Biotechnology Innovation Organization

May 25, 2018

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

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

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on FDA's Draft Guidance for Industry "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (Draft Guidance).

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

General Comments

BIO believes that compounded drugs can serve an important role for patients who have clinical needs that cannot be met by an FDA-approved drug product. As BIO has noted before, access to medically-needed compounded medicines is highly important; but access cannot and should not come at the expense of product quality and patient safety. As such, we strongly encourage and support FDA's allocation of resources to enable the safety of these compounded products. Drug products compounded under the conditions in Section 503B should be inspected for current good manufacturing practice (CGMP) requirements and there should be a well-supported pharmacovigilance approach to enable specific adverse event reporting to help mitigate the risk of these compounded products.

Although outsourcing facilities must comply with CGMP requirements and are inspected by FDA according to a risk-based schedule, their drug products still lack the rigor of a premarket inspection of manufacturing quality that is part of the drug approval process. Providing a patient with a compounded product when they could otherwise use an FDA-approved, commercially available product, subjects that patient to unnecessary health risks. As such, compounded products should only be used by patients whose medical needs cannot be met by an FDA-approved drug. BIO is pleased to see that FDA continues to include this important concept in its regulatory documents, including in this Draft Guidance.[1]

[1] FDA Draft Guidance "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug and Cosmetic Act" March 2018, lines 96-102.

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When unauthorized versions of drugs - including drugs subject to patent protection – are compounded, it weakens incentives for companies to conduct clinical testing and bring a new drug to market via the traditional FDA-approval pathways for innovative as well as generic drugs. Over the long term, this can lead to fewer new drugs, less clinical information available to prescribers about the safety and effectiveness of these products, and fewer approved medical options for patients. As such, we are pleased to see FDA discuss the criticality of the drug approval process in this Draft Guidance.[2]

The drug compounding provisions of the Drug Quality and Security Act (DQSA) did not alter current law with regard to biologics and therefore there is still no applicable exemption in the Federal Food Drug & Cosmetic Act (FD&C Act) compounding provisions for entities that compound or repackage biological products. Accordingly, these products must meet all of the long-standing requirements in the Public Health Service Act (PHSA) and the FD&C Act designed to protect the public health. As such, BIO is pleased to see FDA include in the Draft Guidance language indicating that "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*…" (emphasis added).[3]

BIO thanks FDA for this Draft Guidance, which clearly lays out the process for determining whether a bulk drug substance should be included on the Bulks List and urges FDA to finalize the Guidance as soon as feasible in order to ensure all stakeholders understand the process and FDA can begin placing substances on the list.

Process for Nomination and Review for the 503B List for Bulk Compounding

BIO encourages FDA to put a sustainable framework in place to ensure requirements under the 503B exemptions are met. There needs to be a clear and transparent process for registering facilities with the FDA as 503B bulk compounding outsourcing facilities, knowledgeable and competent reviewers to review the applications, a quick and accurate method to communicate final decisions, and a system for identifying fraudulent outsourcing facilities.

There also needs to be a clear set of guidelines for outsourcing facilities to follow to provide relevant information and for FDA reviewers to follow for what constitutes acceptable CGMP conditions and justifiable clinical need. Consistency and clarity is needed for the application. We encourage FDA to provide adequate resources to train reviewers.

BIO believes it is critical for FDA to publish a notice for public comment in the Federal Register that describes its proposed position on each bulk substance along with the rationale for that position, and consider any comments on FDA's proposals regarding whether to include nominated substances on the 503B bulk list. This is especially important because as these are not FDA-approved products that have findings of safety, efficacy, and quality. Additionally, there needs to be a timely publication of FDA's final decision so stakeholders including physicians and patients understand both what is acceptable and what is not acceptable to compound.

[2] Draft Guidance, lines 180-186.
[3] Draft Guidance, lines 253-255.

