effectiveness of the products and present unacceptable risks to patients. For these reasons, GSK believes that AEDs, including the following GSK products, should be included in FDA's difficult-to-compound list:

- Lamictal® (lamotrigine) Chewable Dispersible Tablets
- Lamictal® (lamotrigine) Tablets
- Lamictal® XR (lamotrigine) Extended-Release Tablets
- Potiga® (ezogabine) Tablets [Controlled Substance – Schedule V]

Again, we appreciate the opportunity to provide input on this important topic. GSK looks forward to participating in FDA's continued development of the difficult-to-compound list, including the advisory committee and rulemaking processes. Please contact me via e-mail at leo.j.lucisano@gsk.com or telephone at (919) 483-5848 with any questions or comments.

Sincerely,



Leo Lucisano
Senior Director GPAR - NA
Global CMC Regulatory Affairs
RD Chief Regulatory Office
5 Moore Drive, P.O. Box 13398
Research Triangle Park, North Carolina 27709



1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

March 4, 2014

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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

Re: Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Nominations; Docket Number FDA-2013-N-1523

Dear Commissioner Hamburg and Dr. Woodcock:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, submits these comments in response to the Food and Drug Administration (FDA) request for nominations for Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FDCA; Docket Number FDA-2013-N-1523).

We wish to express our concern that the FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded because they present demonstrable difficulties for compounding. Sections 503A and 503B of the FDCA, which create exemptions from new drug approval and other requirements for compounding pharmacies and outsourcing facilities, respectively, each separately authorize the FDA to publish a distinct list identifying drug products that present demonstrable difficulties for compounding and therefore

cannot be produced under the exemptions. We believe two separate lists are necessary, because drugs compounded at compounding pharmacies under a Section 503A exemption will be subject to reduced regulatory standards and fewer enforcement mechanisms relative to drugs compounded at outsourcing facilities under a Section 503B exemption. (Although it is important to note that drugs qualifying for either type of exemption will be subject to reduced requirements relative to drugs that undergo new drug approval, and therefore in general pose greater risk to patients than FDA-approved drugs).

We urge the FDA to classify products involving nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding under 503A, but not under 503B. Production of drugs using this inherently high-risk process should be carried out only by a facility that is regularly inspected to verify compliance with current federal Good Manufacturing Practices (cGMP) requirements. Compounding pharmacies regulated under 503A are not required to follow cGMP, will rarely—if ever—be inspected by the FDA, and may or may not be regularly inspected by state officials, depending on the pharmacy regulations in each state, and any such state inspections are likely to be far less rigorous than those conducted by the FDA. By contrast, 503B outsourcing facilities, while not required to obtain new drug approval for their drug products, are nevertheless required to comply with cGMP and will be inspected by FDA officials on a risk-based schedule.

Alternatively, if the FDA chooses to proceed with its proposed plan of establishing only one list, we urge the agency to identify compliance with cGMP and the requirements of 503B as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding, and to require such conditions for high-risk nonsterile-to-sterile compounding. Outsourcing facilities that register under Section 503B and comply fully with the FDCA will be permitted to compound such products, whereas compounding pharmacies regulated under 503A would not be allowed to compound such products.

We also recommend designation of several additional product categories as presenting demonstrable difficulties for compounding, and which therefore cannot be produced under 503B and/or 503A exemptions. A full list of product categories we urge the FDA to identify as demonstrably difficult to compound, along with our recommendations for their appropriate regulatory classification, is summarized as follows:

1. Nonsterile-to-sterile compounding (non-exempt under 503A only)
2. Metered dose inhaler (MDI) products (non-exempt under 503A and 503B)
3. Dry powder inhaler (DPI) products (non-exempt under 503A and 503B)
4. Transdermal Delivery Systems (TDSs) (non-exempt under 503A and 503B)
5. Sustained or time-release dosage forms (non-exempt under 503A and 503B)
6. Enteric-coated preparations (non-exempt under 503A and 503B)

I. Regulatory Background and Relevant Statutory Authority

Section 503A of the FDCA, created under the Food and Drug Administration Modernization Act of 1997 (FDAMA),¹ describes the conditions under which a human drug product, compounded for an identified individual based on a prescription, is entitled to an exemption from the federal requirements for new drug approval, compliance with cGMP, and specific federal labeling requirements.² Rather than follow cGMP requirements, pharmacies qualifying for a 503A exemption must produce drug products under conditions that comply with the United States Pharmacopoeia (USP) chapter on pharmacy compounding, including USP Chapter 797, addressing sterile compounding.^{3,4}

Pharmacies may qualify for a Section 503A exemption only when producing a drug product “not . . . identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.”⁵ Section 503A requires that the FDA consult an advisory committee on pharmacy compounding prior to identifying such products, absent urgent public health need.⁶

Following passage of FDAMA, the FDA initiated an administrative process aimed at creating a list of drugs presenting demonstrable difficulties for compounding. In 2000, the FDA requested comments on a concept paper describing the agency’s preliminary thoughts on the matter (FDA Concept Paper).⁷ However, these preliminary efforts were suspended following a 2002 Supreme Court decision holding portions of Section 503A unconstitutional.⁸

Regulation under Section 503A has been revived by the Drug Quality and Security Act of 2013, which verified the constitutionality of the portions Section 503A that had not been addressed in the Supreme Court’s 2002 decision, including the relevant sections addressing the difficult-to-compound list, by removing the provisions deemed unconstitutional by the Court.⁹ The 2013 Act also added Section 503B to the FDCA, creating a new category of drug producers, known as

¹ Pub. Law No. 105-115.

² FDCA Section 503A, *codified as* 21 U.S.C. § 353a.

³ 21 U.S.C. § 353a (b)(1)(A)(i).

⁴ Food and Drug Administration Draft Guidance: Pharmacy compounding of human drug products under Section 503A of the Federal Food, Drug and Cosmetics Act. December 2013.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377052.pdf>. Accessed February 18, 2014.

⁵ 21 U.S.C. § 353a (b)(3)(A).

⁶ 21 U.S.C. § 353a (c)(1).

⁷ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

⁸ 78 Fed. Reg. 72,840, 72,840 (Dec 4, 2013).

⁹ *Ibid.*

“outsourcing facilities.”¹⁰ Like compounding pharmacies regulated under 503A, outsourcing facilities that qualify for Section 503B are exempt from new drug approval and specific federal labeling requirements, and are therefore subject to lighter federal regulation than manufacturers of FDA-approved drugs. However, unlike Section 503A compounding pharmacies, Section 503B outsourcing facilities will be required to comply with cGMP. Outsourcing facilities must also comply with additional requirements, including federal registration and periodic reporting requirements, as well as federal inspections of facilities and records, conducted on a risk-based schedule.

Like Section 503A, Section 503B excludes drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs.¹¹ However, rather than cross-reference the same list of products identified under Section 503A, Section 503B outlines distinct procedural steps for the FDA to follow in identifying drugs that are difficult to compound, including a specific timeline and process for creating a list of such products.¹² Section 503B also requires the FDA to “tak[e] into account the risks and benefits to patients” when identifying products for the list and authorizes the agency to identify “conditions that are necessary to prevent the drug or category of drugs from presenting demonstrable difficulties [for compounding].”¹³

Neither Section 503A nor Section 503B require that the FDA develop and publish a single list of drug products that present demonstrable difficulties for compounding. If anything, Congress, having identified two distinct processes and two slightly different sets of requirements and authorities for each section, appears to have contemplated that the FDA would create two separate lists. Moreover, even if two separate lists are not statutorily required, the FDA can certainly exercise its discretion to promulgate two separate lists. Separate lists would represent sound public health policy because the conditions for compounding in each type of facility are markedly different, with 503A compounding pharmacies subject to significantly lower regulatory standards than 503B outsourcing facilities.

Alternatively, if the FDA proceeds with its proposed plan to promulgate only one list, the agency has the authority to identify compliance with 503B and cGMP requirements as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding. Outsourcing facilities that register under Section 503B and comply fully with cGMP would then be permitted to compound such products, whereas compounding pharmacies that qualify for exemption under 503A that have not verified compliance with cGMP would not be allowed to compound such products.

¹⁰ Section 503B, *not yet codified*. Pub. Law 113-54. -

¹¹ Pub. Law 113-54. Sec. 503B (a)(6). -

¹² Pub. Law 113-54. Sec. 503B (c)(2). -

¹³ Pub. Law 113-54. Sec. 503B (a)(6). -

II. Specific Drug Product Categories

We propose six categories of drug products for placement on the list or lists of products presenting demonstrable difficulties for compounding under Sections 503B and/or 503A.

1. Nonsterile-to-sterile compounding

Certain drugs must be sterile (in other words, free from all living microorganisms) in order to be administered safely. These include dosage forms administered parenterally (injections, infusions, or implants), aqueous-based inhalation solutions, and ophthalmic products.¹⁴ As stated in the 2000 FDA Concept Paper, “[s]terility is absolute and should never be considered in a relative manner -- a product cannot be partially or almost sterile.”¹⁵

Problems that develop in compounding sterile products can have serious and far-reaching consequences for patient safety. In September 2012, the Centers for Disease Control and Prevention (CDC) and the FDA announced the beginning of what would become the largest outbreak of infection linked to a medical product in more than four decades: healthcare facilities in 23 states received three lots of contaminated preservative-free injectable methylprednisolone acetate produced by the New England Compounding Center (NECC), a compounding pharmacy in Framingham, Massachusetts.¹⁶ Over the next year, the CDC tracked 751 cases of infection, including meningitis, paraspinal/spinal infection, stroke, and joint infection. Sixty-four of those cases resulted in death.¹⁷

While the NECC-linked outbreak was by far the largest ever associated with a compounding pharmacy, it was by no means an isolated event. Table 1 contains a list of infection outbreaks linked to compounding pharmacies since 2004. Many more small-scale outbreaks or isolated infections caused by compounded products likely went undetected because the source of such infections is often not suspected or challenging to identify.

Table 1: Infection Outbreaks Associated with Compounded Products, 2004-2013

Date of Outbreak	Type of Injury	Pharmacy	Source
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¹⁴ Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

¹⁵ *Ibid.*

¹⁶ Centers for Disease Control. Multistate outbreak of fungal meningitis and other infections – healthcare facilities. October 23, 2013. <http://www.cdc.gov/hai/outbreaks/meningitis-facilities-map.html>. Accessed February 21, 2014.

¹⁷ Centers for Disease Control. Multistate outbreak of fungal meningitis and other infections – case count. October 23, 2013. http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html#casecount_table. Accessed February 21, 2014.

Dec 2004 – Feb 2005	Bloodstream infections; 36 cases, including at least 13 children	Anonymous	CDC2005 ¹⁸
Jun – Jul 2004	Bloodstream infections; 2 children	Anonymous	Held2006 ¹⁹
Jan – Mar 2005	11 cases of bacteremia, including 5 cases of sepsis	PharMEDium	CDC2005 ²⁰
Mar 2005	6 cases of sepsis; 1 resulting in death	PharMEDium	FDA2007(1) ²¹
Dec 2004 – Aug 2005	Eye infection resulting in permanent loss of vision; 6 cases	Anonymous	Sunenshine2009 ²²
Dec 2006	70 complaints indicating signs of infection	Med-South Pharmacy	FDA2007(2) ²³
Oct – Nov 2007	7 bloodstream infections	Anonymous	Maragakis2009 ²⁴
Mar 2011	19 bloodstream infections	Meds IV	FDA2011 ²⁵
Jul 2011	12 eye infections; 11 resulting in vision loss	Infupharma	Goldberg2013 ²⁶
Aug 2011 – Mar 2012	47 eye infections; 39 resulting in vision loss	Franck's Compounding Lab	Mikosz2014 ²⁷

¹⁸ Centers for Disease Control. Pseudomonas bloodstream infections associated with a heparin/saline flush --- missouri, new york, texas, and michigan, 2004—2005. *MMWR* 2005;54(11):269-272. - <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm>. Accessed February 26, 2014. -

¹⁹ Held MR, BegierEM, Beardsley DS, et al. Life-threatening sepsis caused by *Burkholderia cepacia* from - contaminated intravenous flush solutions prepared by a compounding pharmacy in another state. *Pediatrics* - 2006;118(1):e212-5. -

²⁰ Centers for Disease Control. Health Advisory: *Serratia marcescens* blood stream infections associated with - contaminated magnesium sulfate solutions. March 18, 2005. - http://www.randolphcountyhealth.org/docs/educ/pr/031805_CDC.html. Accessed February 21, 2014. -

²¹ Food and Drug Administration. Warning Letter to PharMEDium. April 13, 2007. - <http://www.fda.gov/iceci/enforcementactions/warningletters/2007/ucm076357.htm>. Accessed February 21, - 2014. -

²² Sunenshine R, Schultz M, Lawrence MG, et al. An outbreak of postoperative gram-negative bacterial endophthalmitis associated with contaminated trypan blue ophthalmic solution. *Clin Infect Dis* 2009;48:1580-3. -

²³ Food and Drug Administration. Warning Letter to Med-South Pharmacy. September 28, 2007. - <http://www.fda.gov/iceci/enforcementactions/warningletters/2007/ucm076516.htm>. Accessed February 21, - 2014. -

²⁴ Maragakis LL, Chaiwarith R, Srinivasan A, et al. *Sphingomonas paucimobilis* bloodstream infections associated - with contaminated intravenous fentanyl. *Emerg Infect Dis* 2009;15(1):12-18. -

²⁵ Food and Drug Administration. CDC and ADPH investigate outbreak at Alabama hospitals; products recalled. - March 29, 2011 (republished from Alabama Department of Public Health). - <http://www.fda.gov/safety/recalls/archiverecalls/2011/ucm249068.htm>. Accessed February 21, 2014. -

²⁶ Goldberg RA, Flynn HW, Miller D, et al. *Streptococcus* endophthalmitis outbreak after intravitreal injection of - Bevacizumab: One-year outcomes and investigative results. *Ophthalmology* 2013; 120(7):1448-53. -

²⁷ Mikosz CA, Smith RM, Kim M, et al. Fungal endophthalmitis associated with compounded products. *Emerg Infect Dis* 2014;20(2):248-256. -

Mar 2013	5 eye infections	Clinical Specialties	FDA2013(1) ²⁸
May 2013	7 skin abscesses	Main Street Family Pharmacy	FDA2013(2) ²⁹

In addition to being free of microorganisms, injectable compounded pharmaceuticals must also be free from pyrogens (the byproducts of microorganisms that can cause reactions when introduced into humans) and particulate matter, which can cause harmful blood clots, particularly when a product is administered in large quantities.³⁰

Sterile-to-sterile compounding, described as “low” or “medium” risk compounding by the U.S. Pharmacopeial Convention, involves manipulating sterile ingredients entirely within an ISO Class 5 or better environment (a “clean room” carefully controlled to exclude microbial growth) using only sterile ingredients, products, components, and devices.³¹ Depending on the number of sterile products and aseptic manipulations involved, sterile-to-sterile compounding may involve low or medium risk of microbial contamination.³²

Nonsterile-to-sterile compounding, described as “high” risk compounding by the U.S. Pharmacopeial Convention, involves compounding using nonsterile ingredients or materials, including nonsterile active pharmaceutical ingredients (API), finished FDA-approved products not intended for sterile routes of administration (e.g., oral), or nonsterile devices or packaging.³³ It also includes sterile contents of commercially manufactured products that have been exposed to conditions that would render them nonsterile (e.g., exposure to air quality worse than ISO Class 5 for more than one hour). To engage in this process safely, an appropriate sterilization method must be used to ensure that such products are sterile and free of pyrogens and particulate matter prior to distribution.³⁴

The high-risk process of nonsterile-to-sterile compounding is not appropriate for compounding pharmacies exempt under Section 503A, as these entities are not held to cGMP standards and

²⁸ Food and Drug Administration. Clinical Specialties Compounding Pharmacy announces voluntary nationwide - recall of all lots of sterile products repackaged and distributed by Clinical Specialties Compounding due to lack of - sterility assurance. March 20, 2013. <http://www.fda.gov/safety/recalls/ucm344786.htm>. Accessed February 21, - 2014. -

²⁹ Food and Drug Administration. Main Street Pharmacy, LLC issues voluntary nationwide recall of all sterile - compounded products. May 28, 2013. <http://www.fda.gov/safety/recalls/ucm354182.htm>. Accessed February 21, - 2014. -

³⁰ Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for - Compounding Because of Reasons of Safety or Effectiveness. - <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments-to-the-FDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014. -

³¹ <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008. -

³² *Ibid.*

³³ *Ibid.*

³⁴ *Ibid.*

instead must comply with USP standards only. USP standards for sterile compounding, laid out in Chapter 797 of the USP, are set by the U.S. Pharmacopeial Convention, a private organization that sets standards for drugs, food ingredients, and dietary supplements.³⁵ While USP standards have advanced over time, they remain relatively lax compared to the cGMP standards developed and enforced by the FDA. One key difference is that cGMP requires a drug manufacturer to validate and periodically re-validate each step in the production process through direct testing, whereas USP Chapter 797 routinely allows pharmacists to base production design on review of available literature and the pharmacist's prior experience.

For example, in determining sterilization methods, cGMP requires that any sterilization process used to prevent microbial contamination be validated through appropriate direct studies,³⁶ and offers detailed guidance on the design and conduct of such validation studies.³⁷ Once production begins, a single contaminated product in any batch smaller than 5,000 should trigger an investigation and revalidation of the entire manufacturing process.³⁸ USP, by contrast, does not generally require product-specific validation, instead allowing the pharmacist to select a method based on "experience and appropriate information sources," stating that the sterilization method should "preferably" be verified "whenever possible."³⁹

Similarly, federal cGMP regulations require a detailed written stability testing program to determine appropriate storage conditions and expiration dates.⁴⁰ By contrast, USP describes the practice of establishing "beyond use dating (BUD)," and the especially high-risk practice of "theoretical beyond use dating," both of which can be based on a review of general literature and do not require direct product testing.⁴¹ The USP acknowledges that "[t]heoretically predicted beyond-use dating introduces varying degrees of assumptions and, hence, a likelihood of error or at least inaccuracy," yet USP Chapter 797 does not require direct stability testing to avoid such problems. Indeed, actual testing is only "strongly urged" to support dating periods exceeding 30 days.⁴²

³⁵ U.S. Pharmacopeial Convention. <http://www.usp.org/about-usp>. Accessed February 28, 2014. -

³⁶ 21 CFR 211.113(b). -

³⁷ Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice. September 2004. -

³⁸ Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice. September 2004. -

³⁹ <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008. -

⁴⁰ 21 CFR § 211.166. ("There shall be a written testing program designed to assess the stability characteristics of - drug products. The results of such stability testing shall be used in determining appropriate storage conditions and - expiration dates. The written program shall be followed and shall include: (1) Sample size and test intervals based - on statistical criteria for each attribute examined to assure valid estimates of stability; (2) Storage conditions for - samples retained for testing; (3) Reliable, meaningful, and specific test methods; (4) Testing of the drug product in - the same container-closure system as that in which the drug product is marketed; (5) Testing of drug products for - reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.") -

⁴¹ <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008. -

⁴² *Ibid.*

We are aware that the FDA previously issued a preliminary conclusion in its Concept Paper published in 2000, which indicated that sterile compounding could be carried out by compounding pharmacies compliant with USP requirements for sterile compounding.⁴³ We urge the FDA to reconsider this preliminary conclusion, which addressed all sterile compounding, rather than focusing separately on, and requiring more stringent standards for, especially high-risk nonsterile-to-sterile compounding.

The FDA's earlier preliminary conclusion was also based in part on a perceived "substantial need for compounded sterile products, especially in the area of extemporaneous compounding."⁴⁴ While a general need for extemporaneously compounded sterile products may have existed under the conditions that the FDA considered in 2000, no substantial need exists for high-risk nonsterile-to-sterile compounding to be performed in compounding pharmacies exempt under Section 503A. First, most needs for sterile compounded products can be met through modifying federally regulated commercially available sterile products, a low- to medium-risk form of sterile compounding, rather than through high-risk compounding from nonsterile-to-sterile ingredients. Second, following the passage of the Drug Quality and Security Act, any residual needs requiring nonsterile-to-sterile compounding (in other words, making products from bulk API rather than modifying FDA-approved sterile products) are more appropriately met by carrying out such high-risk compounding in outsourcing facilities compliant with Section 503B and federal cGMP requirements (as opposed to relying on 503A compounding pharmacies exempt from cGMP requirements).

