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

Guidance for Industry

DRAFT GUIDANCE

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

March 2018
Compounding and Related Documents

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 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.[3]

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

[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 be take into account the factors described in this guidance.

[3] FDA previously solicited nominations of bulk drug substances to be considered for the 503B Bulks List and issued the guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* regarding certain interim regulatory policies for outsourcing facilities that compound drug products using bulk drug substances while the 503B Bulks List is being developed. That interim policy remains in effect while FDA evaluates substances for the 503B Bulks List. 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 https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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. 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).[4]

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.[5] 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.[6] 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.[7]

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.[8]

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)."[9] *Active pharmaceutical ingredient* is

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

[5] Compare Section 503A(a) of the FD&C Act (exempting drugs compounded in accordance with that section) to Section 503B(a) of the Act (not providing the exemption from CGMP requirements).

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

[7] Section 503B(d)(4)(C).

[8] Section 503B(a)(2)(A) of the FD&C Act.

[9] 21 CFR 207.3.

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."[10,11]

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, National Formulary, 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.[12]

B. Compounding, Generally

Compounded drugs can serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product, 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. 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.[13] 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.[14] Drug products compounded by

[10] Section 503B(a)(2) and 21 CFR 207.1.

[11] 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 United States Pharmacopeia or National Formulary monograph, if a monograph exists.

[12] 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 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*.

[13] See http://www.cdc.gov/HAI/outbreaks/meningitis.html.

[14] 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 an outsourcing facility

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.[15] Because compounded drug products are not FDA-approved, they have not undergone FDA premarket review for safety, effectiveness, and quality. Although outsourcing facilities must 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 only be used by patients whose medical needs cannot be met by an FDA-approved drug.

C. Compounding Drugs From Bulk Drug Substances

Outsourcing facilities sometimes compound drug products using bulk drug substances to meet the medical needs of patients that cannot be met by an approved drug product or by a drug product compounded from an FDA-approved drug product. A patient may 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 inactive ingredients or additional active ingredients that are inappropriate for the patient population. For example, certain inactive ingredients that may be appropriate for the route of administration of the FDA-approved drug product may not be appropriate for another route of administration. Similarly, an outsourcing facility might compound a drug product from a bulk drug substance when patients have an allergy to an inactive ingredient in the approved drug product containing that bulk drug substance. In situations such as these, compounding from bulk drug substances could meet an important patient medical need.

In other situations, however, compounding using the FDA-approved drug product instead of a bulk drug substance would meet patients' medical needs and present less risk. For example, outsourcing facilities often dilute FDA-approved drug products to produce intravenous bags for hospitals. Similarly, when pediatric or elderly patients are unable to swallow an FDA-approved tablet, outsourcing facilities can sometimes manipulate (e.g., crush) the tablet to produce a liquid. In general, compounding using bulk drug substances presents a greater risk than compounding using FDA-approved drug products.

The source, safety, and quality of the starting material are better known and established when an FDA-approved drug product is used instead of bulk drug substance for compounding. FDA-approved drug products are subject to 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-

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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.

[15] Section 503B(a).

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 sponsor'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 levels of impurities are not unsafe and the bulk drug substance will be stable through the product's expiration date. In contrast, the quality standards, specifications, and controls for bulk drug substances used in compounding have not been assessed by FDA, and such bulk drug substances may be manufactured by a facility that is not subject to FDA premarket assessment, including premarket site inspection to verify manufacturing operations are in control.

Compounding from bulk drug substances also involves more complex and numerous inter-related manipulations by the compounder than compounding drugs from FDA-approved drug products, and involves the compounder addressing risks related to ingredient quality. For example, to compound a sterile drug product from a non-sterile bulk drug substance, the outsourcing facility first acquires ingredients that were made under conditions that result in low and known bioburden levels, including limits on endotoxins. It handles the materials to avoid contamination by harmful microorganisms or compounds and then performs a sterilization process, such as sterile filtration followed by aseptic filling. The outsourcing facility then either maintains the sterility of the material through subsequent manipulations or performs terminal sterilization. If an outsourcing facility performs any of the sterilization steps improperly, such as by failing to control air quality or maintain aseptic conditions, the drug may fail to achieve sterility or be further contaminated. If a terminal sterilization step is performed improperly, the drug could fail to achieve sterility, or the conditions of the sterilization process could cause the drug to degrade, resulting in a lower strength (sub-potent) and an increase in impurities. In contrast, compounding a sterile drug product using an FDA-approved sterile drug product does not entail sterilizing a non-sterile substance. Rather, the outsourcing facility would ensure that the sterile drug product being compounded retains its sterility.

