4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. FDA-2018-N-4845]

RIN 0910-AH81

Amendments to the List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) has issued a regulation creating a list of bulk drug substances (active pharmaceutical ingredients) that can be used to compound drug products in accordance with certain compounding provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act), although they are neither the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. This proposed rule would amend that list by placing five additional bulk drug substances on the list. This proposed rule also identifies 26 bulk drug substances that FDA has considered and proposes not to include on the list. Additional substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of a future rulemaking.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. See section VI for the proposed effective date of a final rule based on this proposed rule.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time on the comment due date provided in the DATES section. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2018-N-4845 for "Amendments to the List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover

sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Rosilend Lawson, Center for Drug Evaluation and Research, Office of Unapproved Drugs and Labeling Compliance, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5197, Silver Spring, MD 20993, 240-402-6223, Rosilend.Lawson@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to amend its regulations to add substances to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (21 U.S.C. 353a) (referred to as "the 503A Bulks List"). Bulk drug substances that appear on the 503A Bulks List can be used to compound drug products subject to the conditions of section 503A, even though those substances are not the subject of an applicable USP or NF monograph or components of approved drug products.

B. Summary of the Major Provisions of the Proposed Rule

Based on the results of its evaluation of nominated bulk drug substances to date, as well as consultation with the Pharmacy Compounding Advisory Committee (PCAC), and the United States Pharmacopoeia Convention, Incorporated, FDA is proposing to amend the 503A Bulks List to include five additional bulk drug substances: glutaraldehyde, glycolic acid, L-citrulline, pyruvic acid, and trichloroacetic acid (TCA). FDA is also proposing that 26 other substances not be included on the list: 7-keto dehydroepiandrosterone (DHEA), acetyl-L-carnitine (ALC), alanyl-L-glutamine, Aloe vera 200:1 freeze dried, artemisinin, astragalus extract 10:1, *boswellia serrata* extract (BWSE), cesium chloride, chondroitin sulfate, chrysin, curcumin, D-ribose, deoxy-D-glucose, diindolylmethane, domperidone, epigallocatechin gallate (EGCG), germanium sesquioxide, glycyrrhizin, kojic acid, nettle, nicotinamide adenine dinucleotide (NAD), nicotinamide adenine dinucleotide disodium reduced (NADH), rubidium chloride, sodium dichloroacetate, vanadyl sulfate, and vasoactive intestinal peptide (VIP).

C. Legal Authority

Section 503A of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serves as our principal legal authority for this proposed rule.

D. Costs and Benefits

FDA evaluated 31 bulk drug substances for this proposed rule, proposing to place 5 bulk drug substances on the 503A Bulks List, and not to place 26 substances on the 503A Bulks List. The primary estimate of the present value of the costs over 10 years is $1.03 million. The primary estimate of the annualized costs is $0.15 million at a 7 percent discount rate and $0.12 million at a 3 percent discount rate. Because we lack sufficient information to quantify most of the costs and benefits of this proposed rule, we also include a qualitative description of potential

benefits and potential costs. We expect that the rule will affect compounding pharmacies and other producers that market the affected substances or drug products made from the affected substances, consumers of drug products containing the affected substances, and payers that cover these drug products or alternative treatments.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
ALC	Acetyl-L-carnitine
BWSE	*Boswellia serrata* extract
CFR	Code of Federal Regulations
CFS	Chronic fatigue syndrome
CIRS	Chronic inflammatory response syndrome
DHEA	Dehydroepiandrosterone
EGCG	Epigallocatechin gallate
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GAIT	Glucosamine/Chondroitin Arthritis Intervention Trial
GRAS	Generally recognized as safe
HSV	Herpes simplex virus
IND	Investigational new drug
IV	Intravenous
MS	Multiple sclerosis
NAICS	North American Industry Classification System
NAD	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide disodium reduced
NF	National Formulary
NPRM	Notice of proposed rulemaking
OA	Osteoarthritis
PCAC	Pharmacy Compounding Advisory Committee
RA	Rheumatoid arthritis
RFA	Regulatory Flexibility Analysis
SBA	Small Business Administration
TCA	Trichloroacetic acid
UCD	Urea cycle disorder
USP	United States Pharmacopeia
VIP	Vasoactive intestinal peptide

III. Background

Section 503A of the FD&C Act describes the conditions under which a compounded drug product may qualify for an exemption from certain sections of the FD&C Act. Those conditions include that a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed

physician compounds the drug product using bulk drug substances that: (1) comply with the standards of an applicable USP or NF monograph,[1] 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 of the Department of Health and Human Services (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, appear on the 503A Bulks List. (See section 503A(b)(1)(A)(i) of the FD&C Act.)

On February 19, 2019, FDA published a final rule establishing the criteria for evaluating substances for inclusion on the 503A Bulks List, placing six substances on the list, and identifying four other substances that were evaluated and not included on the 503A Bulks List (84 FR 4696). That final rule noted that additional substances were under evaluation, and that new substances may be added to the list through subsequent rulemaking. This proposed rule would amend that list by adding five additional substances. It also identifies 26 other substances that FDA has evaluated and proposes not to include on the list.

Section 503A of the FD&C Act adopts the definition of "bulk drug substance" in FDA's drug establishment registration and listing regulations, which was codified at § 207.3(a)(4) (21 CFR 207.3(a)(4)) at the time section 503A was enacted. (See section 503A(b)(1)(A) of the FD&C Act.) Under the definition, bulk drug substance means any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug,

[1] FDA has interpreted the statutory language "applicable United States Pharmacopoeia or National Formulary monograph" to refer only to official USP or NF monographs for drug substances. Therefore, a substance that is the subject of a dietary supplement monograph, but not a USP or NF drug substance monograph, does not satisfy the condition regarding bulk drug substances in section 503A(b)(1)(A)(i)(I) of the FD&C Act. Such a substance may only be used as a bulk drug substance under section 503A of the FD&C Act if it is a component of an FDA-approved drug product or is on the 503A Bulks List.

becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.

On August 31, 2016, FDA published a final rule in the *Federal Register* to update its registration and listing regulations in part 207 (21 CFR part 207), which included minor changes to the definition of bulk drug substance and moved the definition to § 207.3 (see 81 FR 60170 at 60175). This definition became effective on November 29, 2016. As set forth in § 207.3, "bulk drug substance," as referenced in section 503A(b)(1)(A) of the FD&C Act, means the same as "active pharmaceutical ingredient" as defined in § 207.1 (21 CFR 207.1). An "active pharmaceutical ingredient" is any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. The term "active pharmaceutical ingredient" does not include intermediates used in the synthesis of the substance (§ 207.1).

Inactive ingredients used in compounded drug products, such as flavorings, dyes, or diluents, need not appear on the 503A Bulks List to be eligible for use in compounding drug products and will not be included on the list.

For regulatory history of the 503A Bulks List, see 81 FR 91071 (December 16, 2016).

IV. Legal Authority

As described in Section III. Background, section 503A of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from three sections of the FD&C Act (sections 501(a)(2)(B), 502(f)(1), and 505 (21 U.S.C. sections 351(a)(2)(B), 352(f)(1), and 355)). One of the conditions that must be satisfied for a compounded drug to qualify for the exemptions under section 503A

of the FD&C Act is that a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician compounds the drug product using bulk drug substances that: (1) comply with the standards of an applicable USP or 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, appear on the 503A Bulks List. (See section 503A(b)(1)(A)(i) of the FD&C Act.) Section 503A(c)(1) of the FD&C Act also states that the Secretary shall issue regulations to implement section 503A, and that before issuing regulations to implement section 503A(b)(1)(A)(i)(III) pertaining to the 503A bulks list, among other sections, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. Section 503A(c)(2) of the FD&C Act requires the Secretary to issue the regulations in consultation with the USP, and to include in the regulation the criteria for such substances that shall include historical use, reports in peer-reviewed journals, or other criteria the Secretary identifies. Thus, section 503A of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act, serves as our principal legal authority for this proposed rule.

V. Description of the Proposed Rule

FDA proposes to amend § 216.23 (21 CFR 216.23) to include 5 of the bulk drug substances that were considered on the 503A Bulks List and to identify 26 substances that were considered and would not be included on the list. The criteria and methodology for evaluating bulk drug substances for inclusion on the list, and FDA's proposals regarding the substances addressed in this notice of proposed rulemaking (NPRM) are described in the paragraphs that

follow.