Furthermore, more information is now available on the actual conditions of practice in compounding pharmacies, historically subject to minimal federal oversight. Recent FDA inspections of compounding pharmacies have revealed widespread sterility concerns, some of which may violate USP standards in addition to cGMP standards, suggesting that the safety of high-risk nonsterile-to-sterile compounding cannot be assured without increased federal oversight.⁴⁵ Some of these violations are discussed in greater detail below.

Companies that have registered as outsourcing facilities under Section 503B will now be held to higher federal standards, and we hope that conditions in these facilities will improve. However, the FDA cannot reasonably expect these conditions to improve substantially in compounding pharmacies exempt from federal oversight under Section 503A, as the current regulatory environment does not provide for appropriate oversight of compounding pharmacies that qualify for this exemption. While the FDA does have authority to inspect and take enforcement action against compounding pharmacies for violations of federal law, the agency has no plans to carry

⁴³ Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

⁴⁴ *Ibid.*

⁴⁵ Food and Drug Administration. Compounding: Inspections, recalls, and other actions. February 6, 2014. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm>. Accessed February 24, 2014.

out regular inspections, leaving day-to-day oversight up to state boards of pharmacy.⁴⁶ Many compounding pharmacies are not routinely monitored by state boards to verify compliance with USP Chapter 797 requirements for sterile compounding. A 2012-2013 survey of state boards of pharmacy published by the office of U.S. Rep. Edward J. Markey (now Senator Markey), indicated that 37 state boards of pharmacy do not routinely track which pharmacies are providing sterile compounding services, and only 19 state boards of pharmacy provide inspectors with special training to identify problems with sterile compounding.⁴⁷

For these reasons, as well as our comments on more specific factors below, we urge the FDA to identify nonsterile-to-sterile compounding as a category presenting demonstrable difficulties for compounding under Section 503A, but not necessarily Section 503B.

The FDA has requested comment on specific relevant factors, including the complexity of compounding, facilities and equipment, personnel training, and testing and quality assurance. We now address each of these factors in turn with regard to nonsterile-to-sterile compounding:

Complexity of Compounding

Nonsterile-to-sterile compounding involves extremely complex production processes. As stated in the FDA's Concept Paper:

The preparation of sterile products is often unavoidably complex, involving many steps and manipulations. Each step poses an opportunity for microbial contamination. The manipulation of a sterile drug product may contaminate it, especially when nonsterile components are used (e.g., if the product is packaged into a nonsterile syringe or vial purported to be sterile), nonsterile equipment is used, or novel, complex, or prolonged aseptic processes are employed.⁴⁸

Even a relatively small change in the production process, such as a switch to new packaging material, may result in unanticipated and far-reaching consequences. The largest infection outbreak associated with a pharmaceutical product in United States history occurred as the result of one such seemingly minor change: Between April and September 1970, Abbott Laboratories began phasing in a new type of cap liner that relied on synthetic plastic, rather than natural

⁴⁶ Food and Drug Administration. Compounding and the FDA: Questions and Answers. December 2, 2013. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm#regulates>. Accessed February 24, 2014. -

⁴⁷ Report of the US House of Representatives. State of Disarray. How states' inability to oversee compounding pharmacies puts public health at risk. April 15, 2013. -

⁴⁸ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. - <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentsToTheFDCAct/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

rubber.⁴⁹ The rubber previously used in the caps had antibacterial properties that synthetic liners lacked. Inadequate environmental control and sampling protocols contributed to microbial contamination of the liners, which thrived on the new synthetic medium. The result was catastrophic: Abbott Laboratories distributed approximately 45 percent of all intravenous fluids sold in the United States at the time, and the outbreak is estimated to have led to between 2,000 and 8,000 cases of infection, and between 200 and 800 deaths.⁵⁰

Both USP and cGMP standards have been updated dramatically over the ensuing decades, yet complex production processes remain challenging to monitor.⁵¹ Any change in the production process should be validated through direct testing to ensure that it does not result in unforeseen consequences. This type of direct validation can only be ensured in facilities verified as fully compliant with cGMP. Nonsterile-to-sterile compounding, therefore, presents demonstrable difficulties for compounding under any other conditions.

Facilities and Equipment

Nonsterile-to-sterile compounding requires sophisticated facilities and equipment that must be maintained to rigorous standards. As stated in the FDA's concept paper:

To maintain the essential characteristics of sterile products (i.e., sterility and freedom from particulate matter and pyrogens), the products and their components must be manipulated in a suitable environment using aseptic techniques. ... It is important to minimize bioburden during the production process even when terminal sterilization is used. Therefore, the production facilities and associated procedures must meet exacting standards.⁵²

While USP and cGMP have developed harmonized standards regarding appropriate levels of bioburden (the accumulation of potential biological contaminants during the production process) in the environment, recent FDA inspections of compounding pharmacies have revealed repeated failures in maintaining the environmental monitoring necessary to meet these standards. In 2013, FDA inspectors cited dozens of compounding pharmacies for failing to assess airflow patterns with adequate smoke studies performed under dynamic conditions and/or failing to conduct appropriate environmental monitoring.⁵³ While FDA inspectors focused on violations of cGMP

⁴⁹ Centers for Disease Control. Epidemiologic notes and reports nosocomial bacteremias associated with intravenous fluid therapy – USA. MMWR Weekly. December 26, 1997/46(51);1227-1233.

<http://www.cdc.gov/mmwr/preview/mmwrhtml/00050554.htm>. Accessed February 18, 2014.

⁵⁰ *Ibid.*

⁵¹ *Ibid.*

⁵² FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

⁵³ Food and Drug Administration. Compounding: Inspections, recalls, and other actions. February 6, 2014.

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm>. Accessed February 24, 2014.

standards, many of the conditions identified would be unacceptable under either cGMP or USP standards. For example, FDA inspectors also noted visible dust, stains, splatters, residue, rust, live or dead insects, and other sources of potential contamination in a disturbing number of facilities.^{54,55,56,57,58,59,60,61,62}

Some of the pharmacies cited by FDA inspectors in 2013 have subsequently registered as outsourcing facilities.⁶³ While we remained concerned that outsourcing facilities will not be required to undergo new drug approval or verify compliance with cGMP prior to producing sterile products, we assume that the FDA will make every effort to ensure that these facilities comply with cGMP standards moving forward. (If this assumption proves to be incorrect, then nonsterile-to-sterile compounding by outsourcing facilities will also pose unacceptable risks to patients.)

By contrast, many pharmacies that have not registered as outsourcing facilities continue to claim that their compounding facilities adequately comply with applicable state and USP standards

⁵⁴ Food and Drug Administration. Axiom Healthcare Pharmacy dba Balanced Solutions Compounding. March 15, 2013. -

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM345694.pdf>. Accessed February 24, 2014. -

⁵⁵ Food and Drug Administration. 483 Inspection Report. Custom Compounding Centers, LLC. December 13, 2012. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348232.pdf>. Accessed February 24, 2014. -

⁵⁶ Food and Drug Administration. 483 Inspection Report: Anazahealth Corporation. February 22, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM341368.pdf>. Accessed February 24, 2014. -

⁵⁷ Food and Drug Administration. 483 Inspection Report: University Pharmacy, Inc. February 26, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM342275.pdf>. Accessed February 24, 2014. -

⁵⁸ Food and Drug Administration. 483 Inspection Report: College Pharmacy Incorporated. March 15, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM345701.pdf>. Accessed February 24, 2014. -

⁵⁹ Food and Drug Administration. 483 Inspection Report: The Compounding Shop, Inc. March 22, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM345933.pdf>. Accessed February 24, 2014. -

⁶⁰ Food and Drug Administration. 483 Inspection Report: Pentec Health, Inc. April 1, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM346817.pdf>. Accessed February 24, 2014. -

⁶¹ Food and Drug Administration. 483 Inspection Report: Pallimed Solutions, Inc. April 9, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348236.pdf>. Accessed February 24, 2014. -

⁶² Food and Drug Administration. 483 Inspection Report: Central Admixture Pharmacy Services, Inc. February 19, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348237.pdf>. Accessed February 24, 2014. -

⁶³ Food and Drug Administration. Registered Outsourcing Facilities. Updated as of February 21, 2014. - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm>. - Accessed February 28, 2014. -

even when they have been informed by the FDA of sterility concerns, making them unlikely to adjust their practices or upgrade their current facilities. In fact, one pharmacy, NuVision, recently refused a request by the FDA to recall all sterile products after the agency identified safety concerns related to sterility during a facility inspection.^{64,65} The pharmacy still claims on its website to adhere to USP standards for sterile compounding.⁶⁶ In addition, three other compounding pharmacies have responded following FDA inspections with their opinion (without citing verification by independent inspectors) that the current facilities satisfy USP requirements, in spite of the fact that federal inspectors had identified serious sterility concerns.^{67,68,69} Regardless of whether these pharmacies do, in fact, comply with USP requirements (a claim that has not been confirmed through independent inspections), it is clear that they are unlikely to dramatically upgrade their facilities in the near future. Appropriately, at least one of these compounding pharmacies has reported that it does not engage in nonsterile-to-sterile compounding.⁷⁰ We urge the FDA to ensure that all compounding pharmacies exempt under 503A avoid this type of high-risk compounding, which cannot be performed safely except in a facility that has been regularly inspected for compliance with cGMP standards.

Personnel Training

Specialized, highly technical training is essential to ensure proper compounding of nonsterile-to-sterile drug products. As stated in the FDA's Concept Paper:

The processes used in pharmacies to prepare sterile products are highly personnel-intensive. The contamination of pharmacy-prepared products (e.g., intravenous admixtures and prefilled syringes) by aseptic processing most likely will be caused by personnel-associated factors. These factors may include the shedding of contaminants from people into the controlled environment, improper procedures under laminar air flow, and the use of poor aseptic technique. Therefore, pharmacy personnel involved in compounding

⁶⁴ FDA reminds health care providers not to use sterile products from NuVision Pharmacy. August 16, 2013. - <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm365402.htm>. Accessed February 26, 2014. -

⁶⁵ Food and Drug Administration. Warning Letter. NuVision Pharmacy. Jul 26, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM363761.pdf>. Accessed February 28, 2014. -

⁶⁶ Nuvision. Sterility Testing. <http://nuvisionpharmacy.com/sterility-testing/>. Accessed February 26, 2014. -

⁶⁷ Foundation Care. Reponse Letter to the Food and Drug Administration. April 9, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM349684.pdf>. Accessed February 24, 2014. -

⁶⁸ IV Solutions of Lubbock. Response Letter to the Food and Drug Administration. April 25, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM349813.pdf>. Accessed February 24, 2014. -

⁶⁹ Pharmacy Creations. Response Letter to the Food and Drug Administration. September 3, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM371359.pdf>. Accessed February 24, 2014. -

⁷⁰ Foundation Care. Reponse Letter to the Food and Drug Administration. April 9, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM349684.pdf>. Accessed February 24, 2014.

sterile products must have sufficient knowledge, training, and experience to perform the task correctly and safely. Furthermore, a pharmacy's quality assurance program for sterile products must include requirements that personnel consistently adhere to performance standards; that performance problems be monitored, detected, and corrected; and that personnel undergo initial and periodic certification.⁷¹

Appropriate training is essential to ensure that sterile solutions do not become contaminated during preparation. A study of pharmacy students by Isanhart et al, published in 2008, assessed procedures performed at the beginning and end of a 16-week parenterals laboratory course offering instruction in aseptic technique.⁷² Prior to undergoing training, 21 of 504 syringes (4 percent) prepared by the students were contaminated during media fill tests, a number that was reduced to 0 of 498 by the end of the course.

While zero contamination is clearly possible with appropriate technique, reports from the FDA and published literature suggest that use of inadequate technique is widespread. Rates of contamination during medium and low risk compounding operations remain highly variable and unacceptably high in practice, ranging from 0 percent to over 6 percent among experienced, practicing pharmacists and technicians.^{73,74,75,76,77} FDA inspection reports from 2013 also document numerous examples of inappropriate aseptic technique and inadequate monitoring of pharmacy personnel. Observations included inadequate gowning that leaves skin exposed, failure to adequately monitor employees for microbial contamination during aseptic operations, uncontrolled movement of employees in and out of the ISO Class 5 clean room where sterile drugs are prepared, inappropriate use of nonsterile objects in aseptic operations, and failure to adequately clean and sanitize equipment and surfaces in the clean room.^{78,79,80,81} Such high-risk

⁷¹ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons - of Safety or Effectiveness. -

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments-to-the-FDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014. -

⁷² Isanhart CM, McCall KL, Kretschmer D, Grimes BA, Parenterals laboratory course to reduce microbial contamination rates in media fill tests performed by pharmacy students. *Am J Pharm Educ.* 2008;72(2):27. -

⁷³ Reiter PD. Sterility of intravenous fat emulsion in plastic syringes. *Am J Health Syst Pharm* 2002;59:1857-9. -

⁷⁴ van Grafhorst JP, Foudraire NA, Nooteboom F, Crombach WH, Oldenhof NJ, van Doorne H. Unexpected high risk - of contamination with staphylococci species attributable to standard preparation of syringes for continuous - intravenous drug administration in a simulation model in intensive care units. *Crit Care Med.* 2002;30:833-6. -

⁷⁵ Trissel LA, Ogundele AB, Ingram DS et al. Using medium-fill simulation to establish a benchmark microbiological contamination rate for low-risk-level compounding. *Am J Health-Syst Pharm.* 2003; 60:1853-5. -

⁷⁶ Thomas M, Sanborn M, Couldry R. IV admixture contamination rates: traditional practice site versus a class 100 cleanroom. *Am J Health-Syst Pharm.* 2005;62:2386-92.

⁷⁷ Trissel LA, Gentempo JA, Anderson RW, Lajeunesse JD. Using a medium-fill simulation to evaluate the microbial contamination rate for USP medium-risk-level compounding. *Am J Health-Syst Pharm.* 2005;62:285-8. -

⁷⁸ Food and Drug Administration. 483 Inspection Report: Avella of Deer Valley, Inc. February 25, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OR/OR-AElectronicReadingRoom/UCM342276.pdf>. Accessed February 26, 2014. -

⁷⁹ Food and Drug Administration. 483 Inspection Report: FVS Holdings, Inc. dba Green Valley Drugs. March 15, - 2013. -

nonsterile-to-sterile compounding by improperly trained personnel poses unacceptable risk to patients. To avoid this risk, nonsterile-to-sterile compounding must be carried out only in facilities that are regularly inspected for compliance with cGMP.

Testing and Quality Assurance

Testing and quality assurance are especially important in nonsterile-to-sterile compounding as a means of verifying that sterility has been successfully achieved. As the FDA stated in its Concept Paper:

All compounded sterile products should be inspected prior to use in patients. Low-risk compounded sterile products (e.g., sterile products prepared from sterile components using proper techniques and equipment) should, at a minimum, be inspected physically and visually for cloudiness and particulate matter. High-risk compounded sterile products (e.g., sterile products prepared from nonsterile components using proper techniques and equipment) should undergo end-product sterility and pyrogen testing before they are dispensed from the pharmacy.⁸²

Sterility testing is required under cGMP, with samples taken at the beginning, middle, and end of the aseptic processing operation.⁸³ Any positive test result is considered a serious cGMP issue requiring thorough investigation.⁸⁴ Under USP standards, only high-risk sterile products prepared in groups of 25 or more or that are exposed to certain temperatures for varying lengths of time must be tested for sterility prior to release, and the pharmacy need not await test results before dispensing the products to patients.⁸⁵ Moreover, products intended for inhalation or ophthalmic administration need not be tested for bacterial endotoxins (pyrogens) prior to release.⁸⁶

As might be expected, a disturbing number of compounding pharmacies forgo testing and quality assurance measures that would be required under cGMP. FDA inspection reports of

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OR/OR-AElectronicReadingRoom/UCM348241.pdf>. Accessed February 26, 2014. -

⁸⁰ Food and Drug Administration. University Pharmacy, Inc. February 26, 2013. -

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OR/OR-AElectronicReadingRoom/UCM342275.pdf>. Accessed February 26, 2014. -

⁸¹ Food and Drug Administration. 483 Inspection Report: Lowlyn Pharmacies, Inc. March 8, 2013.

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OR/OR-AElectronicReadingRoom/UCM345695.pdf>. Accessed February 26, 2014. -

⁸² FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons - of Safety or Effectiveness. -

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014. -

⁸³ Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice. September 2004. -

⁸⁴ *Ibid.*

⁸⁵ <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008.

⁸⁶ *Ibid.*

compounding pharmacies in 2013 identified widespread failure to conduct sterility, endotoxin, and potency testing on all end products. Many pharmacies also failed to document adequate investigation after identifying particulates, discoloration, microbial contamination, leaking product, or other issues with finished samples. In two cases, particulate matter was discovered in products from lots that had already been shipped to customers.^{87,88} Half a dozen pharmacies were also cited for failing to adequately follow up on complaints, including reports indicating mislabeling, particulate matter, and other serious concerns with drug products, including fever, injection-site redness, abscess, and other disturbing adverse events in patients.^{89,90,91,92,93,94}

Based on the factors identified above, high-risk nonsterile-to-sterile compounding cannot be conducted safely in compounding pharmacies that are not regularly inspected for full compliance with cGMP standards. We therefore urge the FDA to identify nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Section 503A, but not necessarily Section 503B.

Alternatively, if the FDA creates a single unified list, we urge the FDA to identify nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for

⁸⁷ Food and Drug Administration. 483 Inspection Report: Village Fertility Pharmacy, Inc. March 13, 2013. <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348242.pdf>. Accessed February 24, 2014. -

⁸⁸ Food and Drug Administration. 483 Inspection Report: Axiom Healthcare Pharmacy dba Balanced Solutions - Compounding. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM345694.pdf>. Accessed February 24, 2014. -

⁸⁹ Food and Drug Administration. 483 Inspection Report: MedPREP Consulting, Inc. April 3, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348230.pdf>. Accessed February 24, 2014. -

⁹⁰ Food and Drug Administration. 483 Inspection Report: Wedgewood Village Pharmacy, Inc. February 11, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM342543.pdf>. Accessed February 24, 2014. -

⁹¹ Food and Drug Administration. 483 Inspection Report: PharMEDium Services LLC (Parsippany, NJ). February 28, - 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM342271.pdf>. Accessed February 24, 2014. -

⁹² Food and Drug Administration. 483 Inspection Report: Village Fertility Pharmacy, Inc. March 13, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348242.pdf>. Accessed February 24, 2014. -

⁹³ Food and Drug Administration. 483 Inspection Report: NuVision Pharmacy, Inc. April 17, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348772.pdf>. Accessed February 24, 2014. -

⁹⁴ Food and Drug Administration. 483 Inspection Report: Central Admixture Pharmacy Services (Chicago, IL). - February 22, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM341365.pdf>. Accessed February 24, 2014.

compounding except under conditions present in outsourcing facilities compliant with Section 503B and cGMP requirements.

2. Metered dose inhaler (MDI) products

The FDA's Concept Paper published in 2000 recommended that MDI products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

The MDI is one of the most complicated drug delivery systems currently marketed by the pharmaceutical industry ...MDI products are primarily used by patients suffering from chronic lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Individuals suffering from asthma and COPD tend to have airways that are hyper-reactive to inhalants. It is therefore critical that the contents and the delivery characteristics of MDI products be carefully controlled to ensure that the product will be safe and effective. Even slight changes in the formulation, drug substance particle size, valve, or actuator can have a major effect on the aerosol delivery and potency characteristics. This effect can significantly alter the safety and effectiveness of the device. For example, a change in particle size distribution may lead to greater systemic absorption of a beta agonist drug, which can increase the amount of systemic side effects and may also decrease the local effectiveness of the drug in the lungs.⁹⁵

The FDA concluded that MDI products present demonstrable difficulties in compounding because:

- Metered dose inhalers are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility, and product-to-product uniformity is critical for dosing accuracy and is usually difficult to achieve.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of MDI products is complex.
- Sophisticated facilities and equipment are required to ensure proper compounding of the drug product.
- Specialized, technical training is essential to ensure proper compounding of the drug product.
- Sophisticated, difficult to perform testing of the compounded drug product is required to ensure potency and purity.⁹⁶

⁹⁵ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

⁹⁶ *Ibid.*

We agree with the FDA's prior analysis and conclusions with respect to MDI products and urge the agency to identify MDI products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

3. Dry powder inhaler (DPI) products

The FDA's Concept Paper published in 2000 also recommended that DPI products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

DPIs are complex drug products that differ in many aspects from more conventional drug products. ... There is a wide array of potential DPI designs, all complex in their design and function and many with characteristics unique to the particular design.

