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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-1309 — Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry; Availability.

ASHP is pleased to submit comments to the U.S. Food and Drug Administration (FDA) regarding the draft guidance about what constitutes a copy of a commercially available drug under Section 503A of the Food, Drug, and Cosmetic Act.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 appreciates FDA's efforts to clarify the types of products pharmacies can permissibly compound under 503A. Greater clarity around terms used in Section 503A may reduce confusion and assist pharmacies with compliance. Although ASHP is supportive of FDA's work, our review of the draft guidance, as well as discussions with our members, indicates potential issues with interpretation and application of some guidance provisions. Specifically, the scope of the drug shortages provision, the interpretation of "commercially available," and the documentation requirements raise concerns. To assist FDA in refining the guidance document, ASHP offers the following recommendations.

I. Interpretation of "Commercially Available"

ASHP urges FDA to clarify in writing that the prohibition on the copying of commercially available products is not intended to prohibit the preparation of a commercially available approved drug in accordance with package labeling, regardless of whether a ready-to-administer or premixed version exists. We request that FDA further clarify that the guidance does not demand that pharmacies purchase ready-to-administer products if they are available. While ASHP's understanding is that preparation of a commercially available approved drug does not constitute compounding under FDA's definition, the inconsistency between the FDA and USP compounding definitions generates understandable confusion among pharmacists.

As ASHP has noted in previous comment letters, a clear, universally understood definition of what compounding is (and is not) is fundamental to the pharmacist's understanding of the requirements of 503A and FDA's interpretive guidances. USP <795>, <797>, and <800> are the foundation of hospital and health-system practice. Hospital and health-system pharmacists are trained on USP, which treats any

manipulation of a sterile drug, including preparation according to package instructions, as compounding. Thus, FDA's unique definition requires pharmacists to review their activity under two competing definitions — FDA's and USP's — while simultaneously ensuring compliance with CMS and other state regulations. Without harmonization or, at minimum, a clearer FDA definition of compounding, the overlapping FDA and USP frameworks will present an ongoing problem. ASHP strongly recommends that FDA work with USP to reconcile the disparate compounding definitions.

II. Drug Shortage Provision

ASHP appreciates the inclusion of drug shortage protections in the draft guidance, but 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 does not appear on FDA's shortage list, we encourage the FDA to consider other sources of shortage information, including the ASHP Drug Shortage list. Because FDA's shortage determinations are based on national drug production and utilization data, they do not always accurately reflect real-time 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 the ASHP Drug Shortage list will be essential to addressing shortages throughout the country.

To further ensure that the shortage provisions adequately protect patient access, ASHP recommends that the FDA institute a grace period before and after a drug appears on the FDA shortage list. During the grace period, pharmacies could compound the drug without violating the prohibition on copying. As FDA is aware, by the time a drug appears on the FDA shortage list, the shortage may already be adversely impacting patient access. Further, even after production of a drug in shortage is resumed, it often takes weeks to push the drug back into the system at quantities sufficient to meet patient need. Thus, these grace periods before and after a product appears on the shortage list could significantly 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 Drug Shortage list (or another authoritative shortage list) or a history of unsuccessful attempts to obtain the approved drug (e.g., purchase orders marked "backordered").

Lastly, ASHP encourages the FDA to consider two issues associated with documenting drug shortages — access to historical shortage data and the treatment of drugs that do not appear on the FDA shortage list but are, nevertheless, unavailable. First, to ensure that pharmacies can comply with the shortage documentation requirement, we ask that FDA confirm with its Drug Shortages staff that drug shortage historical data is accessible to pharmacies and regulators. Without this information, it will be difficult for pharmacists and oversight authorities to verify records. Second, we request that FDA provide a means to exempt drugs that meet the guidance's two criteria for commercial availability, but are still not available

to patients, from the copying prohibitions. ASHP has identified at least eight drugs that do not appear on FDA's shortage list, but which are nevertheless unavailable from any commercial source:

- Chlorothiazide Oral Suspension
- Dexpanthenol Injection
- Erythromycin Lactobionate Injection
- Methylphenidate Transdermal Patch
- Morrhuate Sodium Injection
- Reteplase Injection
- Torsemide Injection
- Vinblastine Injection

We recognize that the guidance offers a safe harbor, which allows pharmacies to fill four or fewer prescriptions for drugs that are considered copies per month. However, a pharmacy can easily exceed that threshold if it has even one patient requiring a medication listed above. For example, in the case of chlorothiazide oral suspension, which is commonly used in pediatrics, a pediatric hospital will need to supply the medication for every patient who needs it, for as long as that patient needs it. Optimal patient care and best practices may also dictate the compounding of the medication on a set schedule, in contravention of the guidance's prohibition against compounding copies on a regular basis or at set intervals. We request that FDA provide additional guidance regarding the appropriate handling and documentation of the types of medications listed above.

III. Documentation of Significant Difference

The guidance's requirements for documenting a "significant difference" require substantial revision to be workable in the hospital and health-system settings. As drafted, the requirements are premised on the community pharmacy model of prescribing, wherein a pharmacy receives a prescription, fills it, and retains the prescription as part of its patient records. In such cases, including a notation on a prescription is a viable documentation option. However, in the hospital/health-system context, a notation may not be possible in all instances.

Hospital pharmacies do not fill prescriptions, but rather issue a daily 24-hour supply of medications pursuant to a valid medication order that remains in effect until the order is changed or the patient discharged. Thus, there is no discrete paper or electronic record that is received and retained in the hospital/health-system pharmacy. Instead, medication orders are either entered into an electronic medical record by prescribers or written in a paper record. The pharmacy receives a copy, transcription, or electronic transmission of the order, but the original remains a permanent part of the patient record. Pharmacists may also be prohibited by state scope of practice acts or hospital policy from writing in the patient chart or altering the electronic health record. Given these facts, it is unclear how hospitals and health systems can comply with the guidance's requirements regarding notation of significant difference.