A. Criteria for Evaluating Bulk Drug Substances for the 503A Bulks List

Section 503A(c)(2) of the FD&C Act provides that the criteria for determining which substances should appear on the 503A Bulks List shall include historical use, reports in peer-reviewed medical literature, or other criteria the Secretary may identify. Under § 216.23, the following criteria are used to evaluate the nominated substances:

- The physical and chemical characterization of the substance;
- Any safety issues raised by the use of the substance in compounded drug products;
- The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
- 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.

In evaluating candidates for the 503A Bulks List under these criteria, the Agency uses a balancing test. Specifically, the Agency considers each criterion in the context of the others and balance them, on a substance-by-substance basis, to decide whether a particular substance is appropriate for inclusion on the 503A Bulks List. The criteria are discussed in further detail in the Agency's previous rulemaking on the 503A Bulks List (81 FR 91071; 84 FR 4696).

B. Methodology for Developing the 503A Bulks List

FDA reviewed the substances addressed in this proposed rule in the context of adequately supported uses that were proposed with the nomination. In certain circumstances, FDA also reviewed substances in the context of uses that were not proposed with the nomination or proposed uses that were inadequately supported because, for example, such uses appear to be

widespread, are intended to treat serious conditions, or pose serious risks to patients. The information that FDA assessed to evaluate the substances addressed in this proposed rule under each of the evaluation criteria was obtained from publicly available sources, including peer-reviewed medical literature. Some of this information was referenced in the nominations, and the remainder FDA gathered through independent searches of medical and pharmaceutical databases. FDA did not review raw data. The nature, quantity, and quality of the information FDA assessed varied considerably from substance to substance. In some cases, there were very little data. For other substances, reports in the literature were more plentiful and sometimes comprised hundreds or thousands of articles. In those cases, generally the Agency limited its review to a sample of the best literature sources available (e.g., review articles in widely known, peer-reviewed journals; meta-analyses; reports of randomized controlled trials).

FDA's evaluation of the nominated substances was, necessarily, far less rigorous and less comprehensive than the Agency's review of drugs as part of the new drug approval process. The new drug approval process is conducted based on extensive data compiled and submitted with new drug and abbreviated new drug applications, which are not available for the nominated substances. Additionally, the Agency's review during the drug approval process includes premarket evaluation of a specific drug formulation, the applicant's chemistry and manufacturing controls, and inspection of the establishments where approved drugs will be manufactured. In contrast, these bulk drug substances will be evaluated only for possible use in compounded drugs.

Therefore, the proposed inclusion of a drug substance on the 503A Bulks List should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded

using the substances on the proposed list has been proven to be safe and effective under the standards required for Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears on this list is approved by FDA, or otherwise endorsed by FDA generally, or for a particular indication, will cause the drug to be misbranded under section 502(a) (labeling) and/or 502(bb) (advertising or promotion) of the FD&C Act.

On October 27 and 28, 2015, March 8, 2016, June 23, 2016, November 3, 2016, May 8 and 9, 2017, and November 20, 2017, FDA consulted with the PCAC created under section 503A(c)(1) of the FD&C Act about the 31 substances that are addressed in this proposed rule (Refs. 1 to 11). The Agency considered the PCAC's recommendations in developing this proposed rule, and the Agency intends to continue to consult with the PCAC in evaluating future candidates for the 503A Bulks List. Going forward, FDA intends to publish NPRMs proposing additional substances be included on the list or not included on the list on a rolling basis as evaluations are completed. Depending on the length of time it takes to complete a rulemaking, multiple rulemakings may be ongoing simultaneously.

Section 503A of the FD&C Act also requires that FDA create the 503A Bulks List in consultation with the USP. (See section 503A(c)(2) of the FD&C Act.) To this end, FDA has consulted with USP about the substances that are the subject of this proposed rule (Refs. 12 to 16). After publication of this NPRM, the public will have an opportunity to submit comments on the proposed rule to the docket. After considering those comments, FDA will publish a final rule amending the 503A Bulks List codified at § 216.23. The final version of the rule may include all, none, or only some of the substances proposed here for inclusion on the 503A Bulks List, based upon the Agency's consideration of the comments received, and will also identify those substances the Agency has determined should not be included on the list. The Agency may

amend the 503A Bulks List to add or delete substances after further notice and comment rulemaking.

With respect to any substance already addressed in a final rule, individuals and organizations may petition FDA to amend the 503A Bulks List (to add or delete those bulk drug substances or to consider information about those bulk drug substances that is different from that which FDA presented to the PCAC) (see 21 CFR 10.30). With respect to substances that have not been addressed in rulemaking, individuals and organizations may submit nominations of new substances or comments on nominated substances to Docket No. FDA-2015-N-3534.

C. Substances Proposed for Inclusion on the 503A Bulks List

Under section 503A(c)(2) of the FD&C Act, FDA is proposing that the following five bulk drug substances, which are neither the subject of an applicable USP or NF monograph nor components of FDA-approved drugs, be included on the 503A Bulks List, and the drug products compounded with those substances may qualify for the exemptions provided for in section 503A of the FD&C Act (i.e., from sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act). When a salt or ester of an active moiety is listed, only that particular salt or ester may be used for compounding under section 503A of the FD&C Act. The base compound and other salts or esters of the same active moiety must be evaluated separately for inclusion on the 503A Bulks List. Additionally, when a bulk drug substance is included on the 503A Bulks List subject to certain restrictions (for example, for a particular route of administration (e.g., topical)), only drug products that conform to that restriction may qualify for the 503A exemptions.

The following bulk drug substances are being proposed for placement on the 503A Bulks List, to appear in § 216.23(a) of title 21 of the CFR:

(1) *Glutaraldehyde.* Glutaraldehyde[2] was evaluated for topical use in the treatment of warts. Glutaraldehyde is well characterized physically and chemically. Glutaraldehyde is reasonably safe to use topically in 0.1 percent to 10 percent solutions for the treatment of warts. Nonclinical studies do not show safety issues in vivo other than irritation and skin sensitization. Skin discoloration has been observed with the use of glutaraldehyde in the treatment of warts, which eventually subsides after treatment. Other risks, such as allergic contact dermatitis, skin ulceration, and necrosis, were observed when high strengths of glutaraldehyde were used. These risks should be managed by the use of glutaraldehyde in strengths of 10 percent or lower.

Although there is no standard regimen for its use, there is available evidence from uncontrolled clinical studies and one randomized controlled trial demonstrating the effectiveness of glutaraldehyde in nongenital cutaneous wart treatment. There are no approved prescription therapies for warts outside of the genital area. Glutaraldehyde has been used in compounded drug products for over 40 years, primarily in the treatment of nongenital warts.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of glutaraldehyde weigh in favor of inclusion of this substance on the list. FDA recommended to the PCAC that this substance be included on the 503A Bulks List for topical use, at concentrations of 10 percent or lower (Ref. 17). At its meeting on October 28, 2015, the PCAC voted to include glutaraldehyde on the list (Ref. 3). We have also consulted with USP regarding

[2] Note that there is a USP monograph for glutaral concentrate (glutaraldehyde in a 50 percent aqueous solution), which is a different concentration than that proposed in the nominations. USP Guidelines state that "[s]ome drug substances are available as concentrated solutions … and are intended to be used as intermediates for final formulations." USP Nomenclature Guideline Outline, available at https://www.usp.org/sites/default/files/usp/document/about/expert-volunteers/expert-committees/nomenclature-guideline.pdf. The glutaral concentrate that is the subject of the USP monograph is intended to be used as an intermediate for a final formulation; the USP monograph for glutaral concentrate states that it should be labeled with the statement that it is not intended for direct administration to humans or animals. Under § 207.3(a)(4), the definition of "bulk drug substance" excludes intermediates used in the synthesis of the bulk drug substance. Therefore, we are proposing glutaraldehyde for inclusion on the list in forms or concentrations other than those provided in the USP monograph.

placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would place glutaraldehyde on the 503A Bulks List for topical use at concentrations of 10 percent or lower.

(2) *Glycolic Acid.* Glycolic acid for topical use was evaluated for use in the treatment of hyperpigmentation and photodamaged skin. Glycolic acid, also known as hydroxyacetic acid, is physically and chemically well characterized. When used in high concentrations, glycolic acid causes local effects that are typical of a strong acid, such as dermal and eye irritation. Reported adverse reactions were generally limited in duration and readily manageable. There is no information available on long-term outcomes. The available data on short-term outcomes do not raise major safety concerns associated with the topical use of glycolic acid.

