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Evaluation of Bulk Drug
Substances Nominated for Use in
Compounding Under Section
503B 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)**

**March 2019
Compounding and Related Documents**

Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act **Guidance for Industry**

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 **TABLE OF CONTENTS**

- I. INTRODUCTION AND SCOPE 1**
- II. BACKGROUND 2**
 - A. Section 503B of the FD&C Act 2**
 - B. Compounding, Generally 3**
 - C. Compounding Drugs From Bulk Drug Substances 4**
 - D. Process for Developing the 503B Bulks List 6**
- III. POLICY 8**
 - A. Bulk Drug Substance for Which There Is a Clinical Need 9**
 - B. Evaluating Nominated Bulk Drug Substances Under the Statutory Standard 10**

Guidance for Industry¹

Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B 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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION AND SCOPE

This guidance sets forth FDA's policy for evaluating bulk drug substances nominated for use in compounding by outsourcing facilities registered under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b).² Section 503B of the FD&C Act directs FDA to develop a list of bulk drug substances for which there is a clinical need (the 503B Bulks List). Drug products compounded using bulk drug substances on the 503B Bulks List qualify for certain exemptions from the FD&C Act provided the other conditions in section 503B are met. This guidance addresses FDA policies for developing the 503B Bulks List, including the Agency's interpretation of the phrase *bulk drug substances for which there is a clinical need*, as it is used in section 503B. This guidance also addresses the factors and processes by which the Agency intends to evaluate and list bulk drug substances.

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.

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 This guidance addresses FDA's evaluation of bulk drug substances nominated by members of the public for use in compounding under section 503B. FDA may also evaluate bulk drug substances for other reasons, including on its own initiative, and in that case expects that its analysis would generally take into account the factors described in this guidance.

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II BACKGROUND

A. Section 503B of the FD&C Act

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 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications); section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and section 582 (21 U.S.C. 360eee-1) (concerning drug supply chain security requirements).³

Drug products compounded under the conditions in section 503B are not exempt from current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act. Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound.⁴

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for exemptions under section 503B is that the outsourcing facility may not compound a drug using a bulk drug substance unless (a) the bulk drug substance appears on a list established by the Secretary 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.⁵

For purposes of section 503B, *bulk drug substance* is defined to mean “the same as an active pharmaceutical ingredient as defined in 21 CFR 207.1(b).”⁶ *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.”^{7,8}

³ Section 503B(a) of the FD&C Act.

⁴ Section 503B(b)(4), 503B(b)(5), *passim*.

⁵ Section 503B(a)(2)(A) of the FD&C Act.

⁶ 21 CFR 207.3.

⁷ Section 503B(a)(2) and 21 CFR 207.1.

⁸ Inactive ingredients are not subject to section 503B(a)(2) of the FD&C Act and will not be included in the 503B Bulks List because they are not included within the definition of a bulk drug substance. Pursuant to section 503B(a)(3), inactive ingredients used in compounding must comply with the standards of an applicable USP or NF monograph, if a monograph exists.

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Bulk drug substances used in compounding under section 503B must also meet certain other statutory requirements, including the following: (1) if an applicable monograph exists under the United States Pharmacopeia (USP), National Formulary (NF), or another compendium or pharmacopeia recognized by the Secretary under section 503B, the bulk drug substance must comply 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.⁹

B. Compounding, Generally

Compounded drugs can serve an important role for patients for whom an FDA-approved drug product is not appropriate, such as patients who have an allergy and need a medication to be made without a certain dye or hospital inpatients who need infusions of a drug combined with a particular diluent not specified in the approved product labeling. However, they also pose a higher risk to patients than FDA-approved drugs. In 2012, contaminated injectable drug products that a state-licensed compounding pharmacy shipped to patients and health care practitioners across the country caused a fungal meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection.¹⁰ This was the most serious of a long history of outbreaks and other serious adverse events, including overdoses, associated with contaminated, superpotent, or otherwise poor quality compounded drugs.

In response to this outbreak, Congress enacted the Drug Quality and Security Act (DQSA), which, among other things, added new section 503B to the FD&C Act and created the new category of compounders known as outsourcing facilities.¹¹ Drug products compounded by outsourcing facilities in accordance with the conditions of section 503B are exempt from FDA drug approval requirements and the requirement that they be labeled with adequate directions for use.¹² Because compounded drug products are not FDA-approved, they have not undergone FDA premarket review for safety, effectiveness, and quality. Although outsourcing facilities must

⁹ Section 503B(a)(2) of the FD&C Act. A compounded drug product only qualifies for the exemptions in section 503B if it is compounded by an outsourcing facility that compounds all of its drugs, both sterile and nonsterile, in accordance with all of the conditions of section 503B. Sections 503B(a)(11), (d)(4)(A)(iii). A complete list of the statutory conditions that must be met for a drug product to qualify for the exemptions in section 503B appears in the guidance *For Entities Considering Whether to Register as Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

¹⁰ See <http://www.cdc.gov/HAI/outbreaks/meningitis.html>.

