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BY ELECTRONIC SUBMISSION: www.regulations.gov
Division of Dockets Management (HFA-305)
Food and Drug Administration
56320 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA Draft Guidance: Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act (Docket No. FDA-2018-D-1067-0001)

Dear Sir or Madam:

The Pew Charitable Trusts is pleased to offer comments on the draft guidance issued by the Food and Drug Administration (FDA) on March 26, 2018 regarding compounding under section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA). Pew is an independent, nonpartisan research and policy organization with a longstanding focus on drug quality and safety, including that of compounded drugs.

Pew supports the FDA's actions to implement the Drug Quality and Security Act (DQSA) and Section 503B of the FDCA, including the guidance document discussed here: *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. While we highlight several potential areas of concern, the policies detailed in the draft guidance will overwhelmingly promote public health by helping ensure the quality of compounded drugs produced by Outsourcing Facilities (OF) registered under Section 503B of the FDCA. The Agency's approach balances the needs of individuals for whom an approved or commercially available medication is not available and the health risks that compounded drugs can pose.

Importance of the Bulks List

Compounding plays an important role in health care for patients whose medical needs cannot be met by an approved drug. For example, as FDA describes in the draft guidance, patients who are allergic to a component of a commercially available product will need a compounded version without that ingredient, and patients who cannot swallow pills may need a compounded liquid formulation.

There are, however, inherent risks in using compounded drugs. Because compounded drugs are intended to be customized to meet an individual patient's need, they are not subject to the same rigorous efficacy, safety, and quality testing as FDA-approved drugs. Without this testing,

patients and their providers may not know the risks a compounded drug poses. For example, a compounded formulation of an FDA-approved drug may or may not be absorbed in the body in the same way as the approved product. Given these risks, compounded drugs should be substituted for approved drugs only when a compounded product is necessary to meet the patient’s clinical need.

Outsourcing facilities create stock supplies of compounded drugs and distribute them to health care providers—such as hospitals or physicians’ offices—for administration to patients. These facilities may manipulate FDA-approved products, e.g., by diluting them or putting them into a different dosage form for patients who need these alternatives. They may also copy FDA-approved products by making those products from bulk ingredients when the FDA-approved drug is on the Agency’s list of drugs that are in shortage. When manufacturers cannot fulfil patient need for approved drugs, outsourcing facilities are permitted to supplement that supply. Finally, and most relevant to this guidance document, outsourcing facilities can compound drugs from bulk substances when compounded options are clinically necessary. They may do this when it is necessary to start from a bulk drug substance to create a needed form of an FDA-approved product, such as a drug product that is preservative-free or allergen-free, or when there is no approved drug product containing an active ingredient that meets the patient’s need. Outsourcing facilities are permitted to fill stock orders for large quantities of compounded drug products for purchasers without first obtaining prescriptions for individual patients, and thus production at these sites can reach significant scale.

Given the potential for this form of compounding to reach a significant number of patients, DQSA set guardrails for bulk compounding by outsourcing facilities, limiting them to an approved list of compounded drug products, referred to as the bulks list. FDA creates the bulks list, but, under the statute, may only place substances “for which there is a clinical need” onto the list.¹

As envisioned by DQSA, the bulks list permits large-scale compounding of medications for which there is a clinical need, while preventing compounded drugs from undercutting the incentive for manufacturers to seek FDA approval. To obtain FDA approval, an applicant must submit a new drug application that contains data to demonstrate that the drug product is safe and effective and will be manufactured in such a way as to ensure a quality product. Conversely, compounded drugs do not go through the FDA approval process. Furthermore, although both pharmaceutical manufacturers and outsourcing facilities are subject to current Good Manufacturing Practice (cGMP) requirements, and inspected according to those standards, the cGMP requirements applicable to outsourcing facilities are different from those applicable to conventional manufacturers, and outsourcing facilities need not be inspected prior to distributing product. This means that compounded drugs may be sold by facilities that have never been inspected. Thus, federal law appropriately restricts the use of bulk drug substances by outsourcing facilities to circumstances where there is a clinical need, unless the drug is in shortage.

¹ FDCA 503B(a)(2)(A); 21 U.S.C. 353b(a)(2)(A).