Data from controlled clinical trials have shown consistently positive results in the treatment of epidermal melasma or other forms of hyperpigmentation. The available evidence suggests that there is a role for glycolic acid in the treatment of melasma, typically as a second line treatment. There is also some evidence indicating that glycolic acid may be effective for the mitigation of manifestations of photodamaged skin. Historically, glycolic acid has been used in compounded drug products for several decades.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of glycolic acid weigh in favor of inclusion of this substance on the list. FDA recommended to the PCAC that this substance be included on the 503A Bulks List, for topical use in concentrations up to 70 percent (Ref. 18). At its meeting on November 3, 2016, the PCAC voted to include glycolic acid for topical use on the list (Ref. 8). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional

quality concerns related to this substance (Ref. 15). This proposed rule would place glycolic acid for topical use, in concentrations up to 70 percent, on the 503A Bulks List.

(3) *L-citrulline.* L-citrulline for oral use was evaluated for use in the treatment of certain urea cycle disorders (UCDs). L-citrulline, a non-essential amino acid, is well characterized physically and chemically. The available nonclinical and clinical data are inadequate to evaluate the safety of L-citrulline for oral use, but no serious adverse events have been linked to its use.

Regarding effectiveness, we found no clinical trials supporting the effectiveness of the use of L-citrulline for UCDs. This lack of data is expected given the small number of patients with UCDs. However, there is a strong mechanistic rationale supporting the use of L-citrulline for UCDs, based on the pathophysiology of the disorder and the goals of treatment. There have also been anecdotal reports of successful treatment of certain UCDs with L-citrulline. Historically, the duration of use of L-citrulline in compounded drug products is not clear. L-citrulline has been used clinically in the treatment of certain UCDs for approximately 30 to 40 years. Oral L-citrulline is part of the standard of care for certain UCDs.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of L-citrulline weigh in favor of inclusion of this substance on the list. FDA recommended to the PCAC that this substance, for oral use, be included on the 503A Bulks List (Ref. 19). At its meeting on November 20, 2017, the PCAC voted to include L-citrulline for oral use on the list (Ref. 10). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). This proposed rule would place L-citrulline for oral use on the 503A Bulks List.

(4) *Pyruvic Acid.* Pyruvic acid for topical use was evaluated for use in the treatment of acne, melasma, and warts. It is physically and chemically well characterized, but it is unlikely to

be stable in ambient conditions. Stability concerns can be addressed by carefully sealing the drug product and isolating it from moisture and light. Regarding safety, we identified no significant safety concerns related to the topical use of pyruvic acid in compounded drug products. The available data indicate that the topical use of pyruvic acid is associated with local irritancy, but reported adverse reactions were generally limited in duration and readily manageable. The most serious risk reported was upper respiratory tract irritation due to inhaled vapors, which can be avoided when patients and healthcare providers take appropriate precautionary measures (e.g., ensuring the product is administered in a room with adequate ventilation) to protect against inhalation.

Regarding effectiveness, limited data derived from small, open-label trials indicate that the topical use of pyruvic acid might be somewhat effective in the treatment of acne, melasma, and warts, which are not serious or life-threatening conditions. There are no approved prescription therapies for warts outside of the genital area. Pyruvic acid has been used in compounded drug products for approximately 30 years.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of pyruvic acid weigh in favor of inclusion of this substance on the list. FDA recommended to the PCAC that this substance be included on the 503A Bulks List for topical administration (Ref. 20). At its meeting on June 23, 2016, the PCAC voted to include pyruvic acid for topical use on the list (Ref. 7). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would place pyruvic acid for topical use on the 503A Bulks List.

(5) *TCA.* TCA for topical use was evaluated for the treatment of warts and as a chemical peeling agent. TCA is well characterized physically and chemically and is likely to be stable when refrigerated. The safety profile shows that TCA commonly causes erythema, crusting, hyperpigmentation and hypopigmentation, burning, and pain at the application site. The reported incidents of adverse effects have increased in correlation with the concentration of TCA used (e.g., adverse reactions were observed more frequently with a 95 percent TCA solution as compared with 85 percent or 50 percent solutions), and more adverse effects have been reported when TCA was used in the facial and genital areas. At higher concentrations, the potential for ulceration and subsequent absorption through open wounds increases. Ulcerations have been reported in most studies of TCA in the treatment of genital warts.

Regarding effectiveness, the available information suggests that TCA may have some effectiveness for the treatment of warts when used at higher concentrations (e.g., in one comparative study, more subjects had a "good" response with an 80 percent TCA solution as compared with a 35 percent solution) or in conjunction with an additional wart treatment, and thus may have a role in treating refractory warts or patients intolerant of other therapies. Warts generally are not a serious or life-threatening condition. There are no approved prescription therapies for warts outside of the genital area. Historically, TCA has been used in compounded drug products for at least 20 years.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of TCA weigh in favor of inclusion of this substance on the list. FDA recommended to the PCAC that this substance be included on the 503A Bulks List for topical use (Ref. 18). At its meeting on November 3, 2016, the PCAC voted to include TCA on the list for topical use (Ref. 8). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and

USP did not identify any additional quality concerns related to this substance (Ref. 15). This proposed rule would place TCA on the 503A Bulks List for topical use.

D. Substances Considered and Not Proposed for Inclusion on the 503A Bulks List

FDA is proposing that 26 of the bulk drug substances that it has evaluated not be included on the 503A Bulks List. Bulk drug substances that are considered for the 503A Bulks list, but not placed on the list, cannot be used to compound drug products that would qualify for the exemptions in section 503A.[3]

The 26 bulk drug substances that have been evaluated and that FDA is proposing not be placed on the list, and the reasons for that proposal, are as follows:

(1) *7-keto DHEA*. 7-keto DHEA was evaluated for use in the treatment of Raynaud's phenomena and weight loss. 7-keto DHEA is physically and chemically well characterized. Although we did not identify a safety signal from available information, there are minimal data available, and we could not adequately assess whether it is safe to use 7-keto DHEA in compounded drug products. Similarly, there are insufficient data to establish whether 7-keto DHEA would be effective in the treatment of Raynaud's phenomena or obesity. Historically, it appears that 7-keto DHEA has been used in compounded drug products for approximately 7 years.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of 7-keto DHEA weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 19). At its meeting

[3] If a prescribing practitioner nevertheless believes that a patient should be treated with a drug product compounded from such a bulk drug substance, it may be possible to obtain the drug under an investigational new drug (IND) application. For information about the requirements for proceeding under an IND application, visit FDA's website at https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm.

on November 20, 2017, the PCAC voted not to include 7-keto DHEA on the list (Ref. 11). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place 7-keto DHEA on the 503A Bulks List.

(2) *ALC.* ALC was evaluated for use in the treatment of Alzheimer's disease, chemotherapy-induced peripheral neuropathy, and hepatic encephalopathy. ALC is well characterized physically and chemically but given that hydrolysis may occur on its ester group in aqueous solutions, it is unlikely to be stable when formulated as an aqueous solution. But it is likely to be stable in solid dosage forms. Regarding safety, the available information, which is limited, did not indicate toxicity, and it appears to be well-tolerated when given orally up to 3 grams daily. However, the labeling of FDA-approved products that contain L-carnitine, a closely related drug substance, indicates that those products may affect blood clotting and pose a risk for seizures. There may be similar risks with the use of ALC.

There is insufficient evidence to indicate that ALC is effective for the treatment of the evaluated conditions. FDA-approved drug products have been demonstrated to be safe and effective under the conditions of use set forth in their labeling for the treatment of Alzheimer's disease, chemotherapy-induced peripheral neuropathy, and hepatic encephalopathy, which are serious conditions. The history of ALC use in compounded drug products is unknown.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of ALC weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 21), and at its meeting on March 8, 2016, the PCAC voted not to include ALC on the list (Ref. 6). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any

additional quality concerns related to this substance (Ref. 14). This proposed rule would not place ALC on the 503A Bulks List.

(3) *Alanyl-L-Glutamine.* Alanyl-L-glutamine was evaluated for use in nutritional support and reducing rates of infectious complications in critically ill and surgical patients. Alanyl-L-glutamine is well characterized physically and chemically, but there are toxicity concerns with potential impurities, specifically, solvents, endotoxins, bioburden, and heavy metal impurities linked to the source of the starting material and the reagents used in processing. Exposure to elemental impurities such as heavy metals has been associated with proven toxicities, such as irreversible neurological impairment and hepatotoxicity. We could not adequately assess whether the substance would be sufficiently free of such impurities to be suitable for compounding into parenteral solutions for intravenous (IV) administration, which would result in 100 percent bioavailability of impurities. Additionally, safety concerns were observed in a large, randomized controlled trial of critically ill patients who received glutamine supplementation, the results of which demonstrated the potential toxicity of alanyl-L-glutamine, including increased frequency of increased serum urea levels and an increase of in-hospital, 28-day, and 6-month mortality rates.

