



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. FDA-2016-N-3464]

RIN 0910-AH29

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) is proposing a regulation to identify an initial list of bulk drug substances that can be used to compound drug products in accordance with certain compounding provisions of the Federal Food, Drug, and Cosmetic Act (the 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. Specifically, the Agency proposes to place six bulk drug substances on the list. This proposed rule also identifies four 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 bulk drug substances list 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:

### Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://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 <http://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): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, 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-2016-N-3464 for "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 will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management 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 <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. 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 docket, see 80 FR

56469, September 18, 2015, or access the information at:

<http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://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 Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: James Flahive, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5108, Silver Spring, MD 20993-0002, 301-796-9293.

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### I. Executive Summary

#### A. Purpose of the Proposed Rule

FDA is proposing to amend its regulations to add a 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, although those substances are not the subject of a USP or NF monograph or components of approved drug products.

### B. Summary of the Major Provisions of the Proposed Rule

FDA is proposing to establish the criteria by which bulk drug substances will be evaluated for inclusion on the 503A Bulks List. 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), FDA is also proposing to include six bulk drug substances on the list: Brilliant Blue G, also known as Coomassie Brilliant Blue G-250; cantharidin (for topical use only); diphenylcyclopropanone (for topical use only); N-acetyl-D-glucosamine (for topical use only); squaric acid dibutyl ester (for topical use only); and thymol iodide (for topical use only) and that four other substances not be included on the list: Oxitriptan, piracetam, silver protein mild, and tranilast.

### 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 is proposing to place six bulk substances on the 503A Bulks List and not to place four bulk substances on the 503A Bulks List. Because we lack sufficient information to quantify the costs and benefits of this proposed rule, we include a qualitative description of potential benefits and potential costs. We expect that the rule would affect compounding pharmacies and other entities that market the affected substances or drug products made from the affected substances, consumers of drug products containing the affected drug substances, and payers that cover these drug products or alternative drug products.

## II. Table of Abbreviations and Acronyms Commonly Used in This Document

Abbreviation/Acronym	What It Means
5-HTP	5-hydroxytryptophan
BLA	Biologics License Application
CFR	Code of Federal Regulations
CSA	Controlled Substances Act
DPCP	Diphenylcyclopropenone
DQSA	Drug Quality and Security Act
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
IND	Investigational New Drug
NAG	N-acetyl-D-glucosamine
NAICS	North American Industry Classification System
NF	National Formulary
NPRM	Notice of Proposed Rulemaking
OTC	Over-The-Counter
PCAC	Pharmacy Compounding Advisory Committee
PHS Act	Public Health Service Act
PRESTO	Prevention of REStenosis with Tranilast and its Outcomes
RFA	Regulatory Flexibility Analysis
SADBE	Squaric acid dibutyl ester
SBA	Small Business Administration
UGT1A1	Uridine diphosphate glucuronosyltransferase 1A1
UK	United Kingdom
USP	United States Pharmacopeia

## III. Background

### A. Statutory and Regulatory Background

Section 503A of the FD&C Act (21 U.S.C. 353a) 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,<sup>1</sup> if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are

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<sup>1</sup> FDA has interpreted the statutory language "applicable USP or NF monographs" to refer to official USP or NF drug substance monographs. 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 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.

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, that appear on the 503A Bulks List. See section 503A(b)(1)(A)(i) of the FD&C Act. This proposed rule proposes criteria for evaluating substances for inclusion on the 503A Bulks List and identifies six substances the Secretary proposes to place on the list. The Agency considered four other substances and is proposing not to include those substances on the 503A Bulks List. Additional substances are under evaluation, and new substances may be added to the list through subsequent rulemaking.

Section 503A 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, 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). This definition becomes 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(b). 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. 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.

#### B. Regulatory History of the 503A Bulks List

Section 503A of the FD&C Act was enacted in 1997. In the Federal Register of April 7, 1998 (63 FR 17011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the 503A Bulks List. In 1998, FDA received nominations for 41 different drug substances. Ten of these drug substances were the subject of an applicable USP or NF monograph or were components of FDA-approved drugs and did not need to go on the list to be used in compounding. After evaluating the nominated drug substances and consulting with the PCAC as required by section 503A(c)(2), FDA published a proposed rule listing 20 drug substances for potential inclusion on the initial section 503A Bulks List (64 FR 996, January 7, 1999) (the 1999 Proposed 503A Bulks List). The proposed rule also described 10 nominated drug substances that were still under consideration for the 503A Bulks List. The PCAC reconvened in May 1999 to discuss bulk drug substances included in the proposed rule, in addition to other bulk drug substances (see 64 FR 19791, April 22, 1999).

In February 2001, the U.S. Court of Appeals for the Ninth Circuit held that certain provisions of section 503A of the FD&C Act were unconstitutional restrictions on commercial speech. (See Western States Med. Ctr. v. Shalala, 238 F.3d 1090 (9th Cir. 2001).) Furthermore, the Ninth Circuit held that the advertising and solicitation provisions could not be severed from

the rest of section 503A and, as a result, found section 503A of the FD&C Act to be invalid in its entirety. In April 2002, the U.S. Supreme Court affirmed the Ninth Circuit's decision that the advertising and solicitation provisions were unconstitutional; it did not, however, rule on the severability of section 503A of the FD&C Act. (See Thompson v. Western States Med. Ctr., 535 U.S. 357 (2002).) In 2008, the U.S. Court of Appeals for the Fifth Circuit held that compounded drugs are subject to regulation by FDA, and that the advertising and solicitation provisions are severable from the rest of section 503A of the FD&C Act. (See Medical Ctr. Pharm. v. Mukasey, 536 F.3d 383 (5th Cir. 2008).)