Compounding from bulk drug substances also increases the potential for errors that could result in a sub-potent or super-potent product. Such compounding involves certain operations, such as weighing, handling, or mixing, that depend, in part, on the unique characteristics of different types of bulk drug substances (e.g., powders, liquids) such as powder flow properties, hygroscopicity, and liquid viscosity. Failure to take into account these characteristics can adversely impact weighing, handling, mixing, or other compounding operations. In addition, these operations are generally conducted under circumstances in which cross-contamination is more likely to occur. For example, these operations may involve the use of powders, which are often similar in appearance and challenging to control. This can result in mix-ups (e.g., accidental use of wrong materials or contaminated equipment), carryover of residues, and airborne transfers of potential contaminants. In contrast, compounding drug products using FDA-approved drug products generally does not present the same degree of risk. For example, when an FDA-approved product is not a powder, compounding with the approved drug will not involve several of the considerations and steps described above and is therefore less likely to lead to errors.

Finally, compounding a drug product from a bulk drug substance that is a component of an FDA-approved drug when there is no clinical need to do so, perhaps because of economic incentives, undermines the drug approval process. For example, use of bulk drug substances to compound a formulation of a needed concentration, route of administration or dosage form rather than simply diluting or otherwise manipulating the approved drug reduces the incentive for sponsors to invest in and seek FDA-approval of such drugs. The drug approval process is critical to ensure patient access to pharmaceuticals whose quality, safety and effectiveness have been established.

In light of the foregoing concerns about drug quality and the integrity of the drug approval process, 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 drugs that have not been demonstrated to be safe and effective, and that may be of substandard quality, to those situations in which the drug is necessary for patient treatment. Second, it preserves the incentives for sponsors to invest in the research and testing required to obtain FDA approval, 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 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.

If the information provided by the nominator did not include sufficient supporting information for FDA to evaluate,[16] the nominator should re-nominate the substance with sufficient supporting information if it wishes to ensure that the bulk drug substance will be reviewed for potential inclusion on the 503B Bulks List.

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*. 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.

[16] If the substance was not nominated with adequate supporting information, it will appear in Category 3, as described in FDA's guidance, *Interim Policy on Compounding Using Bulk Drug Substance Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

As explained in the interim guidance, 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.[17] After considering any comments on FDA's proposals regarding whether to include nominated substances on the 503B Bulks List, FDA will 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 will seek PCAC input.[18] Depending on its review of the docket comments and other relevant information before the Agency, the Agency may finalize its proposed determination without change, 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 that there is 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.

FDA intends to evaluate the substances nominated for the 503B Bulks List on a rolling basis. FDA will 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.

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.

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

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

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.

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

1. Clinical Need Standard

Section 503B authorizes FDA to publish a list identifying "bulk drug substances for which there is a clinical need." FDA interprets this 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 the drug product, and

(2) the drug product must be compounded using the bulk drug substance.

This interpretation is consistent with the text of section 503B(a)(2)(A), and the purpose of the 503B Bulks List, which is to identify the bulk drug substances that can be used in compounding under the exemptions in section 503B, provided the other conditions in that section are met. The Agency's interpretation also furthers the broader purposes of the Act by (1) helping to protect patients from risks of compounding from bulk drug substances where there is no clinical need to do so and (2) protecting the integrity of the drug approval process. FDA intends to use the analysis discussed below in determining whether there is a clinical need for a nominated bulk drug substance.

The Agency does not interpret supply issues, such as backorders, to be within in the meaning "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."

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

There may be situations in which FDA's finding of clinical need is limited to the use of the bulk drug substance to make drug products with certain attributes, such as specific strengths, routes of administration, or dosage forms. In such a case, the Agency may tailor the proposed entry on the 503B Bulks List to the use of the bulk drug substance to compound a drug product with those attributes. For example, if the Agency were to find a clinical need for a bulk drug substance to be used to compound a drug product for topical use, it may limit the entry of that bulk drug substance on the 503B Bulks List to use of the substance to compound drug products 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 nominated substances 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 compounded drug product when it evaluates whether there is a clinical need to compound using the nominated bulk drug substance.