Regarding effectiveness, a meta-analysis published in the literature suggests that parenteral supplementation with alanyl-L-glutamine may benefit certain populations, including through potential decrease in rates of infection or infectious complications; however, the available data are limited, and some other analyses indicated unfavorable outcomes. Alanyl-L-glutamine has been used in compounded drug products for approximately 15 years.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of alanyl-L-glutamine weigh against inclusion of this substance on the list. FDA recommended to

the PCAC that this substance not be included on the 503A Bulks List (Ref. 17), and at its meeting on October 27, 2015, the PCAC voted not to include alanyl-L-glutamine on the list (Ref. 2). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would not place alanyl-L-glutamine on the 503A Bulks List.

(4) *Aloe Vera 200:1 Freeze Dried.* Aloe vera 200:1 freeze dried[4] was evaluated as treatment for burns, cuts, and wounds. We found no information to differentiate "Aloe vera 200:1 freeze dried" from other Aloe vera extracts. Aloe vera extract is not well characterized physically and chemically. Rather, it is a complex mixture that may contain various classes of chemical compounds, such as polysaccharides, organic acids, and anthraquinones.

Regarding safety, nonclinical data show that Aloe vera has abortifacient activity when taken orally and induced skeletal malformations in an oral embryofetal toxicity study in rats. Clinical data indicate that the topical use of Aloe vera gel can be tolerated for short durations without serious toxicity, although it is unclear whether those data are based on 200:1 freeze dried Aloe vera. The anthraquinone derivative in Aloe vera latex can pose safety concerns, including potential carcinogenicity, particularly when used repeatedly at high doses. We found no data on the safety of the long-term use of Aloe vera.

Regarding effectiveness, there is limited and conflicting information from controlled clinical trials regarding the effectiveness of Aloe vera topical products in the treatment of cuts, burns, and wounds. It is not clear whether these trials used 200: 1 freeze dried Aloe vera. Historically, Aloe vera has been used in herbal remedies in many parts of the world. However,

[4] A USP dietary supplement monograph exists for Aloe (USP 38-NF33, Aloe). However, no USP or NF monograph exist for Aloe vera *200:1 freeze-dried* or Aloe vera *gel 200:1 freeze-dried*. See Ref. 21 for additional information.

we do not have sufficient information to evaluate the historical use of compounded drug products that include 200:1 freeze dried Aloe vera.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of 200:1 freeze dried Aloe vera weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 21), and at its meeting on March 8, 2016, the PCAC voted not to include 200:1 freeze dried Aloe vera on the list (Ref. 6). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule proposes not to include Aloe vera 200:1 freeze dried on the 503A Bulks List.

(5) *Artemisinin.* Artemisinin was evaluated for use in the treatment of malaria, helminthic infections, protozoal (particularly toxoplasmosis) infections, stomach ulcers, and cancer. Artemisinin is well characterized physically and chemically. However, it has a short half-life and poor oral bioavailability due to excess first pass metabolism and is poorly soluble in water and oil. Regarding safety, artemisinin has clinically significant effects on different cytochrome P450 enzymes. It is possible that artemisinin acts as a perpetrator to change the exposure of other concomitantly administered drug products that are substrates of these cytochrome P450 isoforms in patients. These effects may lead to significant drug-drug interactions when artemisinin is used with other concomitant medications that are substrates of these cytochrome P450 isoforms on a daily basis. For use in the treatment of malaria, when dosing is limited to 1 or 2 days, we did not identify significant safety concerns associated with the use of artemisinin in compounded drug products. However, with repeat dosing (as would be used in the treatment of the other conditions evaluated), there is evidence of serious adverse

events, the most concerning being drug-induced hepatitis. There are numerous reports in the literature of elevations of transaminases and bilirubin in patients taking repetitive doses of artemisinin leading to hospitalization.

Regarding effectiveness, there is evidence indicating that artemisinin is likely an effective therapy for the treatment of malaria. However, there are numerous FDA-approved drug products that have been demonstrated to be safe and effective under the conditions of use set forth in their labeling for the treatment of malaria. Additionally, because of concerns about resistance, artemisinin is not appropriate for use for prophylaxis of malaria when traveling to countries where malaria is endemic. For the other uses evaluated, there is insufficient information to evaluate the effectiveness of artemisinin. We found no information regarding the historical use of artemisinin in compounded drug products. It does not appear to be currently used in compounding in the United States.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of artemisinin weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 22). At its meeting on May 9, 2017, the PCAC voted not to include artemisinin on the list (Ref. 9). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place artemisinin on the 503A Bulks List.

(6) *Astragalus Extract 10:1*. Astragalus Extract 10:1 (astragalus) was evaluated for use in the treatment of diabetes mellitus, allergic rhinitis, wound healing, asthma, and herpes simplex keratitis. It is not physically or chemically well characterized. Rather, it contains hundreds of known and unknown chemical entities, particularly polysaccharides, most of which would be

difficult to characterize and quantify. Nonclinical data regarding the safety of astragalus are limited, and the significance of the available data is unknown given the variability between astragalus compounds. Based on limited clinical data, it appears that astragalus may be well-tolerated; however, the limited data are insufficient to allow evaluation of potential adverse outcomes associated with the use of astragalus.

Regarding effectiveness, there have been numerous investigations of astragalus extracts in the treatment of diabetes. Some of these studies indicate that some formulations of astragalus extracts reduced plasma glucose and insulin sensitivity. However, as noted above, the significance of the data from these studies is unknown given the variability between astragalus compounds. Studies in allergic rhinitis, wound healing, and asthma were inadequate to assess effectiveness, and no studies in herpes simplex keratitis were found that assessed clinically meaningful endpoints. Historically, astragalus has been used as an herbal treatment for a variety of conditions, but there is insufficient information to determine whether astragalus has been used in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of astragalus weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 19). At its meeting on November 20, 2017, the PCAC voted not to include astragalus on the list (Ref. 11). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place astragalus on the 503A Bulks List.

(7) *BWSE.* BWSE was evaluated as treatment for rheumatoid arthritis (RA) and osteoarthritis (OA). BWSE is not physically or chemically well characterized. Rather, because

it is a naturally derived, botanical substance, BWSE's physical and chemical characteristics can vary according to the source and extraction method and cannot adequately be controlled to ensure a consistent composition absent proper controls of the botanical raw materials and manufacturing processes. Regarding safety, there are reports that resin from *Boswellia* may be an emmenagogue and induce abortion. BWSE has also been associated with gastrointestinal adverse events, including diarrhea, abdominal pain, and nausea. There are reports of an increase in anticoagulant effect when BWSE interacts with oral anticoagulants.

There is some evidence that BWSE might improve symptoms of OA in some patients, but BWSE has not been shown to be effective in inhibiting radiographic progression of RA. There are numerous FDA-approved drug products that have been demonstrated to be safe and effective under the conditions of use set forth in their labeling for both RA and OA. Regarding its historical use, *Boswellia* has been used for millennia, particularly in Ayurvedic and traditional Chinese medicine, for a variety of uses, including wound care, pain, and arthritis, although we don't know how long it has been used in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of BWSE weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 21), and at its meeting on March 8, 2016, the PCAC voted not to include BWSE on the list (Ref. 6). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would not place BWSE on the 503A Bulks List.

(8) *Cesium Chloride.* Cesium chloride, an inorganic chloride salt, was evaluated for use in the treatment of cancer. It is well characterized physically and chemically. Both nonclinical

and clinical studies give rise to significant safety concerns related to the use of cesium chloride in compounded drug products. Those concerns include links between cesium chloride use and hypokalemia, seizures, QT prolongation, and cardiac arrhythmias. There is no evidence that cesium chloride would be effective in the prevention or treatment of cancer. In contrast, there are numerous FDA-approved drug products that have been demonstrated to be safe and effective under the conditions of use set forth in their labeling for the treatment of cancer. We found no evidence regarding the historical use of cesium chloride in compounded drug products, although it appears to have been used for the treatment of cancer. Literature discussing studies of the substance date back to the 1980s

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of cesium chloride weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 20). At its meeting on June 23, 2016, the PCAC voted not to include cesium chloride on the list (Ref. 7). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). The proposed rule would not place cesium chloride on the 503A Bulks List.