Following a fungal meningitis outbreak in September 2012, FDA sought legislation to, among other things, resolve the split in the Circuits to clarify that section 503A of the FD&C Act was valid nationwide. On November 27, 2013, President Obama signed the Drug Quality and Security Act (Pub. L. 113-54) (DQSA), which contains important provisions relating to the oversight of human drug product compounding. Among other things, the DQSA removed from section 503A of the FD&C Act the provisions that had been held unconstitutional by the U.S. Supreme Court in 2002. By removing these provisions, the DQSA clarified that section 503A of the FD&C Act applies nationwide.

### C. Requests for Nominations

Because of the amount of time that had passed between the publication of the 1999 proposed rule and the enactment of the DQSA, FDA felt it was necessary to begin again to develop the 503A Bulks List. In the Federal Register of December 4, 2013 (78 FR 72841), FDA published a notice withdrawing the 1999 proposed rule and inviting all interested persons to nominate bulk drug substances for inclusion on the 503A Bulks List.

Over 2,000 substances were nominated. However, many of those nominations were for a substance that is the subject of an applicable USP or NF monograph or a component of an FDA-approved drug, were not for substances used in compounding as active ingredients, or did not include sufficient information for FDA to evaluate whether the substances should be proposed for inclusion on the 503A Bulks List. To improve the efficiency of the process for developing the 503A Bulks List, FDA reopened the nomination process in July 2014 (79 FR 37747, July 2, 2014) and provided a more detailed description about what information should be included in a nomination to support the Agency's evaluation. FDA stated that bulk drug substances that were previously nominated would not be further considered unless they were renominated and the new nominations were adequately supported. Substances that were already eligible for use in compounding or that were not adequately supported would not be placed on the list.

In response to that solicitation, approximately 740 unique substances were nominated. Of those substances, approximately 315 are components of an FDA-approved drug product or the subject of an applicable USP or NF monograph. Such substances can be used in compounding under section 503A(b)(1)(A)(i)(I) and (II) of the FD&C Act and, therefore, are not eligible for inclusion on the 503A Bulks List.

At least one of the nominated substances is a finished drug product that was nominated by its brand name. Finished drug products are not eligible for the 503A Bulks List because they do not meet the definition of a bulk drug substance in § 207.3(4).

At least one of the nominated substances is a biological product subject to approval in a biologics license application (BLA) under section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262) when used for the indication proposed in the nomination. This substance is not eligible for the 503A Bulks List because biological products subject to approval in a BLA under

section 351 of the PHS Act are not eligible for the exemptions in section 503A of the FD&C Act. No biological products subject to approval in a BLA will be considered for the 503A Bulks List.

At least four of the nominated substances appear on the list published by FDA of substances that have been withdrawn or removed from the market because the drug products or components of the drug products have been found to be unsafe or not effective (section 503A(b)(1)(C) of the FD&C Act) (Withdrawn or Removed List). Such substances cannot be used in compounding under section 503A of the FD&C Act, and therefore, are not eligible for inclusion on the 503A Bulks List.

One of the nominated substances has no currently accepted medical use and is included on Schedule I of the Controlled Substances Act (CSA) (21 U.S.C. 812(c)). The CSA does not allow possession or distribution of Schedule I substances (see 21 U.S.C. 841(a)(1) and 829), except for research purposes (see 21 U.S.C. 823(f)), and Schedule I substances will not be considered for the 503A Bulks List. Those desiring to do research on a Schedule I substance may apply to do so under an investigational new drug (IND) application.

Of the substances that are not components of an approved drug product or the subject of an applicable USP or NF monograph, finished drug products, biological products subject to licensure in a BLA, and do not appear on the Withdrawn or Removed List or Schedule I of the CSA, about 350 substances were nominated with insufficient supporting evidence for FDA to evaluate them.

The remaining substances may be eligible for inclusion on the 503A Bulks List and were nominated with sufficient supporting information for FDA to evaluate them. Ten of those substances have been evaluated and are discussed in section V. The rest will be discussed in future notices of proposed rulemaking (NPRMs) after they have been evaluated. Once the

Agency completes its review of the substances that were nominated for the 503A Bulks List with adequate supporting information under the July 2, 2014, request for nominations, FDA will consider additional substances nominated for inclusion on the list if they are eligible and adequate supporting information is submitted to permit FDA to meaningfully evaluate them (see section III).

With regard to the substances nominated with sufficient supporting information for FDA to evaluate them, including the 10 nominated substances discussed in this proposed rule, FDA generally does not intend to take regulatory action against a State-licensed pharmacy, Federal facility, or licensed physician for compounding a drug product using a bulk drug substance that is not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug product, provided that the other conditions in section 503A and the FD&C Act are met, until the substance is addressed in a final rule. FDA is not applying this interim policy to a nominated substance however, if the Agency has identified the substance as posing a significant safety risk,<sup>2</sup> or if the substance was nominated without adequate support. For further information on this subject, see the guidance for industry entitled "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act" (Ref. 1). As described in the guidance, the following categories of bulk drug substances are identified on FDA's Web site at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf>: (1) The substances nominated with sufficient supporting information that are under evaluation, (2) the substances nominated with sufficient supporting information but with which FDA has identified significant safety risks relating to the use of these

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<sup>2</sup> This is not a determination regarding whether the substances will be added to the 503A Bulks list. FDA intends to make that determination after notice and comment rulemaking, as set forth in this proposal.

bulk drug substances in compounding, and (3) the substances nominated with insufficient supporting evidence for FDA to evaluate them.

