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

Guidance for Industry

DRAFT GUIDANCE

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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

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Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 the Agency) interim regulatory policy concerning compounding by outsourcing facilities registered under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [2] using bulk drug substances. Section 503B of the FD&C Act (21 U.S.C. 353b) includes certain restrictions on the bulk drug substances that outsourcing facilities can use 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 that list of bulk drug substances (the 503B bulks list), and this guidance describes FDA's interim regulatory policy regarding outsourcing facilities that compound human drug products using bulk drug substances while the list is being developed.[3,4]

This draft guidance, when finalized, will revise FDA's current interim policy.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FDA's policy with respect to bulk drug substances that are nominated for inclusion on the 503B bulks list before the draft guidance is finalized. In contrast, bulk drug

[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] *Outsourcing facility* refers to a facility that meets the definition of an outsourcing facility under section 503B(d)(4) of the FD&C Act.

[3] 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.

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

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 503B bulks list consistent with the process and clinical need standard established in the FD&C Act.

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 503B

Section 503B of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by an outsourcing facility 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 582 (concerning drug supply chain security requirements).

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for these exemptions is that the outsourcing facility does not compound drug products using a bulk drug substance unless (a) it appears on a list established by the Secretary of Health and Human Services identifying bulk drug substances for which there is a clinical need, or (b) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FD&C Act at the time of compounding, distribution, and dispensing (section 503B(a)(2)(A) of the FD&C Act).

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 503B(a)(2) and 21 CFR 207.3).[5,6]

Bulk drug substances used in compounding under section 503B must also meet certain other requirements, including: (1) if an applicable monograph exists under the United States Pharmacopeia (USP), National Formulary (NF), or another compendium or pharmacopeia recognized by the Secretary for purposes of this paragraph, the bulk drug substance complies with the monograph; (2) the bulk drug substance must be manufactured by an establishment that is registered under section 510 of the FD&C Act; and (3) the bulk drug substance must be accompanied by a valid certificate of analysis (COA) (section 503B(a)(2) of the FD&C Act).

B. Section 503B Bulks List

1. Section 503B Bulks List History

Section 503B, added to the FD&C Act by the Drug Quality and Security Act in 2013, requires that FDA create a list of bulk drug substances for which there is a clinical need by publishing a notice in the *Federal Register* proposing bulk drug substances for inclusion on the list, providing a public comment period of 60 calendar days, and then publishing a notice in the *Federal Register* designating bulk drug substances for inclusion on the list. See section 503B(a)(2)(A)(i) of the FD&C Act. In the December 4, 2013, *Federal Register* (78 FR 72838), FDA published a notice 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 503B of the FD&C Act.

2. Nominations for the 503B Bulks List

In response to the December 2013 *Federal Register* notice, over 2,000 substances were nominated for the 503B bulks list. However, many of the nominations for the 503B bulks list were not for substances used in compounding as active ingredients, or they did not include sufficient information to allow FDA to evaluate the nominated substances for placement on the list. To improve the efficiency of the process for developing the 503B bulks list, FDA reopened the nomination process in July 2014 (79 FR 37750) and provided more detailed information on what it needs to evaluate nominations for the list. FDA stated that bulk drug substances that were previously nominated would not be further considered unless they were renominated, and

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[5] Section 503B references the definition of bulk drug substance in FDA's drug establishment registration and listing regulations, which was codified at 21 CFR 207.3(a)(4) at the time section 503B was enacted. On Aug 31, 2016, FDA published a final rule in the Federal Register to update its registration and listing regulations in 21 CFR part 207, which made minor changes to the definition of bulk drug substance and moved the definition to 21 CFR 207.3. The definition is also found in 21 CFR 207.1. 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 503B(a)(2) 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 503B(a)(3), inactive ingredients used in compounding must comply with the standards of an applicable United States Pharmacopeia or National Formulary monograph, if a monograph exists.

those nominations were adequately supported. Substances that were not adequately supported would not be evaluated by FDA to be placed on the 503B bulks list. The notice stated that the following information about clinical need is necessary to provide adequate support for nominations to the 503B bulks list:

- A statement describing the medical condition(s) that the drug product to be compounded with the nominated bulk drug substances is intended to treat;

- A list of FDA-approved drug products, if any, that address the same medical condition;

- If there are any FDA-approved drug products that address the same medical condition, an explanation of why a compounded drug product is necessary;

- If the approved drug product is not suitable for a particular patient population, an estimate of the size of the population that would need a compounded drug product;

- A bibliography of safety and efficacy data for the drug product compounded using the nominated substance, if available, including any relevant peer-reviewed medical literature; and

- If there is an FDA-approved drug product that includes the bulk drug substance nominated, an explanation of why the drug product proposed to be compounded must be compounded from bulk rather than with the FDA-approved drug product.