Regardless of design, the most crucial attributes of DPIs are the reproducibility of the dose and particle size distribution. It is difficult to maintain these qualities through the expiration date and to ensure the functionality of the device during the period of patient use. The unique characteristics of DPIs must be considered in their preparation, particularly with respect to the product's formulation, container closure system, and testing.⁹⁷

The FDA concluded that DPI products present demonstrable difficulties in compounding because:

- Dry powder inhalers are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility, and the product-to-product uniformity that is critical for dosing accuracy is usually difficult to achieve.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of DPI products is complex.
- Sophisticated facilities and equipment are required to ensure proper compounding of the drug product.
- Specialized, technical training is essential to ensure proper compounding of the drug product.
- Sophisticated, difficult to perform testing of the compounded drug product is required to ensure potency and purity.⁹⁸

⁹⁷ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAAct/SignificantAmendmentsToTheFDCAAct/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

⁹⁸ *Ibid.*

We agree with the FDA's prior analysis and conclusions with respect to DPI products, and urge the agency to identify DPI products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

4. Transdermal Delivery Systems (TDSs)

Finally, the FDA's Concept Paper published in 2000 recommended that TDS products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

TDS products are complex to develop and may require the use of new technologies. Each system is formulated to meet specific biopharmaceutical and functional criteria. The materials of construction, configurations, and combination of the drug with the proper cosolvents, excipients, penetration enhancers, and membranes must be carefully selected and matched to optimize adhesive properties and drug delivery requirements. The equipment and the technology required for the manufacture of TDS products limit their preparation to properly equipped manufacturers.⁹⁹

The FDA concluded that TDS products present demonstrable difficulties in compounding because:

- TDSs are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of TDS products is complex.
- Sophisticated facilities and equipment are needed to ensure proper compounding of TDS products.
- Specialized technical training is essential to ensure proper compounding of TDS products
- Sophisticated, difficult to perform testing of the compounded product is required to ensure potency, purity, and quality of the drug product prior to dispensing.¹⁰⁰

We agree with the FDA's prior analysis and conclusions with respect to TDS products and urge the agency to identify TDS products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

⁹⁹ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentsToTheFDCAct/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

¹⁰⁰ *Ibid.*

5. Sustained or time-release dosage forms

Public Citizen previously submitted comments on the FDA's Concept Paper published in 2000.¹⁰¹ In those comments, we recommended that the FDA evaluate sustained or time-release dosage forms for categorization as products presenting demonstrable difficulties for compounding. As we stated previously:

Because there is no requirement to test [compounded sustained or time-release] products, it is no known if 90 percent of the active ingredient is released within the first 30 minutes after the dose is taken, or if 90 percent of the active ingredient remains in the dosage form after the dose is taken.¹⁰²

Variation in rates of release of the active ingredient could impact bioavailability, potentially reducing the drug's efficacy or increasing safety risks. Clinical testing is necessary to ensure appropriate bioavailability for sustained or time-release dosage forms. Such clinical testing is not required under either Section 503A or Section 503B and can only be required for drug products that undergo premarket approval by the FDA. We therefore urge the FDA to categorize sustained or time-released dosage forms as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

6. Enteric-coated preparations

Public Citizen also previously recommended that the FDA evaluate enteric-coated preparations for categorization as products presenting demonstrable difficulties for compounding.¹⁰³ Enteric-coated preparations are preparations intended for drugs that are either destroyed by gastric acidity or that cause gastric irritation. As we previously stated, "enteric-coated preparations may, if not properly formulated, resist dissolution in the intestine, and very little if any of the active drug may be absorbed into the blood stream."¹⁰⁴

As with sustained-release dosage forms, improperly formulated enteric-coated preparations could impact bioavailability, potentially reducing the drug's efficacy or increasing safety risks. Clinical testing is necessary to prevent these problems. Because such testing is not required under either Section 503A or Section 503B, we urge the FDA to categorize enteric-coated preparations as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

¹⁰¹ Public Citizen. Comments on Drugs that Present Difficulties for Compounding. August 2, 2000.

<http://www.citizen.org/Page.aspx?pid=3626>. Accessed March 3, 2014.

¹⁰² *Ibid.*

¹⁰³ *Ibid.*

¹⁰⁴ *Ibid.*

III. Conclusion

We are concerned that the FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded because they present demonstrable difficulties for compounding, and urge the agency to withdraw its proposal and instead develop two separate lists. Drugs compounded at compounding pharmacies under a Section 503A exemption should be treated differently than those subject to Section 503B, as the regulations governing each category of facility are different.

Alternatively, if the FDA chooses to proceed with its proposed plan of establishing only one list, we urge the agency to identify compliance with cGMP and the requirements of 503B as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding.

Regardless of whether one or two lists is used, we urge the FDA to classify high-risk nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding under compounding pharmacies exempt under Section 503A, but not necessarily outsourcing facilities exempt under 503B. This high-risk process may be safely carried out only by a facility that is regularly inspected to verify compliance with federal cGMP requirements.

We have also recommended designation of several additional product categories as presenting demonstrable difficulties for compounding.

A full list of product categories that we urge the FDA to identify as demonstrably difficult to compound, along with our recommendations for their appropriate regulatory classification, is summarized as follows:

1. Nonsterile-to-sterile compounding (non-exempt under 503A only)
2. Metered dose inhaler (MDI) products (non-exempt under 503A and 503B)
3. Dry powder inhaler (DPI) products (non-exempt under 503A and 503B)
4. Transdermal Delivery Systems (TDSs) (non-exempt under 503A and 503B)
5. Sustained or time-release dosage forms (non-exempt under 503A and 503B)
6. Enteric-coated preparations (non-exempt under 503A and 503B)

Thank you for your consideration of these comments.

Sincerely,



Sarah Sorscher, J.D., M.P.H.
Attorney
Public Citizen's Health Research Group

A handwritten signature in black ink, appearing to read "Michael Carome". The signature is fluid and cursive, with a long horizontal stroke at the end.

Michael Carome, M.D.
Director
Public Citizen's Health Research Group

Tab 8b

Metered Dose Inhalers (MDIs)

FDA Review



DATE: February 9, 2016

FROM: Brian Rogers, CMC Reviewer, DP/II/Office of Process and Facilities/Office of Pharmaceutical Quality

THROUGH: Richard Lostritto, Acting Associate Director for Science, Office of Policy for Pharmaceutical Quality

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Metered dose Inhalers for Inclusion on the Difficult to Compound List

I. INTRODUCTION

Section 503A of the Food, Drug, and Cosmetic Act (21 U.S.C. 353a) (FD&C Act or the Act) generally governs the application of federal law to pharmacy compounding. Under section 503A of the Act, compounded drug products are exempt, under certain conditions, from three key provisions of the Act: (1) the adulteration provision of section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements); (2) the misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications).

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

Both sections 503A and 503B require compounded drug products to satisfy several requirements to qualify for the statutory exemptions from the FD&C Act. One of those requirements is that the compounded drug product is not one that the Agency has identified as being demonstrably difficult to compound. *See* sections 503A(b)(3)(A); 503B(a)(6).

Specifically, section 503A states that the compounded drug product may not be one that “presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.” *See* section 503A(b)(3)(A).

Similarly, section 503B states that the compounded drug, or category of drugs, either is not one that “present[s] demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into the account the risks and benefits to patients,” or is compounded in accordance with “conditions that are necessary to prevent the drug or category of drugs from presenting [such] demonstrable difficulties.” *See* section 503B(a)(6).

In response to FDA’s request in the Federal Register of December 4, 2013 (FDA-2013-N-1523-0001) for nominations for drug products or categories of products that are considered difficult to compound, three specific metered dose inhaler (MDI) products were nominated, and one nominator also nominated the category of MDI products. Because all MDIs share common characteristics that are relevant to whether they should be considered difficult to compound, we are considering MDIs as a category rather than the individual products for placement on the list of drug products that are considered difficult to compound.

We have reviewed available data on the formulation, drug delivery mechanism, dosage form, bioavailability, compounding process complexity, physicochemical and/or analytical testing complexity, safety, effectiveness, and historical complications in manufacturing this category of drug products. For the reasons discussed below, we recommend that the category of MDIs be included on the list of difficult to compound drug products under sections 503A and 503B of the FD&C Act.

II. BACKGROUND

MDIs are used for the treatment of a variety of lung diseases characterized by obstruction of airflow and shortness of breath, including asthma and chronic obstructive pulmonary disease (COPD). These drug products are also used to treat patients with respiratory infections and cystic fibrosis. In addition, MDIs may be used for systemic drug delivery, because the lungs are increasingly the target organs for absorption of drug products not necessarily intended for the treatment of diseases of the lungs.

The necessary performance characteristics of the MDI dosage form are the ability to deliver a reproducible and specific quantity of the active pharmaceutical ingredient (API) in an aerosol to the targeted portion of the lungs. If the necessary characteristics of the dosage form are not achieved and maintained, the safety and efficacy of the product can be affected. The necessary physical characteristics of an MDI dosage form include a pressurized container consisting of a canister sealed by a metering valve, and an attached actuator/mouthpiece.

MDIs consist of one or more APIs dissolved or suspended in a propellant (liquefied gas under pressure), a mixture of propellants, or a mixture of solvents, propellants, and/or other excipients, in compact aerosol dispensers. An MDI product may discharge up to several hundred metered actuations of one or more drug substances. Depending on the product, the dispensed formulation in each actuation may contain a few micrograms (μg) or up to a milligram (mg) of the active ingredients in a metered volume, typically between 25 and 100 microliters (μL). Individual doses range from one to eight actuations.

The general design of an MDI is shown in Figure 1. The details of a typical valve design are shown in Figure 2 below.

Figure 1. Design of a Typical Metered Dose Inhaler

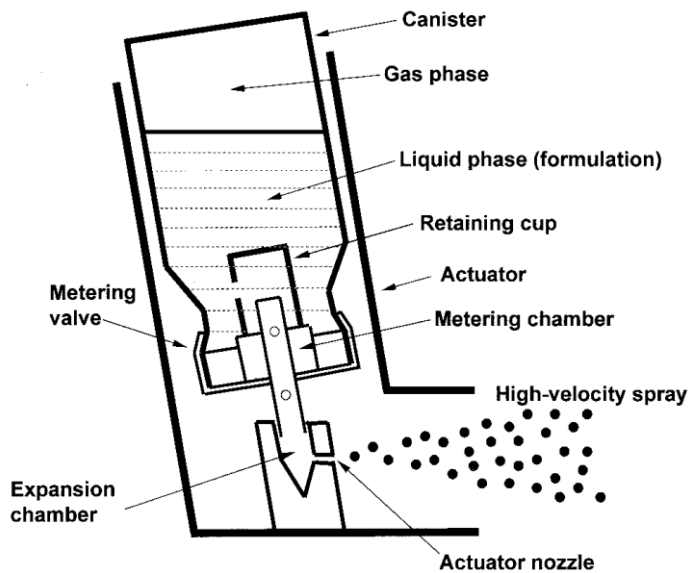
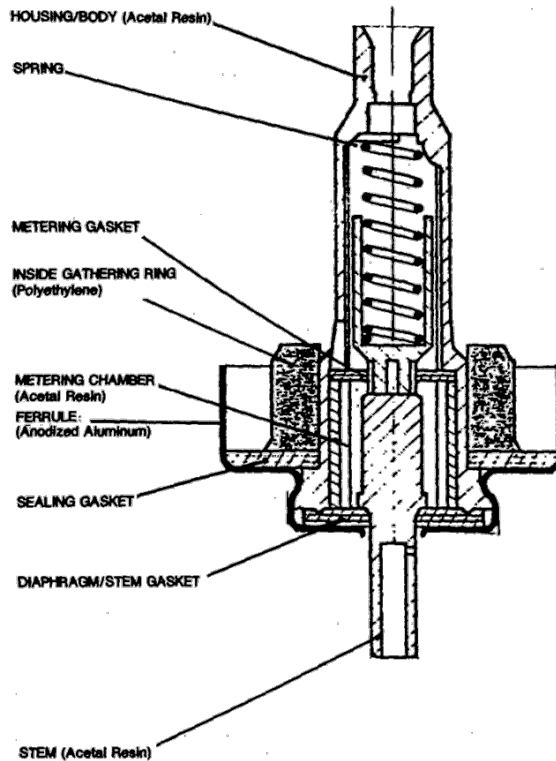


Figure 2. Details of a Typical MDI Metering Valve



An MDI is positioned for actuation (for either priming or dosing) with the canister/metering valve assembly inserted in the inverted orientation into the actuator as shown in Figure 1 above.

Although similar in some respects to other drug products, MDIs have unique characteristics with regard to formulation and container closure systems that require specialized manufacturing procedures, in-process and final controls, and stability testing. Inadequate control or understanding of any of these characteristics can adversely affect the ability of the product to deliver consistent doses to patients throughout the product's shelf life, which includes the period during which it will be used. These unique features of MDIs are discussed below.

III. EVALUATION CRITERIA

FDA has determined that the following criteria should be used for evaluating whether drug products or categories of drug products are demonstrably difficult to compound:

1. Does the drug product or category of drug products have a **complex formulation** that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?
2. Does the drug product or category of drug products have a **complex drug delivery mechanism** that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?

3. Does the drug product or category of drug products involve a **complex dosage form** that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?
4. Does **bioavailability** of the drug product or category of drug products present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?
5. Does compounding the drug product or category of drug products involve a **complex compounding process** that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?
6. Does compounding the drug product or category of drug products necessitate **physicochemical or analytical testing** that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?

IV. ANALYSIS

A. **Metered dose inhalers have a complex formulation that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on safety or effectiveness of the metered dose inhaler.**

MDI formulations are typically either solutions or suspensions and have unique physical characteristics that must be controlled. MDI formulations are uniquely co-developed with a specific drug delivery system associated with the product, to perform a pre-determined drug delivery function, and they require comprehensive characterization of the chemical and physical properties of the formulation's components to assure the stability and performance of the drug product.

1. API

Several properties of the API may affect drug product performance which presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on safety or effectiveness of the MDI. These properties include, but are not limited to, the API's polymorphic form such as amorphous or crystalline (e.g., solvates, hydrates, or clathrates), solubility (solvent system consisting of propellant, and/or co-solvent, and/or surfactant), bulk density, particle size, particle morphology, purity (e.g. moisture and/or residual solvent content). Some of these are discussed below.

a. **Polymorphic Form**

An individual MDI formulation may require the API to exist in a specific polymorphic form. If the amorphous form of the API is desired in the formulation, then the content of other polymorphic forms needs to be limited and controlled by understanding and

avoiding the manufacturing conditions that have the potential to induce/catalyze the natural tendency of phase transition to revert to a thermodynamically more stable crystalline form from the thermodynamically less stable amorphous form.

The presence of an undesired polymorph can affect safety and efficacy because changes in the polymorphic form of the micronized API in the formulation may influence the rate of absorption and dissolution, as well as how the API interacts physically with other API particles, excipients, and the container closure systems.

b. Particle Size

The particle size distribution (PSD) of the API not only affects the homogeneity of an MDI suspension formulation but also the aerodynamic particle size distribution (APSD, a critical quality attribute) of the emitted API mass delivered to the patient. Inadequate control of API particle size can cause unit-to-unit content variability during filling of the MDIs, and unreliable dose deposition in lungs, resulting in a subtherapeutic or suprathapeutic dose to the patient. An API processed to have a large proportion of fine particles—as is critical to have in an MDI—will have a much higher surface area per gram and will result in substantially higher surface energy. The higher energy of these particles makes them unstable relative to the API raw material with respect to increased propensity for particle size growth in the formulation and deposition on the container closure surfaces. The use of an API having a PSD with a high percentage of particles of sizes greater than 5 μm will cause a corresponding increase in the emitted APSD of the drug and will reduce the amount of API deposited in the lungs.

c. Particle Morphology

The surface condition of the API affects its cohesive and adhesive properties, surface activity, specific surface area, and static charge properties, and is important in ensuring suspension stability in MDIs. An unstable suspension formulation will not provide a consistent dose or APSD to the patient, and as a result, the surface condition of the API needs to be carefully characterized and adequately controlled to ensure efficacy and safety.

d. Solubility

Certain APIs may have a high solubility or pH partition profile (partition coefficient and/or dissociation constant) which makes a suspension MDI unstable with respect to physical stability because of its propensity to undergo recrystallization from the formulation. An API with low solubility in a solution formulation may pose a challenge to formulation because of its propensity to precipitate from the formulation at low temperature and it may require the use of a co-solvent to maintain the formulation solution properties.

e. Purity

The purity of the API (assay) and its impurity profile (organic¹ and inorganic² impurities) are critical quality attributes that affect the safety and efficacy of the drug product. However, there are no compendial monographs suitable for APIs for the oral inhalation route of administration.

2. Excipients

Excipients (e.g., propellant, co-solvent, surfactant) and in particular propellants (currently HFA-134a and HFA-227) comprise a significant portion of the MDI formulation. Solution formulations may require co-solvents (e.g., dehydrated alcohol) to help dissolve the API in the propellant. Surfactants (e.g., lecithin, oleic acid) may be used in suspension formulations to stabilize the suspension of particles. Proper selection and quality control of excipients is necessary to achieve and maintain physical stability of the formulation and performance characteristics of the MDI. For example, temperature-induced precipitation of the API may occur due to improper solvent selection or quantity. Solvents may be inappropriate due to insolubility in the propellant, interaction with the elastomeric components in the container closure, water or impurity content, or their acidic or basic nature. Chemical degradation of the API is also potentially an important issue.

3. Formulation Stability

Suspension formulations need to be both physically and chemically stable through careful control of the composition and quality including the physical attributes (e.g., density, PSD) of the APIs and excipients. Physical stability of the formulation is substantially affected by the propensity of the API to: (i) cream or settle in the liquid formulation, (ii) adhere to components of the container closure or other formulation particles, (iii) change in PSD due to Ostwald ripening (recrystallization which increases particle size distribution), or (iv) change to a more stable polymorphic form. Extensive characterization studies are necessary to explore, detect, and avoid the potential for creaming, settling, adhering to container closure components, or change in physical properties. Characterization studies help to prevent physical instability of the formulation by optimizing the concentration of additives such as surfactants, excipient particles of an intermediate density, or use of propellant mixtures. If the formulation is unstable, the amount of drug delivered to the patient may be sub-therapeutic or supra-therapeutic, or the MDI may not deliver drug at all.

Conclusion

MDIs have a complex formulation because of the requirement that the formulation deliver the same amount of drug in the same size droplets or particles when administered from the metering valve as an aerosol over the life of the product. The formulation in a suspension MDI is complex because it must be created from unique components that must have predictable and controllable chemical composition and physical stability, notwithstanding the fact that the solid components are normally in a high-energy physical form (micron-sized particles). If the formulation is not made correctly, taking into

¹ Organic impurities are synthesis and degradation related products.

² Inorganic impurities may include, for example, reagents, heavy metals, and catalysts.

account the numerous properties required of the API, the excipients, the stability of the formulation, and the container closure system, it will not aerosolize correctly and could deliver too much or too little drug. Accordingly, the complex formulation of MDIs presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the MDI.

B. Metered dose inhalers have a complex drug delivery mechanism that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the metered dose inhaler.

The safety or effectiveness of the MDI is directly dependent on the design of the drug delivery mechanism and its ability to function as intended. MDIs require a complex drug delivery mechanism to accurately measure and reproducibly deliver a complex liquid formulation to the patient without undesirable impurities or environmental components (e.g., oxygen or water). In addition, to ensure consistent efficacy without safety concerns from variable dosing, the formulation must be delivered in the form of an accurately and reproducibly generated aerosol plume with a consistent and extremely fine APSD of the API. As described below, dosing accuracy and consistency are difficult to achieve due to the critical function and complexity of the drug delivery mechanism.