(9) *Chondroitin Sulfate.* Chondroitin sulfate was evaluated for use in the treatment of OA. Chondroitin sulfate is an unspecified mixture, composed mainly of chondroitin 4-sulfate and chondroitin 6-sulfate in varying percentages. The relative amounts of chondroitin sulfate A and chondroitin sulfate C in the mixture are not well defined and can vary.

The data available are inadequate to evaluate the safety of the use of chondroitin sulfate in compounded drug products, although there have been no significant safety signals associated with the use of topical chondroitin sulfate. While most adverse events reported in the literature

with the use of chondroitin sulfate orally have not been serious in nature, there have been adverse event reports of concern, including reports of increased effectiveness of anticoagulants (leading to a risk of bleeding) when given in combination with chondroitin sulfate and reports of abnormal liver function. Regarding effectiveness, a large, well-controlled trial, the NIH-sponsored "Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)" (Ref. 21), showed that, whether alone or in combination with glucosamine, the oral use of chondroitin sulfate appears to be ineffective for the treatment of pain associated with OA. Other trials reported positive results, including with the topical use of chondroitin sulfate, but those trials were generally smaller and of shorter duration, and suggest that, at best, any effect may be transient. As noted above, there are numerous FDA-approved drug products that have been demonstrated to be safe and effective under the conditions of use set forth in their labeling for the treatment of OA.

Regarding historical use, the use of chondroitin sulfate has been reported in medical literature dating back to the 1980s, but that discussion was not specific to its use in compounded drug products. We found no information regarding how long chondroitin sulfate has been used in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of chondroitin sulfate weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 21), and at its meeting on March 8, 2016, the PCAC voted not to include chondroitin sulfate on the list (Ref. 6). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would not place chondroitin sulfate on the 503A Bulks List.

(10) *Chrysin.* Chrysin was evaluated for use as an aromatase inhibitor.[5] Chrysin is well characterized physically and chemically. Regarding safety, limited nonclinical studies show chrysin has the potential for mutagenicity and neurotoxicity. Clinically, systemic exposure to chrysin is low due to poor oral bioavailability and rapid metabolism and elimination. We found insufficient information about the topical or oral use of chrysin to evaluate its safety.

Regarding effectiveness, in vitro data shows that chrysin inhibits aromatase at high concentrations, but we found no clinical data indicating that chrysin would be effective in the treatment of cancer, which is the use for which FDA-approved aromatase inhibitors are indicated, specifically, for the treatment of breast cancer in women. There are also FDA-approved products indicated for testosterone replacement, another common use of compounded chrysin products. We found insufficient information to evaluate the historical use of chrysin in compounded drug products. It is currently being compounded for use in drug products promoted for bodybuilding and "men's health."

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of chrysin weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 20). At its meeting on June 23, 2016, the PCAC voted not to include chrysin on the list (Ref. 7). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). The proposed rule would not place chrysin on the 503A Bulks List.

(11) *Curcumin.* Curcumin, a dye obtained from turmeric, was evaluated as treatment for familial adenomatous polyposis, gastric metaplasia, and oral leukoplakia. Although curcumin

[5] Chrysin was proposed for use "as an aromatase inhibitor which prevents the conversion of testosterone to estrogen" for the treatment of "high estrogen and low testosterone." (Ref. 20).

and its major components are well characterized physically and chemically, the term "curcumin" is used to refer to a wide range of substances comprised of different amounts of different curcuminoids, which might have different physical and chemical characteristics.

Curcumin appears to be mostly well tolerated for short durations, and the most common adverse events were mild. However, the evaluated conditions can be chronic, requiring treatment for years. There are limited data about the safety of curcumin in compounded drug products given its poor bioavailability, lack of exposure-response for safety, lack of uniformity of the curcumin used, and lack of information from well-designed clinical trials. Although preliminary signs of activity related to curcumin (generally related to biomarkers or effects on disease processes) have been reported in small and uncontrolled studies, there is insufficient evidence that it would be effective for the proposed conditions. Further, there is a risk that patients might use curcumin to treat the conditions reviewed in lieu of FDA-approved products that have been demonstrated to be safe and effective under the conditions of use set forth in their labeling, or that they might delay the use of such products. Familial adenomatous polyposis in particular is a serious condition; virtually all patients will develop colon cancer if it is left untreated. Turmeric has historically been used in traditional Indian medicine, but we found no information on the length of time curcumin has been used in compounded drug products. It has been used in an IV dosage form to treat eczema and thrombocytopenia (Ref. 23).

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of curcumin weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 17), and at its meeting on October 27, 2015, the PCAC voted not to include curcumin on the list (Ref. 2). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did

not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would not place curcumin on the 503A Bulks List.

(12) *D-Ribose.* D-Ribose was evaluated as treatment for heart disease and chronic fatigue syndrome (CFS).[6] D-ribose is well characterized physically and chemically. It is commercially available for use as a food additive and has been designated as Generally Recognized as Safe (GRAS). However, a substance that is safe when used as a food might not be safe as an active ingredient in a drug product, for example, when used for a route of administration other than oral. In addition, a GRAS determination does not indicate that a substance would have any effectiveness for a proposed use when used in a compounded drug product. 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.[7] The use of D-ribose in compounded drug products poses a particular safety concern to patients with diabetes mellitus, since they often have concomitant coronary artery disease or ischemic cardiac myopathy/ischemic heart failure. 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.

Regarding effectiveness, there is a lack of proven benefit associated with D-ribose for the treatment of either heart disease or CFS. The reported studies of the utility of D-ribose for the treatment of cardiovascular disease provide no convincing evidence of a meaningful clinical benefit. There are many FDA-approved drug products that have been demonstrated to be safe

[6] Currently, FDA does not recognize a particular definition or name as appropriate for use in clinical trials of drug products for CFS, which is also referred to as myalgic encephalomyelitis or systemic exertion intolerance disease. CFS is used in this NPRM because it was the term used in the nomination for D-ribose.

[7] Food products that contain D-ribose as a food additive at ≥1 percent per volume or weight also contain other sources of carbohydrates (and thus glucose), and thus might not pose the same risk of false hypoglycemia.

and effective under the conditions of use set forth in their labeling for the treatment of heart disease, which is a serious condition. While we recognize that there are no FDA-approved therapies indicated for CFS, the treatment of CFS with D-ribose has been evaluated in only a single small uncontrolled, unblinded study (Ref. 24). We do not believe that this study demonstrates that there is a benefit to CFS patients that would outweigh the risks of using D-ribose outlined above.

Regarding the historical use of D-ribose, we do not know how long it has been used as a compounded drug product. It first appeared in the medical literature in 1946.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of D-ribose weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 21), and at its meeting on March 8, 2016, the PCAC voted not to include D-ribose on the list (Ref. 6). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would not place D-ribose on the 503A Bulks List.

(13) *Deoxy-D-Glucose.* Deoxy-D-glucose, also known as 2-deoxy-D-glucose, was evaluated for use in the treatment of cancer and herpes simplex virus (HSV). Deoxy-D-glucose is physically and chemically well characterized. Regarding safety, in rats, dietary supplementation with deoxy-D-glucose showed cardiac toxicity, developmental and reproductive toxicity, carcinogenicity, and decreased median survival. In humans, the safety profile of deoxy-D-glucose was only manageable at lower doses used with combination treatments; when used as a single agent, based on limited clinical evidence, the high dose of deoxy-D-glucose required was unacceptably toxic.

Regarding effectiveness, we found no evidence indicating that deoxy-D-glucose would be effective as a treatment for cancer or HSV. In the reported clinical trials that studied the use of deoxy-D-glucose for the treatment of cancer, toxicity was reached before there was evidence of effectiveness. We located only one clinical trial that studied deoxy-D-glucose in the treatment of HSV, from which no conclusions regarding efficacy could be drawn due to the quality of the study. Each of these serious conditions has a number of FDA-approved drug products that have been demonstrated to be safe and effective under the conditions of use set forth in their labeling. We found insufficient evidence to evaluate the historical use of deoxy-D-glucose in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of deoxy-D-glucose weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 17), and at its meeting on October 27, 2015, the PCAC voted not to include deoxy-D-glucose on the list (Ref. 2). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would not place deoxy-D- glucose on the 503A Bulks List.

(14) *Diindolylmethane.* Diindolylmethane was evaluated for use in the treatment of cancer. It is well characterized physically and chemically. Oral administration of diindolylmethane caused white pulp atrophy and decreased immune cell counts in the spleen of neonatal mice and increased serum cytokines in adult mice. Diindolylmethane induced hepatic CYP1A1, CYP1A2, and CYP3A2 in rats, suggesting that drug-drug interactions might occur with its use in patients. While the nonclinical data are limited, the available data suggest that there may be a safety concern with the use of diindolylmethane in compounded drug products.