#### IV. Legal Authority

As described in the Background section, 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. 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, that 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, and any 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 is proposing to add § 216.23 to title 21 of the Code of Federal Regulations (CFR) to set forth criteria to evaluate bulk drug substances for inclusion on the 503A Bulks List.

Additionally, after considering 10 bulk drug substances for the 503A Bulks List, FDA proposes to codify the initial 503A Bulks List to include 6 of the bulk drug substances that were considered and to identify 4 substances that were considered and would not be placed on the list. The criteria and the bulk drug substances considered for inclusion on the list 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 of Health and Human Services may identify. Consistent with the July 2, 2014, Federal Register notice (79 FR 37747) soliciting nominations for this list, and as presented to and discussed with the PCAC in February 2015 (Ref. 2), FDA proposes that the following criteria be 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 proposes to use a balancing test. Specifically, the Agency proposes to consider 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.

Under the first criterion, the physical and chemical characterization of the substance, FDA would consider each substance's purity, identity, and quality. Based on attributes such as the substance's molecular structure, stability, melting point, appearance, likely impurities, and solubilities, FDA would determine whether the substance can be identified consistently based on its physical and chemical characteristics. If a substance cannot be well characterized chemically and physically, the Agency proposes that this criterion weigh against its inclusion on the 503A Bulks List because there can be no assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities reported in the literature and considered by the Agency.

Under the second criterion, FDA would consider the safety issues raised by the use of each substance in pharmacy compounding. Based on FDA's review of the substances nominated to date, it is unlikely that candidates for the 503A Bulks List will have been thoroughly investigated in in vitro or in animal toxicology studies, or that there will be well-controlled clinical trials to substantiate their safe use in humans. Thus, in evaluating list candidates, the Agency is likely to have at its disposal very limited information, or in some cases no

information, of the type and quality that is ordinarily required and evaluated as part of the drug approval process.

To evaluate the safety of the substances then, the Agency proposes to rely on available information, including reports in peer-reviewed medical literature, about each substance's pharmacology, acute toxicity, repeat dose toxicity, mutagenicity, developmental and reproductive toxicity, and carcinogenicity. The Agency would also rely on reports and abstracts in the literature about adverse reactions the substances have caused in humans. In applying the safety criterion, FDA also proposes to consider the availability of approved drug products or drug products that follow an OTC monograph (OTC monograph products). The existence of approved drug products or OTC monograph products would likely weigh against inclusion on the proposed list when the toxicity of a particular substance appears to be significant or where there are other safety concerns associated with the use of the substance in compounded drug products.

Under the third criterion, FDA proposes to consider the available evidence of the substance's effectiveness or lack of effectiveness for a particular use, including reports in peer-reviewed medical literature, if any such evidence exists. In the new drug approval process, applicants are required to demonstrate effectiveness under the substantial evidence standard described in section 505(d) of the FD&C Act. FDA recognizes that few, if any, of the candidates for the 503A Bulks List will have been studied in adequate and well-controlled investigations sufficient to satisfy this standard. Thus, in its balancing of the relevant criteria, the Agency would take into account whatever relevant evidence concerning effectiveness is available.

For example, for substances that have been widely used for a long period of time, the literature may include anecdotal reports of effectiveness for a particular use or reports of one or

more trials suggesting possible effectiveness. Conversely, the literature may contain anecdotal or clinical evidence that a particular bulk drug substance was not effective for a particular use (negative effectiveness data). When evaluating a bulk drug substance that is proposed for the treatment of a less serious illness, FDA would generally be more concerned about the safety of the substance than about its effectiveness. Thus, the availability of minimal effectiveness data, or the existence of mere anecdotal reports, would be less likely to preclude inclusion of the substance on the list. However, for a bulk drug substance that is proposed to treat a more serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy, particularly when there are approved drug products or OTC monograph products. In those cases, the existence of approved drug products or OTC monograph products would likely weigh against inclusion on the proposed list, and the availability of minimal effectiveness data, or the presence of negative effectiveness data, would weigh more heavily against placement on the list in FDA's balancing of the relevant criteria.

Under the fourth criterion, the historical use of the substance in pharmacy compounding, FDA proposes to consider the length of time the substance has been used in pharmacy compounding, the medical conditions it has been used to treat, how widespread its use has been, including use in other countries, and any references in peer-reviewed medical literature. The Agency proposes that the longer a substance has been used in pharmacy compounding and the broader its use, the more this criterion will weigh in favor of inclusion of the substance on the list.

#### B. Methodology for Developing the 503A Bulks List

FDA reviewed the substances addressed in this proposed rule in the context of adequately supported nominated uses. In certain circumstances, FDA also reviewed substances in the

context of unnominated or inadequately supported uses 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 proposed 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 premarketing evaluation of a specific drug formulation, the sponsor's chemistry and manufacturing controls, and 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 FDA approved, or otherwise endorsed by FDA generally, or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act.

