Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 30 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Compounding Quality and Compliance at 301-796-3100.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2023
Compounding and Related Documents
Revision 2

Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2023
Compounding and Related Documents
Revision 2

TABLE OF CONTENTS

Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION AND SCOPE

This guidance sets forth the Food and Drug Administration's (FDA or Agency) interim regulatory policy concerning compounding using bulk drug substances under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a). Section 503A of the FD&C Act includes certain restrictions on the bulk drug substances that can be used in compounding and directs FDA to develop a list of bulk drug substances that can be used in compounding under that section. FDA is developing this list of bulk drug substances (the 503A bulks list), and this guidance describes FDA's interim regulatory policy for licensed pharmacists in State-licensed pharmacies and Federal facilities and for licensed physicians that compound human drug products using bulk drug substances while the list is being developed.[2,3]

This draft guidance, when finalized, will revise FDA's current interim policy. The revision would not change FDA's policy with respect to bulk drug substances that are nominated for inclusion on the 503A bulks list before the draft guidance is finalized. In contrast, bulk drug substances that are nominated on or after the date of publication of the final guidance would not be within the scope of the policy described in Section III.A of this guidance. FDA intends to continue to receive and evaluate new nominations of bulk drug substances for inclusion on the

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER), in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] Drugs compounded from bulk drug substances for use in animals are not within the scope of this guidance. For policies pertaining to compounding drug products from bulk drug substances for use in animals, see the Center for Veterinary Medicine guidance for industry *#256 Compounding Animal Drugs From Bulk Drug Substances* (August 2022). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] FDA is developing a separate list of bulk drug substances that can be used in compounding under section 503B of the FD&C Act. Because section 503B contains different criteria for that list and provides for a different process for its development, the section 503B bulks list is discussed in a separate guidance (see the guidance for industry, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (January 2017)).

503A bulks list consistent with the process and criteria established in the FD&C Act and FDA regulations.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Compounding From Bulk Drug Substances Under Section 503A of the Act

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

One of the conditions that must be met for a compounded drug product to qualify for these exemptions is that a licensed pharmacist, or licensed physician compounds the drug product using bulk drug substances that:

(1) Comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding;

(2) If such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or

(3) If such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appears on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A.[4]

A *bulk drug substance* is defined as meaning "the same as active pharmaceutical ingredient as defined in 21 CFR 207.1." See 21 CFR 207.3. Active pharmaceutical ingredient is defined as "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," but the term "does not include intermediates used in the synthesis of the substance" (see section

[4] See section 503A(b)(1)(A)(i) of the FD&C Act.

503A(b)(1)(A) and 21 CFR 207.3).[5,6] FDA has interpreted "an applicable USP or NF monograph" to mean an official USP or NF **drug substance** monograph.[7] Accordingly, FDA does not consider USP monographs for dietary supplements to be "applicable" USP or NF monographs within the meaning of section 503A(b)(1)(A)(i)(I).

Under section 503A(c)(1), before developing this list through regulation, FDA must convene and consult an advisory committee on compounding unless FDA determines that the issuance of such regulation before consultation with the advisory committee is necessary to protect the public health. FDA must also consult with USP when promulgating the regulations.[8] The criteria for determining which bulk drug substances should appear on the section 503A bulks list "shall include historical use, reports in peer-reviewed medical literature, or other criteria the Secretary may identify."[9]

Bulk drug substances used in compounding under section 503A must also meet certain other requirements, including: (1) the bulk drug substance must be manufactured by an establishment registered under section 510 of the FD&C Act and (2) the bulk drug substance must be accompanied by a valid certificate of analysis (COA).[10]

In July 2014, FDA issued a guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*, that stated:

> Until a bulk drug substances list is published in the *Federal Register* as a final rule, human drug products should be compounded using only bulk drug substances that are components of drugs approved under section 505 of the FD&C Act, or are the subject of USP or NF monographs.[11]

---

[5] Section 503A references the definition of bulk drug substances in FDA's drug establishment registration and listing regulations, which was codified at 21 CFR 207.3(a)(4) when section 503A was enacted. On Aug 31, 2016, FDA published a final rule in the Federal Register to update its registration and listing regulations in Part 207, which made minor changes to the definition of bulk drug substance and moved the definition to 21 CFR 207.3. See 81 FR 169 (Aug 31, 2016). Under the previous definition, bulk drug substance was defined to mean "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."