¹¹ See Pub.L. No.113-54, §102(a), 127 Stat. 587, 587-588 (2013). Other compounders, which are not the subject of this guidance, are regulated under section 503A of the FD&C Act. These include licensed pharmacists in State-licensed pharmacies or Federal facilities, and licensed physicians, who have not registered as an outsourcing facility with FDA. Drug products compounded by section 503A compounders are exempt from sections 505 (new drug approval requirements), 502(f)(1) (labeling with adequate directions for use), and 501(a)(2)(B) (CGMP requirements) if the conditions of section 503A are met, including that compounding is based on the receipt of valid prescriptions for identified individual patients (section 503A(a)). In general, section 503A compounders do not register with and are not routinely inspected by FDA, and they are primarily overseen by the states.

¹² Section 503B(a).

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comply with CGMP requirements and are inspected by FDA according to a risk-based schedule, their drug products lack a premarket inspection and finding of manufacturing quality that is part of the drug approval process. Because compounded drug products are subject to a lower regulatory standard than FDA-approved drugs, they should not be used by patients who could use an FDA-approved drug.

Outsourcing facilities may or may not obtain prescriptions for identified individual patients and can, therefore, distribute compounded drugs to healthcare practitioners for “office stock” to hold in their offices in advance of patient need.¹³ Given that outsourcing facilities can engage in non-patient specific compounding and distribution of compounded drugs, and given that section 503B does not place conditions on interstate distribution that are applicable to other compounded drugs,¹⁴ the conditions in section 503B, including the limitation on use of bulk drug substances, are critical to prevent outsourcing facilities from growing into conventional manufacturing operations making unapproved new drug products without complying with critical requirements, such as new drug approval.

C. Compounding Drugs From Bulk Drug Substances

An outsourcing facility may be able to prepare a compounded drug product by using an FDA-approved drug product as a starting material. For example, outsourcing facilities may dilute FDA-approved drug products to produce solutions in intravenous bags for infusion by hospitals. Similarly, when pediatric or elderly patients are unable to swallow an FDA-approved tablet, outsourcing facilities sometimes manipulate (e.g., crush) the tablet to produce a liquid.

On other occasions, it may be necessary to compound a drug product using a bulk drug substance for a patient who cannot use an FDA approved drug product or a drug product compounded from an FDA-approved drug product. This may be the case, for example, if certain inactive ingredients that are appropriate for the route of administration of the FDA-approved drug product are not appropriate for another route of administration. Similarly, an outsourcing facility might compound a drug product from a bulk drug substance if there is a well-known, serious allergy in some patients to an inactive ingredient in the approved drug product containing that bulk drug substance.

Section 503B limits the bulk drug substances that outsourcing facilities can use in compounding to those that are used to compound drugs in shortage or that appear on a list developed by FDA of bulk drug substances for which there is a clinical need.¹⁵ Section 503B subjects any bulk drug substance used by an outsourcing facility—irrespective of whether it is a component of an approved drug product—to these conditions.

¹³ Section 503B(d)(4)(C). Compare section 503A(a) (requiring licensed pharmacies and physicians to compound pursuant to patient specific prescriptions); see also *infra* n. 16.

¹⁴ Compare section 503A(b)(3)(B) (describing conditions on interstate distribution applicable to drugs compounded in accordance with section 503A); see also *infra* n. 17.

¹⁵ Section 503B(a)(2)(A)(i), (ii).

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Section 503B includes this limitation, among others, to help ensure that outsourcing facilities do not grow into conventional manufacturing operations making unapproved new drug products without complying with critical requirements, such as new drug approval. Outsourcing facilities, as opposed to other compounders, may compound and distribute drug products for office stock or office use without first receiving a prescription for an individually identified patient¹⁶ and without conditions on interstate distribution that are applicable to other compounded drugs.¹⁷ Because of these differences and others, section 503B places additional or different conditions on drugs compounded by outsourcing facilities, including limitations on the outsourcing facilities' use of bulk drug substances, which are more stringent than those placed on other compounders' use of bulk drug substances.¹⁸ Section 503B requires FDA review of bulk drug substances before outsourcing facilities may use them in compounding outside of the context of a drug shortage. FDA review is not required for the large majority of the bulk drug substances that other pharmacy and physician compounders use, such as components of FDA-approved drug products and drugs that are the subject of an applicable USP or NF monograph. FDA's review provides an important safeguard to help ensure that outsourcing facilities do not use bulk drug substances to compound drug products when there is no clinical need to do so, which, in turn, reduces the potential for them to operate as conventional manufacturers of unapproved new drug products.

