October 11, 2016

[Submitted electronically to www.regulations.gov]
Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA Docket FDA-2016-D-1267 — Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry; Availability.

ASHP is pleased to submit comments to the U.S. Food and Drug Administration (FDA) regarding the draft guidance about what constitutes a copy of a commercially available drug under Section 503B of the Food, Drug, and Cosmetic Act. ASHP represents pharmacists who serve as patient care providers in acute and ambulatory settings. The organization's more than 43,000 members include pharmacists, student pharmacists, and pharmacy technicians. For over 70 years, ASHP has been at the forefront of efforts to improve medication use and enhance patient safety.

ASHP advocates for a strong compounding framework. We believe that a robust 503B outsourcing facility program is essential to realizing the goals of the Drug Quality and Security Act (DQSA). For many of our members, 503Bs are a vital link in their compounding supply chain. ASHP appreciates FDA's efforts to clarify the types of products 503B outsourcing facilities can permissibly compound under 503B. Greater clarity around certain terms used in Section 503B may reduce confusion and assist with compliance. Although ASHP is supportive of FDA's work, our review of the draft guidance, as well as discussions with our members, indicate potential issues with interpretation and application of some guidance provisions. Specifically, the scope of the drug shortages provision, the definition of bulk drug substances to include approved drugs, and the documentation requirements raise concerns. To assist FDA in refining the guidance document, ASHP offers the following recommendations.

I. Definition of Bulk Drug Substances

ASHP urges FDA to further clarify its definition of the term "bulk drug substance" as used in the draft guidance. In the guidance, FDA states "if a component of the compounded drug is a bulk drug substance that is also a component of an approved drug, the compounded drug product is essentially a copy of an approved drug and cannot be compounded under section 503B, unless there is a prescriber determination of clinical difference...".[1] The guidance further notes that "[t]his provision applies to a compounded drug whether it was compounded from bulk drug substances or from drugs in finished form."[2] The application of the bulk substances prohibition to "drugs in finished form," which we understand to mean approved drugs, is confusing and contrary to statutory differentiation between bulk

[1] FDA, *Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (July 2016), at lines 275-278.
[2] *Id.*

drug substances and approved drugs.[3] Based on our interpretation of the bulk substances provision, any sterile-to-sterile compounding undertaken by a 503B would require a documentation of clinical difference — despite the fact that sterile-to-sterile compounding uses only approved drugs in final form.

Confusion regarding which products 503Bs may compound under the guidance is likely to be amplified by the inconsistency between the FDA's definition of compounding and the USP definition of compounding. As noted above, hospitals and health systems rely on 503Bs to provide sterile products for administration to patients. Most of the sterile-to-sterile compounding done by 503Bs is preparing non-patient-specific medications for administration according to manufacturers' instructions in approved labeling. Such activities clearly fall within USP's definition of a compounded sterile product,[4] but it is unclear whether they fall within FDA's definition of compounding, because the compounded products are not immediately administered to patients. If FDA intends to treat these activities as compounding for the purposes of the draft guidance, then it is, in essence, treating 503Bs like hospitals and health systems. Imposing this type of administrative burden on 503Bs threatens their operations by removing some of the incentive for hospitals and health systems to outsource products, rather than simply compounding them internally. Thus, we also strongly recommend that FDA work with USP to reconcile their disparate compounding definitions.

II. Drug Shortage Provision

ASHP appreciates the inclusion of shortage protections in the draft guidance. In particular, we thank FDA for including a 60-day grace period for dispensing and distributing a drug after a drug shortage is resolved. However, we are concerned that the narrow focus on the FDA shortage list will not adequately address the potential impact of shortages on care. Thus, ASHP recommends a broader scope for the drug shortages provision in the draft guidance. Specifically, in cases where patients cannot obtain a drug, and it is not listed by FDA, we encourage the FDA to consider other sources of shortage information, including the ASHP Shortage List. Because FDA's shortage determinations are based on national drug production and utilization data, they do not always accurately reflect real-time point of care shortage status. In particular, the FDA shortage list may not reflect low allocation of shortage drugs by distributors to entities with limited buying power, contractual obligations prohibiting or strictly limiting off-contract purchasing or selling, limited distribution systems, and/or geographic areas with only one distributor or wholesaler. Thus, a comprehensive picture of shortages requires the use of multiple lists. If the FDA's intent is to address all shortages, the additional information offered by other sources such as the ASHP Drug Shortage list will be essential to addressing shortages throughout the country.