Aerosolization of the metered formulation is initiated by releasing the energy stored in the compressed (liquefied) propellant and is controlled by the actuator orifice in conjunction with the metering valve stem and the metering chamber. The orifice dimensions are critical to and impact the spray characteristics (velocity and geometry of the *aerosol plume*), which in turn are important for consistent drug delivery and efficacy of the delivered dose. If the orifice develops deposits from evaporation of the volatile components of the formulation or is incorrectly designed or defective, the shape and density of the resulting aerosol plume and thus the emitted dose will be unpredictable, and will fail to consistently provide adequate medication.

The aerosolization of a formulation from a pressurized MDI container is a complex and rapid sequence of events. Creating an accurate and consistent aerosol plume from the actuator (dose to the patient) requires knowledge of the following:

- a) Drug product-specific valve priming characteristics and cleaning requirements for the actuator.
- b) Extent of drug product variability based on the physical characteristics and controls of the API and any solid excipients.
- c) Optimization of the formulation, the valve and actuator design, the manufacturing process, process parameters, in-process controls, and packaging including canister-valve seal integrity.

In part for reasons stated elsewhere in the consult, this presents difficulties for compounders.

Conclusion

MDIs have a complex drug delivery mechanism because the physical form of the delivered dose (the aerosol plume) to the patient is critically dependent on the formulation composition, characteristics of the formulation components, and the container closure composition and design. The complexity of this drug delivery mechanism presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the MDI.

C. Metered dose inhalers are a complex dosage form that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the metered dose inhaler.

A sophisticated container closure system is required to ensure an MDI performs as intended. The intended function of the MDI container closure and actuator is to precisely, accurately, and consistently measure a volume of liquid formulation, consistently aerosolize it, and then deliver the API in the aerosol plume with a specific and consistent drug content and physical form so as to deposit it in the appropriate portion of the patient's lungs.

The safety and effectiveness of the MDI is dependent on the inertness (i.e., non-absorptive and non-additive properties) of the canister surface in contact with the formulation, as well as the canister design, specifications, and tolerances. Both physical and chemical compatibility between the formulation components and the canister inner surface are necessary.

For a consistent and accurate dose to be delivered over the life of the drug product, the canister must be sealed to the metering valve tightly with the sealing gasket by a precisely crimped ferrule around the canister neck – creating an adequate seal to minimize moisture and oxygen ingress and loss of volatile formulation components. The ingress of moisture or oxygen may adversely affect particle size of an API in the bulk formulation, and in the emitted formulation as measured by the APSD. Loss of propellant will increase the concentration of the API in the formulation, increasing the dose delivered to the patient per actuation.

The canister inner wall and the metering valve components' surfaces are required to be inert (non-absorptive and non-additive) to the formulation. Insufficient understanding of formulation physical and chemical properties can lead to inadequate design (especially a poor choice of material of construction, more so than dimensions), rendering the inner surfaces of these components reactive to the formulation, and thereby affecting the availability of an API in the suspension or introducing impurities in the form of leachable chemical entities into the formulation. If the surfaces interact with the formulation, the unpredictable deposition of the API on these surfaces will cause a decrease in the concentration of the suspended drug in the bulk formulation, thus decreasing both the emitted dose and the fine particle fraction mass that is delivered to the appropriate portion of the lungs. Conversely, flaking off of the API from these surfaces will result in potentially super-potent dosing. Efficacy and safety will both be affected by these processes.

Since the propellant and any co-solvent form a high percentage of an MDI formulation, normal physical contact between the formulation and the container closure components results in migration of impurities as leachable chemical entities from the container closure system components into the formulation. Given the fact that MDIs are used chronically and often in patients with sensitive/compromised lung function, leachables are a potential safety concern and need to be characterized and controlled to minimize patients' exposure.

The fact that MDIs commonly need secondary protective packaging in the form of a foil pouch to maintain the stability of the product over time also demonstrates the complexity of the MDI dosage form and its sensitivity to impurities. Secondary protective packaging is needed when there is a demonstrated degradation in the dosage form performance over time owing to the ingress of water from the atmosphere. This sensitivity to atmospheric moisture must be evaluated by storing the dosage form under a complex range of conditions which have varying humidity levels. When the dosage form performance is found to be humidity dependent, then the use of protective secondary packaging is the most commonly utilized corrective measure.

If the dose delivery of the API is not achieved and maintained throughout its life, the variation in dosing is likely to cause low delivered doses that will be reasonably likely to result in a lack of efficacy. In the case of rescue medication, a low delivered dose will cause safety concerns because it would fail to meet the patient's need for immediate and sufficient dosing to prevent further bronchospasm or airway constriction. The same clinical effects may occur when the emitted dose to the patient cannot penetrate to the targeted part of the lungs, such as when the APSD of the formulation particles in the emitted dose are too large for adequate penetration.

Conclusion

The process of achieving and maintaining necessary performance characteristics is controlled by the precise functioning of the container closure components. Failure of these components to consistently function, or a poor choice of component composition (such as use of plastic in the metering valve which swells when in contact with the formulation, or an uncoated canister which has an affinity for the drug particles), will result in variable emitted dose and/or APSD. The complexity of the dosage form presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the MDI.

D. Bioavailability of drugs in metered dose inhalers is difficult to achieve and assess, and presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on safety or effectiveness of the metered dose inhaler.

The concept of classical bioavailability (that is, the fraction of the administered dose of unchanged drug that reaches the systemic circulation) is usually not applicable to oral inhalation aerosols, which are designed to act locally in the lungs. Currently there is no simple methodology to assess bioavailability at the site of action in the lungs because of the complexity of the target organ.

In addition to difficulties in measuring bioavailability at the site of action, it would likely be difficult to achieve targeted and consistent drug delivery to the site of action for an MDI because of the inherent formulation and delivery system challenges described in sections A and B. As described previously, attaining and maintaining the necessary PSD, polymorphic form, and other critical physical properties of the API can affect the absorption of the delivered dose. Absorption obstruction decreases systemic bioavailability of the compounded drug product. The MDI product is a complex system for which any small change in performance characteristics can have a significant impact upon the local and systemic bioavailability and efficacy of the product. Currently, in vitro assessments such as APSD and single actuation content, alone, are not sufficient to accurately predict lung deposition, bioavailability, and overall clinical effect. As an example, the cascade impactor device used to measure the drug product APSD claims it can also be used for quantitation of drug deposited in the lungs, but at this time, current scientific understanding only supports impactor data being used for quality testing of MDI units.

Because comparative clinical studies and in vitro and pharmacokinetic assessments are typically required to assess the local bioavailability of MDI drug products, this complex weight-of-evidence approach necessary for product development would present a demonstrable difficulty to compounding. The dose administered is typically so small that blood or serum concentrations are generally low, and may only be detectable for a few hours post-dose. The systemic exposure alone may not distinguish the absorption from the lungs or GI tract, and current methodologies cannot clearly differentiate the regional lung deposition. Thus, there is no single, easily reproducible, reliable method of measurement that can quantitate the dose delivered by the dosage form and received by the patient, which would be necessary to enable the compounder to consistently make product with delivered dose uniformly falling within acceptable ranges.

Conclusion

For locally acting drugs applied to the lungs at low doses, as is typical of MDI dosage forms, measuring local bioavailability, which would be determined by measuring the levels of drug deposited at the critical site within the lungs, does not currently have a single, easily reproducible method of quantitation. Measurement of blood levels alone, as accomplished historically for bioavailability testing for solid oral dosage forms, is generally challenging for MDIs. Furthermore, bioavailability of MDIs would also likely be difficult to achieve because of the product characteristics described above for MDIs. The MDI is a complex system for which any small change in performance characteristics can have significant impact upon the overall bioavailability and performance of the product. Therefore, bioavailability of MDIs is difficult to achieve and assess, and presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the MDI.

E. Compounding metered dose inhalers requires a complex compounding process that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of metered dose inhalers.

1. API Processing

MDI formulations, in particular the suspension formulations, require the API and any excipient(s) to be micronized in specialized equipment to a sufficiently small particle size so that they can be inhaled and deposited in the appropriate airways. The micronization process is typically followed by a conditioning or aging step,³ which makes the physical form of the substrate more uniform. Although MDI solution formulations are less dependent on the particle size of the API and excipients than are MDI suspension formulations, they pose additional problems in the form of: (i) potential routes of API or excipient degradation related to water and oxygen ingress; and (ii) absorption of the dissolved formulation components by the valve gaskets, which would decrease the levels of the components in the formulation.

2. Formulation Compounding

The overall unit-to-unit and batch-to-batch uniformities are dependent on the variability of the formulation filled into the canisters. The dispensed formulation variability is in-turn dependent on the variability of the bulk formulation in the filling system, the uniformity of the blending process used to create the solid phase of the formulation, and the rate of addition of any make-up propellant.

MDIs may be prepared by one of two methods: cold-filling or pressure-filling. Either of these operations may be one-stage or two-stage.

In one-stage cold-filling, the entire formulation is chilled to approximately -50°C so that the propellants remain in the liquid state. Specialized equipment is needed to maintain the cold temperature within the correct range. All circulation and associated filling lines must be designed and set up for this process. As filling occurs, the head space in the chiller tank increases, which in turn allows propellant to evaporate. Without proper formulation and manufacturing technique (e.g., incremental addition of fresh propellant), super-potent MDI units may occur at the end of preparation.

In two-stage cold-filling, the propellant(s) is chilled to a liquefied state of approximately -50°C. The drug and other non-volatile excipients are dissolved or dispersed in alcohol and filled into the container, which is then cold-filled.

³ Conditioning (aging) is the storing of a solid under controlled conditions of temperature and humidity to promote a physical change in the solid from a less stable to more stable physical form (e.g., conversion of an unstable polymorph to the most stable polymorph, or agglomeration to produce a more reproducible PSD.)

Pressure-filling may also be done in one or two stages. The one-stage method involves filling the entire formulation into a sealed unit-of-use canister, while the two-stage method involves pre-loading the containers with the drug and all non-volatile excipients dissolved or dispersed in ethanol.

Note that moisture (which can radically alter particle size distributions) is challenging to control during manufacturing in both cold-filling and pressure-filling. For example, in cold-filling operations, condensation of atmospheric moisture must be controlled. The alcohol used also is typically dehydrated to remove as much water as feasible.

In both cold-filling and pressure-filling operations, compounding of an MDI formulation would require specialized equipment including a homogenizer, formulation tank, filling tank, and filling heads. In addition, adequate mixing and circulation are necessary to achieve uniformity of formulation fill into individual units. This equipment is specialized for MDI filling. It also is difficult to set up and validate because of the large number of parameters involved. Without this equipment, a suspension formulation will not be uniform in particle size or concentration, and the filling process will introduce unpredictable variability into the drug product performance and have a significant effect on safety and efficacy. Solution formulations also have a critical uniformity requirement, but do not need to maintain a suspension.

Changes in polymorphic form and PSD during liquid formulation blending and filling are possible when the API has some solubility in an intermediate formulation and the mixing or blending are not accomplished at a sufficiently low temperature to minimize Ostwald Ripening.

The physical properties of the bulk formulation are difficult to measure because the entire system must remain sealed to the atmosphere and pressurized once the bulk formulation compounding begins. This is necessary to prevent ingress of moisture or oxygen, or loss of volatile propellant or co-solvent, which otherwise could be harmful to the physical properties of the micronized API, specifically the PSD and the propensity of the API to interact with the container closure components. Changes in the extent of these interactions may cause significant batch-to-batch variability and have a deleterious effect on safety and efficacy.

3. Filling and Valve Sealing

Formulation filling into the MDI is a critical and complex procedure. During filling, the container closure is normally either evacuated or purged with propellant to eliminate atmospheric moisture and oxygen, the valve is then sealed to the canister by crimping, and finally the formulation is filled into the canister. Critical filling parameters to assure batch-to-batch uniformity include: propellant purge weight, crimping dimensions, fill volume (for cold-fill operations), API content uniformity in the formulation, assay, and pressure testing when co-solvents or propellant mixtures are used.

Conclusion

Any errors in formulation compounding or filling of the MDI are reasonably likely to result in delivered dose variability in either the quantity of the emitted drug or its APSD. Insufficient drug delivered to the appropriate part of the lungs (as measured by these two parameters) would pose an efficacy concern, and potentially a safety concern, especially for rescue medications. For the reasons discussed above, compounding an MDI involves a complex compounding process that presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the MDI.

F. Metered dose inhalers necessitate complex physicochemical or analytical testing that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the metered dose inhaler.

A large number of tests are needed to assure satisfactory performance of MDIs. Furthermore, extensive characterization and developmental studies on the specific formulation, the container closure system, and the manufacturing process are necessary to develop the specifications and in-process controls that would be used to ensure the satisfactory properties of the raw materials, container closure components, and manufacturing consistency, all of which determine the performance characteristics of the dosage form. In addition, such characterization and developmental studies on the specific formulation are necessary to develop the specifications for end-product testing. It is reasonably likely that the failure to appropriately conduct the necessary testing would lead to an adverse effect on the safety or effectiveness of the compounded drug product.

1. Raw Materials Testing

Appropriate acceptance criteria and tests for routine control (i.e., release, stability, and retest) must be instituted for APIs before and after any additional processing, including micronization. These controls are critical to maintain consistent API physicochemical properties in the formulation, such as the percentage of amorphous content, moisture content, PSD, levels of residual solvents and degradation products, bulk density, contaminants and foreign particulates, and morphology. This ensures consistent drug product performance necessary to achieve efficacy and avoid safety concerns related to variability in strength and bioavailability.

The purchased API needs to be tested prior to further processing (micronization and conditioning) because the micronization conditions depend critically on the characteristics of the API. Furthermore, testing of the API after additional processing is critical to establishing the physical characteristics of the API. As described previously, the physical properties of the API after additional processing are critical in ensuring the stability of the formulation, and the consistent drug content, APSD, and bioavailability of the emitted dose. Finally, the physical stability of the reprocessed API during storage must be established through stability studies with appropriate testing of both the API and the finished dosage form.

2. In-Process Testing

Critical in-process tests/controls required to assure accurate and reproducible dose delivery include API assay, consistency of filling of the concentrate and the propellant, valve crimp measurements, propellant purge weight, check-weighing (fill weight), spray testing, leakage, and visual appearance.

It is very common for suspension MDI dosage forms to have very low mass loading of the API in the formulation. It is also difficult to sample the uniformity of the bulk formulation in the formulation mixing vessel or in the recirculating loop due to the need to maintain the internal pressure of the system to keep the formulation in the liquid state. Due to the high non-uniformity risk associated with low drug loading of the suspension formulation, periodic in-process testing is necessary to ensure manufacturing consistency. Validation of the process from beginning-to-end of filling uniformity and unit-to-unit variability is necessary.

3. Lot Release Testing

The APSD and delivered dose uniformity are two of the most critical attributes to consider in determining the batch-to-batch uniformity, potency, and quality of an MDI dosage form. The measurement of the APSD requires a cascade impactor analysis of the label number of actuations in a single dose. It is considerably more complex to correctly assemble, perform a determination, disassemble, and clean the apparatus than other conventional analytical methods. Furthermore, the complexity of the operation increases with the number of operators, each of whom would have to achieve the same results consistently. The quantitation of chemical impurities leached from the container closure components and other impurities in the formulation resulting from API degradation are critical tests necessary to demonstrate purity of the formulation in the dosage form. This testing provides assurance of the safety of the drug product. Furthermore, the chemical impurities leached from the container closure components must be quantitated through various sensitive analytical techniques developed specifically for these impurities.

Leakage in filled MDI units in a batch is tested by a heat stress (pressure) test⁴ prior to equilibration and quarantine storage (e.g., 3 - 4 weeks), after which 100% testing for fill weight (check weighing), spray testing (valve function), and batch release testing are necessary.

4. Stability Testing

MDIs require both product quality and product performance testing to determine appropriate in-use periods and should be studied throughout their in-use period to ensure that product performance is maintained during storage and administration. The effect of resting time, number of priming actuations, and other performance tests are necessary at the beginning and end of a MDI's in-use period. Additional testing is necessary to

⁴ Heat stress testing (normally in a hot water bath) is meant to reveal units with a marginal seal, but not damage those with adequate sealing. For testing, all components of the filled canister (valve, canister and formulation) should achieve both a minimum temperature of 55°C and the corresponding equilibrium pressure. The requirement for establishing appropriate internal conditions during testing makes the validation process and testing procedure complex and precise.

determine the appropriate in-use period, which is the time period from the point the patient removes the MDI from its protective packaging until it has delivered its labeled number of actuations or must be discarded.

Conclusion

MDIs require complex physicochemical and analytical testing because the formulation components' physical and chemical properties and product-critical performance parameters (such as APSD and delivered dose) require complex analytical devices and procedures for accurate measurement. Furthermore, chemical impurities from both the degradation of the API and leached from the container closure components must be quantitated through various sensitive analytical techniques developed specifically for these impurities. In-process testing of MDIs and control of their manufacturing process, using methods unique to MDI manufacturing procedures, are critical to minimizing unit-to-unit and batch-to-batch variability, and to ensuring accurate performance throughout the product shelf life and in-use life.

The physicochemical or analytical testing required for MDIs is so complex that it presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the MDI.

V. PATIENT RISK AND BENEFIT CONSIDERATIONS

MDIs have grown in popularity since their introduction in the late 1950s. They are an indispensable dosage form used for the treatment of a variety of lung diseases including asthma, COPD, respiratory infection, and cystic fibrosis, and other lung diseases characterized by obstruction of airflow and shortness of breath.

There are currently approximately 19 MDI products on the market. These products are all drug products approved under a new drug application or abbreviated new drug application submitted to the FDA. The safety profile for the products is monitored by the FDA to identify drug safety concerns and recommend actions to improve product safety and protect the public health. There is currently an adequate supply of approved MDI products on the market and thus there is limited, if any, benefit to expanding the market to compounding MDI products. In fact, any benefit derived is outweighed by the risks, discussed above, associated with allowing a compounder to attempt to produce these complex drug products.

Unlike most other drug products, the dosing and performance and, therefore, the clinical efficacy of an MDI, is directly dependent on the design of the device which also acts as a container closure system. Also unique to MDIs is that the dosage form is for a local effect in the lungs. Unlike most other dosage forms (e.g., tablet, capsule, solution, suspension), bioequivalence of an MDI to a reference drug product cannot be established solely by conducting typical bioavailability studies and quality control tests alone, because pharmacokinetic data in this instance primarily measures the amount of systemic absorption, which may not correlate with topical drug deposition and/or clinical effect. The demonstration of efficacy and safety (or alternately, bioequivalence) of an MDI product is based upon a complex assessment of in vitro performance characteristics of the MDI, in vivo data, and evidence of clinical effect, where small variations in any one of these complex parameters may have profound effects upon product performance. This

complex product development is a challenge for MDI development programs, given that all these parameters need to be carefully controlled to ensure consistent product quality and stability over the shelf-life of the product. This is the most critical reason why there would be demonstrable difficulties for compounding.

Conclusion

MDIs are a complex category of drug products that are effective and safe when manufactured properly to ensure, amongst other things, that the product has the proper formulation, the drug delivery mechanism is designed correctly, appropriate bioavailability is achieved and the necessary physicochemical and analytical testing is performed. The product quality of an MDI is critical and the complexity of compounding this category eclipses any benefit of allowing an outsourcing facility or pharmacy to compound MDIs. The drug products currently on the market are available to consumers with safety profiles the FDA continues to monitor, and thus the advantage of access, efficacy, and safety benefit the patient greater than exposing them to the myriad risks associated with allowing compounders to attempt to produce MDI drug products.

VI. RECOMMENDATION

Based on an analysis of the evaluation criteria, we conclude that MDIs present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product and that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the category of drugs, taking into account the risks and benefits to patients. Accordingly, we recommend that the category of MDIs be included on the list of difficult to compound drug products under sections 503A and 503B of the FD&C Act.