In addition, allowing outsourcing facilities to compound a drug product from a bulk drug substance that is a component of an FDA-approved drug product because of, for instance, economic incentives, when the approved drug product, or a drug product compounded from the approved drug product, would be medically appropriate for the patient, would reduce the

¹⁶ By contrast, section 503A of the FD&C Act, concerning compounding by licensed pharmacists in State-licensed pharmacies or Federal facilities, or by licensed physicians, requires that compounding under that section be based on the receipt of a valid prescription for an individually identified patient. This means that the pharmacist or physician compounding under section 503A must compound either: (1) after receiving a valid prescription for an identified, individual patient, or (2) before receiving a patient-specific prescription, in limited quantities, based on a history of receiving valid orders generated solely within the context of an established relationship with the patient or prescriber. See FDA's *Guidance for Industry: Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

¹⁷ Under section 503A, drug products must be compounded in a State (i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or (ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

¹⁸ Licensed pharmacies and physicians that compound drugs under the conditions of section 503A, including the requirement to compound drugs only pursuant to a prescription for an identified individual patient, may use many bulk drug substances by operation of the statute, without action by FDA. See section 503A(b)(1)(A)(i)(I)-(II)(providing that a drug product may be compounded consistent with the exemptions in section 503A if the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances . . . that comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; or if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary.).

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incentive for applicants to seek FDA approval of drugs product. For example, use of bulk drug substances instead of an approved drug product to compound a different formulation, strength, route of administration, or dosage form, rather than simply diluting or otherwise manipulating the approved drug product, reduces the incentive for applicants to invest in and seek FDA approval of such drug products. Furthermore, applicants might not have an incentive to continue marketing their FDA-approved drug products if they face competition from similar drug products compounded from bulk drug substances that have not had to demonstrate safety and efficacy. Limiting outsourcing facilities' use of bulk drug substances to situations in which an approved drug product or a drug product compounded from the approved drug product would not meet an identified medical need helps retain important incentives for applicants to conduct the research and testing necessary to obtain FDA approval and continue to market the approved drug product.

When it is feasible to compound a drug product by starting with an approved drug product, there are also certain benefits of doing so over starting with a bulk drug substance. Approved drug products used in compounding have undergone premarket review for safety, effectiveness, and quality, and are manufactured by a facility that is subject to premarket assessment, including site inspection. After the premarket assessment, FDA conducts routine, risk-based inspections to verify that the manufacturer has systems in place to assure proper design, monitoring, and control of manufacturing processes and facilities. In addition, during pre-market review of FDA-approved drug products, the quality standards and controls with respect to ingredients, and the specific processes and facilities used to produce the bulk drug substance and drug products, are similarly assessed. This includes a review of evidence to evaluate the safety of the bulk drug substance and any inactive ingredients used in the product. For example, FDA evaluates whether the applicant's proposed specifications for purity, potency, and other attributes of the bulk drug substance are appropriate for its use in the drug product, and whether studies demonstrate that the safety of the impurities' levels and the stability of the bulk drug substance through the product's expiration date. In contrast, FDA does not conduct a premarket review of the quality standards, specifications, and controls for bulk drug substances used in compounding. In addition, FDA does not conduct a premarket assessment of the manufacturer of the bulk drug substance, including a premarket site inspection to verify manufacturing operations are under control, prior to bulk drug substances from that facility being used in a compounded drug product.

In sum, section 503B's limitation on the 503B Bulks List to substances for which there is a clinical need serves important public health functions. First, it helps to 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. Second, it preserves the incentives for applicants to invest in the research and testing required to obtain FDA approval and continue to manufacture FDA-approved drug products, thereby helping to maintain a supply of high-quality, safe, and effective drugs.

D. Process for Developing the 503B Bulks List

In the *Federal Register* of December 4, 2013 (78 FR 72838), FDA requested nominations for specific bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List. In response to that request, interested groups and individuals nominated a wide variety of

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substances. However, many of those nominations were not for substances used in compounding as active pharmaceutical ingredients or did not include sufficient information to allow FDA to evaluate the nominated substance. To improve the efficiency of the process for the development of the list of bulk drug substances, FDA reopened the nomination process in the *Federal Register* of July 2, 2014 (79 FR 37750) and provided more detailed information on what it needs to evaluate nominations for the list. On October 27, 2015 (80 FR 65770), the Agency opened a new docket, FDA- 2015-N-3469, to provide an opportunity for interested persons to submit new nominations of bulk drug substances or to re-nominate substances with sufficient information. This docket is currently open.

In June 2016, FDA published the guidance for industry *Interim Policy on Compounding Using Bulk Drug Substance Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.¹⁹ This guidance, which was revised in January 2017, sets forth interim regulatory policies for outsourcing facilities compounding using bulk drug substances and provides information about the Agency's procedures for establishing the 503B Bulks List.

As FDA evaluates bulk drug substances, it intends to publish a notice for public comment in the *Federal Register* that describes its proposed position on each substance along with the rationale for that position.²⁰ After considering any comments on FDA's proposals regarding whether to include nominated substances on the 503B Bulks List, FDA intends to consider whether input from the Pharmacy Compounding Advisory Committee (PCAC) on the nominations would be helpful to the Agency in making its determination, and if so, it may seek PCAC input.²¹ Depending on its review of the docket comments and other relevant information before the Agency, the Agency may finalize its proposed determination without change, it may issue a new proposal, or it may finalize a modification to its proposal to reflect new evidence or analysis regarding clinical need. FDA will then 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 final determination. FDA will also publish in the *Federal Register* a list of those substances it considered but found no clinical need to use in compounding and FDA's rationale in making this decision.