In the *Federal Register* of October 27, 2015 (80 FR 65770), FDA established a docket (October 2015 docket) where new nominations for these substances can be submitted with sufficient supporting 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 2,590 unique substances were nominated. Of those nominated substances:

- Approximately 1,740 are biological products (these are individual allergenic extracts) subject to approval in a biologics license application (BLA) under section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262).

  These products are not eligible for the 503B 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 503B.[7] No biological products subject to approval in a BLA will be considered for the 503B bulks list.

[7] 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.

- At least one[8] 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 503B bulks list because they do not meet the definition of a bulk drug substance in 21 CFR 207.3.

- At least five of the nominated substances appear on the list of drugs 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).

  Such substances cannot be used in compounding under section 503B of the FD&C Act, and therefore are not eligible for inclusion on the 503B bulks list.[9]
- 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)).[10]

  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 (21 U.S.C. 823(f)), and these substances will not be considered for the 503B bulks 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 may be eligible for use in compounding under section 503B, approximately 650 substances were nominated without sufficient supporting evidence for FDA to evaluate them.

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

FDA's website identifies the following categories of substances nominated for the 503B bulks list:[11]

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

[9] See section 503B(a)(4) of the FD&C Act. See also 21 CFR 216.24. The five substances are: chloroform reagent, cobalt chloride hexahydrate, cobalt gluconate, methapyrilene fumarate, and phenacetin.

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

[11] https://www.fda.gov/drugs/human-drug-compounding/bulk-drug-substances-used-compounding-under-section-503b-fdc-act. As discussed in the July 2014 *Federal Register* notice requesting nominations for the 503B bulks list (79 FR 37747), 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

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

503B 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 503B 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 the communication on FDA's human drug compounding website[12] advising that the substance has been added to Category 2 and, is not within the scope of the policies regarding substances in Category 1.

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

3. Process for Developing the 503B Bulks List

FDA is currently evaluating the bulk drug substances nominated for the 503B bulks list with sufficient supporting information for evaluation. FDA is considering a number of factors in prioritizing the order in which it reviews these 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

subject to the conditions in section 503B(a)(2) 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 503B(a)(2), and need not appear on the 503B 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 503B(a)(3), which applies to ingredients other than bulk drug substances used in compounded drugs.

[12] 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/human-drug-compounding/information-outsourcing-facilities#subscribe.

- 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 drug substances that raise similar issues (e.g., vitamins or botanicals) or that are nominated for the treatment of the same condition (e.g., warts).

FDA intends to publish a notice in the *Federal Register* that describes its proposed position on each substance it has evaluated along with the rationale for that proposal, for public comment. We note that there is no requirement in section 503B to consult the Pharmacy Compounding Advisory Committee (PCAC) before developing a 503B bulks list, as is required by section 503A(c)(1) for the 503A bulks list. However, after considering public comment on the nominated substances, FDA will determine whether PCAC input on any of the substances would be helpful to the Agency in making its determination, and if so, it will seek PCAC input. Once FDA makes a determination, it will publish in the *Federal Register* a list identifying the bulk drug substances for which it has determined there is a clinical need and FDA's rationale in making that determination. FDA will also publish in the *Federal Register* a list of those substances it considered but found that there is no clinical need to use in compounding and FDA's rationale in making this determination.

Once FDA publishes a 503B bulks list in the *Federal Register* that reflects its determination regarding particular bulk drug substances, drug products compounded with substances on the 503B bulks list will be eligible for the 503B exemptions, provided the drug products are compounded in compliance with the other conditions of section 503B.[13] Once FDA has published in the *Federal Register* its decision not to place a particular substance on the 503B bulks list, the substance is no longer within the scope of the policy described in this guidance.