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Tab 9

Dry Powder Inhalers (DPIs)

Tab 9a

Dry Powder Inhalers (DPIs)

Nominations



4 March 2014

Food and Drug Administration
Division of Dockets Management (HFA-301)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Comments [Docket No. FDA-2013-N-1523]

Dear Sir or Madam:

Reference is made to the notice published by the Food and Drug Administration (FDA) in the Federal Register on 4 December 2013 (78 Fed. Reg. 72840), encouraging interested parties to nominate specific drug products or categories of drug products for inclusion in the Agency's list of products that present demonstrable difficulties for compounding (the difficult-to-compound list). The purpose of this submission is to note several drug products and categories of drug products that GlaxoSmithKline (GSK) believes warrant inclusion in the difficult-to-compound list.

GSK is a research-based pharmaceutical and biotechnology company. Our company is dedicated to the discovery, development, manufacture, and distribution of medicines and vaccines that enable people to live longer, healthier, more productive lives. GSK appreciates the opportunity to provide comments on this important topic. While GSK recognizes the importance of preserving access to compounded drugs when patients cannot be treated with FDA-approved products, inappropriate compounding activities can present significant risks. The timely issuance, and rigorous enforcement, of FDA's difficult-to-compound list is critically important to protect patients from these risks.

As described in the Federal Register notice, for a drug product to be compounded under either Section 503A or Section 503B of the Food, Drug, and Cosmetic Act (FDCA), it must (among other things) not be a drug product identified by the Secretary as one that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that product, taking into account the risks and benefits to patients. After evaluating the responses to its request for nominations, and after consulting with the Pharmacy Compounding Advisory Committee, FDA has stated that it plans to develop and publish a single list for compounding under both Sections 503A and 503B, using notice-and-comment rulemaking procedures.

In its request for nominations, the Agency lists a number of factors that may be relevant in assessing whether a certain drug product or category of products should be included in the difficult-to-compound list, including factors that may impact the potency, purity, or quality of a drug product, and thereby affect its safety or effectiveness. The factors listed by FDA include those related to: the drug delivery system; drug formulation and consistency; bioavailability; the complexity of compounding; facilities and equipment; training; and testing and quality assurance. Below, we list a number of drug products and categories of products that we believe should be included in the list, based on our assessment of these and other factors. GSK reserves the right to expand upon these comments or nominate additional drug products or categories of products in the future.

I. Respiratory Drug Products

Respiratory products often incorporate sophisticated drug delivery systems, such as dry powder or metered dose inhalers, which are precisely engineered and tightly controlled to deliver their active ingredients to local sites of action within the body. In addition to their device components, the formulations of respiratory medicines are often complex, using active and inactive ingredients with defined particle size profiles and other qualities that are intended to interact with those components in specific ways. The manufacturing of respiratory products thus requires sophisticated facilities and equipment, and highly trained personnel, beyond the capabilities of drug compounding operations. Post-manufacture, ensuring the quality and performance of such drug/device combination products requires difficult-to-perform testing, such as aerodynamic particle size distribution and emitted dose assessments.

Failure in any of these numerous elements – from device design and formulation work, to manufacturing, to quality assurance – would threaten the safety and effectiveness of the drug product. Moreover, these medicines generally cannot be compounded into more common dosage forms, such as tablets or capsules, because of concerns with dosing accuracy and bioavailability at the local sites of action. For these reasons, GSK believes that respiratory drug products, including the following GSK products, should be included in FDA's difficult-to-compound list:

- Advair Diskus® (fluticasone propionate and salmeterol) Inhalation Powder
- Advair HFA® (fluticasone propionate and salmeterol) Inhalation Aerosol
- Anoro™ Ellipta™ (umeclidinium and vilanterol) Inhalation Powder
- Beconase AQ® (beclomethasone dipropionate, monohydrate) Nasal Spray
- Breo® Ellipta™ (fluticasone furoate and vilanterol) Inhalation Powder
- Flonase® (fluticasone propionate) Nasal Spray
- Flovent Diskus® (fluticasone propionate) Inhalation Powder
- Flovent HFA® (fluticasone propionate) Inhalation Aerosol
- Relenza® (zanamivir) Inhalation Powder
- Serevent Diskus® (salmeterol xinafoate) Inhalation Powder
- Ventolin HFA® (albuterol sulfate) Inhalation Aerosol
- Veramyst® (fluticasone furoate) Nasal Spray

II. Modified Release Drug Products

Modified release products, including delayed, sustained, and extended release tablets and capsules, are generally manufactured using complex, often patent-protected, technologies. The failure of a drug compounding operation to understand, have access to, and utilize these technologies appropriately could result in products with poor dosing accuracy, bioavailability, or product-to-product uniformity – any of which may affect safety or effectiveness. The failure of a release mechanism, for example, may present a safety issue, if it leads to dose dumping, or an effectiveness issue, if the drug is not released into the circulation in a timely manner. For these reasons, GSK believes that modified release drug products, including the following GSK products, should be included in FDA's difficult-to-compound list:

- Coreg CR® (carvedilol phosphate) Extended-Release Capsules
- Requip XL® (ropinirole) Extended Release Tablets
- Rythmol SR® (propafenone hydrochloride) Extended-Release Capsules
- Wellbutrin SR® (bupropion hydrochloride) Sustained-Release Tablets
- Zyban® (bupropion hydrochloride) Sustained-Release Tablets
- Lamictal® XR (lamotrigine) Extended-Release Tablets

III. Drug Products Presenting Increased Risks

Certain drugs and drug products, including but not limited to those subject to Risk Evaluation and Mitigation Strategies (REMS), present increased risks. Adequate mitigation of these risks requires careful and consistent manufacturing, enhanced labeling and risk communications, and even restricted distribution. Compounded products containing drugs associated with teratogenicity, mutagenicity, or carcinogenicity may also present increased occupational risks to those performing the manufacturing operations themselves, through respiratory or skin exposure. These products therefore require sophisticated facilities and equipment, and highly trained personnel, to ensure not only the potency, purity, and quality of the drug products, but also the safety of those working with them. For these reasons, GSK believes that certain increased risk drug products, including the following GSK products, should be included in FDA's difficult-to-compound list:¹

A. Drug Products with Approved REMS²

- Potiga® (ezogabine) Tablets [Controlled Substance – Schedule V]
- Promacta® (eltromopag olamine) Tablets
- Zyban® (bupropion hydrochloride) Sustained-Release Tablets
- Avandamet® (rosiglitazone maleate and metformin hydrochloride) Tablets
- Avandaryl® (rosiglitazone maleate and glimepiride) Tablets
- Avandia® (rosiglitazone maleate) Tablets

B. Drug Products Presenting Occupational Risks

- Avodart® (dutasteride) Capsules
- Jayln® (dutasteride and tamsulosin hydrochloride) Capsules
- Tafinlar® (dabrafenib) Capsules
- Votrient® (pazopanib) Tablets
- Soriatane® (acitretin) Capsules
- Veltin® (clindamycin phosphate and tretinoin) Gel

IV. Anti-Epileptic Drug Products

Certain drugs are characterized by narrow margins between their effective and toxic doses. Others require careful dose selection and titration, because even small differences in dose or bioavailability can have clinical consequences for patients. Anti-epileptic drugs (AEDs) are perhaps the most well-known such products. Consistency of manufacturing, dosing uniformity, and reliable bioavailability are critical for these drug products. Any potential compounding of such products is highly complex, with significant potential for

¹ GSK understands that biological products, licensed under the Public Health Service Act, are not covered by the new drug application exemption provisions of Sections 503A and 503B of the FDCA. For this reason, biological products may not be compounded or distributed without an approved biologics license application. If FDA interprets Sections 503A and 503B to apply to biological products, however, such products – including the GSK products Benlysta® (belimumab) Injection, Arzerra® (ofatumumab) Injection, and raxibacumab injection – should be included in the do-not-compound list. Biological products are uniquely challenging to manufacture, handle, and distribute, and the inappropriate compounding of biological products would present significant risks to patients.

² Section 503B(a)(7) of the FDCA prohibits the compounding by outsourcing facilities of certain drugs subject to REMS (those approved with elements to assure safe use), unless the facilities demonstrate prior to beginning compounding that they will utilize controls comparable to the controls applicable under the relevant REMS. This does not address, however, compounding under Section 503A of the FDCA, or the compounding of other drugs presenting increased risks.

GSK Comment
Docket No. FDA-2013-N-1523
4 March 2014

errors that may affect the safety or effectiveness of the products and present unacceptable risks to patients. For these reasons, GSK believes that AEDs, including the following GSK products, should be included in FDA's difficult-to-compound list:

- Lamictal® (lamotrigine) Chewable Dispersible Tablets
- Lamictal® (lamotrigine) Tablets
- Lamictal® XR (lamotrigine) Extended-Release Tablets
- Potiga® (ezogabine) Tablets [Controlled Substance – Schedule V]

Again, we appreciate the opportunity to provide input on this important topic. GSK looks forward to participating in FDA's continued development of the difficult-to-compound list, including the advisory committee and rulemaking processes. Please contact me via e-mail at leo.j.lucisano@gsk.com or telephone at (919) 483-5848 with any questions or comments.

Sincerely,



Leo Lucisano
Senior Director GPAR - NA
Global CMC Regulatory Affairs
RD Chief Regulatory Office
5 Moore Drive, P.O. Box 13398
Research Triangle Park, North Carolina 27709



1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

March 4, 2014

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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

Re: Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Nominations; Docket Number FDA-2013-N-1523

Dear Commissioner Hamburg and Dr. Woodcock:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, submits these comments in response to the Food and Drug Administration (FDA) request for nominations for Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FDCA; Docket Number FDA-2013-N-1523).

We wish to express our concern that the FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded because they present demonstrable difficulties for compounding. Sections 503A and 503B of the FDCA, which create exemptions from new drug approval and other requirements for compounding pharmacies and outsourcing facilities, respectively, each separately authorize the FDA to publish a distinct list identifying drug products that present demonstrable difficulties for compounding and therefore

cannot be produced under the exemptions. We believe two separate lists are necessary, because drugs compounded at compounding pharmacies under a Section 503A exemption will be subject to reduced regulatory standards and fewer enforcement mechanisms relative to drugs compounded at outsourcing facilities under a Section 503B exemption. (Although it is important to note that drugs qualifying for either type of exemption will be subject to reduced requirements relative to drugs that undergo new drug approval, and therefore in general pose greater risk to patients than FDA-approved drugs).

We urge the FDA to classify products involving nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding under 503A, but not under 503B. Production of drugs using this inherently high-risk process should be carried out only by a facility that is regularly inspected to verify compliance with current federal Good Manufacturing Practices (cGMP) requirements. Compounding pharmacies regulated under 503A are not required to follow cGMP, will rarely—if ever—be inspected by the FDA, and may or may not be regularly inspected by state officials, depending on the pharmacy regulations in each state, and any such state inspections are likely to be far less rigorous than those conducted by the FDA. By contrast, 503B outsourcing facilities, while not required to obtain new drug approval for their drug products, are nevertheless required to comply with cGMP and will be inspected by FDA officials on a risk-based schedule.

Alternatively, if the FDA chooses to proceed with its proposed plan of establishing only one list, we urge the agency to identify compliance with cGMP and the requirements of 503B as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding, and to require such conditions for high-risk nonsterile-to-sterile compounding. Outsourcing facilities that register under Section 503B and comply fully with the FDCA will be permitted to compound such products, whereas compounding pharmacies regulated under 503A would not be allowed to compound such products.

We also recommend designation of several additional product categories as presenting demonstrable difficulties for compounding, and which therefore cannot be produced under 503B and/or 503A exemptions. A full list of product categories we urge the FDA to identify as demonstrably difficult to compound, along with our recommendations for their appropriate regulatory classification, is summarized as follows:

1. Nonsterile-to-sterile compounding (non-exempt under 503A only)
2. Metered dose inhaler (MDI) products (non-exempt under 503A and 503B)
3. Dry powder inhaler (DPI) products (non-exempt under 503A and 503B)
4. Transdermal Delivery Systems (TDSs) (non-exempt under 503A and 503B)
5. Sustained or time-release dosage forms (non-exempt under 503A and 503B)
6. Enteric-coated preparations (non-exempt under 503A and 503B)

I. Regulatory Background and Relevant Statutory Authority

Section 503A of the FDCA, created under the Food and Drug Administration Modernization Act of 1997 (FDAMA),¹ describes the conditions under which a human drug product, compounded for an identified individual based on a prescription, is entitled to an exemption from the federal requirements for new drug approval, compliance with cGMP, and specific federal labeling requirements.² Rather than follow cGMP requirements, pharmacies qualifying for a 503A exemption must produce drug products under conditions that comply with the United States Pharmacopoeia (USP) chapter on pharmacy compounding, including USP Chapter 797, addressing sterile compounding.^{3,4}

Pharmacies may qualify for a Section 503A exemption only when producing a drug product “not . . . identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.”⁵ Section 503A requires that the FDA consult an advisory committee on pharmacy compounding prior to identifying such products, absent urgent public health need.⁶

Following passage of FDAMA, the FDA initiated an administrative process aimed at creating a list of drugs presenting demonstrable difficulties for compounding. In 2000, the FDA requested comments on a concept paper describing the agency’s preliminary thoughts on the matter (FDA Concept Paper).⁷ However, these preliminary efforts were suspended following a 2002 Supreme Court decision holding portions of Section 503A unconstitutional.⁸

Regulation under Section 503A has been revived by the Drug Quality and Security Act of 2013, which verified the constitutionality of the portions Section 503A that had not been addressed in the Supreme Court’s 2002 decision, including the relevant sections addressing the difficult-to-compound list, by removing the provisions deemed unconstitutional by the Court.⁹ The 2013 Act also added Section 503B to the FDCA, creating a new category of drug producers, known as

¹ Pub. Law No. 105-115.

² FDCA Section 503A, *codified as* 21 U.S.C. § 353a.

³ 21 U.S.C. § 353a (b)(1)(A)(i).

⁴ Food and Drug Administration Draft Guidance: Pharmacy compounding of human drug products under Section 503A of the Federal Food, Drug and Cosmetics Act. December 2013.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377052.pdf>. Accessed February 18, 2014.

⁵ 21 U.S.C. § 353a (b)(3)(A).

⁶ 21 U.S.C. § 353a (c)(1).

⁷ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

⁸ 78 Fed. Reg. 72,840, 72,840 (Dec 4, 2013).

⁹ *Ibid.*

“outsourcing facilities.”¹⁰ Like compounding pharmacies regulated under 503A, outsourcing facilities that qualify for Section 503B are exempt from new drug approval and specific federal labeling requirements, and are therefore subject to lighter federal regulation than manufacturers of FDA-approved drugs. However, unlike Section 503A compounding pharmacies, Section 503B outsourcing facilities will be required to comply with cGMP. Outsourcing facilities must also comply with additional requirements, including federal registration and periodic reporting requirements, as well as federal inspections of facilities and records, conducted on a risk-based schedule.

Like Section 503A, Section 503B excludes drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs.¹¹ However, rather than cross-reference the same list of products identified under Section 503A, Section 503B outlines distinct procedural steps for the FDA to follow in identifying drugs that are difficult to compound, including a specific timeline and process for creating a list of such products.¹² Section 503B also requires the FDA to “tak[e] into account the risks and benefits to patients” when identifying products for the list and authorizes the agency to identify “conditions that are necessary to prevent the drug or category of drugs from presenting demonstrable difficulties [for compounding].”¹³

Neither Section 503A nor Section 503B require that the FDA develop and publish a single list of drug products that present demonstrable difficulties for compounding. If anything, Congress, having identified two distinct processes and two slightly different sets of requirements and authorities for each section, appears to have contemplated that the FDA would create two separate lists. Moreover, even if two separate lists are not statutorily required, the FDA can certainly exercise its discretion to promulgate two separate lists. Separate lists would represent sound public health policy because the conditions for compounding in each type of facility are markedly different, with 503A compounding pharmacies subject to significantly lower regulatory standards than 503B outsourcing facilities.

Alternatively, if the FDA proceeds with its proposed plan to promulgate only one list, the agency has the authority to identify compliance with 503B and cGMP requirements as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding. Outsourcing facilities that register under Section 503B and comply fully with cGMP would then be permitted to compound such products, whereas compounding pharmacies that qualify for exemption under 503A that have not verified compliance with cGMP would not be allowed to compound such products.

¹⁰ Section 503B, *not yet codified*. Pub. Law 113-54. -

¹¹ Pub. Law 113-54. Sec. 503B (a)(6). -

¹² Pub. Law 113-54. Sec. 503B (c)(2). -

¹³ Pub. Law 113-54. Sec. 503B (a)(6). -

II. Specific Drug Product Categories

We propose six categories of drug products for placement on the list or lists of products presenting demonstrable difficulties for compounding under Sections 503B and/or 503A.

1. Nonsterile-to-sterile compounding

Certain drugs must be sterile (in other words, free from all living microorganisms) in order to be administered safely. These include dosage forms administered parenterally (injections, infusions, or implants), aqueous-based inhalation solutions, and ophthalmic products.¹⁴ As stated in the 2000 FDA Concept Paper, “[s]terility is absolute and should never be considered in a relative manner -- a product cannot be partially or almost sterile.”¹⁵

Problems that develop in compounding sterile products can have serious and far-reaching consequences for patient safety. In September 2012, the Centers for Disease Control and Prevention (CDC) and the FDA announced the beginning of what would become the largest outbreak of infection linked to a medical product in more than four decades: healthcare facilities in 23 states received three lots of contaminated preservative-free injectable methylprednisolone acetate produced by the New England Compounding Center (NECC), a compounding pharmacy in Framingham, Massachusetts.¹⁶ Over the next year, the CDC tracked 751 cases of infection, including meningitis, paraspinal/spinal infection, stroke, and joint infection. Sixty-four of those cases resulted in death.¹⁷

While the NECC-linked outbreak was by far the largest ever associated with a compounding pharmacy, it was by no means an isolated event. Table 1 contains a list of infection outbreaks linked to compounding pharmacies since 2004. Many more small-scale outbreaks or isolated infections caused by compounded products likely went undetected because the source of such infections is often not suspected or challenging to identify.

Table 1: Infection Outbreaks Associated with Compounded Products, 2004-2013

Date of Outbreak	Type of Injury	Pharmacy	Source
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¹⁴ Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments/totheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

¹⁵ *Ibid.*

¹⁶ Centers for Disease Control. Multistate outbreak of fungal meningitis and other infections – healthcare facilities. October 23, 2013. <http://www.cdc.gov/hai/outbreaks/meningitis-facilities-map.html>. Accessed February 21, 2014.

¹⁷ Centers for Disease Control. Multistate outbreak of fungal meningitis and other infections – case count. October 23, 2013. http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html#casecount_table. Accessed February 21, 2014.