FDA intends to maintain a current list of all bulk drug substances it has evaluated on its website, with separate lists for bulk drug substances it has placed on the 503B Bulks List and those it has decided not to place on the list. FDA will only place a bulk drug substance on the 503B Bulks List where it has determined there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance. If a clinical need to compound drug products using the bulk drug substance has not been demonstrated, based on the information submitted by the nominator and the information considered by the Agency, the Agency will not place a substance on the 503B Bulks List.

¹⁹ We update guidances periodically. To make sure you have the most recent version of a guidance, be sure to check the Agency's guidance website at <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>.

²⁰ This procedure is set forth in section 503B(a)(2)(A)(i).

²¹ Section 503B does not require FDA to consult the PCAC before developing a 503B Bulks List.

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FDA intends to evaluate the substances nominated for the 503B Bulks List on a rolling basis. FDA intends to evaluate and publish in the *Federal Register* its proposed and final determinations in groups of bulk drug substances until all nominated substances that were sufficiently supported have been evaluated and either placed on the 503B Bulks List or identified as bulk drug substances that were considered but determined not to be appropriate for inclusion on the 503B Bulks List.

FDA will not consider a substance for inclusion on the 503B Bulks List if the substance is not eligible for the exemptions available under section 503B, such as biological products subject to licensure in a biologics license application under section 351 of the Public Health Service Act or substances that 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 ineffective.

FDA may take action to remove a bulk drug substance from the 503B Bulks List or modify a listing where appropriate. For example, if a drug product containing the bulk drug substance is approved and there is no longer a clinical need to use the bulk drug substance in compounding, then FDA may remove the bulk drug substance from the 503B Bulks List. Or if a new study reveals significant safety risks associated with a particular strength of the drug product that tips the balance against use of the bulk drug substance in compounding a drug product with that strength, FDA may modify the listing for the bulk drug substance to specify a particular strength. FDA generally intends to make such modifications by issuing a *Federal Register* notice for public comment before finalizing a change.²² Alternatively, individuals and organizations may petition FDA to amend the list (to add or remove bulk drug substances, or to modify a listing) at any time after the substance is addressed in a final *Federal Register* notice (see 21 CFR 10.30).

Below, we discuss the Agency's interpretation of *clinical need* as used in section 503B(a)(2), factors the Agency intends to use to evaluate bulk drug substances that have been nominated, and certain additional procedures the Agency intends to follow during its review.

III. POLICY

In the next section, we discuss how we interpret *bulk drug substances for which there is a clinical need*, and in the following section we provide a more detailed discussion of the analysis we intend to conduct in evaluating bulk drug substances that have been nominated for inclusion on the 503B Bulks List.

²² Different procedures may be appropriate in certain circumstances, e.g., if a listed bulk drug substance is added to the withdrawn and removed list or if drug products compounded with the bulk drug substance are added to the difficult-to-compound list.

A. Bulk Drug Substance for Which There Is a Clinical Need

1. Interpretation of Statutory Standard

Section 503B of the FD&C Act directs FDA to publish a list identifying “bulk drug substances for which there is a clinical need.” FDA interprets this statutory language consistent with the text of section 503B(a)(2)(A) and the purpose of the 503B Bulks List, to mean that the 503B Bulks List may include a bulk drug substance if:

- (1) there is a clinical need for an outsourcing facility to compound a drug product, and
- (2) the drug product must be compounded using the bulk drug substance.

The statutory requirement to create a 503B Bulks List reflects a judgment by Congress that it is necessary for FDA to determine which bulk drug substances are eligible for use in compounding by outsourcing facilities under section 503B outside the context of a drug shortage. FDA’s clinical need assessments are critical safeguards for drug products that qualify for the section 503B exemptions and thus are not subject to requirements of premarket approval, labeling with adequate directions for use, and drug supply chain security. They are one of the checks in section 503B that helps ensure outsourcing facilities do not operate like conventional manufacturers of unapproved new drug products without complying with these requirements. As noted previously, outsourcing facilities can distribute drug products without first receiving prescriptions for individually identified patients and without conditions on interstate distribution applicable to other compounded drugs. As explained above section II.C., FDA’s clinical need assessments help limit patient exposure to compounded drug products that have not been demonstrated to be safe and effective to those situations in which the compounded drug product is necessary for patient treatment, and serve an important role in preserving the integrity of the drug approval process.

The Agency does not interpret supply issues, such as backorders, to be within the meaning of “clinical need” for compounding with a bulk drug substance. We note that section 503B of the FD&C Act already allows compounding from bulk drug substances if the drug product compounded from such bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing. Similarly, FDA does not interpret considerations of cost to be within the meaning of “clinical need.”