[6] Inactive ingredients are not subject to section 503A(b)(1)(A)(i) or the policies described in this guidance because they are not included within the definition of a bulk drug substance. See 21 CFR 207.3. Pursuant to section 503A(b)(1)(B), inactive ingredients used in compounding must comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding.

[7] See 84 FR 4696, 4705 (2019).

[8] See section 503A(c)(2) of the FD&C Act.

[9] See section 503A(c)(2) of the FD&C Act.

[10] See section 503A(b)(1)(A) of the FD&C Act.

[11] See page 5 of the 2014 guidance *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*, available at https://www.regulations.gov/docket/FDA-2013-D-1444/document.

FDA has received comments that this policy could be causing unnecessary and inappropriate disruptions in patient care because there are patients receiving drugs compounded with bulk drug substances that are not components of FDA-approved drugs, or the subject of an applicable USP or NF monograph, but that may ultimately be included on the 503A bulks list, and those patients' care should not be disrupted while the list is under development. After considering this issue, FDA has decided to use this guidance to describe its interim policy concerning compounding with bulk drug substances while the 503A bulks list is being developed. FDA revised the July 2014 guidance to state:

> FDA's interim policy concerning bulk drug substances that are not components of drugs approved under section 505 of the FD&C Act or that are not the subject of applicable USP or NF monographs can be found in the guidance, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug and Cosmetic Act*.[12]

FDA seeks to avoid unnecessary disruption to patient treatment while the Agency considers the bulk drug substances that were nominated with sufficient support to permit FDA to evaluate them and promulgates the regulations required under section 503A. Therefore, as described further below, FDA is issuing this interim guidance stating that it does not intend to take regulatory action for compounding drug products under section 503A using a bulk drug substance when an applicable USP or NF monograph for the substance does not exist and the substance is not a component of an FDA-approved product if, among other conditions, the bulk drug substance appears on Category 1 on FDA's website, as described below.

B. Efforts to Develop the List of Bulk Drug Substances Under Section 503A

1. Section 503A Bulks List — Early History

Section 503A was enacted in 1997 as part of the Food and Drug Administration Modernization Act. 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 list of bulk drug substances that can be used in compounding under section 503A and received nominations for 41 different drug substances. In November 1998, FDA published a guidance for industry, *Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act.* In this guidance, FDA announced that it would not normally take regulatory action relating to a drug product that had been compounded with a bulk drug substance that had been nominated for inclusion on the bulk drug substances list on or before November 21, 1999, while the substance was being evaluated, as long as the compounding complied with the other effective requirements in section 503A and did not appear to present a significant safety risk.[13]

---

[12] See the guidance *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (June 2016) at section III.B.2.

[13] The 1998 guidance was withdrawn in the *Federal Register* notice announcing the availability of the draft guidance *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*. See 78 FR 72901 (Dec. 4, 2013). The final guidance was published in July 2014.

In January 1999, after evaluating the nominated drug substances and consulting with the Pharmacy Compounding Advisory Committee (PCAC) as required by section 503A, FDA published a proposed rule listing 20 drug substances on the section 503A bulks list (64 FR 996, January 7, 1999). The preamble to the proposed rule indicated that 10 of the 41 nominated drug substances were the subject of a USP or NF monograph, or components of FDA-approved drugs and did not need to be considered for inclusion on the list.[14] The proposed rule also described 10 nominated drug substances that were still under consideration for the bulk drug substances list and stated that one of the substances was withdrawn by its nominator at the first meeting of the PCAC. The PCAC reconvened in May 1999 to discuss bulk drug substances included in the proposed rule, in addition to other bulk drug substances (64 FR 19791; April 22, 1999).

However, after a 2002 U.S. Supreme Court decision holding that certain provisions of section 503A were unconstitutional,[15] FDA suspended its efforts to develop the bulk drugs list under section 503A.

Because of the amount of time that had passed between the publication of the proposed rule and the enactment of the 2013 Drug Quality and Security Act, which removed the provisions of the FD&C Act that the U.S. Supreme Court held to be unconstitutional in 2002, FDA felt it was necessary to begin again to develop the section 503A bulk drug substance list. In the December 4, 2013, *Federal Register* (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 a list of bulk drug substances that can be used for compounding under section 503A of the FD&C Act.