Dec 2004 – Feb 2005	Bloodstream infections; 36 cases, including at least 13 children	Anonymous	CDC2005 ¹⁸
Jun – Jul 2004	Bloodstream infections; 2 children	Anonymous	Held2006 ¹⁹
Jan – Mar 2005	11 cases of bacteremia, including 5 cases of sepsis	PharMEDium	CDC2005 ²⁰
Mar 2005	6 cases of sepsis; 1 resulting in death	PharMEDium	FDA2007(1) ²¹
Dec 2004 – Aug 2005	Eye infection resulting in permanent loss of vision; 6 cases	Anonymous	Sunenshine2009 ²²
Dec 2006	70 complaints indicating signs of infection	Med-South Pharmacy	FDA2007(2) ²³
Oct – Nov 2007	7 bloodstream infections	Anonymous	Maragakis2009 ²⁴
Mar 2011	19 bloodstream infections	Meds IV	FDA2011 ²⁵
Jul 2011	12 eye infections; 11 resulting in vision loss	Infupharma	Goldberg2013 ²⁶
Aug 2011 – Mar 2012	47 eye infections; 39 resulting in vision loss	Franck's Compounding Lab	Mikosz2014 ²⁷

¹⁸ Centers for Disease Control. Pseudomonas bloodstream infections associated with a heparin/saline flush --- missouri, new york, texas, and michigan, 2004—2005. *MMWR* 2005;54(11):269-272. - <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm>. Accessed February 26, 2014. -

¹⁹ Held MR, BegierEM, Beardsley DS, et al. Life-threatening sepsis caused by *Burkholderia cepacia* from - contaminated intravenous flush solutions prepared by a compounding pharmacy in another state. *Pediatrics* - 2006;118(1):e212-5. -

²⁰ Centers for Disease Control. Health Advisory: *Serratia marcescens* blood stream infections associated with - contaminated magnesium sulfate solutions. March 18, 2005. - http://www.randolphcountyhealth.org/docs/educ/pr/031805_CDC.html. Accessed February 21, 2014. -

²¹ Food and Drug Administration. Warning Letter to PharMEDium. April 13, 2007. - <http://www.fda.gov/iceci/enforcementactions/warningletters/2007/ucm076357.htm>. Accessed February 21, - 2014. -

²² Sunenshine R, Schultz M, Lawrence MG, et al. An outbreak of postoperative gram-negative bacterial endophthalmitis associated with contaminated trypan blue ophthalmic solution. *Clin Infect Dis* 2009;48:1580-3. -

²³ Food and Drug Administration. Warning Letter to Med-South Pharmacy. September 28, 2007. - <http://www.fda.gov/iceci/enforcementactions/warningletters/2007/ucm076516.htm>. Accessed February 21, - 2014. -

²⁴ Maragakis LL, Chaiwarith R, Srinivasan A, et al. *Sphingomonas paucimobilis* bloodstream infections associated - with contaminated intravenous fentanyl. *Emerg Infect Dis* 2009;15(1):12-18. -

²⁵ Food and Drug Administration. CDC and ADPH investigate outbreak at Alabama hospitals; products recalled. - March 29, 2011 (republished from Alabama Department of Public Health). - <http://www.fda.gov/safety/recalls/archiverecalls/2011/ucm249068.htm>. Accessed February 21, 2014. -

²⁶ Goldberg RA, Flynn HW, Miller D, et al. *Streptococcus* endophthalmitis outbreak after intravitreal injection of - Bevacizumab: One-year outcomes and investigative results. *Ophthalmology* 2013; 120(7):1448-53. -

²⁷ Mikosz CA, Smith RM, Kim M, et al. Fungal endophthalmitis associated with compounded products. *Emerg Infect Dis* 2014;20(2):248-256. -

Mar 2013	5 eye infections	Clinical Specialties	FDA2013(1) ²⁸
May 2013	7 skin abscesses	Main Street Family Pharmacy	FDA2013(2) ²⁹

In addition to being free of microorganisms, injectable compounded pharmaceuticals must also be free from pyrogens (the byproducts of microorganisms that can cause reactions when introduced into humans) and particulate matter, which can cause harmful blood clots, particularly when a product is administered in large quantities.³⁰

Sterile-to-sterile compounding, described as “low” or “medium” risk compounding by the U.S. Pharmacopeial Convention, involves manipulating sterile ingredients entirely within an ISO Class 5 or better environment (a “clean room” carefully controlled to exclude microbial growth) using only sterile ingredients, products, components, and devices.³¹ Depending on the number of sterile products and aseptic manipulations involved, sterile-to-sterile compounding may involve low or medium risk of microbial contamination.³²

Nonsterile-to-sterile compounding, described as “high” risk compounding by the U.S. Pharmacopeial Convention, involves compounding using nonsterile ingredients or materials, including nonsterile active pharmaceutical ingredients (API), finished FDA-approved products not intended for sterile routes of administration (e.g., oral), or nonsterile devices or packaging.³³ It also includes sterile contents of commercially manufactured products that have been exposed to conditions that would render them nonsterile (e.g., exposure to air quality worse than ISO Class 5 for more than one hour). To engage in this process safely, an appropriate sterilization method must be used to ensure that such products are sterile and free of pyrogens and particulate matter prior to distribution.³⁴

The high-risk process of nonsterile-to-sterile compounding is not appropriate for compounding pharmacies exempt under Section 503A, as these entities are not held to cGMP standards and

²⁸ Food and Drug Administration. Clinical Specialties Compounding Pharmacy announces voluntary nationwide - recall of all lots of sterile products repackaged and distributed by Clinical Specialties Compounding due to lack of - sterility assurance. March 20, 2013. <http://www.fda.gov/safety/recalls/ucm344786.htm>. Accessed February 21, - 2014. -

²⁹ Food and Drug Administration. Main Street Pharmacy, LLC issues voluntary nationwide recall of all sterile - compounded products. May 28, 2013. <http://www.fda.gov/safety/recalls/ucm354182.htm>. Accessed February 21, - 2014. -

³⁰ Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for - Compounding Because of Reasons of Safety or Effectiveness. - <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments-to-the-FDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014. -

³¹ <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008. -

³² *Ibid.*

³³ *Ibid.*

³⁴ *Ibid.*

instead must comply with USP standards only. USP standards for sterile compounding, laid out in Chapter 797 of the USP, are set by the U.S. Pharmacopeial Convention, a private organization that sets standards for drugs, food ingredients, and dietary supplements.³⁵ While USP standards have advanced over time, they remain relatively lax compared to the cGMP standards developed and enforced by the FDA. One key difference is that cGMP requires a drug manufacturer to validate and periodically re-validate each step in the production process through direct testing, whereas USP Chapter 797 routinely allows pharmacists to base production design on review of available literature and the pharmacist's prior experience.

For example, in determining sterilization methods, cGMP requires that any sterilization process used to prevent microbial contamination be validated through appropriate direct studies,³⁶ and offers detailed guidance on the design and conduct of such validation studies.³⁷ Once production begins, a single contaminated product in any batch smaller than 5,000 should trigger an investigation and revalidation of the entire manufacturing process.³⁸ USP, by contrast, does not generally require product-specific validation, instead allowing the pharmacist to select a method based on "experience and appropriate information sources," stating that the sterilization method should "preferably" be verified "whenever possible."³⁹

Similarly, federal cGMP regulations require a detailed written stability testing program to determine appropriate storage conditions and expiration dates.⁴⁰ By contrast, USP describes the practice of establishing "beyond use dating (BUD)," and the especially high-risk practice of "theoretical beyond use dating," both of which can be based on a review of general literature and do not require direct product testing.⁴¹ The USP acknowledges that "[t]heoretically predicted beyond-use dating introduces varying degrees of assumptions and, hence, a likelihood of error or at least inaccuracy," yet USP Chapter 797 does not require direct stability testing to avoid such problems. Indeed, actual testing is only "strongly urged" to support dating periods exceeding 30 days.⁴²

³⁵ U.S. Pharmacopeial Convention. <http://www.usp.org/about-usp>. Accessed February 28, 2014. -

³⁶ 21 CFR 211.113(b). -

³⁷ Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice. September 2004. -

³⁸ Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice. September 2004. -

³⁹ <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008. -

⁴⁰ 21 CFR § 211.166. ("There shall be a written testing program designed to assess the stability characteristics of - drug products. The results of such stability testing shall be used in determining appropriate storage conditions and - expiration dates. The written program shall be followed and shall include: (1) Sample size and test intervals based - on statistical criteria for each attribute examined to assure valid estimates of stability; (2) Storage conditions for - samples retained for testing; (3) Reliable, meaningful, and specific test methods; (4) Testing of the drug product in - the same container-closure system as that in which the drug product is marketed; (5) Testing of drug products for - reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted."). -

⁴¹ <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008. -

⁴² *Ibid.*

We are aware that the FDA previously issued a preliminary conclusion in its Concept Paper published in 2000, which indicated that sterile compounding could be carried out by compounding pharmacies compliant with USP requirements for sterile compounding.⁴³ We urge the FDA to reconsider this preliminary conclusion, which addressed all sterile compounding, rather than focusing separately on, and requiring more stringent standards for, especially high-risk nonsterile-to-sterile compounding.

The FDA's earlier preliminary conclusion was also based in part on a perceived "substantial need for compounded sterile products, especially in the area of extemporaneous compounding."⁴⁴ While a general need for extemporaneously compounded sterile products may have existed under the conditions that the FDA considered in 2000, no substantial need exists for high-risk nonsterile-to-sterile compounding to be performed in compounding pharmacies exempt under Section 503A. First, most needs for sterile compounded products can be met through modifying federally regulated commercially available sterile products, a low- to medium-risk form of sterile compounding, rather than through high-risk compounding from nonsterile-to-sterile ingredients. Second, following the passage of the Drug Quality and Security Act, any residual needs requiring nonsterile-to-sterile compounding (in other words, making products from bulk API rather than modifying FDA-approved sterile products) are more appropriately met by carrying out such high-risk compounding in outsourcing facilities compliant with Section 503B and federal cGMP requirements (as opposed to relying on 503A compounding pharmacies exempt from cGMP requirements).

Furthermore, more information is now available on the actual conditions of practice in compounding pharmacies, historically subject to minimal federal oversight. Recent FDA inspections of compounding pharmacies have revealed widespread sterility concerns, some of which may violate USP standards in addition to cGMP standards, suggesting that the safety of high-risk nonsterile-to-sterile compounding cannot be assured without increased federal oversight.⁴⁵ Some of these violations are discussed in greater detail below.

Companies that have registered as outsourcing facilities under Section 503B will now be held to higher federal standards, and we hope that conditions in these facilities will improve. However, the FDA cannot reasonably expect these conditions to improve substantially in compounding pharmacies exempt from federal oversight under Section 503A, as the current regulatory environment does not provide for appropriate oversight of compounding pharmacies that qualify for this exemption. While the FDA does have authority to inspect and take enforcement action against compounding pharmacies for violations of federal law, the agency has no plans to carry

⁴³ Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

⁴⁴ *Ibid.*

⁴⁵ Food and Drug Administration. Compounding: Inspections, recalls, and other actions. February 6, 2014. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm>. Accessed February 24, 2014.

out regular inspections, leaving day-to-day oversight up to state boards of pharmacy.⁴⁶ Many compounding pharmacies are not routinely monitored by state boards to verify compliance with USP Chapter 797 requirements for sterile compounding. A 2012-2013 survey of state boards of pharmacy published by the office of U.S. Rep. Edward J. Markey (now Senator Markey), indicated that 37 state boards of pharmacy do not routinely track which pharmacies are providing sterile compounding services, and only 19 state boards of pharmacy provide inspectors with special training to identify problems with sterile compounding.⁴⁷

For these reasons, as well as our comments on more specific factors below, we urge the FDA to identify nonsterile-to-sterile compounding as a category presenting demonstrable difficulties for compounding under Section 503A, but not necessarily Section 503B.

The FDA has requested comment on specific relevant factors, including the complexity of compounding, facilities and equipment, personnel training, and testing and quality assurance. We now address each of these factors in turn with regard to nonsterile-to-sterile compounding:

Complexity of Compounding

Nonsterile-to-sterile compounding involves extremely complex production processes. As stated in the FDA's Concept Paper:

The preparation of sterile products is often unavoidably complex, involving many steps and manipulations. Each step poses an opportunity for microbial contamination. The manipulation of a sterile drug product may contaminate it, especially when nonsterile components are used (e.g., if the product is packaged into a nonsterile syringe or vial purported to be sterile), nonsterile equipment is used, or novel, complex, or prolonged aseptic processes are employed.⁴⁸

Even a relatively small change in the production process, such as a switch to new packaging material, may result in unanticipated and far-reaching consequences. The largest infection outbreak associated with a pharmaceutical product in United States history occurred as the result of one such seemingly minor change: Between April and September 1970, Abbott Laboratories began phasing in a new type of cap liner that relied on synthetic plastic, rather than natural

⁴⁶ Food and Drug Administration. Compounding and the FDA: Questions and Answers. December 2, 2013. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm#regulates>. Accessed February 24, 2014. -

⁴⁷ Report of the US House of Representatives. State of Disarray. How states' inability to oversee compounding pharmacies puts public health at risk. April 15, 2013. -

⁴⁸ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. - <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentsToTheFDCAct/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

rubber.⁴⁹ The rubber previously used in the caps had antibacterial properties that synthetic liners lacked. Inadequate environmental control and sampling protocols contributed to microbial contamination of the liners, which thrived on the new synthetic medium. The result was catastrophic: Abbott Laboratories distributed approximately 45 percent of all intravenous fluids sold in the United States at the time, and the outbreak is estimated to have led to between 2,000 and 8,000 cases of infection, and between 200 and 800 deaths.⁵⁰

Both USP and cGMP standards have been updated dramatically over the ensuing decades, yet complex production processes remain challenging to monitor.⁵¹ Any change in the production process should be validated through direct testing to ensure that it does not result in unforeseen consequences. This type of direct validation can only be ensured in facilities verified as fully compliant with cGMP. Nonsterile-to-sterile compounding, therefore, presents demonstrable difficulties for compounding under any other conditions.

Facilities and Equipment

Nonsterile-to-sterile compounding requires sophisticated facilities and equipment that must be maintained to rigorous standards. As stated in the FDA's concept paper:

To maintain the essential characteristics of sterile products (i.e., sterility and freedom from particulate matter and pyrogens), the products and their components must be manipulated in a suitable environment using aseptic techniques. ... It is important to minimize bioburden during the production process even when terminal sterilization is used. Therefore, the production facilities and associated procedures must meet exacting standards.⁵²

While USP and cGMP have developed harmonized standards regarding appropriate levels of bioburden (the accumulation of potential biological contaminants during the production process) in the environment, recent FDA inspections of compounding pharmacies have revealed repeated failures in maintaining the environmental monitoring necessary to meet these standards. In 2013, FDA inspectors cited dozens of compounding pharmacies for failing to assess airflow patterns with adequate smoke studies performed under dynamic conditions and/or failing to conduct appropriate environmental monitoring.⁵³ While FDA inspectors focused on violations of cGMP

⁴⁹ Centers for Disease Control. Epidemiologic notes and reports nosocomial bacteremias associated with intravenous fluid therapy – USA. MMWR Weekly. December 26, 1997/46(51);1227-1233.

<http://www.cdc.gov/mmwr/preview/mmwrhtml/00050554.htm>. Accessed February 18, 2014.

⁵⁰ *Ibid.*

⁵¹ *Ibid.*

⁵² FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

⁵³ Food and Drug Administration. Compounding: Inspections, recalls, and other actions. February 6, 2014.

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm>. Accessed February 24, 2014.

standards, many of the conditions identified would be unacceptable under either cGMP or USP standards. For example, FDA inspectors also noted visible dust, stains, splatters, residue, rust, live or dead insects, and other sources of potential contamination in a disturbing number of facilities.^{54,55,56,57,58,59,60,61,62}

Some of the pharmacies cited by FDA inspectors in 2013 have subsequently registered as outsourcing facilities.⁶³ While we remained concerned that outsourcing facilities will not be required to undergo new drug approval or verify compliance with cGMP prior to producing sterile products, we assume that the FDA will make every effort to ensure that these facilities comply with cGMP standards moving forward. (If this assumption proves to be incorrect, then nonsterile-to-sterile compounding by outsourcing facilities will also pose unacceptable risks to patients.)

By contrast, many pharmacies that have not registered as outsourcing facilities continue to claim that their compounding facilities adequately comply with applicable state and USP standards

⁵⁴ Food and Drug Administration. Axiom Healthcare Pharmacy dba Balanced Solutions Compounding. March 15, 2013. -

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM345694.pdf>. Accessed February 24, 2014. -

⁵⁵ Food and Drug Administration. 483 Inspection Report. Custom Compounding Centers, LLC. December 13, 2012. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348232.pdf>. Accessed February 24, 2014. -

⁵⁶ Food and Drug Administration. 483 Inspection Report: Anazahealth Corporation. February 22, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM341368.pdf>. Accessed February 24, 2014. -

⁵⁷ Food and Drug Administration. 483 Inspection Report: University Pharmacy, Inc. February 26, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM342275.pdf>. Accessed February 24, 2014. -

⁵⁸ Food and Drug Administration. 483 Inspection Report: College Pharmacy Incorporated. March 15, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM345701.pdf>. Accessed February 24, 2014. -

⁵⁹ Food and Drug Administration. 483 Inspection Report: The Compounding Shop, Inc. March 22, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM345933.pdf>. Accessed February 24, 2014. -

⁶⁰ Food and Drug Administration. 483 Inspection Report: Pentec Health, Inc. April 1, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM346817.pdf>. Accessed February 24, 2014. -

⁶¹ Food and Drug Administration. 483 Inspection Report: Pallimed Solutions, Inc. April 9, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348236.pdf>. Accessed February 24, 2014. -

⁶² Food and Drug Administration. 483 Inspection Report: Central Admixture Pharmacy Services, Inc. February 19, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348237.pdf>. Accessed February 24, 2014. -

⁶³ Food and Drug Administration. Registered Outsourcing Facilities. Updated as of February 21, 2014. - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm>. - Accessed February 28, 2014. -

even when they have been informed by the FDA of sterility concerns, making them unlikely to adjust their practices or upgrade their current facilities. In fact, one pharmacy, NuVision, recently refused a request by the FDA to recall all sterile products after the agency identified safety concerns related to sterility during a facility inspection.^{64,65} The pharmacy still claims on its website to adhere to USP standards for sterile compounding.⁶⁶ In addition, three other compounding pharmacies have responded following FDA inspections with their opinion (without citing verification by independent inspectors) that the current facilities satisfy USP requirements, in spite of the fact that federal inspectors had identified serious sterility concerns.^{67,68,69} Regardless of whether these pharmacies do, in fact, comply with USP requirements (a claim that has not been confirmed through independent inspections), it is clear that they are unlikely to dramatically upgrade their facilities in the near future. Appropriately, at least one of these compounding pharmacies has reported that it does not engage in nonsterile-to-sterile compounding.⁷⁰ We urge the FDA to ensure that all compounding pharmacies exempt under 503A avoid this type of high-risk compounding, which cannot be performed safely except in a facility that has been regularly inspected for compliance with cGMP standards.

Personnel Training

Specialized, highly technical training is essential to ensure proper compounding of nonsterile-to-sterile drug products. As stated in the FDA's Concept Paper:

The processes used in pharmacies to prepare sterile products are highly personnel-intensive. The contamination of pharmacy-prepared products (e.g., intravenous admixtures and prefilled syringes) by aseptic processing most likely will be caused by personnel-associated factors. These factors may include the shedding of contaminants from people into the controlled environment, improper procedures under laminar air flow, and the use of poor aseptic technique. Therefore, pharmacy personnel involved in compounding

⁶⁴ FDA reminds health care providers not to use sterile products from NuVision Pharmacy. August 16, 2013. - <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm365402.htm>. Accessed February 26, 2014. -

⁶⁵ Food and Drug Administration. Warning Letter. NuVision Pharmacy. Jul 26, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM363761.pdf>. Accessed February 28, 2014. -

⁶⁶ Nuvision. Sterility Testing. <http://nuvisionpharmacy.com/sterility-testing/>. Accessed February 26, 2014. -

⁶⁷ Foundation Care. Reponse Letter to the Food and Drug Administration. April 9, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM349684.pdf>. Accessed February 24, 2014. -

⁶⁸ IV Solutions of Lubbock. Response Letter to the Food and Drug Administration. April 25, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM349813.pdf>. Accessed February 24, 2014. -

⁶⁹ Pharmacy Creations. Response Letter to the Food and Drug Administration. September 3, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM371359.pdf>. Accessed February 24, 2014. -

⁷⁰ Foundation Care. Reponse Letter to the Food and Drug Administration. April 9, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM349684.pdf>. Accessed February 24, 2014.

sterile products must have sufficient knowledge, training, and experience to perform the task correctly and safely. Furthermore, a pharmacy's quality assurance program for sterile products must include requirements that personnel consistently adhere to performance standards; that performance problems be monitored, detected, and corrected; and that personnel undergo initial and periodic certification.⁷¹

Appropriate training is essential to ensure that sterile solutions do not become contaminated during preparation. A study of pharmacy students by Isanhart et al, published in 2008, assessed procedures performed at the beginning and end of a 16-week parenterals laboratory course offering instruction in aseptic technique.⁷² Prior to undergoing training, 21 of 504 syringes (4 percent) prepared by the students were contaminated during media fill tests, a number that was reduced to 0 of 498 by the end of the course.