Clarification for What Constitutes "Clinical Need"

BIO believes that further clarification of "clinical need" is necessary. As "clinical need" is a key element to implementing this provision, there is a need for more clarity regarding what constitutes "clinical need" and what does *not* constitute "clinical need". While the interpretation discussed in the Draft Guidance is consistent with the relevant legislative text, additional details and examples may be helpful for stakeholders to fully understand FDA's thinking regarding "clinical need".

For example, acceptable "clinical need" may be a patient who has difficulty swallowing solids and semi-thick liquids, but who can swallow thin liquids, who could benefit from a less viscous form of the medication. In this example, the liquid formulation remains intact in its FDA-approved form except for the addition of a diluent. The risk to the patient is minimal.

Alternatively, BIO believes that convenience is not an acceptable "clinical need". An example where three single agents becomes a triple combination for ease and convenience of drug administration undermines the FDA drug regulations and approval process. These compounded multiple drug combinations have no data to assure efficacy, safety, and quality. There are no data regarding drug-drug active ingredient interactions, drug-drug excipient interactions, or that the combination of single agents are as effective as each of the single agents when administered separately, as required under the Combination Rule where each of the components of a combination must demonstrate their individual contribution to the overall effect of the drug.

Accordingly, FDA should not permit drugs to be compounded under 503B for reasons of supply issues, costs, or convenience. While the Draft Guidance mentions supply issues or costs as not meeting the "clinical need" threshold, it does not specifically address convenience. We ask FDA to include a discussion that articulates that convenience does not meet FDA's standard of "clinical need".

Non-Biologic Complex Drugs and Narrow Therapeutic Index Drugs

Non-Biologic Complex Drugs (NBCDs) are highly complex drugs which contain unique drug delivery systems, active ingredients and/or dosage forms. There are currently no reliable techniques or regulatory pathways to establish and ensure bioequivalence between a NBCD and any proposed compounded version. Consequently, alteration of complex drugs, in any way, may diminish their efficacy or worse, subject patients to unnecessary danger. While there is currently no formal definition of what constitutes a NBCD, the Non-Biologics Complex Drugs Working Group defines NBCDs as "medicinal products, not being a biological medicine, where the active substance is not a homo-molecular structure, but consists of different structures that cannot be isolated and fully quantitated, characterized and/or described by physico-chemical analytical means. The composition, quality, and in vivo performance of NBCDs are highly dependent on the manufacturing processes of the active ingredient as well as the formulation".[4] As such, BIO believes that there should never be a clinical need to add bulk substances onto the bulk substances list for the purposes of

[4] Non-Biological Complex Drugs (NBCD) Working Group https://www.lygature.org/non-biological-complex-drugs-nbcd-working-group

compounding a drug considered to be a NBCD, as the safety risks significantly outweigh any perceived patient benefit.

Similar concerns are raised with drugs with a narrow therapeutic index. A drug or other therapeutic agent with a narrow therapeutic range has little difference between toxic and therapeutic doses.[5] Precise manufacturing, controls of excipients used and qualification of personnel are even more critical for narrow therapeutic index drugs than for other products. The margin of error for differences before patient safety is impacted is much smaller, so that the acceptable range of variability between the approved brand product and a compounded version will be slight. This is especially magnified for highly potent drugs that are administered at a low dose.

In addition, differences in release profiles for drugs with a narrow therapeutic index (e.g., between immediate and extended release formulations, or between different extended release preparations) can result in higher or more or less sustained concentrations of drug plasma levels in patients, affecting safety and/or efficacy. Differences in excipients could also affect product absorption by the patient, likewise affecting safety and/or efficacy.

As with NBCDs, BIO believes there should never be a clinical need to compound a drug with a narrow therapeutic index.

Conclusion

BIO appreciates this opportunity to comment on 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." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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[5] 21 CFR 320.33 defines a drug product as having a narrow therapeutic ratio if there is less than a two-fold difference in minimum toxic concentration and minimum therapeutic concentration in the blood. Also, any drug where safe and effective use requires careful titration and monitoring or where there is a less than two-fold difference