Preference for Starting from Approved Product

In the draft guidance, FDA proposes to require that when an outsourcing facility has the option of starting from approved product, it must. In other words, when compounding from a bulk drug substance is not necessary to fulfill a clinical need (or to remedy a drug shortage), the outsourcing facility cannot compound from bulk. We welcome the Agency's clarity on this matter; it is a key component of the new guidance.

A preference for compounding from approved product will reduce the risk of compounding a poor quality product, and therefore limit risk to patients. The quality and quantity of the active ingredients and excipients in an approved product have been established during the review process, as has the ability of the manufacturer to consistently produce a quality product. If the initial product is required to be sterile, the manufacturer will have been required to show during the approval process that it can consistently manufacture a sterile product. 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. (Page 5, lines 146-159)

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 product is particularly concerning. By requiring these facilities to manufacture from an FDA-approved product whenever possible, the Agency minimizes the risk of compounding errors—not only through contamination, but also through the production of sub- or super-potent compounded drugs.

As Pew considered the guidance and its potential impact on the delivery of health care, we interviewed stakeholders from across the compounding sector. Over the course of those discussions, some stakeholders indicated that there may be circumstances where compounding from bulk substances is preferable because it is safer.

The basis for this reasoning is that, in some instances, compounding from approved product may also involve many manipulations—for example, obtaining the necessary quantity of an approved product may involve opening multiple small vials or ampules, and with each manipulation the risk of contamination increases. However, Pew has not found evidence of any specific circumstance where it is safer to create a sterile product from a non-sterile product, rather than starting with a sterile product and then maintaining its sterility during compounding. Thus, we

consider a preference for compounding from approved product wherever possible to be a policy that will promote patient safety.

Some may also argue that certain other circumstances dictate the need to compound from bulk substances. Because some populations—e.g., neonates—may require an uncommonly high degree of precision in measuring an active ingredient, it may preclude the use of approved products, which are permitted to fall within a range of values. To the extent that circumstances like these can be documented and legitimately present a clinical need to compound from bulk substances, FDA’s guidance would, appropriately, allow for the bulk substance to be placed on the list.

These examples illustrate a key implementation challenge. As FDA places bulk drug substances that are active ingredients in approved drugs on the bulks list to meet clinical needs like those described above, it will need a mechanism to ensure that it does not facilitate compounding from bulk when clinical needs do not require substituting bulk ingredient for approved drug. In the neonate example above, a compounder might be permitted to use bulk to compound for neonates, but should not start with bulk when compounding for populations tolerant of the range of active ingredient in approved product. FDA might address this by requiring the outsourcing facility to obtain documentation from the purchaser regarding the clinical need for the full quantity of compounded drug contained within the order, submitting the outsourcing facility to an expectation that it utilize reasonable judgment in fulfilling orders (e.g., if the quantity ordered for neonatal use far exceeds that required by the neonatal population, the facility would have reason to inquire whether some portion of the order could be created from approved drug rather than bulk), and using its authority to promulgate labeling requirements to require that the outsourcer label the drug for the clinical circumstance that necessitated compounding from bulk (e.g., “For Neonatal Use” or “For Use in the Treatment of XX Condition”, where “XX Condition” has been identified by FDA as a condition demonstrating the clinical need for medications compounded from bulk substances).

Meanwhile, some stakeholders have also made note that compounding from bulk substances is generally less expensive. While this may be true, substituting unproven, compounded versions of FDA-approved drugs exposes patients to unknown risks and undermines the incentive for pharmaceutical companies to do the testing necessary to protect patients.

Access to affordable medications is vital. Policymakers and others, including Pew, are working to find solutions to high drug costs. However, the answer is not to undermine the FDA approval process or to ask patients to accept potentially substandard products by turning to compounding. So, we are glad to see that in the guidance, FDA distinguishes between the need for a lower cost drug and clinical need. Through DQSA, Congress specified that clinical need should inform the composition of the bulks list, and FDA’s clear stance in the guidance adheres to that statutory requirement.