Therefore, the inclusion of a 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 otherwise endorsed by FDA 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. Analysis for Evaluating Nominated Bulk Drug Substances

1. Overview of Proposed 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 Part 1 of this two-part evaluation, 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.[19]

If the bulk drug substance is not a component of an FDA-approved product, FDA will proceed to Part 2 of its evaluation to determine whether the substance is clinically necessary.

[19] The active pharmaceutical ingredient is as defined in the approved product labeling.

If the bulk drug substance is a component of an FDA-approved drug, FDA intends to conduct a threshold review based on 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 from the 503B Bulks List. If the Agency answers "yes" to both questions, it intends to proceed to Part 2 of the analysis.

The Agency intends to use Part 2 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 proposes to conduct a balancing test, described more fully below, under which FDA would consider each factor in the context of the others and to balance 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
(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 uses of the bulk drug substances that were not described in the nomination, such as those that are described in public comments submitted to the Agency or that are otherwise identified during the Agency's review, if the Agency concludes they 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.

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, there is no clinical need to compound using that bulk drug substance. Rather, it would unnecessarily expose patients to the risks associated with drug products that do not 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 will 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 inactive ingredients or additional active ingredients that are inappropriate for the 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 the patient population. For these examples, FDA will evaluate whether the inactive ingredients, additional active ingredients, the route of administration, or the dosage forms are attributes of the FDA-approved products that make them unsuitable and impart unacceptable risk for certain patients for the conditions that FDA is evaluating. If so, FDA will consider whether the compounded drug products 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.[20] Accordingly, 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).

[20] See Footnote 21.

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 an acceptable reason for compounding from bulk drug substances, unless the preservative is well known to be a clinically significant allergen for some patients who are administered the drug. Similarly, 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.

To make this assessment, FDA intends to consider the difference or differences between the proposed compounded drug product and the FDA-approved product. Whether the compounded drug product must be prepared by starting from a bulk drug substance will be assessed case by case, considering the proposed differences between the products, 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, including the type and number of manipulations necessary to produce the proposed drug from the FDA-approved product versus the bulk drug substance and their potential impact on the overall quality of the resultant drug product. 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 because of the difficulties and complexities likely to be associated with removing an ingredient from a finished 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) should be compounded from the FDA-approved product because a more dilute drug product can often be formulated from an approved drug product with minimal, simple manipulations (e.g., adding a diluent to an approved drug).

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's analysis of bulk drug substances that are not components of FDA-approved drugs will start with Part 2.

In Part 2 of its evaluation, FDA intends to balance the four factors described below. 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, the physical and chemical characterization of 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 inclusion as an active ingredient in an FDA-approved product. However, bulk drug substances that are components of FDA-approved drug products may present different challenges. 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 stability or bioavailability concerns, when they 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 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 relates to safety. The Agency may also rely on reports and abstracts in the literature or reported 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 drug products that follow an over-the-counter monograph (OTC monograph products) as treatment options for the conditions being considered. The existence of such approved drug products or OTC monograph products would likely weigh against inclusion on the proposed 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 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 proposes 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 any 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 sufficient to satisfy the standard in the drug approval process. In evaluating these bulk drug substances, the Agency would consider relevant evidence concerning effectiveness that is available.

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 trial. 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 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, 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 such effectiveness concerns are associated with use of the bulk drug substance to compound a particular drug product.

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,[21] particularly to compound drug products for office stock,[22] 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.