2. Current Nominations for the 503A Bulks List

In response to the December 2013, *Federal Register* notice, over 2,000 substances were nominated for the 503A bulks list. However, many of the substances nominated for the 503A list were for substances that can be compounded without being on the list because they are the subject of an applicable USP or NF monograph or are a component of an FDA-approved drug. In addition, many of the nominations were not for bulk drug substances used in compounding as active ingredients or did not include sufficient information for FDA to evaluate the nominated substances for inclusion on the 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) and provided more detailed information on what it needs to evaluate nominations for the 503A bulks list (July 2014 docket). FDA stated that bulk drug substances that were previously nominated would not be considered further unless they were re-nominated with adequate support to permit a meaningful evaluation. Substances that were already eligible for use in compounding or that were not adequately supported would not be evaluated for placement on the 503A bulks list.

In the *Federal Register* of October 27, 2015, FDA established a docket (October 2015 docket) where new nominations for these substances can be submitted with sufficient supporting

[14] See 64 FR 996, at 997 (Jan 7, 1999).

[15] For additional legal history of section 503A, see the guidance *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

information or where nominations for substances that were not previously nominated can be submitted.

In response to this request for nominations, as of publication of the June 2016 guidance, approximately 740 unique substances were nominated. Of those nominated substances:

- Approximately 315 substances are already eligible for use in compounding under section 503A.

  These are the subject of an applicable USP or NF monograph or components of an FDA-approved drug product, which can be used in compounding pursuant to sections 503A(b)(1)(A)(i)(I) and (II) and, therefore, can be compounded without being included on the 503A bulks list. To determine if a bulk drug substance is the subject of an applicable USP or NF monograph, see the *USP-NF* available at https://www.uspnf.com. To determine if a bulk drug substance is a component of an FDA-approved drug, see the FDA's *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.[16]

- At least one[17] of the nominated substances is not a bulk drug substance.

  This 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 21 CFR 207.3.

- 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 such drug products or components of such drug products have been found to be unsafe or not effective (withdrawn or removed list).[18]

  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)).[19]

---

[16] Biological products subject to approval in a biologics license application (BLA) under section 351 of the Public Health Service (PHS) Act are not eligible for the exemptions in section 503A of the FD&C Act (21 USC 353a). Biological products subject to approval in a BLA under section 351 of the PHS Act will not be considered for the 503A bulks list. See the guidance for industry *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* (January 2018) for FDA's policies regarding State-licensed pharmacies, Federal facilities, and outsourcing facilities that mix, dilute, or repackage biological products outside the scope of an approved BLA.

[17] The nonprescription finished drug product Maalox was nominated. Maalox is not a bulk drug substance.

[18] See section 503A(b)(1)(C) of the FD&C Act. See also 21 CFR 216.24. The four substances are: chloroform reagent, cobalt chloride hexahydrate, cobalt gluconate, and phenacetin.

[19] An extract of cannabidiol (CBD) and tetrahydrocannabinol (THC) derived from marijuana (marihuana) was nominated. This is a Schedule I substance.

The CSA does not allow possession or distribution of Schedule I substances (21 USC 841(a)(1) and 829), except for research purposes (21 U.S.C. 823(f)), and these substances will not be considered for the 503A bulk drug substances list at this time. Those desiring to do research on a Schedule I substance can apply to do so under an investigational new drug application (IND).

- Of the substances that are not components of an approved drug or the subject of an applicable USP or NF monograph, that are not included on Schedule I of the CSA, and do not appear on the withdrawn or removed list, approximately 350 substances were nominated without sufficient supporting evidence for FDA to evaluate them.

- The remaining substances may be eligible for inclusion on the 503A list and were nominated with sufficient supporting information for FDA to evaluate them. However, FDA has identified significant safety risks relating to the use of some of these bulk drug substances in compounded drug products.

FDA's website identifies the following categories of substances nominated for the 503A bulks list:[20]

503A Category 1 – Substances Nominated for the Bulks List Currently Under Evaluation: These substances may be eligible for inclusion on the 503A bulks list, were nominated with sufficient supporting information for FDA to evaluate them, and do not appear on any other list.