FDA intends to evaluate the substances nominated for the 503B list on a rolling basis. FDA will begin by publishing a *Federal Register* notice identifying a group of substances (e.g., 10 substances) that it has considered and whether it proposes the substances for inclusion on the list. Under section 503B, an outsourcing facility may only compound using bulk drug substances that are on FDA's 503B bulks list or that are used to compound drugs that appear on the shortage list in effect under section 506E of the FD&C Act at the time of compounding, distribution, and dispensing. To avoid unnecessary disruption to patient treatment while FDA considers the substances that were nominated with sufficient support to permit FDA to evaluate them, FDA is issuing this guidance stating that at this time it does not intend to take action against an outsourcing facility for failing to compound in accordance with section 503B(a)(2) if certain conditions are met. Those conditions include that the nomination for the relevant bulk drug substance appears on Category 1 on FDA's website. As described below, FDA does not intend to categorize bulk drug substances as described in section II.B.2 on or after the date this guidance is finalized.

[13] See section 503B(a)(11) of the FD&C Act.

C. Categorization Under FDA's Interim Policy

Section 503B of the FD&C Act directs FDA to establish a list of bulk drug substances for which there is a clinical need.[14] Stakeholders advised FDA that some of the compounded drug products which patients may have received before enactment of the Drug Quality and Security Act (DQSA) in 2013 were important for patient care. Stakeholders further advised FDA that some of the compounded drug products containing nominated bulk drug substances were important for "office stock" or for "office use" by hospitals, clinics, or health care practitioners to administer to patients who present with an immediate need for a compounded drug product.[15] In 2016, FDA issued a guidance setting forth its interim policy on compounding using bulk drug substances by 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."[16] 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 an outsourcing facility for compounding drug products using those bulk drug substances if certain conditions were met. However, stakeholders advised FDA that, less than three 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 (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) (2017 503B Interim Policy Guidance)) to provide for ongoing categorization of bulk drug substances newly nominated to the October 2015 docket.

As discussed further below, since FDA developed the 2017 503B 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 503B 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 503B bulks list may present particular risks when FDA has not yet completed the process to conclude

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[14] See section 503B(a)(2)(A)(i) of the FD&C Act.

[15] In contrast to compounders operating under section 503A, outsourcing facilities can distribute compounded drug products to healthcare practitioners or healthcare facilities without first receiving a prescription for an identified individual patient. Compare sections 503B(d)(4)(C) and section 503A(a) of the FD&C Act; see also the guidance for industry *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (December 2016).

[16] See the guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (June 2016) at 7, available at https://www.regulations.gov/docket/FDA-2015-D-3539/document.

whether they will be placed on the 503B bulks list. Pursuant to the clinical need standard in section 503B(a)(2)(A) of the FD&C Act, FDA places a bulk drug substance on the 503B bulks list if the Agency concludes that there is a clinical need for an outsourcing facility to compound a drug product, and the drug product must be compounded using the bulk drug substance.[17] Under this standard, FDA proposes adding a bulk drug substance to the 503B bulks list only after Agency medical and scientific experts have, among other things, evaluated the physical and chemical characterization of the substance; any safety issues raised by the use of the substance in compounded drug products; current and 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, and preliminarily concluded that these factors weigh in favor of inclusion of the bulk drug substance on the list. FDA must consider public comment regarding a proposal before making its final determination.[18] Although FDA's evaluation of a substance for the 503B bulks list is, necessarily, far less rigorous and less comprehensive than the Agency's review of drugs as part of the new drug approval process, this evaluation process for clinical need is important to help limit patient exposure to compounded drug products, which have not been demonstrated to be safe and effective, to those situations in which the compounded drug product is necessary for patient treatment, and serves an important role in preserving the integrity of the drug approval process.[19]

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 503B bulks list. In developing the 2017 503B Interim Policy Guidance, FDA weighed these public health interests and concluded that, at that early stage of section 503B 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 6 years since FDA issued the 2017 503B 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

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[17] In addition, with respect to a bulk drug substance that is a component of an FDA-approved drug, FDA considers whether there is an attribute of the FDA-approved drug that makes it medically unsuitable for the proposed condition and the compounded drug is intended to address that attribute, and whether the drug must be compounded from a bulk drug substance. See the guidance for industry *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (March 2019) (503B Evaluation Guidance) at 9.

[18] Sections 503B(a)(2)(A)(i)(II) and (III) of the FD&C Act.

