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DRAFT GUIDANCE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 Sara Rothman, CDER Office of Unapproved Drugs and Labeling Compliance (OUDLC) at 301-796-3110.

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

October 2015
Compounding and Related Documents

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TABLE OF CONTENTS

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 or Act) [2] using bulk drug substances. Section 503B of the FD&C Act 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]

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER) and 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] 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.

[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 Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic 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 identifying bulk drug substances for which there is a clinical need, or (b) the drug product 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.

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 originally 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

New 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 bulk drug 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 37747), 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 re-nominated and those nominations were adequately supported. Substances that were already eligible for use in compounding or 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 response to this request for nominations, approximately 2,590 unique substances were nominated. Of the nominated substances:

- Approximately 1,740 are biological products (all but one[5] are individual allergenic extracts) subject to approval in a biologics license application (BLA) under section 351 of the Public Health Service (PHS) Act. These products are not eligible for the 503B bulks list because biological products subject to approval in a BLA under section 351 of

[5] The product is sodium hexachloroplatinate (IV) hexahydrate.

the PHS Act are not eligible for the exemptions in section 503B.[6] No biological products subject to approval in a BLA will be considered for the 503B bulks list.

- At least one[7] of the nominated substances is not a bulk drug substance. Rather, it 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(4). Outsourcing facilities can compound from finished drug products, provided all of the other conditions of section 503B are met. *See* section 503B(a)(3) of the FD&C Act.

- At least four of the nominated substances are radiopharmaceuticals.[8] Compounding of radiopharmaceutical products will be addressed in a separate guidance document, and radiopharmaceuticals will not be considered for the 503B bulks list.

- 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. See section 503B(a)(4) of the FD&C Act.[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 (see 21 U.S.C. § 823(f)), and these substances will not be considered for the 503B bulk drug substances list at this time. Those desiring to do research on a Schedule I substance may 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.

FDA's website, available at

[6] See the draft guidance, *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (BLA).*

[7] The over-the-counter finished drug product Maalox was nominated. Maalox is not a bulk drug substance.

[8] The four substances are sodium iodide I-131, GHRP-2, GHRP-6, and strontium chloride.

[9] See codified list at 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. Marijuana (marihuana) is a Schedule I substance.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf, contains the following lists of substances nominated for the 503B bulk drug substances list:

503B List 1 – Bulk Drug Substances Under Evaluation: These bulk drug 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 List 2 – Bulk Drug Substances That Raise Safety Concerns: These bulk drug 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, because FDA has identified safety concerns relating to the use of these bulk drug substances, FDA has placed them on a list on FDA's website of substances that may not be used in compounding under section 503B while FDA is considering their placement on the 503B bulks list unless FDA publishes a notice in the *Federal Register* authorizing their use under section 503B.

503B List 3 – Bulk Drug Substances Nominated Without Adequate Support: These bulk drug 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 may be re-nominated with sufficient supporting information through a docket that FDA has established, as discussed below in section III.B.

503B List 4 – Bulk Drug Substances That May Not Be Used to Compound Drug Products Under Section 503B (to be developed): These bulk drug substances were considered for inclusion on the 503B bulks list but after publication of a notice in the Federal Register and public comment, FDA determined that they should not be used in compounding under section 503B.

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 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; and
- 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: either recommending that the bulk drug substance be placed on the 503B bulks list or recommending that it not be placed on the list, along with the rationale for the proposal. FDA will solicit public comment on the proposals. 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 the comments on the nominated substances, FDA will determine whether PCAC input on any of the nominations would be helpful to the Agency in making its determination on the nominated substance, and if so, it will seek PCAC input. FDA then will make a final determination and 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 compound drug products with these bulk drug substances.

Once FDA publishes a 503B bulks list in the *Federal Register* that reflects its final determination regarding particular bulk drug substances, drug products compounded with substances on the list will be eligible for the 503B exemptions, provided the drug products are compounded in compliance with the other conditions of section 503B. Under section 503B(a)(11) of the FD&C Act, a compounded drug product can only qualify for the exemptions provided in section 503B if all of the outsourcing facility's compounded drugs are compounded in accordance with section 503B. Therefore, if an outsourcing facility compounds a drug product using a bulk drug substance that FDA has evaluated, and for which FDA has published in the *Federal Register* its determination that the bulk drug substance will not be placed on the 503B bulks list, none of the human drug products compounded by the outsourcing facility will qualify for the exemptions under section 503B unless the drug product compounded from the bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing).

FDA intends to evaluate the substances nominated for the 503B list on a rolling basis. FDA will evaluate and publish its proposed determination for a group of substances (e.g., 10 substances) until all of the nominated substances that were sufficiently supported have been evaluated and either placed on the 503B bulks list or determined not to be appropriate for the list. The substances that have been evaluated and that FDA will not place on the list will appear on 503B List 4 on FDA's website.

To avoid unnecessary disruption to patient treatment while FDA considers the bulk drug substances that were nominated with sufficient support to permit FDA to evaluate them and promulgates the list required under section 503B, FDA is issuing this guidance stating that it does not intend to take action for compounding drug products under section 503B using bulk drug substances that are not on the FDA drug shortage list at the time of compounding if, among other conditions, the nomination included adequate information for FDA to evaluate the substance and FDA has not identified safety concerns about its use in drug compounding.

