

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

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Office of Compliance/OU DLC**

**January 2017  
Compounding and Related Documents  
Revision 1**

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

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## **Guidance for Industry<sup>1</sup>**

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

This guidance represents 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 office 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 or Act). 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.<sup>2,3</sup>

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.

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<sup>1</sup> 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.

<sup>2</sup> This guidance does not apply to drugs compounded from bulk drug substances for use in animals. For proposed policies pertaining to compounding drug products from bulk drug substances for use in animals, see FDA's draft guidance, *Compounding Animal Drugs from Bulk Drug Substances*.

All FDA guidances are available on the FDA guidance web page. FDA updates guidances regularly. To make sure you have the most recent version of a guidance, always consult the guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>3</sup> 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 covered under a separate guidance (see guidance for industry, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*).

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### **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.<sup>4</sup>

A bulk drug substance is defined as meaning “the same as active pharmaceutical ingredient as defined in 21 CFR 207.1(b).” 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 503A(b)(1)(A) and 21 CFR 207.3).<sup>5,6</sup> FDA has interpreted “an applicable USP or NF

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<sup>4</sup> See Section 503A(b)(1)(A)(i) of the FD&C Act.

<sup>5</sup> 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 August 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 (August 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.”

<sup>6</sup> 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 United States Pharmacopeia or National Formulary monograph, if a monograph exists, and the USP chapter on pharmacy compounding.

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monograph” to mean an official USP or NF **drug substance** monograph. 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.<sup>7</sup> 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.”<sup>8</sup>

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).<sup>9</sup>

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 states:

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.<sup>10</sup>

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 has 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*

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<sup>7</sup> See section 503A(c)(2) of the FD&C Act.

<sup>8</sup> See section 503A(c)(2) of the FD&C Act.

<sup>9</sup> See section 503A(b)(1)(A) of the FD&C Act.

<sup>10</sup> See page 5 of the guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

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### *Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug and Cosmetic Act.*

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, FDA has determined that the nomination for the bulk drug substance included adequate information for FDA to evaluate the substance and at this time, the substance does not appear to present significant safety risks.

### **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.<sup>11</sup>

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 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.<sup>12</sup> The proposed rule also described 10 nominated 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).

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<sup>11</sup> 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.

<sup>12</sup> See 64 FR 996, at 997 (January 7, 1999).

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However, after a 2002 U.S. Supreme Court decision holding that certain provisions of section 503A were unconstitutional,<sup>13</sup> 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 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 37742) and provided more detailed information on what it needs to evaluate nominations for the 503A bulks list. 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 response to this request for nominations, approximately 740 unique substances were nominated. Of the 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 [www.USPNF.com](http://www.USPNF.com). To determine if a bulk drug substance is a component of an FDA approved drug, see the FDA's *Orange Book*:

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<sup>13</sup> 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*.

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*Approved Drug Products with Therapeutic Equivalence Evaluations*, available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

- At least one<sup>14</sup> 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 one of the substances is considered a biological product subject to approval in a biologics license application (BLA) under section 351 of the Public Health Service (PHS) Act 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.<sup>15</sup> 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 such drug products or components of such drug products have been found to be unsafe or not effective (withdrawn or removed list).<sup>16</sup>

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)).<sup>17</sup>

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).

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<sup>14</sup> The over-the-counter finished drug product Maalox was nominated. Maalox is not a bulk drug substance.

<sup>15</sup> The nominated substance is sodium hexachloroplatinate (IV) hexahydrate. See the revised draft guidance, *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* for FDA's proposed policies regarding State-licensed pharmacies, Federal facilities, and outsourcing facilities that mix, dilute, or repackage biological products outside the scope of an approved BLA.

<sup>16</sup> 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.

<sup>17</sup> An extract of cannabidiol (CBD) and tetrahydrocannabinol (THC) derived from marijuana (marihuana) was nominated. Marijuana (marihuana) is a Schedule I substance.

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- Of the substances that are not components of an approved drug or the subject of an applicable USP or NF monograph and that are not biological products subject to licensure in a BLA or 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:<sup>18</sup>

**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 the communication on FDA's human drug compounding website,<sup>19</sup> advising that the substance has been added to Category 2 and is no longer eligible for the policies that apply to 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

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<sup>18</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf>. 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.

<sup>19</sup> <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm>. FDA also encourages compounding facilities to subscribe to FDA's list serve to receive updates at: [http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_429](http://service.govdelivery.com/service/subscribe.html?code=USFDA_429).

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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 discussed at the PCAC meeting on February 23, 2015:

- 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, 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.<sup>20</sup>

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<sup>20</sup> See Section 503A(c)(1) of the FD&C Act.

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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 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 not qualify for the policies described for the substances in Category 1.