On February 23 and 24, 2015, and on June 17, 2015, FDA consulted with the PCAC created under section 503A(c)(1) of the FD&C Act, about the criteria proposed to evaluate substances nominated for the list and about the 10 substances that are addressed in this proposed rule (Refs. 2-4). The Agency has considered all of 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. The first 10 substances evaluated are addressed in this proposed rule. Going forward, FDA intends to publish NPRMs proposing additional substances be placed on the list or not placed 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 requires that FDA create the 503A Bulks List by regulation, in consultation with the USP. See section 503A(c)(2) of the FD&C Act. To this end, FDA has been periodically meeting with USP and discussing the 503A Bulks List (Refs. 5 and 6). After publication of this NPRM, the public will have an opportunity to comment on the proposed rule. After considering the comments on this proposed rule submitted to the docket, FDA will issue the 503A Bulks List as a final rule, which will be codified in the CFR. 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, depending on the comments received, and will also identify those substances the Agency has determined should not be placed on the list. The Agency may amend the 503A Bulks List to add or delete substances after further notice and comment rulemaking.

Individuals and organizations may petition FDA to amend the list (to add or delete bulk drug substances) at any time after the final rule is published (see 21 CFR 10.30). Individuals and organizations may also nominate new substances for the 503A Bulks List or comment on nominated substances that have not yet been addressed in an NPRM via Docket No. FDA-2015-N-3534 while that docket is open.

### 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 six bulk drug substances, which are neither the subject of a current 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. The base compound and other salts or esters of the same active moiety must be evaluated separately for eligibility for 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 dosage forms for that route of administration may be compounded with that bulk drug substance.

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

## 1. Brilliant Blue G

Brilliant Blue G, also known as Coomassie Brilliant Blue G-250,<sup>3</sup> was evaluated for use as a dye used in staining for visualization during ophthalmic procedures. It is well characterized physically and chemically. There are potential mutagenic and carcinogenic concerns associated with Brilliant Blue G; however, those concerns are mitigated in clinical use because the dye is immediately washed out of the eye after administration, and tissue that is stained with the dye is removed as part of the surgical procedure. Published clinical trials provide some evidence for efficacy of Brilliant Blue G in staining the internal limiting membrane. Brilliant Blue has had relatively widespread use for staining the internal limiting membrane during retinal surgery for approximately 10 years. There is one product that is FDA-approved for staining the internal limiting membrane and the anterior capsule.

FDA proposed to the PCAC that Brilliant Blue G be included on the 503A Bulks List (Ref. 7), and at its meeting on June 17, 2015, the PCAC voted to include Brilliant Blue G on the list (Ref. 4). The proposed rule would place Brilliant Blue G on the 503A Bulks List.

## 2. Cantharidin

Cantharidin, which is obtained from various species of blister beetle, was evaluated for topical use<sup>4</sup> in the treatment of warts and molluscum contagiosum. It is well characterized physically and chemically. Cantharidin is extremely toxic, due to its potential for severe irritation. However, clinical data accumulated since 1958 indicate that, with careful use under physician direction, toxicities observed with cantharidin, are no worse than and sometimes less

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<sup>3</sup> While there are other substances referred to by the name "Brilliant Blue," only Coomassie Brilliant Blue G-250 (CAS RN 6104-58-1, UNII M1ZRX790SI) was evaluated, and the Agency is proposing only that substance for inclusion on the 503A Bulks List. The other substances referred to as "Brilliant Blue" would have to be nominated and separately evaluated for consideration for inclusion on the 503A Bulks List.

<sup>4</sup> Except where specified otherwise, "topical use" means for application on the skin only and does not include oral, intravaginal, or ophthalmic use.

severe than those seen with other destructive modalities in the treatment of molluscum contagiosum and warts. Evidence of some efficacy of cantharidin in the treatment of warts and molluscum contagiosum has been reported in the literature. It appears to have been widely used to treat molluscum contagiosum and warts since the 1950s. There are no approved prescription or OTC monograph products for molluscum contagiosum. For warts, there are no prescription drug products approved for use outside of the genital area. A variety of OTC monograph products containing salicylic acid are available.

FDA proposed to the PCAC that cantharidin be included on the 503A Bulks List for topical use only (Ref. 8). At the PCAC meeting on February 24, 2015, the PCAC voted to include cantharidin on the list (Ref. 3). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place cantharidin on the 503A Bulks List for topical use only.

### 3. Diphenylcyclopropanone (DPCP)

DPCP was evaluated for topical use in the treatment of alopecia areata and nongenital warts. It is well characterized physically and chemically but degrades readily by hydrolysis in an alcoholic base or exposure to light. Known safety concerns about the use of DPCP are limited to reported adverse effects primarily due to its action as a contact sensitizer to elicit contact dermatitis. Evidence of some efficacy of DPCP in the treatment of alopecia areata and recalcitrant nongenital warts has been reported in the literature. DPCP has been used to treat resistant non-genital warts and alopecia areata for over 30 years. The only FDA-approved drug product indicated for the treatment of alopecia areata is intralesional injection of corticosteroid suspensions. For warts, there are no approved prescription drug products outside of the genital

area. A variety of OTC monograph products are available containing salicylic acid at percentages varying from 17 to 40 percent.