Creating the List

In general, we support the factors the Agency has proposed to consider in developing the list of approved bulk substances. Through the development of the bulk substances list for 503A compounders, FDA and stakeholders have developed experience with factors impacting that process. Using similar factors in the development of the 503B list enhances predictability, which is particularly helpful over time as alternatives arise and the list must be updated.

The majority of the factors discussed in the guidance will not only ensure the consistency and predictability of the process, but will help to ensure the safety of medications compounded from substances included in the list.

As FDA notes in the guidance, physical and chemical characterization of the substance is important for ensuring that the properties the Agency considered necessary in approving drug products with the same active ingredient will translate to the properties of the compounded product. This requirement helps ensure that the data on which FDA relies to place a substance on the list are relevant to the product ultimately made from that bulk substance.

Similarly, FDA importantly notes that safety information will be less available and less rigorous for most bulk drug substances. Thus, the Agency is right to take into consideration whether there are approved alternatives that can be used in place of a compounded drug. In the interest of limiting risk while promoting access, the Agency's tolerance for uncertainty regarding safety should be higher when patients lack access to alternatives, and lower when they do not.

In addition to safety, FDA appropriately intends to consider the effectiveness of a substance for a particular use, however that has been demonstrated. This factor is especially important for patients with serious or life-threatening diseases, who may forego other treatment options for the compounded drug.

To the extent that the historical use of a substance in compounding can be used to support safety and effectiveness, it makes sense to include this fourth factor. However, it is unclear whether a drug's historical use as office stock imparts any meaningful information related to safety or effectiveness, or clinical need.

Outsourcing facilities can produce drug for both office stock and to fulfill patient prescriptions (except where state law poses a barrier). Considering historical use for office stock as a factor would presumably make it less likely that products without a history of such use could be made by outsourcing facilities. Thus, compounding of products produced according to prescriptions would be pushed into the traditional compounding sector, where they could be made by physicians or pharmacists under state standards. While this may be good policy in circumstances where having a prescription for the product would help ensure that it is used only when clinically necessary, it is unclear that the agency should preferentially seek to have products without a history of office use produced by physicians or pharmacists instead of outsourcing facilities, who operate under higher quality standards and are subject to FDA inspection.

We support FDA's proposal for specificity in the list, which better permits it to be tailored to clinical need. In particular, we appreciate that when a listed bulk substance is a salt or ester of an active moiety, the Agency will specifically list that salt or ester, and not include the base compound and other salts or esters of the same active moiety. This helps to ensure that the safety and effectiveness profile of each variant can be separately considered (to the extent those characteristics are known for substances that have not been through approval) and that patients receive drugs for which the benefits outweigh the risks.

Along those same lines, we are glad to see that the list will allow for specific dosage forms to be nominated. This allows for compounding from bulk substances where necessary without providing an over-broad mandate that provides for compounding in circumstances that may entail undue risk or may not be clinically necessary. As described above, FDA may want to consider additional restrictions, such as allowing compounding from bulk only for specific patient populations (e.g., "For Use by Neonates", "For Use by Patients with Peanut Allergies") to better ensure that a substance on the list to meet a given clinical need is not more broadly produced for patients who would be better served by approved drug or by drug compounded from approved drug.

Potential Issues in Implementation

While this proposal represents an important and positive step forward in realizing the promise of DQSA, we would like to highlight several factors that have the potential to impact both patient safety and access as the Agency works to implement this guidance.

The process for developing the bulks list will necessarily take time to finalize and implement. However, portions of this proposal can be immediately implemented—namely, prohibiting compounding from bulk where compounding from an approved product is a clinically acceptable alternative. To the extent this change may cause disruption in the industry, FDA should set forth an implementation plan that helps ensure patient access during the transition. FDA has been charged to ensure the safety of compounded medications and, where possible, it must do so without delay.

Lastly, we strongly support 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 providers 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.

* * *

Again, we thank you for your consideration of these comments and for your efforts to protect patients through robust implementation of the DQSA. Pew has worked for years on issues related

to drug safety, including work to ensure the safety of compounded medications. This guidance presents strong and necessary safeguards toward meeting our shared goals.

Sincerely,

A handwritten signature in blue ink, appearing to read "Elizabeth Jungman".

Elizabeth Jungman, J.D., M.P.H.
Director, Public Health Programs