### **III. POLICY<sup>21</sup>**

#### **A. Compounding from Bulk Drug Substances under Section 503A**

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 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf>. A Category 1 substance may be eligible for inclusion on the 503A bulks list, was nominated with sufficient supporting information for FDA to

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<sup>21</sup> See the Appendix for a chart summarizing FDA's interim policy.

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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
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.

This policy does not apply to a licensed pharmacist in a State-licensed pharmacy or Federal facility, or a licensed physician, that compounds a drug using a bulk drug substance that does not meet each of the above conditions, and the bulk drug substance is not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug.

#### **B. Substances Not Nominated or Nominated Without Adequate Support**

As stated above, one of the categories of bulk drug substances FDA has identified on its website is substances nominated for the 503A bulks list that may be eligible for inclusion on the 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). In the *Federal Register* of October 27, 2015, FDA established a docket (October docket) where these substances can be re-nominated with sufficient supporting information or where nominations for substances that were not previously nominated can be submitted.

After a substance is nominated to the October docket,<sup>22</sup> FDA will determine whether the nomination is supported with sufficient information to allow FDA to evaluate it. After FDA makes that determination, the nominated substance will be placed in one of the three categories described in section II.B.2 above, and the categorization will be published on the FDA website. Once the category of a substance is published, FDA intends to apply the policy described in Section III.A of this guidance to that substance. FDA generally expects to categorize bulk drug substances nominated to the October docket and to publish updated categories on its website on the first business day of each month. Please note that until substances nominated for the October docket have been categorized, the policy does *not* apply to those substances.

#### **C. Comments about Nominated Bulk Drug Substances**

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<sup>22</sup> This includes re-nominations of substances with sufficient supporting information.

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If you feel that a substance that you nominated does not appear on the appropriate list or category as described in this guidance you can submit your comment to docket number FDA-2015-N-3534. If you have new information on a previously nominated substance that was placed in Category 3, the substance can be re-nominated with the additional information.

A nominator may also submit a comment to the docket requesting withdrawal of any of its nominations. If the party nominating the substance was the sole nominator, FDA will update the categories described in this guidance to reflect the withdrawn nomination.<sup>23</sup> 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 the resulting updates 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.

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<sup>23</sup> 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 to reflect that withdrawal.

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### APPENDIX: SUMMARY OF POLICY

The following table summarizes the interim policy for bulk drug substances set forth in this guidance:

| Category  | FDA Policy   |
|---|--|
| <p>The bulk drug substance appears in 503A Category 1 on FDA's website at <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf</a>.</p> <p>Such 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 to present a significant safety risk.</p> | <p>FDA does not intend to take action for compounding a drug product from a bulk drug substance in Category 1 that does not meet the conditions of section 503A(b)(1)(A)(i), provided that the bulk drug substance was manufactured by an establishment registered with FDA under section 510 of the FD&amp;C Act and is accompanied by a valid COA from the entity that originally produced the bulk drug substance and provided that the drug compounded from the bulk drug substance is compounded in compliance with the other conditions of section 503A.</p> |
| <p>The bulk drug substance is a component of an FDA-approved drug and/or the subject of an applicable USP or NF monograph.</p>  | <p>The bulk drug substance can be used in compounding under section 503A of the FD&amp;C Act, provided it complies with the standards of the monograph (if one exists) and is compounded in compliance with the other conditions of section 503A.</p>  |
| <p>The bulk drug substance appears on the withdrawn or removed list.</p>  | <p>The bulk drug substance cannot be used in compounding under section 503A of the FD&amp;C Act. A drug compounded using the bulk drug substance is subject to regulatory action.</p>  |
| <p>The bulk drug substance appears in 503A Category 2 on FDA's website at <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf</a>. The substance has been identified by FDA as presenting a significant safety risk pending further evaluation.</p>   | <p>The bulk drug substance cannot be used in compounding under section 503A of the FD&amp;C Act unless and until FDA publishes a final rule authorizing its use under section 503A.</p>  |
| <p>The bulk drug substance is a biological product subject to approval in a BLA.</p>  | <p>The bulk drug substance is not eligible for the 503A bulks list. FDA has issued a separate draft guidance document describing the Agency's proposed policies concerning mixing, diluting, and repackaging biological products subject to approval in a BLA.<sup>24</sup></p>  |
| <p>The bulk drug substance appears in 503A Category 3 on FDA's website at <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf</a>. The substance may be eligible for inclusion on the 503A bulks list, but was nominated with insufficient supporting information for FDA to evaluate it.</p>   | <p>The bulk drug substance cannot be used in compounding under section 503A of the FD&amp;C Act. See section III.B of this guidance for information about re-nominating substances that were previously nominated with insufficient supporting information.</p>  |

<sup>24</sup> See FDA's revised draft guidance, *Mixing, Diluting, and Repackaging Biological Products Subject to Approval in a Biologics License Application*.