FDA generally intends to use the analysis discussed in Part III.B., below, when it applies the statutory standard to evaluate nominated bulk drug substances consistent with this interpretation.

2. Inclusion of a Bulk Drug Substance on the 503B Bulks List

There may be situations in which FDA’s findings, particularly in Part 2 of its clinical need analysis discussed below, indicate that the clinical need for drug product compounding using the bulk drug substance is limited. For example, there may be safety risks associated with a drug product compounded using the bulk drug substance at a higher strength that are not associated

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with compounding at a lower strength. Similarly, evidence of some effectiveness may be available for only certain routes of administration or dosage forms. In cases such as these, the Agency may tailor the entry on the 503B Bulks List to reflect its findings related to clinical need. For example, if the Agency were to find a clinical need for a bulk drug substance to be used to compound a drug product at a specific strength for topical use, it could choose to limit the entry of that bulk drug substance on the 503B Bulks List to use of the substance to compound drug products at a specified strength for topical use.

Additionally, when a bulk drug substance that is a salt or ester of an active moiety is listed, FDA intends to include only that particular salt or ester on the 503B Bulks List. The base compound and other salts or esters of the same active moiety are different bulk drug substances and would therefore not be included.

FDA's evaluation of the clinical need for outsourcing facilities to use the nominated bulk drug substances in compounding will be, necessarily, far less rigorous and less comprehensive than the Agency's review of drug products as part of the new drug approval process. The new drug approval process is conducted based on extensive data submitted in new drug and abbreviated new drug applications, which are not available for the nominated substances. Additionally, the Agency's review during the drug approval process includes premarket evaluation of the specific drug product (i.e., the finished dosage form containing the active ingredient and any inactive ingredients); its proposed labeling; the applicant's chemistry, manufacturing, and controls information; and a premarket assessment of the establishments where approved drug products will be manufactured. The Agency will not have the same type, quality, or amount of information about the drug products proposed to be compounded, when it evaluates whether there is a clinical need for outsourcing facilities to compound using the nominated bulk drug substance.

Therefore, the inclusion of a bulk drug substance on the 503B Bulks List should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug product compounded using the substance. Nor should it be assumed that drug products compounded using substances on the 503B Bulks List have been proven to be safe and effective under the standards required for Agency approval. Any person who represents that a compounded drug product made with a bulk drug substance that appears on the 503B Bulks List is FDA-approved, or is otherwise endorsed by the FDA, either generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act.

B. Evaluating Nominated Bulk Drug Substances Under the Statutory Standard

1. Overview of Analysis

FDA intends to use a two-part analysis, described more fully in section III.B.ii., below, in evaluating substances nominated for placement on the 503B Bulks List to determine whether there is a clinical need for outsourcing facilities to compound using the bulk drug substance.

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As a threshold inquiry, in Part 1 of the analysis, FDA intends to determine whether the bulk drug substance is a component of an FDA-approved product. For purposes of this inquiry, FDA will generally consider a bulk drug substance to be a component of an FDA-approved drug product if the bulk drug substance is the same as the active pharmaceutical ingredient in an FDA-approved drug product.²³ In this guidance, unless otherwise specified, the term “approved drug products” refers to FDA-approved drug products that are not in the discontinued section of FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the “Orange Book”). If a bulk drug substance is a component of one or more approved drug products and all of the approved drug products are in the discontinued section of the Orange Book, we generally intend to proceed directly to Part 2 of the evaluation described below.

If the bulk drug substance is not a component of an FDA-approved product, FDA intends to proceed to Part 2 of its evaluation.

If the bulk drug substance is a component of an FDA-approved drug, FDA intends to consider the following questions:

- (a) Is there a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that (i) an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and (ii) the drug product proposed to be compounded is intended to address that attribute?
- (b) Is there a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product?

If FDA answers “no” to either threshold question, the Agency does not intend to include the nominated bulk drug substance on the 503B Bulks List. This is because, as discussed further below, FDA generally expects that, in such a case, there would be no clinical need for outsourcing facilities to use the bulk drug substance in compounding. If the Agency answers “yes” to both questions, it intends to proceed to Part 2 of the analysis.

In Part 2 of the analysis, the agency intends to evaluate bulk drug substances that are components of FDA-approved drugs if the questions in Part 1 are answered in the affirmative, and to evaluate bulk drug substances that are not components of FDA-approved drug products. The Agency intends to conduct a balancing test, described more fully below, under which FDA intends to consider each factor in the context of the others and balances them, on a substance-by-substance basis, to determine whether the substance is appropriate for inclusion on the 503B Bulks List. The balancing test includes the following factors:

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

²³ The active pharmaceutical ingredient is as defined in the approved product labeling.

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- (d) Current and historical use of the substance in compounded drug products, including information about the medical condition(s) that the substance has been used to treat and any references in peer-reviewed medical literature.