While zero contamination is clearly possible with appropriate technique, reports from the FDA and published literature suggest that use of inadequate technique is widespread. Rates of contamination during medium and low risk compounding operations remain highly variable and unacceptably high in practice, ranging from 0 percent to over 6 percent among experienced, practicing pharmacists and technicians.^{73,74,75,76,77} FDA inspection reports from 2013 also document numerous examples of inappropriate aseptic technique and inadequate monitoring of pharmacy personnel. Observations included inadequate gowning that leaves skin exposed, failure to adequately monitor employees for microbial contamination during aseptic operations, uncontrolled movement of employees in and out of the ISO Class 5 clean room where sterile drugs are prepared, inappropriate use of nonsterile objects in aseptic operations, and failure to adequately clean and sanitize equipment and surfaces in the clean room.^{78,79,80,81} Such high-risk

⁷¹ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons - of Safety or Effectiveness. -

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCA/SignificantAmendments/totheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014. -

⁷² Isanhart CM, McCall KL, Kretschmer D, Grimes BA, Parenterals laboratory course to reduce microbial contamination rates in media fill tests performed by pharmacy students. *Am J Pharm Educ.* 2008;72(2):27. -

⁷³ Reiter PD. Sterility of intravenous fat emulsion in plastic syringes. *Am J Health Syst Pharm* 2002;59:1857-9. -

⁷⁴ van Grafhorst JP, Foudraine NA, Nooteboom F, Crombach WH, Oldenhof NJ, van Doorne H. Unexpected high risk - of contamination with staphylococci species attributable to standard preparation of syringes for continuous - intravenous drug administration in a simulation model in intensive care units. *Crit Care Med.* 2002;30:833-6. -

⁷⁵ Trissel LA, Ogundele AB, Ingram DS et al. Using medium-fill simulation to establish a benchmark microbiological contamination rate for low-risk-level compounding. *Am J Health-Syst Pharm.* 2003; 60:1853-5. -

⁷⁶ Thomas M, Sanborn M, Couldry R. IV admixture contamination rates: traditional practice site versus a class 100 cleanroom. *Am J Health-Syst Pharm.* 2005;62:2386-92.

⁷⁷ Trissel LA, Gentempo JA, Anderson RW, Lajeunesse JD. Using a medium-fill simulation to evaluate the microbial contamination rate for USP medium-risk-level compounding. *Am J Health-Syst Pharm.* 2005;62:285-8. -

⁷⁸ Food and Drug Administration. 483 Inspection Report: Avella of Deer Valley, Inc. February 25, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OR/OR-AElectronicReadingRoom/UCM342276.pdf>. Accessed February 26, 2014. -

⁷⁹ Food and Drug Administration. 483 Inspection Report: FVS Holdings, Inc. dba Green Valley Drugs. March 15, - 2013. -

nonsterile-to-sterile compounding by improperly trained personnel poses unacceptable risk to patients. To avoid this risk, nonsterile-to-sterile compounding must be carried out only in facilities that are regularly inspected for compliance with cGMP.

Testing and Quality Assurance

Testing and quality assurance are especially important in nonsterile-to-sterile compounding as a means of verifying that sterility has been successfully achieved. As the FDA stated in its Concept Paper:

All compounded sterile products should be inspected prior to use in patients. Low-risk compounded sterile products (e.g., sterile products prepared from sterile components using proper techniques and equipment) should, at a minimum, be inspected physically and visually for cloudiness and particulate matter. High-risk compounded sterile products (e.g., sterile products prepared from nonsterile components using proper techniques and equipment) should undergo end-product sterility and pyrogen testing before they are dispensed from the pharmacy.⁸²

Sterility testing is required under cGMP, with samples taken at the beginning, middle, and end of the aseptic processing operation.⁸³ Any positive test result is considered a serious cGMP issue requiring thorough investigation.⁸⁴ Under USP standards, only high-risk sterile products prepared in groups of 25 or more or that are exposed to certain temperatures for varying lengths of time must be tested for sterility prior to release, and the pharmacy need not await test results before dispensing the products to patients.⁸⁵ Moreover, products intended for inhalation or ophthalmic administration need not be tested for bacterial endotoxins (pyrogens) prior to release.⁸⁶

As might be expected, a disturbing number of compounding pharmacies forgo testing and quality assurance measures that would be required under cGMP. FDA inspection reports of

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAElectronicReadingRoom/UCM348241.pdf>. Accessed February 26, 2014. -

⁸⁰ Food and Drug Administration. University Pharmacy, Inc. February 26, 2013. -

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAElectronicReadingRoom/UCM342275.pdf>. Accessed February 26, 2014. -

⁸¹ Food and Drug Administration. 483 Inspection Report: Lowlyn Pharmacies, Inc. March 8, 2013.

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAElectronicReadingRoom/UCM345695.pdf>. Accessed February 26, 2014. -

⁸² FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. -

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments-to-the-FDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014. -

⁸³ Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. September 2004. -

⁸⁴ *Ibid.*

⁸⁵ <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008.

⁸⁶ *Ibid.*

compounding pharmacies in 2013 identified widespread failure to conduct sterility, endotoxin, and potency testing on all end products. Many pharmacies also failed to document adequate investigation after identifying particulates, discoloration, microbial contamination, leaking product, or other issues with finished samples. In two cases, particulate matter was discovered in products from lots that had already been shipped to customers.^{87,88} Half a dozen pharmacies were also cited for failing to adequately follow up on complaints, including reports indicating mislabeling, particulate matter, and other serious concerns with drug products, including fever, injection-site redness, abscess, and other disturbing adverse events in patients.^{89,90,91,92,93,94}

Based on the factors identified above, high-risk nonsterile-to-sterile compounding cannot be conducted safely in compounding pharmacies that are not regularly inspected for full compliance with cGMP standards. We therefore urge the FDA to identify nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Section 503A, but not necessarily Section 503B.

Alternatively, if the FDA creates a single unified list, we urge the FDA to identify nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for

⁸⁷ Food and Drug Administration. 483 Inspection Report: Village Fertility Pharmacy, Inc. March 13, 2013. <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348242.pdf>. Accessed February 24, 2014. -

⁸⁸ Food and Drug Administration. 483 Inspection Report: Axiom Healthcare Pharmacy dba Balanced Solutions - Compounding. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM345694.pdf>. Accessed February 24, 2014. -

⁸⁹ Food and Drug Administration. 483 Inspection Report: MedPREP Consulting, Inc. April 3, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348230.pdf>. Accessed February 24, 2014. -

⁹⁰ Food and Drug Administration. 483 Inspection Report: Wedgewood Village Pharmacy, Inc. February 11, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM342543.pdf>. Accessed February 24, 2014. -

⁹¹ Food and Drug Administration. 483 Inspection Report: PharMEDium Services LLC (Parsippany, NJ). February 28, - 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM342271.pdf>. Accessed February 24, 2014. -

⁹² Food and Drug Administration. 483 Inspection Report: Village Fertility Pharmacy, Inc. March 13, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348242.pdf>. Accessed February 24, 2014. -

⁹³ Food and Drug Administration. 483 Inspection Report: NuVision Pharmacy, Inc. April 17, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM348772.pdf>. Accessed February 24, 2014. -

⁹⁴ Food and Drug Administration. 483 Inspection Report: Central Admixture Pharmacy Services (Chicago, IL). - February 22, 2013. - <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAAElectronicReadingRoom/UCM341365.pdf>. Accessed February 24, 2014.

compounding except under conditions present in outsourcing facilities compliant with Section 503B and cGMP requirements.

2. Metered dose inhaler (MDI) products

The FDA's Concept Paper published in 2000 recommended that MDI products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

The MDI is one of the most complicated drug delivery systems currently marketed by the pharmaceutical industry ...MDI products are primarily used by patients suffering from chronic lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Individuals suffering from asthma and COPD tend to have airways that are hyper-reactive to inhalants. It is therefore critical that the contents and the delivery characteristics of MDI products be carefully controlled to ensure that the product will be safe and effective. Even slight changes in the formulation, drug substance particle size, valve, or actuator can have a major effect on the aerosol delivery and potency characteristics. This effect can significantly alter the safety and effectiveness of the device. For example, a change in particle size distribution may lead to greater systemic absorption of a beta agonist drug, which can increase the amount of systemic side effects and may also decrease the local effectiveness of the drug in the lungs.⁹⁵

The FDA concluded that MDI products present demonstrable difficulties in compounding because:

- Metered dose inhalers are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility, and product-to-product uniformity is critical for dosing accuracy and is usually difficult to achieve.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of MDI products is complex.
- Sophisticated facilities and equipment are required to ensure proper compounding of the drug product.
- Specialized, technical training is essential to ensure proper compounding of the drug product.
- Sophisticated, difficult to perform testing of the compounded drug product is required to ensure potency and purity.⁹⁶

⁹⁵ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

⁹⁶ *Ibid.*

We agree with the FDA's prior analysis and conclusions with respect to MDI products and urge the agency to identify MDI products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

3. Dry powder inhaler (DPI) products

The FDA's Concept Paper published in 2000 also recommended that DPI products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

DPIs are complex drug products that differ in many aspects from more conventional drug products. ... There is a wide array of potential DPI designs, all complex in their design and function and many with characteristics unique to the particular design.

Regardless of design, the most crucial attributes of DPIs are the reproducibility of the dose and particle size distribution. It is difficult to maintain these qualities through the expiration date and to ensure the functionality of the device during the period of patient use. The unique characteristics of DPIs must be considered in their preparation, particularly with respect to the product's formulation, container closure system, and testing.⁹⁷

The FDA concluded that DPI products present demonstrable difficulties in compounding because:

- Dry powder inhalers are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility, and the product-to-product uniformity that is critical for dosing accuracy is usually difficult to achieve.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of DPI products is complex.
- Sophisticated facilities and equipment are required to ensure proper compounding of the drug product.
- Specialized, technical training is essential to ensure proper compounding of the drug product.
- Sophisticated, difficult to perform testing of the compounded drug product is required to ensure potency and purity.⁹⁸

⁹⁷ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAct/SignificantAmendmentsToTheFDCAct/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

⁹⁸ *Ibid.*

We agree with the FDA's prior analysis and conclusions with respect to DPI products, and urge the agency to identify DPI products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

4. Transdermal Delivery Systems (TDSs)

Finally, the FDA's Concept Paper published in 2000 recommended that TDS products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

TDS products are complex to develop and may require the use of new technologies. Each system is formulated to meet specific biopharmaceutical and functional criteria. The materials of construction, configurations, and combination of the drug with the proper cosolvents, excipients, penetration enhancers, and membranes must be carefully selected and matched to optimize adhesive properties and drug delivery requirements. The equipment and the technology required for the manufacture of TDS products limit their preparation to properly equipped manufacturers.⁹⁹

The FDA concluded that TDS products present demonstrable difficulties in compounding because:

- TDSs are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
- A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility.
- Reproducible bioavailability of the compounded drug product is difficult to achieve.
- The compounding of TDS products is complex.
- Sophisticated facilities and equipment are needed to ensure proper compounding of TDS products.
- Specialized technical training is essential to ensure proper compounding of TDS products
- Sophisticated, difficult to perform testing of the compounded product is required to ensure potency, purity, and quality of the drug product prior to dispensing.¹⁰⁰

We agree with the FDA's prior analysis and conclusions with respect to TDS products and urge the agency to identify TDS products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

⁹⁹ FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness.

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FDAMA/ucm100205.htm>. Accessed February 18, 2014.

¹⁰⁰ *Ibid.*

5. Sustained or time-release dosage forms

Public Citizen previously submitted comments on the FDA's Concept Paper published in 2000.¹⁰¹ In those comments, we recommended that the FDA evaluate sustained or time-release dosage forms for categorization as products presenting demonstrable difficulties for compounding. As we stated previously:

Because there is no requirement to test [compounded sustained or time-release] products, it is no known if 90 percent of the active ingredient is released within the first 30 minutes after the dose is taken, or if 90 percent of the active ingredient remains in the dosage form after the dose is taken.¹⁰²

Variation in rates of release of the active ingredient could impact bioavailability, potentially reducing the drug's efficacy or increasing safety risks. Clinical testing is necessary to ensure appropriate bioavailability for sustained or time-release dosage forms. Such clinical testing is not required under either Section 503A or Section 503B and can only be required for drug products that undergo premarket approval by the FDA. We therefore urge the FDA to categorize sustained or time-released dosage forms as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

6. Enteric-coated preparations

Public Citizen also previously recommended that the FDA evaluate enteric-coated preparations for categorization as products presenting demonstrable difficulties for compounding.¹⁰³ Enteric-coated preparations are preparations intended for drugs that are either destroyed by gastric acidity or that cause gastric irritation. As we previously stated, "enteric-coated preparations may, if not properly formulated, resist dissolution in the intestine, and very little if any of the active drug may be absorbed into the blood stream."¹⁰⁴

As with sustained-release dosage forms, improperly formulated enteric-coated preparations could impact bioavailability, potentially reducing the drug's efficacy or increasing safety risks. Clinical testing is necessary to prevent these problems. Because such testing is not required under either Section 503A or Section 503B, we urge the FDA to categorize enteric-coated preparations as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

¹⁰¹ Public Citizen. Comments on Drugs that Present Difficulties for Compounding. August 2, 2000.

<http://www.citizen.org/Page.aspx?pid=3626>. Accessed March 3, 2014.

¹⁰² *Ibid.*

¹⁰³ *Ibid.*

¹⁰⁴ *Ibid.*

III. Conclusion

We are concerned that the FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded because they present demonstrable difficulties for compounding, and urge the agency to withdraw its proposal and instead develop two separate lists. Drugs compounded at compounding pharmacies under a Section 503A exemption should be treated differently than those subject to Section 503B, as the regulations governing each category of facility are different.

Alternatively, if the FDA chooses to proceed with its proposed plan of establishing only one list, we urge the agency to identify compliance with cGMP and the requirements of 503B as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding.

Regardless of whether one or two lists is used, we urge the FDA to classify high-risk nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding under compounding pharmacies exempt under Section 503A, but not necessarily outsourcing facilities exempt under 503B. This high-risk process may be safely carried out only by a facility that is regularly inspected to verify compliance with federal cGMP requirements.

We have also recommended designation of several additional product categories as presenting demonstrable difficulties for compounding.

A full list of product categories that we urge the FDA to identify as demonstrably difficult to compound, along with our recommendations for their appropriate regulatory classification, is summarized as follows:

1. Nonsterile-to-sterile compounding (non-exempt under 503A only)
2. Metered dose inhaler (MDI) products (non-exempt under 503A and 503B)
3. Dry powder inhaler (DPI) products (non-exempt under 503A and 503B)
4. Transdermal Delivery Systems (TDSs) (non-exempt under 503A and 503B)
5. Sustained or time-release dosage forms (non-exempt under 503A and 503B)
6. Enteric-coated preparations (non-exempt under 503A and 503B)

Thank you for your consideration of these comments.

Sincerely,



Sarah Sorscher, J.D., M.P.H.
Attorney
Public Citizen's Health Research Group

A handwritten signature in black ink, appearing to read "Michael Carome". The signature is fluid and cursive, with a long horizontal stroke at the end.

Michael Carome, M.D.
Director
Public Citizen's Health Research Group

Tab 9b

Dry Powder Inhalers (DPIs)

FDA Review



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993-0002

DATE: February 9, 2016

FROM: Craig M. Bertha, CMC Lead, Branch IV/Division of New Drug Products II/Office of New Drug Products/Office of Pharmaceutical Quality

THROUGH: Julia Pinto, PhD, Acting Branch Chief, Branch IV/Division of New Drug Products II/Office of New Drug Products/Office of Pharmaceutical Quality

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Dry Powder Inhalers for Inclusion on the Difficult to Compound List

I. INTRODUCTION

Section 503A of the Food, Drug, and Cosmetic Act (21 U.S.C. 353a) (FD&C Act or the Act) generally governs the application of federal law to certain drug compounding. Under section 503A of the Act, compounded drug products are exempt, under certain conditions, from three key provisions of the act: (1) the adulteration provision of section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements); (2) the misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications).

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

Both sections 503A and 503B require compounded drug products to satisfy several requirements to qualify for the statutory exemptions from the FD&C Act. One of those requirements is that the compounded drug product is not one that the Agency has

identified as being demonstrably difficult to compound. *See* sections 503A(b)(3)(A); 503B(a)(6).

Specifically, section 503A states that the compounded drug product may not be one that “presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.” *See* section 503A(b)(3)(A).

Similarly, section 503B states that the compounded drug, or category of drugs, either is not one that “present[s] demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into the account the risks and benefits to patients,” or is compounded in accordance with “conditions that are necessary to prevent the drug or category of drugs from presenting [such] demonstrable difficulties.” *See* section 503B(a)(6).

In response to FDA’s request in the Federal Register of December 4, 2013 (FDA-2013-N-1523-0001), for nominations for drug products or categories of products that are considered difficult to compound, six specific dry powder inhaler (DPI) products were nominated, and one nominator also nominated the category of DPI products. Because all DPIs share common characteristics that are relevant to whether they should be considered difficult to compound, we are considering DPIs as a category rather than the individual products for placement on the list of drug products that are considered difficult to compound.

We have reviewed available data on the formulation, drug delivery mechanism, dosage form, bioavailability, compounding process complexity, physicochemical and/or analytical testing complexity, safety, effectiveness, and historical complications in manufacturing this category of drug products. For the reasons discussed below, we recommend that the category of DPIs be included on the list of difficult to compound drug products under sections 503A and 503B of the FD&C Act.

II. BACKGROUND

DPIs are used for the treatment of a variety of lung diseases characterized by obstruction of airflow and shortness of breath, including asthma and chronic obstructive pulmonary disease. More recently, these drug products have also been developed for treatment of patients with respiratory infections and cystic fibrosis. For these indications and diseases, drugs are topically applied to the lungs for local action, and, as such, there are no reliable pharmacokinetic data that can be related to efficacy. It has recently been recognized that the inhalation route also offers further potential for systemic drug delivery, i.e., the lungs are increasingly the target organs for absorption of drugs not necessarily intended for the treatment of diseases of the lungs (e.g., insulin for treatment of diabetes).

DPIs contain or use formulations with one or more solid active pharmaceutical ingredients (APIs) typically mixed with a solid carrier excipient. Current device designs include **pre-metered** and **device-metered DPIs**, both of which can be driven by patient inspiration alone or with power-assistance of some type for production of the drug formulation in the form intended for inhalation (note that the latter is not commonplace and typically requires devices of considerably greater complexity). **Pre-metered DPIs** contain previously measured amounts of formulation in individual containers (e.g., capsules, blisters) that are each inserted in the device by the patient before use. Pre-metered DPIs may also contain pre-metered dose units enclosed during manufacture as ordered multi-dose assemblies in the delivery system. The pre-metered dose may be inhaled directly or it may be transferred to a chamber before being inhaled by the patient. **Device-metered DPIs** have an internal reservoir containing a sufficient quantity of formulation for multiple doses that are metered by the device itself during actuation by the patient. The wide array of DPI designs, many with unique characteristics, usually present challenges in developing information in support of an application. Depending on the product, the dispensed formulation in each actuation may contain as little as a few micrograms (mcg) but typically less than a milligram (mg) of the active ingredients, and individual doses range from one to multiple actuations by the oral inhalation route of administration.

As indicated above, there are a wide variety of DPI designs and most of these are proprietary and protected by patents. Because these design parameters and operating principles are an integral part of the complex drug-device product function, it is not possible to have a general use DPI device that could be substituted for any approved product. For the same reasons, these facts render these types of drug products difficult or impossible to compound safely and effectively.

Although similar in some features to other types of inhalation drug products (e.g., metered dose inhalers and inhalation sprays), DPIs are unique with respect to formulation, container closure systems/devices, manufacturing procedures, in-process and final controls, and stability testing. Inadequate understanding and control of any of these characteristics can adversely affect the ability of the product to deliver reproducible doses to patients throughout the product's shelf-life, resulting in suprathreshold or subtherapeutic dosing which could impact safety and efficacy. The relative importance of these characteristics is emphasized by the fact that, in general, clinical efficacy studies of DPI products may not be an adequate measure of the ability to deliver reproducible doses to patients due to the variable, subjective, or insensitive nature of clinical measurements, as well as the small number of patients studied relative to the eventual market size for the product. These unique features of DPIs are discussed below.

III. EVALUATION CRITERIA

FDA has determined that the following criteria should be used for evaluating whether drug products or categories of drug products are demonstrably difficult to compound:

1. Does the drug product or category of drug products have a **complex formulation** that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?
2. Does the drug product or category of drug products have a **complex drug delivery mechanism** that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?
3. Does the drug product or category of drug products involve a **complex dosage form** that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?
4. Does **bioavailability** of the drug product or category of drug products present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?
5. Does compounding the drug product or category of drug products involve a **complex compounding process** that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?
6. Does compounding the drug product or category of drug products necessitate **physicochemical or analytical testing** that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product?