Although we identified no serious adverse events reports related to the use of diindolylmethane in humans, the available clinical data are too limited to draw conclusions regarding the safety of diindolylmethane.

Clinical studies published to date show changes in biomarkers, but no clinical publication to date describes an effect of diindolylmethane on any endpoint generally accepted in clinical oncology as being of clinical benefit. There is no evidence that diindolylmethane would be effective in the treatment of cancer. In contrast, there are numerous FDA-approved drug products that have been demonstrated to be safe and effective under the conditions of use set forth in their labeling for the treatment of cancer. We found no evidence regarding the historical use of diindolylmethane in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of diindolylmethane weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 18). At its meeting on November 3, 2016, the PCAC voted not to include diindolylmethane on the list (Ref. 8). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place diindolylmethane on the 503A Bulks List.

(15) *Domperidone.* Domperidone was evaluated as treatment for gastroparesis, nausea and vomiting, and to enhance lactation. Domperidone is well characterized physically and chemically. Serious concerns about the safety of domperidone are raised by both clinical and nonclinical studies. At therapeutic doses approved outside the United States, domperidone carries a serious risk of life-threatening cardiac arrhythmias and sudden cardiac death in all populations, including healthy lactating women, and potentially, their infants. Domperidone has

known risks of QT interval prolongation, and the dose and exposure at which domperidone can cause serious cardiac arrhythmias are not well characterized in patients.

The effectiveness of domperidone as a galactagogue is unknown given the limited evidence available, and evidence suggesting that domperidone may be beneficial for nausea and vomiting and gastroparesis is limited due to the small size of the clinical trials that have been conducted for these uses or design flaws with those trials. Domperidone has been compounded in the United States for at least a decade and has been used in other jurisdictions since at least the 1970s.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of domperidone weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 17), and at its meeting on October 28, 2015, the PCAC voted not to include domperidone on the list (Ref. 4). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 16). This proposed rule would not place domperidone on the 503A Bulks List.

(16) *EGCG.* EGCG, or (-)-epigallocatechin-3-gallate, was evaluated for use in the treatment of obesity, type 1 and type 2 diabetes, cardiac hypertrophy, corneal neovascularization, non-alcoholic fatty liver disease, Parkinson's disease, and wound healing. EGCG is the most abundant type of catechin in green tea. It is well characterized physically and chemically, but degrades significantly within 1 month. It was nominated for use in capsules, topical gels, and ophthalmic solutions, but it is not expected to be stable in formulations other than solid oral dosage forms. Regarding safety, in several nonclinical models, liver and gastrointestinal toxicities were noted. In humans, there are numerous case reports of hepatotoxicity, including

fulminant hepatic failure, the need for liver transplantation, or death associated with products that contain EGCG, which is typically administered as one component of a multicomponent dietary supplement/botanical product. Establishing whether EGCG has a causal link with these existing cases is not feasible, and additional data are needed to evaluate the safety of the use of EGCG in compounded drug products. A review by Health Canada published in December 2017 concluded that there may be a link between the use of green tea extract and a risk of rare and unpredictable liver injury (Ref. 25).

Regarding effectiveness, there are hypotheses regarding the potential therapeutic utility of EGCG, as well as nonclinical and clinical pharmacologic data identifying potential mechanisms of action in various disease states. However, clinical data for EGCG have not been identified to support the effectiveness of EGCG for any of the uses evaluated. We found insufficient information to determine how long EGCG has been used in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of EGCG weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 19). At its meeting on November 20, 2017, the PCAC voted not to include EGCG on the list (Ref. 11). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place EGCG on the 503A Bulks List.

(17) *Germanium Sesquioxide.* Germanium sesquioxide was evaluated as treatment for cancer. It is physically and chemically well characterized. It can, however, include impurities with significant toxicities, specifically, potentially dangerous levels of inorganic germanium salts

(e.g., GeO2, germanium lactate citrate, Ge-lac-cit), which can accumulate in the body. The limited information available about the safety of germanium sesquioxide gives rise to significant concerns about its use in compounded drug products, particularly given the risk of contamination with highly toxic inorganic forms of germanium salts. The nephrotoxicity of inorganic forms of germanium, such as germanium dioxide or germanium citrate lactate, is well established, and prolonged use of germanium products has been associated with cases of renal failure and death. There is currently a restriction on the importation of all germanium compounds, except those used for semiconductors (Ref. 26).

There are very little clinical data regarding the effectiveness of germanium sesquioxide in the treatment of cancer. We located only a single case report, from which no conclusions regarding the effectiveness of germanium sesquioxide could be drawn. In contrast, there are numerous FDA-approved drug products that have been demonstrated to be safe and effective under the conditions of use set forth in their labeling for the treatment of various types of cancer. We found little information regarding the history of the use of germanium sesquioxide in compounded drug products and could not determine whether or how long it has been used in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of germanium sesquioxide weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 17), and at its meeting on October 27, 2015, the PCAC voted not to include germanium sesquioxide on the list (Ref. 2). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would not place germanium sesquioxide on the 503A Bulks List.

(18) *Glycyrrhizin.* Glycyrrhizin, also known as glycyrrhizic acid or glycyrihizinic acid, is a triterpene saponin extracted from licorice. It was evaluated for use in the treatment of hepatitis C by intravenous administration. Although glycyrrhizin's molecular structure can be characterized, the term "glycyrrhizin" is used to refer to a variety of licorice extracts, which are often complex mixtures that are not well characterized physically or chemically. Glycyrrhizin also poses safety concerns. The association between glycyrrhizin use and serious pseudo-hyperaldosterone effects is well established and has been noted in over 100 case reports. Regarding effectiveness, clinical studies of IV administration of glycyrrhizin in patients with chronic hepatitis C have shown no demonstrable antiviral effect.

Regarding its historical use, *Glycyrrhiza* (licorice) has been used for curative and flavoring purposes for 4,000 years, and glycyrrhizin has been used to treat chronic hepatitis in Japan for over 30 years. However, we found no evidence of the use of glycyrrhizin in IV compounded drugs products in the United States.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of glycyrrhizin weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 17), and at its meeting on October 28, 2015, the PCAC voted not to include glycyrrhizin on the list (Ref. 3). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would not place glycyrrhizin on the 503A Bulks List.

(19) *Kojic Acid.* Kojic acid was evaluated for use in the treatment of melasma and as an iron chelator in wound healing and photodamage prevention. Kojic acid is well characterized physically and chemically, but it is a very reactive and unstable compound. Nonclinical data

suggest that kojic acid is potentially genotoxic, and data about its carcinogenicity are equivocal. Data suggest that the use of kojic acid may be associated with local irritancy, but reported adverse reactions appear to have been transient and manageable. There have been no reports of systemic adverse reactions. We identified no major safety concerns related to the use of kojic acid to treat melasma, but we found no data evaluating the safety of the use of kojic acid in open wounds or the prevention of photodamage.

Regarding effectiveness, there is insufficient evidence to show that kojic acid would be an effective treatment for any of the evaluated uses. Most trials evaluating the use of kojic acid for melasma or hyperpigmentation disorders used kojic acid in combination with other topical therapies, and often flaws in trial design prevented the data from being sufficiently reliable. Historically, kojic acid has been used in compounded drug products for decades, often in combination with other substances.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of kojic acid weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 18). At its meeting on November 3, 2016, the PCAC voted not to include kojic acid on the list (Ref. 8). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place kojic acid on the 503A Bulks List.

(20) *Nettle.* Nettle (*Urtica dioica L.*), a botanical substance, was evaluated for use in glycemic control. Nettle is not physically or chemically well characterized. The major and/or active components of nettle are unknown. There is a dearth of reliable information regarding the safety of the use of nettle in compounded drug products. The most frequent adverse effects

appear to be mild gastrointestinal irritation and allergic reactions; however, the available information is based on formulations with poorly characterized compositions. It is unclear how the formulations employed in the existing literature might compare qualitatively or quantitatively to a bulk drug substance used in compounded drug products.

The effectiveness of nettle has not been adequately assessed with well-characterized formulations. A small number of clinical effectiveness investigations of nettle and some nonclinical data in animal models for diabetes suggest that nettle may have some effect in reducing fasting blood sugar and other parameters related to diabetes. However, they do not provide sufficient evidence that nettle would be effective in providing glycemic control. Historically, nettle has been used for centuries as an herbal treatment for a variety of conditions. It has been used in compounded drug products for at least 7 years.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of nettle weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 22). At its meeting on May 8, 2017, the PCAC voted not to include nettle on the list (Ref. 9). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place nettle on the 503A Bulks List.