III. POLICY[11]

A. Compounding from Bulk Drug Substances Under Section 503B

Under section 503B of the FD&C Act, a bulk drug substance cannot be used in compounding unless it appears on the FDA drug shortage list at the time of compounding, distribution, and dispensing, or it appears on a list developed by FDA pursuant to section 503B(a)(2)(A) of the FD&C Act.

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 product compounded from the bulk drug substance appears on the drug shortage list within 60 days of distribution and dispensing.

In addition, until FDA publishes its final determination in the *Federal Register* that a bulk drug substance may or may not be used in compounding under section 503B, FDA does not intend to take action against an outsourcing facility for compounding a drug product using a bulk drug substance that does not appear on the 503B bulks list and is not used to compound a drug product 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 List 1 on FDA's website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf. The 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 safety concerns.

2. The bulk drug substance:

   - Was originally manufactured by an establishment that is registered under section 510 (including a foreign establishment that is registered under section 510(i)) of the FD&C Act (section 503B(a)(2)C of the FD&C Act); and
   - Is accompanied by a valid COA from the original manufacturer. Section 503B(a)(2)(D) 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.

3. If the bulk drug substance is the subject of an applicable USP or NF monograph, the bulk drug substance complies with the monograph. Section 503B(a)(2)(B) of the FD&C Act.

[11] See Appendix A for a summary of FDA's interim policy.

4. 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. Section 503B(a)(11) of the FD&C Act.

An outsourcing facility that compounds a drug product using a bulk drug substance that does not appear on the FDA drug shortage list at the time of compounding, distribution, and dispensing or within 60 days of distribution and dispensing, and that does not meet the four conditions described above is ***not*** eligible for the exemptions in section 503B and could be subject to regulatory action.

B. Bulk Drug Substances Not Nominated or Nominated Without Adequate Support

As stated above, FDA is providing a list on its website of bulk drug substances that may be eligible for inclusion on the 503B bulks list, but that FDA is unable to evaluate for inclusion on the lists because the substances were nominated with insufficient supporting evidence for FDA to evaluate them (503B List 3). In the *Federal Register* of October 27, 2015, FDA has established a docket where these substances can be re-nominated with sufficient supporting information or to receive nominations for substances that were not previously nominated. FDA does not intend to evaluate these submissions until the Agency completes its review of the substances that were nominated for the 503B bulks list with adequate supporting information as described in the July 2, 2014, request for nominations (79 FR 37750).[12]

A. Comments about Nominated Bulk Drug Substances

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-3469.

[12] Patients with medical conditions that need to be treated with drug products that are made from bulk drug substances that cannot be used in compounding may be able to obtain those drug products through FDA's Expanded Access programs. For information about these programs, visit FDA's website at http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm.

APPENDIX: SUMMARY OF POLICY

The following table summarizes the interim policy set forth in this guidance:

Category	FDA Policy
The bulk drug substance appears on 503B List 1 on FDA's website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf. Such substances may be eligible for inclusion on the 503B bulks list, were nominated with adequate supporting information for FDA to evaluate them, and have not been identified by FDA as presenting safety concerns.	FDA does not intend to take action against an outsourcing facility for compounding a drug product from a bulk drug substance that does not meet the conditions of section 503B(a)(2)(A) provided that the bulk drug substance is originally manufactured by an establishment registered with FDA under section 510 of the FD&C Act, is accompanied by a valid COA from the original manufacturer, complies with an applicable USP monograph, if one exists, and provided that the drug compounded from the bulk drug substance is compounded in compliance with the other conditions of section 503B.
The bulk drug substance appears on the withdrawn or removed list.	The bulk drug substance cannot be used in compounding under section 503B of the FD&C Act.
The bulk drug substance appears on 503B List 2 on FDA's website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf. The substance has been identified by FDA as raising safety concerns.	The bulk drug substance cannot be used in compounding under section 503B while FDA is considering its placement on the 503B bulks list unless FDA publishes a notice in the Federal Register authorizing its use under section 503Bof the FD&C Act.
The bulk drug substance is a biological product subject to approval in a BLA.	The substance is not eligible for the 503B 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.[13]
The bulk drug substance is a radiopharmaceutical product.	The substance is not eligible for the 503B bulks list. Compounding radiopharmaceuticals will be addressed in a separate guidance document.
The bulk drug substance appears on 503B List 3 on FDA's website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf. The substance was nominated with insufficient supporting information for FDA to evaluate it.	The bulk drug substance cannot be used in compounding under section 503B of the FD&C Act. See section III.B of this guidance for information about supplementing inadequately supported nominations.
The bulk drug substance appears on 503B List 4 on FDA's website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf.. The substance has been identified by FDA as a substance that should not be used in compounding under section 503B after publication in the *Federal Register* and public comment.	The bulk drug substance cannot be used in compounding under section 503B of the FD&C Act

[13] See FDA's draft guidance, *Mixing, Diluting, and Repackaging Biological Products Subject to Approval in a Biologics License Application (BLA).*