IV. ANALYSIS

- A. Dry powder inhalers (DPIs) have a complex formulation that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of dry powder inhalers.**

DPI formulations require components (APIs and excipients) to have certain unique characteristics or properties to achieve and maintain the proper physical form and stability to assure reproducible dosing performance characteristics of the drug product.

DPI formulations are, by definition, dry powders and have unique physical characteristics that must be controlled. DPI formulations are developed for use with specific devices

that are used by the patient to deliver drug by the oral inhalation route of administration. The reproducibility of delivery performance and product stability, and, thus, safety and efficacy of the drug product, typically requires a comprehensive control strategy for the chemical and physical properties of the formulation's components and the manufacturing process.

1. API

Several properties of the API may affect drug product performance which presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on safety or effectiveness of the DPI. These properties include, but are not limited to, the API's amorphous or crystalline forms including polymorphic forms (e.g., solvates, hydrates, or clathrates), bulk density, particle size, particle morphology, purity (e.g., moisture and/or residual solvent content). Some of these are discussed below.

a. Polymorphic Form

An individual DPI formulation may require the API to exist in an amorphous state or a specific polymorphic form. If the amorphous form of the API is desired in the formulation, then the content of other polymorphic forms needs to be limited and controlled by understanding and avoiding the manufacturing conditions that have the potential to induce/catalyze the natural tendency of phase transition to revert to a thermodynamically more stable crystalline form from the thermodynamically less stable amorphous form.

The presence of an undesired polymorph can affect safety and efficacy because changes in the polymorphic form of the micronized API in the formulation may influence the rate of absorption and dissolution, as well as how the API interacts physically with the excipients, the latter of which can impact the delivery performance and/or drug stability.

Amorphous areas in otherwise crystalline carrier excipient can lead to "high energy" areas on the surface of the carrier that leads to strong interaction with API particles, preventing deagglomeration and release of inhalable-sized API particles during use of the DPI. Specific carrier and/or API surface treatments or conditioning, as well as the use of other additives (e.g., magnesium stearate, finely micronized carrier) can be incorporated into the formulation blending/manufacturing process to mitigate the impact of any amorphous content of the formulation components.

b. Size

Particle size distribution (PSD) of the API and the carrier excipient not only affects the homogeneity of the formulation blend with excipients of a DPI, but also the aerodynamic PSD, a critical quality attribute of the emitted API delivered from the mouthpiece to the patient. Inadequate control of API particle size can cause unit-to-unit content variability

during filling of the blend into DPI pre-metered units or reservoirs, and unreliable dose deposition in lungs, resulting in a subtherapeutic or suprathapeutic dose to the patient.

c. Particle Morphology

The surface condition of the API affects its cohesive and adhesive properties, surface activity, specific surface area, and static charge properties. Thus, it is important in ensuring the right balance of API/carrier excipient interaction to assure reproducible manufacturability but to also allow deagglomeration of inhalable API particles from the carrier (usually much larger sized), and hence, delivery to the lungs during patient use. Surface conditions of both the API and the carrier excipient need to be carefully characterized and adequately controlled to ensure efficacy and safety.

d. Purity

The purity of the API (assay) and its impurity profile [organic (synthesis and degradation related products), and inorganic (e.g., reagents, heavy metals, catalysts) impurities] are critical quality attributes that affect the safety and efficacy of the drug product. However, there are no compendial monographs suitable for APIs for the oral inhalation route of administration.

2. Excipients

Excipients (e.g., carrier, stabilizing agents) and in particular carriers (e.g., lactose) comprise a significant portion of most DPI formulations. Proper selection and quality control of excipients is necessary to achieve and maintain physical stability and performance characteristics of the formulation. Preventing physicochemical changes or degradation of the formulation is highly dependent on choice and quality control of excipients for the specific APIs of these DPI drug products.

3. Formulation Stability

Physicochemical stability of DPI formulations is imperative to assure reproducible dose delivery performance, and, therefore, efficacy and safety. For both APIs and excipients, maintenance of physical form (e.g., crystalline or amorphous forms) and the PSD may be highly dependent on various factors such as moisture/solvent content and temperature, and specific conditioning processes may be necessary as part of the manufacturing process. For example, recrystallization of amorphous material can lead to particle bridging and increase in aerodynamic particle size. Chemical stability of the formulation will depend on the excipients used, which should be selected to minimize the potential for chemical interaction with the API. Extensive formulation characterization studies are necessary during development to assure DPI formulation reproducibility and stability.

Conclusion

In summary, DPIs have complex formulations as the overall dosing performance is highly dependent on the physicochemical properties of the formulation components and their interaction in combination with both the device and the patient. Furthermore, the physical properties of the formulation, as delivered from the device, are crucial in determining the deposition sites of the drug in patients' lungs and, therefore, require full characterization to assure stability and reproducible drug product performance. As particle size requirements for the API of DPI drug products are such that these are high-energy physical forms (micron size range), achieving this reproducibility is challenging from a manufacturing and processing perspective. Finally, the majority of DPI drug products are used for topical treatment of patient lungs for local effect and call for high purity components to avoid unwanted side-effects associated with patient lung sensitivity from their disease. Accordingly, the complex formulation of DPIs presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.

B. Dry powder inhalers have a complex drug delivery mechanism that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of dry powder inhalers.

The complexity of the drug delivery mechanism for DPIs derives from the fact that in the vast majority of cases, it is only the inhalation maneuver of the patient that draws the formulation from the device, deagglomerates the formulation [i.e., turbulence releases fine drug from carrier excipient(s)] to achieve the necessary fine particle size of the drug, and propels the drug to the local site of action in the lungs of the patient. Therefore, device designs need to be intuitive, robust and rugged, provide protection for the formulation in between doses, and provide a mechanism, if necessary, for the patient to keep track of remaining doses available. Poor coordination or inhaler use technique may reasonably result in patients not receiving their necessary dose, with potentially critical consequences. For example, in the case of asthma rescue medication, low delivered dose or insufficient deagglomeration (due to formulation, device, or patient use failures) would be less likely to prevent further bronchospasm or airway constriction. The same clinical effects are noticed when the emitted dose to the patient cannot penetrate to the targeted part of the lungs. Therefore, in addition to precise control of formulation and device components, development of DPIs must include consideration of patient ability to use the DPI and necessary instructions to limit medication errors.

Because of the interaction of the formulations, devices, and patients, DPI devices are not cleared for general use as stand-alone devices, and each DPI drug product is unique. Thus, there are no cleared general-use DPI devices that compounders could purchase for delivery of compounded DPI formulations. Furthermore, unlike metered dose inhalers (inhalation aerosols), DPI device designs vary widely (e.g., pre-metered capsules or blisters to be used in conjunction with a separate delivery device; device-metered DPIs

that contain a reservoir of formulation to be metered each time the patient uses the device), and, therefore, patients must become familiar with each unique type of product. Even if a general use DPI device were available, compounding a dry powder formulation into a different device would present significant variations in performance characteristics, which presents demonstrable difficulties that are reasonably likely to lead to adverse effect on the safety or effectiveness of the DPI.

The vast majority of DPI drug products have very low drug load in the formulation due to the high energy physical state of the API and considerations of manufacturability. In addition, the amounts of formulation that are typically needed for delivery are quite small (i.e., individual doses are typically less than one milligram). Therefore, achieving adequacy of mix (blend uniformity) is more difficult than for more typical drug products, but necessary to attain acceptable dosing accuracy and reproducibility. Metering small quantities of powder formulations also depends on tight control of formulation bulk density as well as the dimensions of the components used in metering the API (either during manufacturing for pre-metered DPIs or by the device itself for device-metered DPIs). In addition, as already discussed above, tight control of formulation component properties is necessary to assure the correct balance of the forces holding the API to the carrier such that it is enough to allow consistent manufacturability (e.g., powder flow), but not so much as to prevent deagglomeration of fine particles of drug from the carrier during actuation of the device by the patients' inhalation maneuvers.

Although DPI devices themselves come in a wide variety of forms, from relatively simple units for delivery of pre-metered doses to highly complex devices that meter the dose upon patient use, all of these drug products are considered to be complex mainly because of the very small particle size necessary to deliver the API to the lungs of patients. Highly reduced particle sizes are necessarily high-energy physical states which require careful selection of formulation excipients, highly specialized production processes, device component composition, and the complex methodology for characterization and quality control of formulation and final product, which includes the device. For example, selection of device component composition can directly affect the amount of fine particles of a drug that can be delivered due to variable or substantial hold-up or loss of the drug through adherence to the inner surfaces of the inhaler (from, for example, electrostatic interactions) and negatively affect dosing reproducibility.

Conclusion

Developing a final DPI drug product that can deliver formulations of very fine API is dependent on the formulation and the associated device, as well as its use by patients. Only when all three of these factors are considered together in development will there be success in producing a product that will correctly deliver the accurate dose of the drug to the biological target organs of patients, i.e., their lungs. Therefore, the drug delivery system for DPIs is considered to be complex and to present a demonstrable difficulty for

compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.

C. Dry powder inhalers are a complex dosage form that present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of dry powder inhalers.

As discussed above in sections A and B, DPIs have complex formulations and drug delivery mechanisms. Specifically, as mentioned above in section B, each DPI drug product is unique. Thus, there are no cleared general-use DPI devices that compounders could purchase for delivery of compounded DPI formulations. Furthermore, unlike metered dose inhalers (inhalation aerosols), DPI device designs vary and, therefore, patients must become familiar with each unique type of product. DPIs are complex dosage forms and compounding a dry powder formulation for use in a different device would present significant variations in performance characteristics. As a result, DPIs are considered complex dosage forms that present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of DPIs.

D. Bioavailability of drugs in dry powder inhalers is difficult to achieve and assess, and presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of dry powder inhalers.

The concept of classical bioavailability (that is, the fraction of the administered dose of unchanged drug that reaches the systemic circulation) is usually not applicable to oral inhalation dry powders, which are designed to act locally in the lungs. Currently, there is no simple methodology to assess bioavailability at the site of action in the lungs, because of the complexity of the target organ.

In addition to difficulties in measuring bioavailability at the site of action, it would likely be difficult to achieve a targeted and consistent local bioavailability for a DPI because of the inherent formulation and delivery system challenges described in sections A and B. As described previously, attaining and maintaining the necessary PSD, polymorphic form, and other critical physical properties of the API can affect the absorption of the delivered dose. Absorption obstruction decreases systemic bioavailability of the compounded drug product. The DPI is a complex system in which any small change in performance characteristics can have significant impact upon local and systemic bioavailability and efficacy of the product. At the current time, in vitro assessments, such as APSD and single actuation content, alone are not sufficient to accurately predict lung deposition, bioavailability, and overall clinical effect, although many of these areas are currently being researched. As an example, the cascade impactor device used to measure the drug product aerodynamic PSD claims it can be used for quantitation of drug

deposited in the lungs, but at this time the science only supports impactor data being used for quality testing of DPI units.

Because comparative clinical studies are typically required to assess the local bioavailability of DPI drug products along with in vitro and pharmacokinetic assessments, this complex weight-of-evidence approach necessary for product development would present a demonstrable difficulty to compounding. The dose administered is typically so small that blood or serum concentrations are generally low, and may only be detectable for a few hours post-dose. The systemic exposure alone may not distinguish the absorption from the lungs or GI tract, and current methodologies cannot clearly differentiate the regional lung deposition. Thus, there is no single, easily reproducible, reliable method of measurement that can quantitate the dose delivered by the dosage form and received by the patient, which would be necessary to enable the compounder to consistently make product with delivered dose uniformly falling within acceptable ranges.

Conclusion

For locally acting drugs applied to the lungs at low doses, as is typical of DPI dosage forms, measuring local bioavailability, which would be determined by measuring the levels of drug deposited at the critical site within the lungs, does not currently have a single, easily reproducible method of quantitation. Measurement of blood levels alone, as accomplished historically for bioavailability testing for solid oral dosage forms, is generally challenging for DPIs. Furthermore, the bioavailability of DPIs would also likely be difficult to achieve because of the product characteristics described above for DPIs. The DPI is a complex system for which any small change in performance characteristics can have significant impact upon the overall bioavailability and performance of the product. Therefore, achieving and assessing bioavailability of DPIs presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of DPIs.

E. Compounding dry powder inhalers requires a complex compounding process that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of dry powder inhalers.

DPI formulations require specialized processing to yield reproducible physicochemical characteristics necessary for use with devices to deliver drug to the patient's lungs. As particles for delivery to lungs are generally thought to require an aerodynamic diameter of about 5 micrometers or less, DPI formulations typically contain micronized drug, which is in a high-energy physical state. Highly micronized drug most often has very poor manufacturability (lack the flow properties necessary for ease of filling/metering), and can have substantial amorphous rather than crystalline structure, which leads to poor

physical stability and associated problems (e.g., particle bridging and increase in particle size, water uptake, and chemical degradation). Because of the low drug loads commonly associated with products for local delivery and action in the lung, achieving adequacy of mix, and thus dose-to-dose uniformity for the patient, is often difficult, and comprehensive development work leading to in-depth understanding of formulation interactions (i.e., adhesion, cohesion) is generally required to achieve formulations with dose uniformity and manufacturability. The development process also requires consideration of the inter-particulate interactions necessary to assure reproducible aerodynamic PSD under the widely variable conditions of patient use. (As noted above, patient inspiration generally provides the energy to produce and deliver the dose to the lungs.)

In conjunction with these formulation considerations, there must also be consideration of the device to be used for formulation delivery. Devices need to be designed to be functional in the patients' hands, and when used, increase the energy from the patient's inhalation air flow sufficiently to deagglomerate and propel the drug for delivery. In addition, devices that meter the formulation must also protect the formulation when not in use and provide an indication of the number of remaining doses.

Conclusion

Errors in formulation compounding or filling of the DPI could reasonably result in delivered dose variability in either the quantity of the emitted drug or its aerodynamic PSD. Insufficient drug delivered to the appropriate part of the lungs (as measured by these two parameters) would pose an efficacy concern, and potentially a safety concern, especially for rescue medications. Compounding a DPI involves a complex compounding process that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.

F. Dry powder inhalers require complex physicochemical or analytical testing that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of dry powder inhalers.

The testing generally used to assess the quality of DPIs is relatively comprehensive and addresses many parameters. Further, in terms of performance, this testing is relatively complex (compared to tablets, capsules, oral solutions, and injectables) and requires specialized instruments and expertise. This is particularly true of the collection of aerosolized PSD data by cascade impaction testing. This latter test requires specialized instruments (e.g., Andersen or Next Generation Impactors) and complex procedures specific to impactor testing to prevent re-entrainment of particles within the impactor and to assure accurate assessment of aerosolized PSD. It is generally accepted that there is likely a correlation between the laboratory-measured aerosolized PSD for DPI products and the lung deposition patterns that occur when patients use these products. However,

direct establishment of these correlations are difficult or are attempted with methodology that is not generally accepted by regulatory agencies (e.g., lung imaging studies with radioactively labeled drug). Therefore, aerodynamic PSD and other quality control tests are useful primarily as a quality measurement, evaluated in conjunction with other key data (such as the results of clinical studies) based on products to which these tests have been applied and the data obtained. Even if compounders are capable of collecting aerodynamic PSD data for compounded DPI products, it is unlikely that they could provide all the other evaluations typically done to prepare a DPI, and failing to do them is reasonably likely to have an adverse effect on the safety and efficacy of the compounded drug products.

Without comprehensive development work, a compounder would not be able to identify the physicochemical properties of formulation components that would need to be controlled nor would they be able to determine the specific testing needed for starting or intermediate materials to assure the reproducibility of these components of the formulation. And because, as mentioned above, there are no DPI devices that have been cleared for general use, compounders would not be able to purchase such devices and use them with minimal testing.

In addition, due to the complexity of typical DPI formulations, they often display unique stability characteristics and require special treatment or protection from the environment that can only be determined by the execution of thorough stability testing. Finally, because of the complexity of DPI drug products and their reliance on the patient for the production of the dose at the time of use, extensive one-time characterization studies are routinely performed by DPI manufacturers to create labeling and patient instructions for use and storage (e.g., in-use studies when protective packaging is used, effect of varying flow rate on product dosing performance, dose build-up and cleaning instructions, orientation effects, need for device priming or preparation prior to first dosing, device ruggedness). It is unlikely that compounders would have the expertise or be able to invest in the specialized instruments necessary to carry out these drug product characterization studies.

Conclusion

DPIs require complex physicochemical and analytical testing because the formulation components' physical and chemical properties and product-critical performance parameters (such as aerodynamic PSD and delivered dose) require complex analytical devices and procedures for accurate measurement. In-process testing of DPIs and control of their manufacturing process are critical to minimizing unit-to-unit and batch-to-batch variability and to ensuring accurate performance throughout the product shelf life and in-use life. Furthermore, because the performance of the DPI depends heavily on proper

patient use of the drug product, testing to determine the adequacy of the labeling and instructions for use must be considered.

The physicochemical and analytical testing and actual use studies typically required for DPIs are extremely complex. For drugs applied to the lungs for local action, there is no well-established correlation of the *in vitro* data collected with these tests, to clinical or other *in vivo* measures in patients. Clinical measures are insensitive, and there is not enough evidence at this time to determine if systemic blood drug levels can reflect drug activity at the local site of action in the lungs. The inability to correlate the clinical effect based on the *in vitro* testing alone increases the likelihood that a product quality defect, which could lead to an adverse effect on safety or effectiveness, would not be detected for a compounded drug product. For the reasons described above, DPIs require complex physicochemical and analytical testing that presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.

V. PATIENT RISK AND BENEFIT CONSIDERATIONS

At present, DPIs are not used as commonly in the United States as are MDIs. There are currently approximately 20 DPI products on the market. These products are all drug products approved under a new drug application or abbreviated new drug application submitted to the FDA. The safety profile for the products is monitored by the FDA to identify drug safety concerns and recommend actions to improve product safety and to protect the public health. There is currently an adequate supply of approved DPI products on the market and thus there is limited, if any, benefit to expanding the market to compounding DPI products. In fact, any benefit derived is outweighed by the risks, discussed above, associated with allowing a compounder to attempt to produce these complex drug products.

Unlike most other drug products, the dosing and performance and, therefore, the clinical efficacy of a DPI, is directly dependent on the design of the device which also acts as a container closure system. Also unique to DPIs is that the dosage form is for a local effect in the lungs. Unlike most other dosage forms (e.g., tablet, capsule, solution, suspension), bioequivalence of a DPI to a reference drug product cannot be established solely by conducting typical bioavailability studies and quality control tests alone because pharmacokinetic data in this instance primarily measures the amount of systemic absorption, which may not correlate with topical drug deposition and/or clinical effect. The demonstration of efficacy and safety (or alternately, bioequivalence) of a DPI product is based upon a complex assessment of *in vitro* performance characteristics of the DPI, *in vivo* data, and evidence of clinical effect, where small variations in any one of these complex parameters may have profound effects upon product performance. This complex product development is a challenge for innovator and generic DPI development programs, given that all these parameters need to be carefully controlled to ensure consistent product quality and stability over the shelf-life of the product. This is the most critical reason why there would be demonstrable difficulties for compounding

Conclusion

DPIs are a complex category of drug products that are effective and safe when manufactured properly to ensure, amongst other things, that the product has the proper formulation, the drug delivery mechanism is designed correctly, appropriate bioavailability is achieved and the necessary physicochemical and analytical testing is performed. The product quality of a DPI is critical and the complexity of compounding this category eclipses any benefit of allowing an outsourcing facility or pharmacy to compound DPIs. The drug products currently on the market are available to consumers with safety profiles the FDA continues to monitor, and thus the advantage of access, efficacy, and safety benefit the patient greater than exposing them to the myriad risks associated with allowing compounders to attempt to produce DPI products.

VI. RECOMMENDATION

Based on an analysis of the evaluation criteria, we conclude that DPIs present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product and that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the category of drugs, taking into account the risks and benefits to patients. Accordingly, we recommend that the category of DPIs be included on the list of difficult to compound drug products under sections 503A and 503B of the FD&C Act.

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