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Food and Drug Administration
Department of Health and Human Services
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Rockville, MD 20852

Comments on the Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act, Draft Guidance for Industry
Docket No. FDA-2018-D-1067

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, submits these comments with regard to the draft guidance for industry "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act," the availability of which was announced by the Food and Drug Administration (FDA) in the *Federal Register* on March 26, 2018 (Docket No. FDA-2018-D-1067).[1]

In general, Public Citizen strongly supports the policies articulated in the draft guidance. These policies would appropriately balance the needs of individual patients for whom an approved or commercially available medication is not available with the health risks that compounded drugs can pose.

Notably, unlike most of the other organizations and health care professionals that have submitted comments about the draft guidance, Public Citizen does not have any relevant financial interests that would influence our views on the matters addressed by the draft guidance.

I. Background

Section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA), which was enacted under the Drug Quality and Security Act in 2013, stipulates the conditions that must be satisfied for human drug products compounded by an outsourcing facility to be exempt from the FDCA requirements concerning (a) the approval of drugs under new drug applications or abbreviated new drug applications, (b) the labeling of drugs with adequate directions for use, and (c) drug supply chain security. Drug products compounded under the conditions in section 503B are not exempt from current Good Manufacturing Practice (cGMP) requirements and must satisfy other requirements.

[1] 83 FR 12952.

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 of Health and Human Services identifying bulk drug substances for which there is a *clinical need* (hereafter, the 503B Bulks List) or (b) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FDCA at the time of compounding, distribution, and dispensing. The draft guidance describes policies that the FDA proposes to use in evaluating bulk drug substances nominated for inclusion on the 503B Bulks List.

II. General Comments

As previously stated, in general, Public Citizen strongly support the policies proposed in the draft guidance document. In particular, the proposed guidance seeks to appropriately limit, under section 503B, the use of bulk drug substances by outsourcing facilities in pharmacy compounding of human drug products that are not on the FDA's drug shortage list. Large-scale compounding by outsourcing facilities can affect large numbers of patients. Thus, limits on such pharmacy compounding under section 503B are critically important to protecting public health for the following reasons highlighted by the FDA in its draft guidance:

> Lines 83-89: **[Compounded drugs] …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. 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. [Emphasis added]
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> Lines 96-102: 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.** [Emphasis added]
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> Lines 119-125: **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. [Emphasis added]

> Lines 188-194: 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.**" [Emphasis added]

Public Citizen strongly agrees with all these reasons.

III. Specific Comments

Public Citizen offers the following comments regarding specific policies proposed in the draft guidance document:

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

1. *Clinical Need Standard* (lines 274-298)

Section 503B explicitly authorizes the FDA to publish a list identifying "bulk drug substances for which there is a clinical need." Public Citizen agrees with the FDA's well-reasoned interpretation that a bulk drug substance may be included on the 503B Bulks List if (a) there is a clinical need for an outsourcing facility to compound the drug product and (b) the drug product must be compounded using the bulk drug substance.

We also agree that the FDA's interpretation is entirely consistent with the relevant text in Section 503B and furthers the broader purposes of the Act by (a) helping to protect patients from risks of compounding from bulk drug substances where there is no clinical need to do so and (b) protecting the integrity of the drug approval process.

We also strongly endorse the agency's conclusion that considerations of cost fall outside the scope of the meaning of "clinical need." Allowing costs to play a role in determining whether there is a clinical need for pharmacy compounding using bulk drug substances could allow pharmacy compounding by outsourcing facilities to undercut the incentive for manufacturers to seek FDA approval of drug products.

2. *Inclusion of a bulk drug substance on the 503B Bulks List* (lines 300-335)

Public Citizen agrees with the FDA's common-sense assessment that there may be situations in which the agency'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 cases, the agency definitely should 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. Public Citizen recommends that proposed entries to the list also be tailored to the

treatment of the specific disease(s) or condition(s) and patient populations for which the clinical need was established.