503A Category 2 – Substances Nominated for the Bulks List That Raise Significant Safety Risks: These substances were nominated with sufficient supporting information to permit FDA to evaluate them, and they may be eligible for inclusion on the 503A bulks list. However, FDA has identified significant safety risks relating to the use of these substances in compounding pending further evaluation, and therefore does not intend to adopt the policy described for the substances in Category 1. If FDA adds a substance to Category 2, it will publish a public communication (e.g., a safety alert) describing the safety risks and will post

[20] See https://www.fda.gov/media/94155/download. As discussed in the July 2014 Federal Register notice requesting nominations for the 503A bulks list (79 FR 37742), nominators were to confirm that all substances nominated for the list are active ingredients that meet the definition of a "bulk drug substance." Inclusion of a substance in any of these categories does not reflect a determination by FDA that the substance is a bulk drug substance. Whether a substance is a bulk drug substance subject to the conditions in section 503A(b)(1)(A) depends on whether it meets the definition of a bulk drug substance in 21 CFR 207.3. If the substance is used in a compounded drug as an inactive ingredient, then it does not meet the definition of a bulk drug substance in 21 CFR 207.3, is not subject to the conditions in section 503A(b)(1)(A), and need not appear on the 503A bulks list to be eligible for use in compounding. Instead, when used as an inactive ingredient, the substance is subject to the conditions in section 503A(b)(1)(B), which applies to ingredients other than bulk drug substances used in compounded drugs.

the communication on FDA's human drug compounding website,[21] advising that the substance has been added to Category 2 and, is no longer within the scope of the policies regarding substances in Category 1.

503A Category 3 – Substances Nominated for the Bulks List Without Adequate Support: These substances may be eligible for inclusion on the 503A bulks list but were nominated with insufficient supporting information for FDA to evaluate them. These substances can be re-nominated with sufficient supporting information through a docket that FDA has established, as discussed below in section III.B.

3. Process for Developing the 503A List

FDA is currently evaluating the substances that were nominated for the 503A bulks list with sufficient information to permit evaluation. FDA is considering a number of factors in prioritizing the order in which it reviews the nominated bulk drug substances, including but not limited to the following:

- Safety concerns about use of the bulk drug substance in compounding
- Whether the bulk drug substance was nominated by multiple parties or identified as necessary by medical professional organizations
- The efficiency with which the evaluation can be completed, based on ease of acquiring the necessary information to conduct the review, available resources, and other logistical issues

FDA may also group some nominated drug substances to facilitate efficient review and discussion. These include drugs that raise similar issues (e.g., vitamins or botanicals) or have been nominated for the treatment of the same condition (e.g., warts).

In conducting its evaluations, FDA reviews the information provided in support of the nomination and other available information to assess each bulk drug substance according to the following four criteria:[22]

- The physical and chemical characterization of the substance
- Any safety issues raised by the use of the substance in compounded drug products

[21] See https://www.fda.gov/drugs/guidance-compliance-regulatory-information/human-drug-compounding. FDA also encourages compounding facilities to subscribe to FDA's list serve to receive updates at: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/human-drug-compounding#subscribe.

[22] See 21 CFR 216.23(c).

- 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

- The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists

In evaluating candidates for the 503A bulks list under these criteria, FDA is using a balancing test. No single one of these criteria is dispositive; rather, FDA is considering each criterion in the context of the others and balancing them, on a substance-by-substance basis, to evaluate whether a particular substance is appropriate for inclusion on the list.

Once the evaluation of a substance is complete, FDA will present the results of its review to the PCAC to obtain its advice on whether to include the substance on the list.[23]

Section 503A requires that FDA create the 503A bulks list by regulation in consultation with the USP. To this end, FDA has been periodically meeting with USP and discussing the list. FDA will publish a notice of proposed rulemaking (NPRM) that identifies substances FDA proposes for placement on the 503A bulks list and the substances FDA has evaluated but is not proposing to include on the 503A bulks list. After publication of the NPRM, the public will have an opportunity to comment on the proposed rule. After considering the comments submitted to the docket, FDA will publish a final rule that establishes the 503A bulks list and identifies the substances that were considered and will not be placed on the list. FDA does not intend to evaluate all of the sufficiently supported nominations before publishing the first NPRM. Instead, after FDA has made a decision on whether to propose a group of substances (e.g., 10 substances) it intends to publish an NPRM with respect to that group of substances and continue to prepare the list on a rolling basis.

A final rule will list the substances that FDA has determined can be used in compounding under section 503A and those substances that have been evaluated and not placed on the section 503A bulks list, if any.