Under Parts 1 and 2 of its analysis, FDA intends to evaluate the nominated bulk drug substances in the context of information provided by the nominators about the drug products proposed to be compounded and the proposed uses of those drug products. The Agency may also consider additional information about the bulk drug substances that was not included in the nomination, such as information described in public comments submitted to the Agency, obtained during outreach to stakeholders such as medical organizations, or that is otherwise identified during the Agency's review, if the Agency concludes it may be relevant to its decision whether to place a bulk drug substance on the 503B Bulks List. The Agency may request additional information from nominators or persons who have submitted relevant docket comments to help inform its review. Nominators or members of the public who believe that different considerations would establish that there is a clinical need for a particular bulk drug substance should present those to the agency.

2. Explanation of Analysis

a. Part 1

i. Subpart 1(a): Need for a Compounded Drug?

Under Subpart 1(a), FDA intends to consider whether there is a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that (i) an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and (ii) the drug product proposed to be compounded is intended to address that attribute.

Unless an attribute of the FDA-approved drug is medically unsuitable for certain patients, and a drug product compounded using a bulk drug substance that is a component of the approved drug is intended to address that attribute, FDA expects that there will be no clinical need for outsourcing facilities to compound using that bulk drug substance. Rather, it would unnecessarily expose patients to the risks associated with drug products that have not been shown to meet the standards applicable to FDA-approved drug products for safety, effectiveness, quality, and labeling and would undermine the drug approval process. Accordingly, unless FDA can answer "yes" to the two questions in Part 1(a) of its analysis, the Agency intends to find there is no clinical need for compounding using the bulk drug substance.

In the Part 1(a) threshold test, FDA intends to focus on the rationale for compounding from a bulk drug substance that appears in the nomination or that FDA otherwise identifies. For example, several nominations state that patients need a drug product compounded using the bulk drug substance because the FDA-approved drug that includes the bulk drug substance as a component also includes certain inactive ingredients or additional active ingredients that are inappropriate for a patient population. Other nominations state that the FDA-approved drug is for use by routes of administration or in dosage forms that are inappropriate for a patient population. For these examples, FDA intends to evaluate whether the inactive ingredients, additional active

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ingredients, the route of administration, or the dosage forms are attributes of the FDA-approved products that make them medically unsuitable for certain patients for the conditions that FDA is evaluating. If so, FDA would consider whether the compounded drug products the nominator proposes to make are intended to address those attributes by, for example, excluding the inactive ingredients or additional active ingredients or using a different route of administration or dosage form.

Whether there is an attribute of the FDA-approved drug product that makes it medically unsuitable for some patients for the conditions that FDA has identified for evaluation and, if so, whether the compounded drug product addresses that attribute, will be determined on a case-by-case basis. For example, if an approved drug product contains peanut oil, patients with a peanut allergy treated with the FDA-approved drug product may develop a serious allergic reaction. In this case, FDA would likely determine that a proposal to produce a compounded drug product without the peanut oil to address the condition described in the nomination would proceed through Part 1(a). Or if a drug product is approved with two active ingredients in a fixed combination, but FDA has received or identified information indicating that it is known, within that specialty, on the basis of competent evidence, that some patients need just one active ingredient and are likely to have an adverse clinical reaction to the second active ingredient, and there is no FDA-approved drug product containing the one active ingredient they need, then FDA would likely determine that a proposal to compound the single-ingredient product from a bulk drug substance would proceed through Part 1(a).

In general, broad statements that a compounded drug product with an attribute that differs from the FDA-approved drug is necessary for certain patients, without sufficient evidence that the attribute makes the FDA-approved drug medically unsuitable for specific patients for the condition that has been identified for evaluation, will not be adequate. For example, general statements that a preservative-free drug needs to be compounded because some patients may have an allergy to the preservative in the approved drug likely would not be sufficient.²⁴ Minor changes in dosage form, such as from tablet to capsule, are unlikely to fulfill a clinical need that cannot be met by the approved drug. Nor is the combination of multiple active ingredients to allow for administration of fewer products likely to represent a clinical need for purposes of this factor.

ii. Subpart 1(b): Need for a Drug Compounded from a Bulk Drug Substance?

Under Subpart 1(b), if there is an FDA-approved drug product that incorporates the nominated bulk drug substance, FDA intends to consider whether there is a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than an FDA-approved drug product. This is because in order to place a bulk drug substance on the 503B Bulks List, FDA must determine that there is a clinical need for outsourcing facilities to compound a drug product *using the bulk drug substance*. Accordingly, the Agency intends to find that there is no clinical need to compound using a bulk drug substance unless the nomination identifies a drug product that must be produced from the bulk drug substance rather than from an FDA-approved drug product.

²⁴ FDA may consider whether the nomination identifies a preservative that is well known to be a clinically significant allergen for some patients under the proposed route of administration and dose.