(21) *NAD.* NAD was evaluated for use in the treatment of fatigue in patients with multiple sclerosis (MS). It is well characterized physically and chemically, but it degrades substantially when exposed to light, moisture, alkaline pH, or standard room temperatures and would not be stable under ordinary storage conditions absent multiple compensatory measures. Nonclinical data found in the literature are inadequate to characterize the potential toxicity

profile for NAD, particularly for use in a chronic disease such as MS. Similarly, we did not find sufficient clinical data about NAD to evaluate whether it is safe for use in compounded drug products.

We identified no published studies that support the use of NAD for the treatment of fatigue in patients with multiple sclerosis. Therefore, we have insufficient information on which to evaluate the effectiveness for NAD for its proposed use. There are FDA-approved drug products that have been demonstrated to be safe and effective under the conditions of use set forth in their labeling for the treatment of MS. We do not have enough information to determine how long NAD has been used in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of NAD weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 22). At its meeting on May 8, 2017, the PCAC voted not to include NAD on the list (Ref. 9). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place NAD on the 503A Bulks List.

(22) *NADH.* NADH was evaluated for use in the treatment of CFS.[8] It is well characterized physically and chemically, but degrades substantially when exposed to light, moisture, alkaline pH, or standard room temperatures and would not be stable under ordinary storage conditions absent multiple compensatory measures. We found no reports of serious adverse events; however, the clinical safety data available for review were minimal. Nonclinical data reported in the literature suggest that NADH is not stable in an acid medium and is likely to

[8] See footnote 5, above, regarding use of the term "CFS."

be degraded before absorption after oral dosing. Nonclinical safety data are insufficient to characterize the potential toxicity profile for NADH, particularly for use in a chronic disease such as CFS.

Regarding effectiveness, there is insufficient information to indicate that NADH would be effective for the evaluated use. The available clinical effectiveness data regarding administration of NADH to patients with CFS failed to provide an assessment of fatigue specifically, and it also failed to show statistically significant improvement on assessment scales of multiple other symptoms. We do not have enough information to determine how long NAD has been used in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of NADH weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 22). At its meeting on May 8, 2017, the PCAC voted not to include NADH on the list (Ref. 9). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place NADH on the 503A Bulks List.

(23) *Rubidium Chloride.* Rubidium chloride, also known as rubidium monochloride or rubinorm, was evaluated for use in the treatment of cancer. Rubidium chloride is physically and chemically well characterized. We found insufficient information to determine whether the use of rubidium chloride in compounded drug products would be safe or effective. Non-clinical studies showed that the administration of rubidium in rats affected their growth, survival times, and behavior. Rubidium chloride in the treatment of cancer appears to have only been studied in clinical trials by one individual in the 1960s and 1970s, but the role of rubidium in the results of

those studies is uncertain since data were reported in the aggregate. Since that time, there have been no documented studies of the safety or effectiveness of rubidium chloride in the treatment of cancer. In contrast, there are numerous FDA-approved drug products that have been demonstrated to be safe and effective under the conditions of use set forth in their labeling in the treatment of various types of cancer. Although rubidium chloride was first discussed in medical literature in the 1960s, we did not find information regarding the history of use of rubidium chloride in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of rubidium chloride weigh against inclusion of this substance on the list. FDA recommended to the PCAC that this substance not be included on the 503A Bulks List (Ref. 17), and at its meeting on October 27, 2015, the PCAC voted not to include rubidium chloride on the list (Ref. 2). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). This proposed rule would not place rubidium chloride on the 503A Bulks List.

(24) *Sodium Dichloroacetate.* Sodium dichloroacetate, also known as dichloroacetate sodium, was evaluated for use in the treatment of cancer. It is well characterized physically and chemically, but unlikely to be stable when formulated as a solution for injection. There are significant safety concerns related to the use of sodium dichloroacetate in compounded drug products, primarily related to its toxicity profile, as observed in both nonclinical and clinical studies. One study of sodium dichloroacetate identified in the literature was closed due to patient deaths and safety concerns (Ref. 27). There is no evidence that sodium dichloroacetate would be effective in the prevention or treatment of cancer. In contrast, there are numerous FDA-approved drug products that have been demonstrated to be safe and effective under the

conditions of use set forth in their labeling for the treatment of cancer. We found no evidence regarding the historical use of sodium dichloroacetate in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of sodium dichloroacetate weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 20). At its meeting on June 23, 2016, the PCAC voted not to include sodium dichloroacetate on the list (Ref. 7). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 14). The proposed rule would not place sodium dichloroacetate on the 503A Bulks List.

(25) *Vanadyl Sulfate.* Vanadyl sulfate was evaluated for use in the treatment of diabetes, hyperlipidemia, and heart disease, and for the prevention of cancer. Vanadyl sulfate, an inorganic vanadium salt, is well characterized physically and chemically. Regarding the safety of vanadyl sulfate in compounded drug products, nonclinical safety data, including toxicokinetic data, chronic toxicity data, reproductive data, and carcinogenicity data, found in the literature suggest the potential for a high toxicity profile. Administration by injection, the proposed dosage form, appears to be associated with greater toxicity than the oral route of administration. Human safety data are limited and do not reveal the same types or degrees of toxicity that are shown in nonclinical testing. The differences between nonclinical and clinical safety findings may be explained by shortcomings in the available clinical data and limited duration of treatment.

Regarding effectiveness, limited clinical effectiveness data provide preliminary evidence that vanadyl sulfate or other vanadium containing compounds could have an effect in treating diabetes or hyperlipidemia. We identified no clinical effectiveness data for the treatment of

cancer or heart disease with vanadyl sulfate. There is insufficient evidence to indicate that vanadyl sulfate has any effectiveness in treating any of the evaluated conditions. Cancer and heart disease are serious conditions for which there are FDA approved drugs that have been found to be safe and effective under the conditions of use set forth in their labeling. We do not have enough information to determine how long vanadyl sulfate has been used in compounded drug products.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of vanadyl sulfate weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 22). At its meeting on May 8, 2017, the PCAC voted not to include vanadyl sulfate on the list (Ref. 9). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place vanadyl sulfate on the 503A Bulks List.

(26) *VIP*. VIP, a 28-amino acid peptide, was evaluated for use in the treatment of a condition described as "chronic inflammatory response syndrome" (CIRS).[9] VIP is well characterized physically and chemically, but absent sufficient controls on its production, synthesis is likely to result in peptides of different lengths or different amino acid sequencing. Although most adverse reactions observed related to the use of VIP appear to be relatively mild, it has been associated with severe immunologic reactions. Regarding effectiveness, we located only one published study of VIP in a condition that appears to be related to CIRS (Ref. 28), which failed to clearly establish benefits of the administration of VIP. We did not find sufficient

[9] CIRS is a term we located in three publications. It appears to be the subject of research. It is not listed in the International Statistical Classification of Diseases and Related Health Problems (ICD-10), a medical classification list by the World Health Organization (Ref. 18). Further, CIRS is not listed in the Medical Dictionary for Regulatory Activities (MedDRA) (id.).

information to determine the historical use of VIP in compounded drug products. However, it appears that VIP is currently used in compounded nasal sprays.

On balance, the physiochemical characteristics, safety, effectiveness, and historical use of VIP weigh against inclusion of this substance on the 503A Bulks List. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 18). At its meeting on November 3, 2016, the PCAC voted not to include VIP on the list (Ref. 8). We have also consulted with USP regarding placement of this substance on the 503A Bulks List, and USP did not identify any additional quality concerns related to this substance (Ref. 15). The proposed rule would not place VIP on the 503A Bulks List.

VI. Proposed Effective Date

The Agency proposes that any final rule based on this proposed rule will become effective 30 days after the date of publication of the final rule in the *Federal Register*.

VII. Preliminary Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. We

believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we do not have enough information about the effect of the proposed rule on small entities, we find that the proposed rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $150 million, using the most current (2017) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

We evaluated 31 bulk drug substances for this proposed rule. We propose to place 5 bulk drug substances on the 503A Bulks List, and we propose not to place 26 substances on the 503A Bulks List. We expect that the rule will affect compounding pharmacies and other producers that market the affected substances or drug products made from the affected substances, consumers of drug products containing the affected substances, and payers that cover these drug products or alternative treatments. Because we lack sufficient information to quantify most of the costs and benefits of this proposed rule, we also include a qualitative description of potential benefits and potential costs.