FDA proposed to the PCAC that DPCP be included on the 503A Bulks List (Ref. 8). At its meeting on February 24, 2015, the PCAC voted to include DPCP on the list (Ref. 3). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place DPCP on the 503A Bulks List for topical use only.

#### 4. N-acetyl-D-glucosamine (NAG)

NAG, also known as acetyl-D glucosamine or N-acetyl glucosamine, was evaluated for topical use in the treatment of hyperpigmentation and other skin conditions. It is well characterized physically and chemically. Topical use of NAG has been associated with relatively minor and infrequent side effects. Studies have indicated that NAG may be effective for reducing diffuse and local facial hyperpigmentation. NAG has been used topically for the treatment of hyperpigmentation since the mid-2000s. There are FDA-approved drug products indicated for the treatment of hyperpigmentation and other skin conditions, which are not serious or life-threatening conditions.

FDA proposed to the PCAC that NAG be included on the 503A Bulks List for topical use only (Ref. 7). At the PCAC meeting on June 17, 2015, the PCAC voted to include NAG on the list (Ref. 4). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place NAG on the 503A Bulks List for topical use only.

#### 5. Squaric Acid Dibutyl Ester (SADBE)

SADBE was evaluated for topical use in the treatment of alopecia areata and recalcitrant nongenital warts. It is well characterized physically and chemically but hydrolyzes readily in the

presence of water. The adverse effects from use of SADBE are primarily related to its action as contact sensitizer. Evidence of some efficacy of SADBE in the treatment of recalcitrant nongenital warts and alopecia areata has been reported in the literature. SADBE has been used in the treatment of resistant nongenital warts and alopecia areata for 30 to 40 years. The only FDA-approved drug product indicated for the treatment of alopecia areata is intralesional injection of corticosteroid suspensions. For warts, there are no prescription drug products approved for use outside of the genital area. A variety of OTC monograph products are available containing salicylic acid at percentages varying from 17 to 40 percent.

FDA proposed to the PCAC that SADBE be included on the 503A Bulks List (Ref. 8). At its meeting on February 24, 2015, the PCAC voted to include SADBE on the list (Ref. 3). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place SADBE on the 503A Bulks List for topical use only.

## 6. Thymol Iodide

Thymol iodide was evaluated for use as a topical treatment for ulcerations and skin infections, as well as an intrapleural treatment for pleural effusions. It is well characterized physically and chemically. Reports indicate that it has been used without major complications. Literature reports some efficacy of thymol iodide for pleural effusions, which are serious and can be life-threatening conditions. Data regarding the effectiveness of thymol iodide in compounding for topical use on wounds or ulcers in various skin conditions is limited; however, these skin conditions generally are not serious or life-threatening. Thymol iodide has been in use for over 100 years. Regarding use as an antiseptic in surgery and use as an external application

to wounds or ulcers in various skin conditions, approved and OTC monograph products are available. There are also FDA-approved products available to treat malignant pleural effusions.

FDA proposed to the PCAC that thymol iodide be included on the 503A Bulks List (Ref. 8). At its meeting on February 23, 2015, the PCAC voted to include thymol iodide on the list (Ref. 2). Because the supported nominations were limited to the topical use of this substance, and because pleural effusions are serious and potentially life-threatening conditions for which there are approved products available, the proposed rule would place thymol iodide on the 503A Bulks List for topical use only.

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

FDA is proposing that four 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. 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 IND. For information about the requirements for proceeding under an IND, visit FDA's Web site at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm>.

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

##### 1. Oxitriptan

Oxitriptan, also known as 5-hydroxytryptophan (5-HTP), was evaluated as a treatment for depression and insomnia. It is a hydroxylated form of a naturally occurring amino acid,

tryptophan. Oxitriptan is well characterized physically and chemically. However, there are significant safety concerns related to its use. Based upon its mechanism of action, concomitant use of oxitriptan with antidepressant drugs could result in serotonin syndrome, a serious and life-threatening drug interaction. Additionally, medications used to treat depression have been linked to an increase in suicidal thinking and behavior. There are no data to suggest that oxitriptan would be free of similar risks, and compounded drugs do not include labeling that would adequately warn physicians and patients of such risks. Other potential adverse reactions include moderate gastrointestinal effects, which are common upon administration of oxitriptan.

Data supporting the efficacy of oxitriptan for depression are limited, and there is no evidence to support long-term efficacy of oxitriptan for the treatment of this chronic disease. Depression is a serious and potentially life-threatening condition, and there are multiple FDA-approved antidepressants that have been shown to be safe and effective in their approved forms that are appropriately labeled. Regarding the use of oxitriptan to treat insomnia, the clinical trials examining insomnia were too poorly designed and/or executed to assess efficacy. There are multiple FDA-approved drug products available for the treatment of insomnia. The length of time oxitriptan has been used in compounding is uncertain, although it has been discussed in scientific journals dating back approximately 40 years.

On balance, the physiochemical characteristics, the safety concerns, lack of evidence of effectiveness, and historical use of oxitriptan weigh against inclusion of this substance on the 503A Bulks List. In particular, the Agency's proposal regarding this substance is based on the seriousness of the safety concerns related to the use of oxitriptan for depression in lieu of, or causing a delay in the use of an approved product, the lack of adequate warnings that would inform patients and prescribers of the risks associated with taking an oxitriptan product, and the

availability of approved drug products for the treatment of depression, a potentially life-threatening condition. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 7). At its meeting on June 17, 2015, the PCAC voted not to include oxitriptan on the list (Ref. 4). The proposed rule would not place oxitriptan on the 503A Bulks List.