[19] 503B Evaluation Guidance at 9.

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 placed in existing Category 1. In addition, FDA intends to continue to receive and evaluate new nominations for inclusion on the 503B bulks list consistent with the process and clinical need standard established in the FD&C Act.

Accordingly, the balance of public health interests relating to categorization of newly nominated bulk drug substances has changed. As discussed above, FDA's process for evaluating and proposing inclusion of bulk drug substances on the 503B bulks list ensures that FDA and the public can carefully consider a bulk drug substance nominated for the 503B bulks list before outsourcing facilities can use it in compounding under section 503B. 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 503B bulks list.[20] FDA also believes that the public health is best served by FDA leveraging its limited resources to develop the 503B 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 503B bulks list. Thus, at this time, FDA is retaining the policy outlined in section III.A of this guidance until the Agency publishes a notice in the *Federal Register* making a final listing determination, 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 503B bulks list on or after the date this guidance is finalized.[19] Although the Agency intends to continue to receive and evaluate new nominations of bulk drug substances for possible inclusion on the 503B 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 503B(a)(2). FDA is evaluating bulk drug substances nominated for the 503B bulks list on a rolling basis.

[20] 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 under the statutory clinical need standard and obtains public comment.

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

Under section 503B of the FD&C Act, a bulk drug substance cannot be used in compounding unless it is used to compound a drug that appears on the FDA drug shortage list at the time of compounding, distribution, and dispensing, or it appears on the 503B bulks list.

FDA does not intend to take action against an outsourcing facility for compounding a drug product using a bulk drug substance that is not on the 503B bulks list if the drug compounded from the bulk drug substance: (i) appeared on FDA's drug shortage list within 60 days of distribution and dispensing, and (ii) was to fill an order that the outsourcing facility received for the drug while it was on FDA's drug shortage list.[21]

In addition, at this time FDA does not intend to take action against an outsourcing facility for compounding a drug using a bulk drug substance that does not appear on the 503B bulks list and that is not used to compound a drug that appears on the FDA drug shortage list at the time of compounding, distribution, and dispensing, provided that the following conditions are met:

(1) The bulk drug substance appears on 503B Category 1 on FDA's website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Pharmacy Compounding/UCM467374.pdf. A Category 1 substance may be eligible for inclusion on the 503B bulks list, was nominated for inclusion on the 503B bulks list with adequate supporting information for FDA to evaluate it, and has not been identified by FDA as a substance that appears to present a significant safety risk in compounding before a determination as to whether to place it on the 503B bulks list has been made;

(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;

(4) If the bulk drug substance is the subject of an applicable USP or NF monograph, the bulk drug substance complies with the monograph; and

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

[21] An outsourcing facility may not be able to predict when a drug shortage will be resolved, and the facility may have orders for a compounded drug in-house that were in progress when the drug was removed from FDA's drug shortage list (e.g., the outsourcing facility may have compounded a drug while it was in shortage, but the shortage ended while the outsourcing facility awaits the results of sterility testing before release). This policy provides some regulatory flexibility where an outsourcing facility fills orders that it received while a drug was in shortage. However, this policy does not pertain to an outsourcing facility continuing to fill orders received after the shortage ends, or if the outsourcing facility continues to fill orders more than 60 days after the drug was removed from FDA's drug shortage list.

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 this policy: (1) substances not nominated for the 503B bulks list or that were nominated on or after [Insert date of final guidance]; (2) substances that are the subject of a final determination as to whether they will be included, or not included, on the 503B bulks list; (3) substances that are used to compound a drug product on FDA's drug shortage list at the time of compounding, distribution, and dispensing;[22] and (4) substances that are used to compound a drug that appeared on the FDA drug shortage list within 60 days of distribution and dispensing.

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

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 503B 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 (503B 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,[23] 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 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 appear in Category 3,[24] 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 substances, provided they are nominated with sufficient supporting information to permit an evaluation, for inclusion on the 503B bulks list pursuant to section 503B(a)(2) of the FD&C Act.[25]

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[22] See section 503B(a)(2)(A)(ii) of the FD&C Act.

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

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

[25] See also the 503B Evaluation Guidance.

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-3469. 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, if the new nomination includes sufficient supporting information to permit an evaluation, FDA expects to consider the substance for inclusion on the 503B 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.[26] 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.

[26] 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.