Furthermore, in the hospital and health-system context, pharmacists review every medication order to determine its appropriateness, including whether a compounded product is necessary for that patient. Information in the patient's medical record nearly always renders the need for a compounded medication self-evident. For instance, a pharmacist would immediately know to substitute a compounded liquid product for a neonate prescribed a drug available only as an oral tablet or to substitute a compounded gluten-free product for a celiac patient prescribed an approved drug that contains gluten. Thus, the need for a notation is effectively nullified in the hospital/health-system context.

We urge FDA to exclude orders that are authorized by hospital policy or protocol from the notation requirement. Although the guidance calls for case-by-case determinations of significant difference, medical staff and formulary committees regularly establish medication-use policy or protocols that apply to more than one patient. These protocols and policies are commonly used to anticipate needs and guide care in hospitals for a particular procedure, diagnosis, symptom, or other clinical need common to a group of patients. In these cases, a pharmacist, nurse, or other professional may initiate an order, including an order for a compounded drug, which is authorized according to approved medical staff protocol or approved medical staff policy. For example, a hospital-wide protocol for patients who have a newly inserted nasogastric or nasojejunal tubing may include the order, "When position of tubing confirmed, convert all oral solid medications to oral liquid form. Contact physician for any medication that can't be converted." Other examples of protocol-driven orders for compounded drugs abound, including orders to "administer all drugs as alcohol-free formulations" in pediatric patients or to supply "only sugar-free medications" for diabetic patients. The significant difference a compounded product makes for these patients is clearly evident to pharmacists — they do not need an additional note or step in the process, and no statement of clinical difference should be required.

Finally, we are concerned that the documentation requirement could create tension between prescribers and pharmacists. The draft guidance states that prescribers are responsible for determining that a compounded product will produce a significant difference for their patient. However, under the current law, prescribers are not held legally responsible for writing a prescription for a copy of a commercially available medication. If such a prescription arrives, a pharmacist can contact the prescriber and request the notation of significant difference. However, the prescriber may, understandably, object to questions regarding their prescribing authority and scope of practice or refuse to disclose the significant difference (likely on the basis of patient privacy). FDA provides no guidance for these situations, and it appears the pharmacist's only recourse is to send the patient away with a potentially valid, but unfilled, prescription. The patient suffers, and the pharmacist is viewed as obstructive, which damages the patient-prescriber-pharmacist relationship and is ultimately detrimental to quality care. ASHP believes that most prescribers will provide a notation once they know about the requirements. However, at present, because the compliance requirements fall squarely on pharmacists, it is unclear that prescribers are aware that these notations will be required.

While ASHP believes that the vast majority of prescribers will comply with the guidance once they are aware of it, the statement of significant difference is unlikely to deter prescribers determined to circumvent the law. Because FDA has stated that it does not intend to question the veracity of the significant difference notations, prescribers are free to prescribe copies of commercially available drugs,

provided they offer some statement of significant difference. If a prescription with a questionable statement of significant difference arrives at the pharmacy, pharmacists are placed in the untenable position of questioning a prescriber's medical judgment or turning away a patient with a potentially valid prescription. Based on the foregoing, we remain concerned that the notation requirement and its corresponding documentation element, as drafted, may not yield the results FDA intends.

IV. FDA Should Further Refine "Essentially A Copy" Provisions

To provide additional clarity, ASHP suggests the following changes to the component elements of the guidance's "essentially a copy" provisions:

- Same Route of Administration — ASHP believes that this category is too broad. We encourage FDA to revise it to apply to the "same, or essentially the same, formulation." The route of administration does not actually distinguish among drugs that are formulated differently for the same route in order to enable administration or ensure absorption by the target system or organ. For example, a drug to be administered "by inhalation" could be given nasally (i.e., a nose spray) or orally (i.e., an inhaler). An oral drug might be swallowed, administered via enteral access tubing as a liquid, or absorbed through the mucous membranes of the mouth as a troche, lozenge, sublingual, or buccal dosing form. Rectal administration might require a solution, suppository, retention enema, or foam.

  These differences in formulation are required for the drug to achieve its therapeutic purpose, not to produce a copy. We support prohibiting copies of these individual dosage forms but do not consider, for example, compounding an oral anti-candidal lozenge to be equivalent to copying an oral tablet, as one may be essentially topical (though in the oral cavity) and the other enteral.

  Similarly, we have concerns with the guidance's statement that a compounded drug will be considered a copy if there is a "commercially available drug product [that] can be used (regardless of how it is labeled) by the route of administration prescribed for the compounded drug."[1] We question the suggestion that the pharmacist should ignore the product labeling in such an instance. Administering a drug by other than its intended route is not without risk of adverse effects, including lack of effectiveness — no pharmacist would automatically make such a substitution without careful evaluation.

- Same Characteristics of Two or More Commercially Available Drug Products — The guidance prohibits compounding a mixture from active pharmaceutical ingredients (API) when two or more commercially available drugs could be used. We request that FDA clarify whether this requirement refers solely to compounding from bulk chemicals or whether it is also applicable

[1] FDA, *Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (July 2016), at lines 251-255.

to combining two or more approved drugs in a mixture (e.g., a mixture of sterile ophthalmic drugs that promotes adherence).

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,

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Director, Federal Regulatory Affairs