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FDA intends to assess whether the compounded drug product must be prepared by starting from a bulk drug substance on a case by case basis, considering the difference or differences between the proposed compounded drug product and the FDA-approved product; the basis provided by the nominator for why it intends to use the bulk drug substance rather than the FDA-approved drug to compound the proposed drug product; and other relevant information. For example, FDA is likely to determine that a drug product that is being proposed to be compounded without an active or inactive ingredient (e.g., an allergen) in the approved product must be compounded from a bulk drug substance rather than the FDA-approved drug, and therefore pass through this part of the analysis, because of the difficulties and complexities likely to be associated with removing an ingredient from an approved drug product. In contrast, FDA is likely to determine that a drug product that is being proposed to be compounded in a lower concentration than an FDA-approved product (e.g., for a pediatric patient) could be compounded from the FDA-approved product because a more dilute drug product can often be formulated from an approved drug product by adding a diluent.

b. Part 2

For bulk drug substances that are components of an FDA-approved drug, FDA only intends to proceed to Part 2 if the Agency answers “yes” to the questions in both subpart 1(a) and subpart 1(b). FDA intends to begin its analysis of bulk drug substances that are not components of FDA-approved drugs with Part 2.

In Part 2 of its evaluation, FDA intends to balance the four factors described below to reach a conclusion about whether there is a clinical need for the bulk drug substance. Whether the factors in Part 2 taken together weigh in favor of or against a finding of clinical need will inform FDA’s proposal to include or exclude nominated bulk drug substances from the 503B Bulks List.

i. Subpart 2(a): Physical and Chemical Characterization

Under the first factor, FDA intends to evaluate the physical and chemical characterization of the bulk drug substance and the drug product proposed to be compounded from the bulk drug substance. FDA intends to consider each substance's purity, identity, and quality. Based on attributes such as the substance's molecular structure, stability, melting point, appearance, likely impurities, and solubilities, FDA would determine whether the substance can be identified or compounded consistently based on its physical and chemical characteristics. If a substance cannot be well-characterized, or is not chemically and physically stable after compounding, or requires conditions to prevent degradation that cannot be accomplished reliably, this factor would weigh against its inclusion on the 503B Bulks List because there would be no assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities considered by the Agency.

With respect to bulk drug substances that are components of FDA-approved drug products, FDA will have already determined the bulk drug substance in a particular drug product possesses chemical and physical characteristics suitable for its use in the FDA-approved product. However, bulk drug substances that are components of FDA-approved drug products may

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present different challenges when they are used in compounding. In addition to concerns related to purity of substances from sources that have not been evaluated during the premarket approval process, there may be physical and chemical characterization concerns, such as complexity of the drug substance, need for a specific polymorphic form, stability or bioavailability concerns when bulk drug substances are used to compound drug products, that differ from the approved product in their formulation, route of administration, strength, or other features. FDA therefore intends to consider whether such concerns, or other physical and chemical characterization concerns, are associated with use of the bulk drug substance to compound a particular drug product.

ii. Subpart 2(b): Safety Issues Raised by Use of the Substance in Compounding

Under the second factor, FDA intends to consider the safety issues raised by the use of a nominated bulk drug substance in compounding. With respect to nominated bulk drug substances that are not components of FDA-approved drug products, based on FDA's review of the substances nominated to date, it is unlikely that the substances will have been thoroughly investigated in *in vitro* or in animal toxicology studies, or that there will be well-controlled clinical trials to substantiate their safe use in humans. Thus, in evaluating these substances, the Agency is likely to have at its disposal very limited information, or in some cases no information, of the type and quality that is ordinarily required and evaluated as part of the drug approval process.

Therefore, to evaluate substances that are not components of FDA-approved drug products, the Agency intends to rely on information, such as reports in peer-reviewed medical literature, about each substance's pharmacology, acute toxicity, repeat dose toxicity, mutagenicity, developmental and reproductive toxicity, and carcinogenicity, or other data that relate to safety. The Agency may also rely on reports and abstracts in the literature or reports to FDA about adverse reactions associated with human use of the substances, or other appropriate information. FDA also intends to consider the availability of approved drug products or unapproved over-the-counter (OTC) drug products as treatment options for the conditions being considered. The existence of such approved drug products or OTC drug products would likely weigh against inclusion on the list when the toxicity of the bulk drug substance appears to be significant or where there are other safety concerns associated with the use of the substance in compounded drug products.

With respect to bulk drug substances that are components of FDA-approved drug products, FDA will have already determined that a drug product that includes the bulk drug substance as a component is shown to be safe for its intended use under the conditions described in its approved product labeling. However, when a bulk drug substance that is a component of an FDA-approved drug product is used in compounding, differences between the resulting compounded drug product and the approved drug product may raise safety concerns (e.g., issues arising from different formulations, routes of administration, or strengths). Additionally, there may be relevant differences between the proposed uses or intended patient population of the FDA-approved drug and a compounded drug product (e.g., if the compounded drug product is specifically proposed for a pediatric population and the FDA-approved drug is indicated for adults). In evaluating the potential impact of such differences on the safety of the compounded drug product, FDA intends to rely on available safety information, such as peer-reviewed

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scientific literature, reports to FDA about adverse reactions relevant to the difference or differences, and FDA's expertise to evaluate safety risks associated with drug products proposed to be compounded from the nominated bulk drug substance.

iii. Subpart 2(c): Available Evidence of Effectiveness or Lack of Effectiveness

Under the third factor, FDA intends to consider evidence of the substance's effectiveness or lack of effectiveness for an identified use, including but not limited to reports in peer-reviewed medical literature, if such evidence exists. In the new drug approval process, applicants are required to demonstrate effectiveness under the substantial evidence standard described in section 505(d) of the FD&C Act. FDA recognizes that few, if any, of the substances nominated for the 503B Bulks List that are not components of approved drug products will have been studied in adequate and well-controlled investigations. In evaluating these bulk drug substances, the Agency would consider relevant available evidence concerning effectiveness.