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[3] 21 U.S.C. § 353b(d)(1); *see also, id. at* § 353b(d)(3).

[4] USP, *Chapter <797>: Pharmaceutical Compounding – Sterile Preparations,* (It is important to note that while FDA states that compounding does not include products prepared according to package labeling, FDA-approved labeling [*i.e.*, the product package insert] rarely describes environmental quality [*e.g.*, ISO Class air designation, exposure durations to non-ISO classified air, personnel garbing and gloving, and other aseptic precautions by which sterile products are to be prepared for administration].)

To further ensure that the shortage provisions adequately protect patient access, ASHP recommends that the FDA also institute a brief grace period before a drug appears on the FDA shortage list. As FDA is aware, a drug shortage may not be national in scope but may already be adversely impacting patient access and hospitals, and health systems may need to rely on compounded medications to ensure patient access. Thus, a grace period before a product appears on the shortage list would ameliorate the impact of shortages on patients. To safeguard against abusive copying during grace periods, FDA could require alternative documentation of shortage, such as appearance of the drug on the ASHP Shortage List (or another authoritative shortage list) or a history of unsuccessful attempts to obtain the approved drug (e.g., purchase orders marked "backordered").

III. Documentation of Significant Difference

ASHP recommends that FDA reconsider the draft guidance's requirements for documenting a "clinical difference" for an unidentified patient. As noted in Section I above, our understanding of the guidance's bulk substances provision would mean that compounding done from both bulk substances and approved drugs would necessitate documentation of clinical difference unless the compounded drug is a copy or essentially a copy of a drug on FDA's shortage list. Thus, under the guidance (and depending on how FDA interprets the definition of compounding), a 503B will need to "obtain a statement from the practitioner that specifies the change between the compounded drug and the comparable approved drug and indicates that the compounded drug will be administered or dispensed only to a patient for whom the change produces a clinical difference, as determined by the prescribing practitioner for that patient."[5] The guidance further suggests that a "hospital pharmacy manager" could make this representation.

While we strongly support efforts to limit abusive copying, we question the necessity and effect of such a requirement. The responsibility for determining significant difference for individual unidentified patients rests with the prescriber. Assigning legal compliance with 503B requirements to vendors and dispensing pharmacists will achieve the letter, but not the intent, of DQSA. Aside from the potential liability associated with asking anyone other than the ultimate prescriber to make representations about how a drug will be used, there are also scope-of-practice ramifications. Physicians retain medical discretion and would not be bound by representations of the hospital pharmacy manager. Physicians could perceive such representations as an infringement upon their medical judgment. Further, FDA has repeatedly pointed to 503B outsourcing facilities as the preferred and, in some instances, sole provider of non-patient-specific compounded medications. By imposing additional documentation requirements on 503Bs, FDA may be undermining the incentive of hospitals and health systems to use 503Bs. As ASHP has previously emphasized, 503Bs are an essential link of the supply chain for many hospitals and health systems. We are concerned that imposing burdensome documentation requirements could threaten their ongoing operations, which would, in turn, threaten patient and facility access to medications. Thus, we encourage FDA to consider either removing this documentation requirement or, at a minimum, substantially revising it to address the concerns listed above.

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[5] FDA, *Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (July 2016), at lines 295-299.

ASHP appreciates the opportunity to provide FDA with feedback on the draft guidance. We look forwarding to continuing to work with FDA to develop a workable and effective compounding regulatory framework. Please contact me at jschulte@ashp.org or (301)-664-8698 if you have any questions or wish to discuss our comments further.

Sincerely,

Jillanne M. Schulte, J.D.
Director, Federal Regulatory Affairs