After a final rule is published, drug products compounded using the substances on the 503A bulks list will be eligible for the section 503A exemptions provided the drug product is compounded in compliance with the other conditions of section 503A. Those substances that have been evaluated and not placed on the 503A bulks list will no longer be within the scope of policies described in this guidance.

C. Categorization Under FDA's Interim Policy

Section 503A of the FD&C Act directs FDA to establish a list of bulk drug substances that can be used in compounding under that section. After enactment of the Drug Quality and Security Act (DQSA) in 2013, FDA engaged in renewed efforts to implement section 503A, including the condition concerning bulk drug substances. However, because FDA had not yet promulgated regulations to develop the 503A bulks list, compounded drug products containing such bulk drug

[23] See section 503A(c)(1) of the FD&C Act.

substances were not eligible for the exemptions in section 503A. Stakeholders advised FDA that some of these compounded drug products, which patients may have received prior to the DQSA's enactment, were important for patient care. In 2016, FDA issued a guidance setting forth its interim policy on compounding using bulk drug substances by State-licensed pharmacies, Federal facilities, and physicians (not registered as outsourcing facilities). The guidance explained that the purpose of the interim policy was to "avoid unnecessary disruption to patient treatment while the Agency considers the bulk drug substances that were nominated with sufficient support to permit FDA to evaluate them."[24] As described in the guidance, FDA categorized bulk drug substances that had been nominated by a certain date and explained an interim policy under which the Agency did not intend to take action against a State-licensed pharmacy, Federal facility, or licensed physician for compounding drug products using those bulk drug substances if certain conditions were met. However, stakeholders advised FDA that, less than 3 years after DQSA was enacted, certain compounded drug products containing bulk drug substances that had not yet been nominated were important for patient care. Accordingly, in 2017, FDA published a guidance revision (guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (January 2017) (2017 503A Interim Policy Guidance)) to provide for ongoing categorization of newly nominated bulk drug substances.

As discussed further below, since FDA developed the 2017 503A Interim Policy Guidance, stakeholders have had substantial opportunity to nominate new bulk drug substances for categorization. As reflected in the updated policy described in section III below, FDA has determined that ongoing categorization of newly nominated substances, as described in the 2017 503A Interim Policy Guidance, no longer serves the interim policy's stated objective of avoiding unnecessary disruption to patient treatment and does not otherwise benefit public health. Categorizing substances nominated on or after the date of finalization of this guidance would unnecessarily expose patients to the risks associated with drugs compounded from such bulk drug substances.

Drug products compounded from bulk drug substances nominated for inclusion on the 503A bulks list may present particular risks when FDA has not yet completed the process to conclude whether they will be placed on the 503A bulks list, and because they are not the subject of an applicable USP or NF monograph or components of an FDA-approved drug. When FDA evaluates bulk drug substances nominated for the list, Agency medical and scientific experts examine the physical and chemical characterization of the substance; any safety issues raised by the use of the substance in compounded drug products; historical use of the substance in compounded drug products; and available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists. FDA considers whether these criteria, on balance, weigh in favor or against inclusion of the bulk drug substance on the 503A bulks list. An advisory committee and the USP provide expert advice, and FDA engages in notice-and-comment rulemaking, taking into consideration any public comments received. Although FDA's evaluation of a substance for the 503A bulks list is, necessarily, far less rigorous and less comprehensive than the Agency's review of drugs as part of the new drug

[24] See the guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (June 2016), available at https://www.regulations.gov/docket/FDA-2015-D-3517/document.

approval process, this evaluation process is important to reduce the risk of patient harm and the risk of patients receiving ineffective treatments.

In the early days of DQSA implementation, FDA recognized that patients may have a medical need for treatment with certain drugs that they may have received prior to enactment of the DQSA, but that were compounded from bulk drug substances that the Agency had not yet evaluated for inclusion on the 503A bulks list. In developing the 2017 503A Interim Policy Guidance, FDA weighed these public health interests and concluded that, at that early stage of section 503A implementation, the potential patient benefits of such a policy outweighed the risks. Importantly, FDA characterized the guidance as an *interim* policy because the Agency intended for it to be temporary. For the reasons that follow, FDA is ending categorization of newly nominated substances because the Agency believes such a policy no longer serves the guidance's stated objective of preventing unnecessary disruption to patient treatment and, therefore, the balance of public health interests supporting the policy has changed.