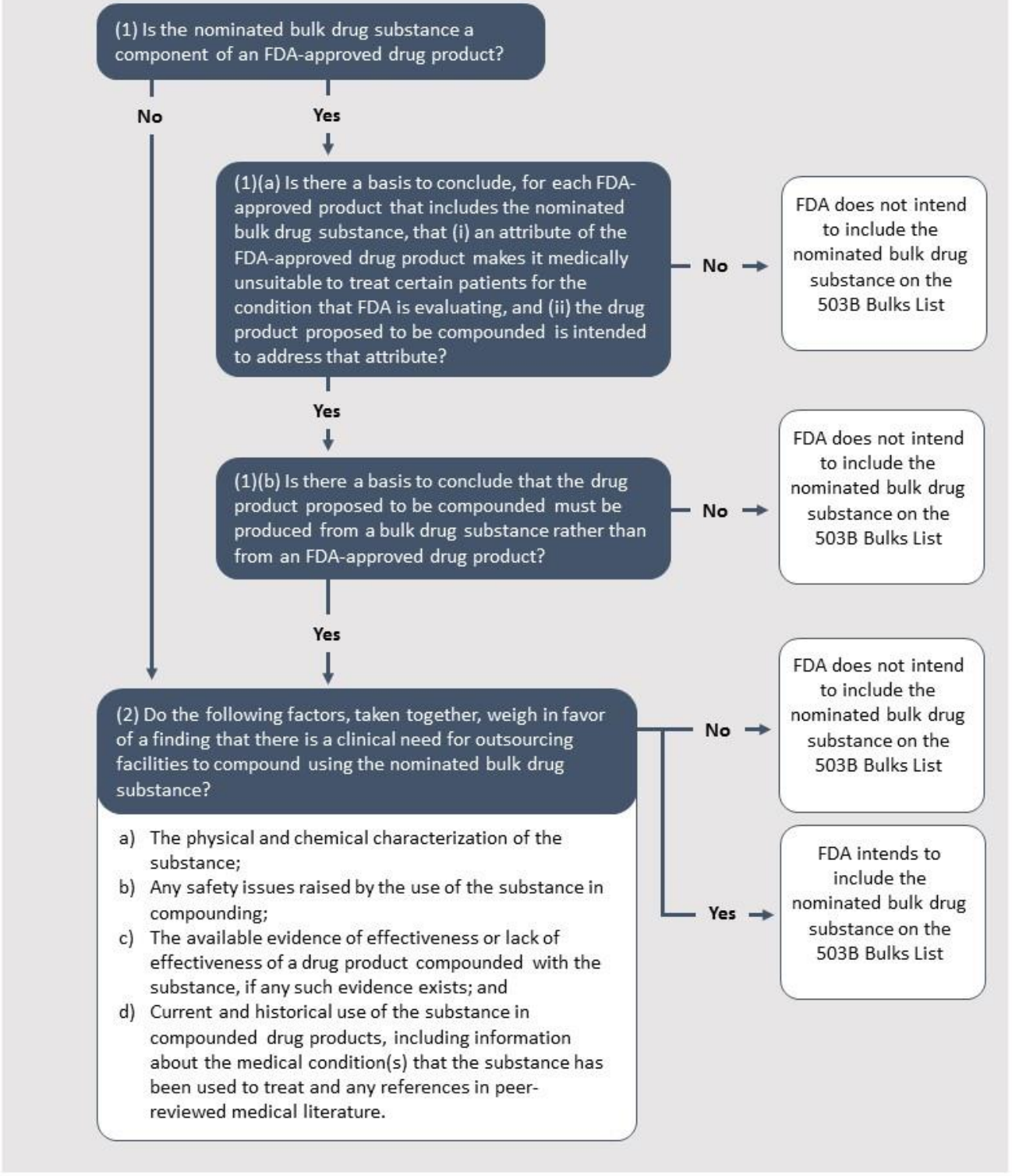
In weighing this factor for bulk drug substances that are components of FDA-approved drug products, FDA intends to consider evidence, if available, of whether the substance has been used to compound drug products that are intended to address an attribute of the FDA-approved drug product that makes it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

[21] For example, in the description of Part 1(a) of this analysis, we noted that an example of a situation in which an attribute of the approved drug product may make it medically unsuitable to treat certain patients for the condition identified for evaluation is when a patient who has a peanut allergy needs to be treated with an approved drug that contains peanut oil. In general, this factor would weigh more heavily in favor of including of the bulk drug substance on the 503B Bulks List if there is information that a significant portion of the population of the United States has a peanut allergy and therefore uses a compounded drug rather than the approved drug, compared to information that a bulk drug substance is to be compounded to treat few patients with an uncommon, non-urgent condition.

[22] In conducting this analysis, the Agency proposes to note 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, if there is information that the drug compounded from the nominated bulk drug substance is maintained in physicians' offices to treat patients who present with infections in emergency situations, this factor may weigh more heavily in favor of including the bulk drug substance on the list, compared to information that a bulk drug substance is used to compound a drug product that does not need to be administered in the office in non-emergency situations.

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



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