For example, for substances that are not components of approved drug products, but have been widely used for a long period of time, the literature may include anecdotal reports of effectiveness for a particular use or reports of clinical trials suggesting possible effectiveness. Conversely, the literature may contain anecdotal or clinical evidence that a substance did not show effectiveness for a particular use in a reasonably designed study. Further, information about other available treatments may affect FDA's evaluation. For a bulk drug substance that is proposed to be used to compound drug products to treat a serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy, particularly when there are approved drug products available that may be appropriate for treatment. In those cases, the existence of drug products approved to treat the condition would likely weigh against inclusion on the 503B Bulks List, and the availability of no or minimal effectiveness data, or trials that do not demonstrate effectiveness, would weigh more heavily against placement on the list in FDA's balancing of the relevant factors.

With respect to bulk drug substances that are components of FDA-approved drug products, FDA will have already determined that a drug product that includes the bulk drug substance as a component is effective for its indicated use under the conditions described in its approved labeling. Additionally, in Part 1(a) of the analysis, the Agency will already have considered whether there is a basis to conclude that an attribute of the FDA-approved drug product makes it unsuitable to treat certain patients for the medical condition described in the nomination. However, when the bulk drug substance that is a component of an FDA-approved drug product is used in compounding, differences between the compounded drug product and the FDA-approved drug product may raise effectiveness concerns arising, e.g., from a different formulation, route of administration, or strength. Additionally, effectiveness concerns may be raised by differences between the FDA-approved drug product and the compounded drug product in terms of their proposed uses or intended patient population. FDA intends to consider whether effectiveness concerns are associated with use of the bulk drug substance to compound a particular drug product.

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iv. Subpart 2(d): Historical and Current Use in Compounding

Under the fourth factor, FDA intends to consider the historical and current use of the substance in compounding drug products, which may include the length of time the substance has been used in compounding; the medical conditions it has been used to treat; the patient population it has been used to treat; how widespread its use is and has been, including use in other countries; whether it is typically used to compound drugs that healthcare providers maintain in their offices in advance of identifying individual patients; and relevant references in peer-reviewed medical literature. Documentation of this information may include reference to past medical textbooks or medical specialty professional organization guidelines that describe the use of the drug.

The longer a substance has been used in compounding drug products and the broader its use,²⁵ particularly to compound drug products for office stock,²⁶ the more this factor will generally weigh in favor of inclusion of the substance on the list. In contrast, if FDA's analysis suggests that the historical and current use of the substance in compounding has been minimal or non-existent, or the nominator has not provided information supporting its historic use in compounding, the more this factor would generally weigh against inclusion of the substance on the 503B Bulks List.

In weighing this factor for bulk drug substances that are components of FDA-approved drug products, FDA also intends to consider evidence, if available, of whether the substance has been used to compound drug products that are intended to address an attribute of the FDA-approved drug product that makes it medically unsuitable to treat certain patients for the condition that FDA has identified for evaluation.

²⁵ For example, this factor would weigh more heavily in favor of including the bulk drug substance on the 503B Bulks List if there is information that a significant portion of the population of the United States can experience a serious allergic reaction to a substance that is a component of the approved drug, and therefore uses a compounded drug rather than the approved drug, than information that a bulk drug substance has been compounded infrequently to treat few patients whose uncommon, non-urgent condition is not well described or well supported in the literature..

²⁶ In conducting this analysis, the Agency intends to note particularly the extent of compounding drug products using a nominated bulk drug substance for office stock, because outsourcing facilities are the only entities that can distribute compounded drug products without first receiving prescriptions for identified individual patients. In contrast, compounding under section 503A must be based on the receipt of a valid prescription for an identified individual patient. Section 503A(a). See FDA's guidance for industry *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

For example, this factor may weigh more heavily in favor of including the bulk drug substance on the list to address emergency situations if there is information that the drug product compounded from the nominated bulk drug substance is maintained in physicians' offices to treat patients who present with infections in emergency situations, than information that a bulk drug substance is used to compound a drug product that does not need to be administered in such situations.

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**APPENDIX A:
HOW FDA GENERALLY INTENDS TO EVALUATE BULK DRUG SUBSTANCES THAT HAVE BEEN
NOMINATED FOR INCLUSION ON THE 503B BULKS LIST**