## 2. Piracetam

Piracetam was evaluated as a treatment for enhancing cognitive skills in treating a variety of cognitive disorders, including Alzheimer's disease. It has also been studied for treatment of coagulation disorders and vertigo. It is well characterized physically and chemically. Piracetam is approved in the United Kingdom (UK) as a prescription drug for the adjunctive treatment of cortical myoclonus. The labeling of the UK product identifies that the drug is renally excreted, that the dosage should be adjusted in the presence of renal disease, and that it is contraindicated in end-stage renal disease. Piracetam acts by multiple mechanisms to prolong bleeding time and is therefore not recommended for use by individuals with medical conditions that prolong bleeding time or that are taking concomitant anticoagulants or other medications that prolong bleeding (Ref. 9). Piracetam is not recommended for women who are pregnant, planning to become pregnant, or breastfeeding, because, according to the UK product's labeling, the drug has been shown to cross the placenta and be excreted in human milk. It is also recommended that individuals required to restrict their salt intake avoid piracetam (id.).

Piracetam was assessed for the treatment of mild cognitive impairment, a potential component of Alzheimer's disease, in a large, well-conducted, controlled clinical trial that failed to demonstrate efficacy. Studies of the efficacy of piracetam for other indications have been inconclusive, many of which were poorly designed or executed, or used flawed statistical

methods to analyze the results. Piracetam's regulatory approval in the UK for the treatment of cortical myoclonus, which is not among the uses for which piracetam was nominated, was based on a single center, retrospective review of 40 patients treated with piracetam (id.). FDA-approved products are available for treatment of the conditions, and conditions related to, those for which piracetam was nominated, for example, for Alzheimer's disease, which is frequently preceded by mild cognitive impairment. Regarding historical use, piracetam has been available for approximately 40 years.

On balance, the physiochemical characteristics, safety concerns, inconclusive evidence of effectiveness, and historical use of piracetam weigh against inclusion of this substance on the list. In particular, the Agency's proposal regarding this substance is based on the limited evidence of benefit associated with piracetam, the seriousness of the conditions for which piracetam was nominated to be used, and the availability of safe and effective FDA-approved medications for many of these uses. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 8). At its meeting on February 24, 2015, the PCAC voted not to include piracetam on the list (Ref. 3). The proposed rule would not place piracetam on the 503A Bulks List.

### 3. Silver Protein Mild

Silver protein mild, also known as mild silver protein, was evaluated for use as an anti-infective agent for ophthalmic use. Silver protein mild is not well characterized because the term "silver protein mild" is used to refer to a variety of different drug products. There are also safety concerns associated with the use of silver protein mild. It can cause argyria, which is a permanent ashen-gray discoloration of the skin, conjunctiva, and internal organs. Regarding effectiveness, silver protein mild has been found to be inferior to another treatment in clinical

trials. A number of FDA-approved anti-infective agents for ophthalmic use are available and have been shown to be both safe and effective. While it has a long history of use, dating back to the early 1900s, the use of silver protein mild declined dramatically after the introduction of FDA-approved ocular anti-infectives.

On balance, the physiochemical characteristics, safety issues, questionable effectiveness, and historical use of silver protein mild weigh against inclusion of this substance on the 503A Bulks List. In particular, the Agency's proposal is based on the facts that silver protein mild is not well characterized, that in clinical trials it has been found to be inferior to another treatment and numerically inferior to no treatment at all, and that chronic use may result in permanent discoloration of the conjunctiva, cornea, and/or lens. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 8). At its meeting on February 23, 2015, the PCAC voted not to include silver protein mild on the list (Ref. 2). The proposed rule would not place silver protein mild on the 503A Bulks List.

#### 4. Tranilast

Tranilast, an antiallergenic agent, was evaluated for the treatment of allergic disorders, arthritis, dry eye syndrome, keloids, and hypertrophic scars. It is approved in South Korea and Japan for the treatment of asthma, keloids, and hypertrophic scarring, and as an ophthalmic solution for allergic conjunctivitis. It is well characterized physically and chemically. However, there are significant safety concerns associated with its systemic administration. In a well-controlled clinical trial with nearly 12,000 participants (the Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) Trial) (Ref. 10), tranilast was associated with significantly elevated liver enzymes (three times the upper limit of normal) in 11 percent of patients within 1

to 3 months of drug initiation, as well as anemia, renal failure, rash, and dysuria.<sup>5</sup> Liver toxicity is of particular concern because many of the conditions for which tranilast was nominated are chronic conditions. While there is some evidence that tranilast may be effective for allergic disorders, evidence of effectiveness for other uses is either not available or inconclusive. For allergy, arthritis, and ophthalmic indications, there are numerous FDA-approved and OTC monograph products. The length of time tranilast has been used in compounding is uncertain, although it has been discussed in scientific journals dating back approximately 40 years.

On balance, the physiochemical characteristics, safety concerns, lack of evidence of effectiveness, and historical use of tranilast weigh against inclusion of this substance on the 503A Bulks List, particularly given the seriousness of the safety concerns related to hepatotoxicity of tranilast and contraindications in pregnant and breastfeeding women, the availability of approved products for most of the proposed uses, and the lack of evidence that tranilast is effective. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 7). However, at its meeting on June 17, 2015, the PCAC voted to include tranilast on the list for topical use only (Ref. 4).