We also agree with the FDA that 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. Therefore, we strongly support the FDA's proposal to consider a drug misbranded if its labeling implies that compounded drugs have been proven to be safe and effective. Such claims are permitted for approved medications that have gone through a rigorous evaluation, where it has been demonstrated that the drug's benefits outweigh its risks. Compounded medications are not submitted to this process and thus the same claims cannot be made. It is especially important for health care professionals to understand this distinction, because they must take into account the full range of factors that present risk to their patients when designing a treatment regimen.

B. Proposed Analysis for Evaluating Nominated Bulk Drug Substances (Lines 337-616)

Public Citizen supports the FDA's proposed two-part analysis for evaluating a bulk drug substance that has been nominated for inclusion on the 503B Bulks List. The factors discussed in the guidance in general will not only ensure the consistency and predictability of the process, but will help to ensure the safety of medications compounded from substances included on the list.

Under part 1, the agency first would determine whether the bulk drug substance is a component of an FDA-approved drug. If it is, the FDA will then conduct a review based on the following two 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?

A preference for compounding from FDA-approved products will reduce the risk of compounding a poor quality product, and therefore limit risk to patients. This is particularly true for sterile compounded drugs that could be produced using FDA-approved sterile drugs as the starting materials. The manufacturers of the FDA-approved products will have been required to show during the approval process that they can consistently manufacture sterile products. As noted in the guidance:

> 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… If an outsourcing facility performs any of the sterilization steps improperly,…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. (Lines 146-162)

Given that outsourcing facilities producing compounded drugs have not necessarily undergone inspection, the risk of contamination associated with creating a sterile drug through multiple manipulations of non-sterile bulk drug substances is particularly concerning. By requiring these facilities to compound using FDA-approved products whenever possible, the FDA minimizes the risk of compounding errors — not only through contamination, but also through the production of sub- or super-potent compounded drugs.

Part 2 of the FDA's proposed analysis would occur for nominated bulk drug substances that are components of FDA-approved drugs, for which questions (a) and (b) under Part 1 are answered affirmatively, and for nominated bulk drug substances that are not components of FDA-approved products. For this part 2 analysis, the FDA would conduct a balancing test under which the agency would consider each of the following factors in the context of the others and balance them, on a substance-by-substance basis, to determine whether the substance is appropriate for inclusion on the 503B Bulks List:

(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.

Importantly, the assessment regarding whether there is a clinical need for outsourcing facilities to produce compounded drugs using a particular bulk drug substance cannot occur in a vacuum. The availability, if any, of other FDA-approved drugs (or other FDA-approved or FDA-cleared medical products) to treat the disease or condition for which the bulk drug substance was nominated must be a key consideration in conducting these assessments. We acknowledge that the FDA's draft guidance document addresses this issue in the discussion of factor (c) above (i.e., the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists). However, we recommend that this factor be elevated to a stand-alone fifth factor in Part 2 of the FDA's proposed analysis.

IV. Responses to Other Commenters

Several commenters challenged the FDA's assertion in the draft guidance document that "In general, compounding using bulk drug substances presents a greater risk than compounding using FDA-approved drug products." In voicing this criticism, some commentators described scenarios in which there likely would be a reasonable 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. Thus, the draft guidance appears to already address these concerns.

Some commenters proposed that any drug that has FDA approval or is listed in the FDA's Orange Book should be eligible for inclusion on the 503B Bulks List. Implementation of these ludicrous suggestions would eviscerate the statutory requirement that authorized the FDA to establish the 503B Bulks List and would be inconsistent with Congress's intent when it passed the Drug Quality and Security Act after extensive consultations with the FDA.

V. Conclusions

In closing, the guidance document, when finalized after minor revisions are made, would appropriately limit, under section 503B, the use of bulk drug substances by outsourcing facilities in pharmacy compounding of human drug products that are not on the FDA's drug shortage list. Public Citizen encourages the FDA to promptly issue final guidance on this topic.

Thank you for the opportunity to comment on this important public health matter.

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