In the approximately 6x years since FDA issued the 2017 503A Interim Policy Guidance providing for ongoing categorization of bulk drug substances newly nominated to the October 2015 docket, nominators have had substantial opportunity to nominate bulk drug substances with sufficient supporting information for placement in Category 1. A substance that has not been used to compound drug products during that period cannot reasonably be considered necessary to avoid disruption to patient treatment. Nor do we expect the policy in section III.B to adversely affect market stability because, among other reasons, FDA intends to retain the policy, described in section III.A of this guidance, for bulk drug substances already categorized. In addition, FDA intends to continue to receive and evaluate new nominations for inclusion on the 503A bulks list consistent with the process and criteria established in the FD&C Act and FDA regulations.

Accordingly, the balance of public health interests relating to categorization of newly nominated bulk drug substances has changed. As discussed above, the statutory and regulatory process for evaluating such bulk drug substances ensures that FDA, independent medical and scientific experts, and the public can carefully consider a bulk drug substance before it may appear on the 503A bulks list. During this process, FDA may, for example, uncover safety risks or effectiveness concerns, or concerns about the physical and chemical characterization of the substance, that could place patients at risk. These concerns may not be apparent until FDA and other experts conduct an in-depth review of the substance for consideration for the 503A bulks list.[25] FDA also believes that the public health is best served by FDA leveraging its limited resources to develop the 503A bulks list rather than to categorize newly nominated substances.

FDA does, however, recognize that certain substances that currently appear in Category 1 may be important for patient care and that the Agency has not yet made a final determination as to whether these substances will appear on the 503A bulks list. Thus, at this time, FDA is retaining the policy outlined in section III.A of this guidance until the Agency addresses these substances

[25] Prior to placing an adequately supported substance in Category 1, it is FDA's practice to preliminarily assess whether the substance appears to present significant safety risks such that it should be placed in Category 2. However, some risks may not be apparent until FDA conducts the complete evaluation in accordance with the established criteria, consults with the advisory committee and USP, and obtains public comment.

in a final rule, or unless the Agency removes the substances from Category 1 based on, for example, information about safety risks.

III. POLICY

As discussed below, FDA does not intend to categorize bulk drug substances that the public nominates for inclusion on the 503A bulks list on or after the date this guidance is finalized.[26] Although the Agency intends to continue to receive and evaluate new nominations of bulk drug substances for possible inclusion on the 503A bulks list, FDA does not intend to place such bulk drug substances in categories published on FDA's website prior to evaluating them in accordance with section 503A(c). FDA is evaluating bulk drug substances nominated for the 503A bulks list on a rolling basis.

A. Compounding From Bulk Drug Substances Nominated for the 503A Bulks List

Under section 503A of the FD&C Act, a bulk drug substance that is not the subject of an applicable USP or NF monograph or is not a component of an FDA-approved drug cannot be used in compounding unless it appears on a list promulgated as a regulation pursuant to section 503A(b)(1)(A)(i)(III) of the FD&C Act. This list will be codified at 21 CFR part 216 subpart E.

However, until a substance has been evaluated and is identified in a final rule as being included or not included on the 503A bulks list, FDA does not intend to take action against a State-licensed pharmacy, Federal facility, or licensed physician compounding a drug product using a bulk drug substance that is not a component of an FDA-approved drug product and that is not the subject of an applicable USP or NF monograph, provided that the following conditions are met:

(1) The bulk drug substance appears in 503A Category 1 on FDA's website at https://www.fda.gov/media/94155/download. A Category 1 substance may be eligible for inclusion on the 503A bulks list, was nominated with sufficient supporting information for FDA to evaluate it and has not been identified by FDA as a substance that presents a significant safety risk in compounding prior to the publication of a final rule;

(2) The original manufacturer and all subsequent manufacturers of the bulk drug substance are establishments that are registered under section 510 (including foreign establishments that are registered under section 510(i) of the FD&C Act);

(3) The bulk drug substance is accompanied by a valid COA; and

[26] FDA recognizes that some compounders and other stakeholders may currently be in the process of compiling a bulk drug substance nomination for submission to the Agency. As noted above, FDA intends to categorize nominations of bulk drug substances received prior to the date FDA announces the availability of the final guidance. FDA believes that this will provide a sufficient amount of time in which to submit nominations that are currently in progress.