Subsequent to that meeting, FDA reviewed the topical use of tranilast further. It obtained the label of the Japanese tranilast product, RIZABEN, but found no information on the transdermal absorption or other pharmacokinetics of tranilast when applied topically to healthy or diseased human skin (Ref. 11). The labeling of the Japanese product identifies a number of safety concerns, including a contraindication in pregnant women, especially during the first trimester of pregnancy, and in those who might be pregnant, due to evidence of teratogenicity in

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<sup>5</sup> During the PCAC meeting on June 17, 2015, the PRESTO trial was criticized by one of the tranilast nominators as having insufficiently accounted for the medical history of the subjects, among other things (see Ref. 4). To the contrary, the five-arm trial design appears to have been properly controlled for the patients' various medical conditions, and signals of liver toxicity were consistent across arms (see Ref. 10).

animal studies (id.). The labeling also states that tranilast is detected in breast milk and should be avoided by breastfeeding women. In addition, the RIZABEN label lists a drug interaction with warfarin and identifies a number of serious adverse events, particularly those that are hematologic in nature (leukopenia, thrombocytopenia, anemia, hemolytic anemia), associated with the oral use of tranilast. Safety information regarding other routes of administration is limited.

FDA also noted evidence that some increases in some liver function tests (bilirubin) are explained by tranilast inhibition of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) especially in patients with a genotype for Gilbert's Disease. Increases in liver transaminases observed with tranilast are not typically seen with inhibition of UGT1A1. It is speculated that tranilast impairs the metabolism of drugs that are metabolized by UGT1A1. If these drugs are associated with transaminase elevations, inhibiting the drug's metabolism may lead to liver transaminitis.

As was found in the Agency's initial review and presented to the PCAC, there is no persuasive information available regarding the safety or effectiveness of topical tranilast. FDA has identified only two reports in the literature describing the efficacy and safety of tranilast administered topically for the treatment of keloids and hypertrophic scars (Refs. 12 and 13). One of those studies was an open-label trial, and the other was a case series. Between the two studies, only five patients were exposed to topical tranilast.

As stated previously, FDA has serious concerns about the safety of tranilast when administered orally. The Agency has insufficient information about the systemic absorption of topical tranilast formulations to determine whether topical administration of the drug product would present the same safety concerns. Given the lack of information available about the safety

and efficacy of topical tranilast, and safety concerns related to the oral use of this product, the proposed rule would not place tranilast on the 503A Bulks List.

#### VI. Proposed Effective Date

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

#### VII. Analysis of Environmental Impact

FDA has 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.

#### VIII. Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, 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). We have developed a comprehensive 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 find little evidence that a substantial number of small entities would be affected by the proposed rule or that the economic

impact on each affected small entity would be significant, we propose to certify that the proposed rule will not 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 \$146 million, using the most current (2015) 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.

Table 1.--Economic Data: Costs and Benefits Statement

Category	Primary Estimate	Low Estimate	High Estimate	Units Year Dollars	Discount Rate	Period Covered	Notes
Benefits							
Annualized Monetized \$ mil/year	Not Estimated (N.E.)				7%	10 years	
Annualized Monetized \$ mil/year	N.E.				3%	10 years	
Annualized Quantified	N.E.				7%		
Annualized Quantified	N.E.				3%		
Qualitative	Not including four bulk drug substances from the 503A Bulks List would limit the use of potentially ineffective or unsafe unapproved drugs						

Costs							
Category	Primary Estimate	Low Estimate	High Estimate	Units Year Dollars	Discount Rate	Period Covered	Notes
Annualized Monetized \$ mil/year	N.E.				7%	10 years	
Annualized Monetized \$ mil/year	N.E.				3%	10 years	
Annualized Quantified	\$118 to \$235 one-time per firm costs			2014	7%		
Annualized Quantified	\$118 to \$235 one-time per firm costs			2014	3%		
Qualitative							
Transfers							
Federal Annualized Monetized \$ mil/year					7%		
Federal Annualized Monetized \$ mil/year					3%		
From/To	From:			To:			
Other Annualized \$ mil/year	N.E.				7%		
Other Annualized Monetized \$ mil/year	N.E.				3%		
From/To	From: Producers of bulk drug substances not proposed for inclusion and compounding pharmacies using these substances			To: Producers of alternative treatments, consumers, using these treatments and payers for these treatments			
Effects							
State, Local, and/or Tribal Government: No effect							
Small Business: Unknown effect							
Wages: No effect							
Growth: No effect							

The Economic Analysis of Impacts of the proposed rule performed in accordance with Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act is available at <http://www.regulations.gov> under the docket

number for this proposed rule (Ref. 14) and at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

We invite comments on this analysis.

#### A. Summary of the Costs of the Rule

We lack data on the scope of the current use of the affected bulk drug substances and the number of firms that would be affected by the rule. Without this information, we cannot quantify the total potential costs of the proposed rule. Potential costs include administrative costs, additional costs for consumers and payers if alternative therapies are more costly than the affected compounded drug products, and a potential loss of producer surplus if producers use additional resources in response to the rule. We estimate that each affected firm would spend 1 to 2 hours on administrative costs to read and understand the rule. The average hourly wage for a pharmacist in 2014 equals about \$57, or \$114 including 100 percent overhead. Thus, each affected firm would incur administrative costs that range from \$118 to \$235. We request comment on the potential costs and number of firms affected by the proposed rule.