In table 1, we summarize the impacts of the proposed rule. The estimated costs are derived from administrative costs related to reading the rule. The primary estimate of the present value of the costs over 10 years is $1.03 million. The primary estimate of the annualized costs is $0.15 million at a 7 percent discount rate and $0.12 million at a 3 percent discount rate.

Table 1.--Summary of Benefits, Costs, and Distributional Effects of the Proposed Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($m/year)							
	Annualized Quantified							
	Qualitative	Potential gains or losses in consumer surplus, depending on consumer preferences for compounded drugs. Potential public health benefits from increased use of other drug products that may be more effective.						
Costs	Annualized Monetized ($m/year)	$0.15	$0.10	$0.20	2017	7%	10 years	
		$0.12	$0.08	$0.16	2017	3%	10 years	
	Annualized Quantified							
	Qualitative	Costs to submit investigational new drug applications (INDs) for some compounded drug products.						
Transfers	Federal Annualized Monetized ($m/year)							
		From:			To:			
	Other Annualized Monetized ($m/year)							
		From:			To:			
Effects	State, Local, or Tribal Government: None Small Business: None Wages: None Growth: None							

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 29) and at https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. *FDA, Transcript of the October 27, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Morning Session), 2015. Available at https://wayback.archive-it.org/7993/20170404155219/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM484905.pdf.

2. *FDA, Transcript of the October 27, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2015. Available at https://wayback.archive-it.org/7993/20170404155220/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM484906.pdf.

3. *FDA, Transcript of the October 28, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Morning Session), 2015. Available at

https://wayback.archive-it.org/7993/20170404155221/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM484907.pdf.

4. *FDA, Transcript of the October 28, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2015. Available at https://wayback.archive-it.org/7993/20170404155222/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM484908.pdf.

5. *FDA, Transcript of the March 8, 2016, Meeting of the Pharmacy Compounding Advisory Committee (Morning Session), 2016. Available at https://wayback.archive-it.org/7993/20170403224125/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM507771.pdf.

6. *FDA, Transcript of the March 8, 2016, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2016. Available at https://wayback.archive-it.org/7993/20170404155209/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM507772.pdf.

7. *FDA, Transcript of the June 23, 2016, Meeting of the Pharmacy Compounding Advisory Committee (Morning Session), 2016. Available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM563843.pdf.

8. *FDA, Transcript of the November 3, 2016, Meeting of the Pharmacy Compounding Advisory Committee (Morning Session), 2016. Available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM563842.pdf.

9. *FDA, Transcript of the May 8-9, 2017, Meeting of the Pharmacy Compounding Advisory Committee, 2017. Available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM565933.pdf.

10. *FDA, Transcript of the November 20, 2017, Meeting of the Pharmacy Compounding Advisory Committee (Morning Session), 2017. Available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM604328.pdf.

11. *FDA, Transcript of the November 20, 2017, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2017. Available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM604329.pdf.

12. *Memorandum to File on FDA Consultations with United States Pharmacopeia, September 26, 2016.

13. *Letter from the United States Pharmacopeia to FDA, October 7, 2016.

14. *Letter I from the United States Pharmacopeia to FDA, August 17, 2018.

15. *Letter II from the United States Pharmacopeia to FDA, August 17, 2018.

16. *Letter III from the United States Pharmacopeia to FDA, August 17, 2018.

17. *FDA Briefing Document for the October 27-28, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015. Available at https://wayback.archive-it.org/7993/20170405230355/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM466380.pdf.

18. *FDA Briefing Document for the November 3, 2016, Meeting of the Pharmacy Compounding Advisory Committee, 2016. Available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM524613.pdf.

19. *FDA Briefing Document for the November 20, 2017, Meeting of the Pharmacy Compounding Advisory Committee, 2017. Available at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm582868.htm.

20. *FDA Briefing Document for the June 23, 2016, Meeting of the Pharmacy Compounding Advisory Committee, 2016. Available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM505041.pdf.

21. *FDA Briefing Document for the March 8-9, 2016, Meeting of the Pharmacy Compounding Advisory Committee, 2016. Available at

https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm486144.htm.

22. *FDA Briefing Document for the May 8-9, 2017, Meeting of the Pharmacy Compounding Advisory Committee, 2017. Available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM553368.pdf.

23. *FDA, August 4, 2017, Statement, "FDA investigates two serious adverse events associated with ImprimisRx's compounded curcumin emulsion product for injection." Available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm570192.htm.

24. Teitelbaum, J. E., et al. "The Use of D-Ribose in Chronic Fatigue Syndrome and Fibromyalgia: A Pilot Study," *Journal of Alternative and Complementary Medicine*, 12:857-862, 2006.

25. * Government of Canada, "Summary Safety Review-Green Tea Extract-Containing Natural Health Products-Assessing the Potential Risk of Liver Injury (Hepatotoxicity)," December 12, 2017. Available at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/green-tea-extract-containing-natural-health-products-assessing-potential-risk-liver-injury.html.

26. *FDA Import Alert 54-07. Available at https://www.accessdata.fda.gov/cms_ia/importalert_139.html.

27. Garon, E. B., et al. "Dichloroacetate Should be Considered with Platinum-based Chemotherapy in Hypoxic Tumors Rather Than as a Single Agent in Advanced

Non-small Cell Lung Cancer," *Journal of Cancer Research and Clinical Oncology*, 140:443, 2014.

28. Shoemaker, R. C., et al. "Vasoactive Intestinal Polypeptide (VIP) Corrects Chronic Inflammatory Response Syndrome (CIRS) Acquired Following Exposure to Water-Damaged Buildings," *Health*, 5:396-401, 2013. Available at https://www.scirp.org/journal/health/. (Open Access)

29. *Amendments to the List of Bulk Drug Substances that Can be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act, Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, Unfunded Mandates Reform Act Analysis, 2018. Available at https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.

List of Subjects in 21 CFR Part 216

Drugs, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 216 be amended as follows:

PART 216--HUMAN DRUG COMPOUNDING

1. The authority citation for part 216 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 353a, 353b, 355, and 371.

2. In § 216.23, revise paragraphs (a) and (b) to read as follows:

§ 216.23 Bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act.

(a) The following bulk drug substances, which are neither the subject of a current applicable United States Pharmacopeia or National Formulary monograph nor components of FDA-approved drugs, can be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.

(1) Brilliant Blue G, also known as Coomassie Brilliant Blue G-250.

(2) Cantharidin (for topical use only).

(3) Diphenylcyclopropenone (for topical use only).

(4) Glutaraldehyde (for topical use only, in concentrations of 10 percent or lower).

(5) Glycolic acid (for topical use only, in concentrations of 70 percent or lower).

(6) L-citrulline (for oral administration only).

(7) N-acetyl-D-glucosamine (for topical use only).

(8) Pyruvic acid (for topical use only).

(9) Squaric acid dibutyl ester (for topical use only).

(10) Thymol iodide (for topical use only).

(11) Trichloroacetic acid (for topical use only).

(b) The following bulk drug substances have been nominated and evaluated for inclusion on the list of substance that can be used in compounding set forth in paragraph (a) of this section, and FDA has determined that they do not meet the criteria for inclusion set forth in paragraph (c) of this section:

(1) 7-keto dehydroepiandrosterone (DHEA).

(2) Acetyl L Carnitine.

(3) Alanyl L Glutamine.

(4) Aloe Vera 200:1 Freeze Dried.

(5) Artemisinin.

(6) Astragalus extract 10:1.

(7) *Boswellia*.

(8) Cesium Chloride.

(9) Chondroitin Sulfate.

(10) Chrysin.

(11) Curcumin.

(12) D-Ribose.

(13) Deoxy-D-Glucose.

(14) Diindolylmethane.

(15) Domperidone.

(16) Epigallocatechin gallate (EGCG).

(17) Germanium Sesquioxide.

(18) Glycyrrhizin.

(19) Kojic acid.

(20) Nettle.

(21) Nicotinamide adenine dinucleotide (NAD).

(22) Nicotinamide adenine dinucleotide disodium reduced (NADH).

(23) Oxitriptan.

(24) Piracetam.

(25) Rubidium Chloride.

(26) Silver Protein Mild.

(27) Sodium dichloroacetate.

(28) Tranilast.

(29) Vanadyl sulfate.

(30) Vasoactive intestinal peptide.

* * * * *

Dated: July 16, 2019.

Norman E. Sharpless,
Acting Commissioner of Food and Drugs.

Dated: August 13, 2019.

Eric D. Hargan,
Deputy Secretary,
Department of Health and Human Services.

[FR Doc. 2019-18951 Filed: 9/4/2019 8:45 am; Publication Date: 9/5/2019]