(4) The drug product compounded using the bulk drug substance is compounded in compliance with all other conditions of section 503A of the FD&C Act.

Original manufacturer means the entity that originally produced the bulk drug substance and not a subsequent packer, repacker, labeler, or distributor.

Drug products compounded using a bulk drug substance that does not meet each of the above conditions are not within the scope of the policy described in this guidance. For example, drug products compounded from the following bulk drug substances are not within the scope of the policy: (1) substances not nominated for the 503A bulks list or that were nominated on or after the date this guidance is finalized; (2) substances that are the subject of a final rule concluding that they will be included, or not included, on the 503A bulks list;[27] and (3) substances that are the subject of an applicable USP or NF monograph or a component of an FDA-approved drug.[28]

B. Substances Not Nominated, Nominated Without Adequate Support, or Nominated On or After the Date of Publication of This Guidance

As stated above, one of the categories of bulk drug substances FDA has identified on its website contains nominated substances that may be eligible for inclusion on the 503A bulks list, but that FDA is unable to evaluate for inclusion on the list at this time because the substances were nominated with insufficient supporting evidence for FDA to evaluate them (503A Category 3). New nominations for these substances with sufficient supporting information or nominations for substances that were not previously nominated can be submitted to the October 2015 docket.

After a substance is nominated to the October 2015 docket,[29] FDA will determine whether the nomination is supported with sufficient information to allow FDA to evaluate it.

Previously, after FDA made that determination, the nominated substance was placed in one of the three categories described in section II.B.2. above, and the categorization was published on the FDA website. Section III.A. of this guidance sets forth a policy that addresses substances once they have been categorized. This guidance retains the policy described in section III.A. with respect to substances that currently appear in the categories described in section II.B.2.

However, with respect to substances nominated on or after the date this guidance is finalized, including new nominations of substances that currently appear in Category 3,[30] FDA no longer intends to place such substances into the categories described in section II.B.2. Accordingly, substances nominated on or after the date this guidance is finalized are not within the scope of the policy described in section III.A of this guidance. FDA intends to continue to evaluate such

[27] See section 503A(b)(1)(A)(i)(III) of the FD&C Act.

[28] These substances are eligible for use in compounding under section 503A without appearing on the 503A bulks list. See section 503A(b)(1)(A)(i)(I), (II) of the FD&C Act.

[29] This includes new nominations of substances submitted with sufficient supporting information.

[30] This includes new nominations of substances in Category 3 that include sufficient supporting information to permit FDA evaluation for the 503A bulks list.

substances, provided they are nominated with sufficient supporting information to permit an evaluation, for inclusion on the 503A bulks list pursuant to section 503A(a)(2)(b)(1)(A)(i)(III) of the FD&C Act.

C. Comments About Nominated Bulk Drug Substances

If you feel that a substance that you nominated prior to finalization of this guidance does not appear on the appropriate category as described in this guidance you can submit your comment to docket number FDA-2015-N-3534. If you have additional information on a previously nominated substance that was placed in Category 3, you can submit a new nomination for the substance that includes the additional information. Consistent with the policy described in section III.B. of this guidance, FDA does not intend to categorize the substance if the new nomination is submitted on or after the date this guidance is finalized. However, provided the new nomination includes sufficient supporting information to permit an evaluation, FDA expects to consider the substance for inclusion on the 503A bulks list.

A nominator may also submit a comment to the docket requesting withdrawal of any of its nominations. If the substance that is the subject of such nomination appears in one of the categories, and the party nominating the substance was the sole nominator, FDA will update the categories described in this guidance to reflect the withdrawn nomination.[31] FDA intends to provide notice to the public before removing any nominated substances from Category 1 or Category 2.

Withdrawal of a nomination upon the nominator's request and, if applicable, a resulting update to the categories described in this guidance, do not reflect a determination by FDA regarding the validity of the nomination or of any reasons given by the nominator for requesting withdrawal. In addition, FDA may continue to evaluate a substance at its discretion even if the nominator submits a comment requesting withdrawal of the nomination.

[31] If multiple parties nominated the same substance, each party that nominated the substance must withdraw its nomination for the nominated substance to be considered withdrawn and for the categories to be updated, if applicable, to reflect that withdrawal.