#### B. Summary of the Benefits of the Rule

The benefits of the rule are unquantified. We include a qualitative discussion of potential benefits. For consumers who switch to more effective treatments, there would be benefits as consumers experience better health outcomes than they do currently.

#### C. Summary of the Impact on Small Entities

The Regulatory Flexibility Act requires a Regulatory Flexibility Analysis (RFA) unless the Agency can certify that the proposed rule would have no significant impact on a substantial number of small entities. The Small Business Administration (SBA) establishes thresholds for small entities by North American Industry Classification System (NAICS); the SBA considers

small any entity below these thresholds. Firms affected by the proposed rule would fall into three major industries, NAICS 325412 Pharmaceutical Preparation Manufacturing, NAICS 424210 Drugs and Druggists' Sundries Merchant Wholesalers, and NAICS 446110 Pharmacies and Drug Stores. The thresholds for these industries are 750 employees for NAICS 325412, 100 employees for NAICS 424210, and annual sales of \$27.5 million for NAICS 446110.

We lack data on the number or size of manufacturers, wholesalers, and compounding pharmacies that would be affected by the proposed rule. Moreover, we find little evidence of widespread use of four bulk drug substances not proposed for inclusion on the 503A Bulks List. This suggests that the impact of the rule would likely not be significant on small entities. Because we find little evidence that a substantial number of small entities would be affected by the proposed rule or that the economic impact on each affected small entity would be significant, we believe that the proposed rule would not have a significant economic impact on a substantial number of small entities, but the impacts are uncertain. We request detailed comments and data on the number of small entities that would be affected by the proposed rule, as well as data on the economic impact of the proposed rule on these small entities.

#### IX. Paperwork Reduction Act of 1995

The submission of comments on this proposed rule would be submissions in response to a Federal Register notice, in the form of comments, which are excluded from the definition of "information" under 5 CFR 1320.3(h)(4) of Office of Management and Budget regulations on the Paperwork Reduction Act (i.e., facts or opinions submitted in response to general solicitations of comments from the public, published in the Federal Register or other publications, regardless of the form or format thereof, provided that no person is required to supply specific information pertaining to the commenter, other than that necessary for self-identification, as a condition of

the Agency's full consideration of the comment). The proposed rule contains no other collection of information.

#### X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the 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. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. FDA, "Guidance for Industry: Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act," (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf>), 2016.
2. FDA, Transcript of the February 23, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2015,

(<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444500.pdf>).

3. FDA, Transcript of the February 24, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015, (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444501.pdf>).

4. Transcript of the June 17, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2015, (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM458513.pdf>).

5. Memorandum to File on FDA Consultations with USP, September 26, 2016.

6. Letter from USP to FDA, October 7, 2016.

7. FDA Briefing Document for the June 17-18, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015, (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf>).

8. FDA Briefing Document for the February 23-24, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015, (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf>).

9. Obeso, J. A., et al., "Piracetam in the Treatment of Different Types of Myoclonus," Clinical Neuropharmacology, 11(6): 529-536, 1988.

10. Holmes, D. R., Jr., M. Savage, J. M. LaBlanche, et al., "Results of Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) Trial," Circulation, 106(10): 1243-1250, 2002.
11. FDA Supplemental Review of Topical Tranilast, April 25, 2016.
12. Shigeki, S., T. Murakami, N. Yata, and Y. Ikuta, "Treatment of Keloid and Hypertrophic Scars by Iontophoretic Transdermal Delivery of Tranilast," Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery, 31(2): 151-159, 1997.
13. Banov, D., F. Banov, and A. S. Bassani, "Case Series: The Effectiveness of Fatty Acids From Pracaxi Oil in a Topical Silicone Base for Scar and Wound Therapy," Dermatology and Therapy, 4(2): 259-269, 2014.
14. Economic Analysis of Impacts.

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, the Food and Drug Administration proposes to amend 21 CFR part 216 as follows:

PART 216--HUMAN DRUG COMPOUNDING

1. The authority citation for part 216 is revised to read as follows:  
Authority: 21 U.S.C. 351, 352, 353a, 353b, 355, and 371.
2. The heading for part 216 is revised to read as set forth above.
3. Section 216.23 is added 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 can be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.

Brilliant Blue G, also known as Coomassie Brilliant Blue G-250.

Cantharidin (for topical use only).

Diphenylcyclopropanone (for topical use only).

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

Squaric acid dibutyl ester (for topical use only).

Thymol iodide (for topical use only).

(b) After balancing the criteria set forth in paragraph (c) of this section, FDA has determined that the following bulk drug substances will not be included on the list of substances that can be used in compounding set forth in paragraph (a) of this section:

Oxitriptan.

Piracetam.

Silver Protein Mild.

Tranilast.

(c) FDA will use the following criteria in evaluating substances considered for inclusion on the list set forth in paragraph (a) of this section:

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

(4) 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.

(d) Based on evidence currently available, there are inadequate data to demonstrate the safety or efficacy of any drug product compounded using any of the drug substances listed in paragraph (a) of this section, or to establish general recognition of the safety or effectiveness of any such drug product. Any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the Federal Food, Drug, and Cosmetic Act.

Dated: December 9, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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