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Advancing Health in America

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December 6, 2021

Janet Woodcock, M.D.
Acting Commissioner of Food and Drugs
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2016-D-0271: Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Draft Guidance for Industry; Notice of Availability (Vol. 86, No. 192), October 7, 2021.

Dear Dr. Woodcock:

On behalf of our nearly 5,000 member hospitals, health systems and other health care organizations, and our clinician partners – including more than 270,000 affiliated physicians, 2 million nurses and other caregivers – and the 43,000 health care leaders who belong to our professional membership groups, the American Hospital Association (AHA) appreciates the opportunity to submit comments on the Food and Drug Administration's (FDA's) revised draft guidance on Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic (FD&C) Act. The AHA appreciates the FDA's efforts to ensure that its compounding regulatory framework allows hospitals and health systems to continue delivery of safe and high-quality care to patients. We also applaud the agency for holding listening sessions to ensure that stakeholders, including hospitals and health systems, have the opportunity to provide in-person input to these issues.

Removal of the One-mile Radius Policy. **We are pleased that the FDA has responded to concerns voiced by the AHA and its members regarding the one-mile radius policy and has determined that it no longer will take into consideration whether compounded drug products are distributed only to health care facilities that are located within a one-mile radius of the compounding pharmacy.**

The one-mile radius policy would not have been workable for hospitals and health systems with centralized compounding pharmacies that provide compounded medications to facilities at other sites outside of that perimeter without similar compounding capabilities. It would have severely curtailed access to compounded products for other health system facilities that may not have the necessary infrastructure and environment to engage in sterile compounding on their own; such facilities include

critical access hospitals, ambulatory surgery centers and satellite emergency departments. Such a policy also would have other negative consequences, particularly as it relates to utilizing to full advantage the skills of highly trained pharmacy staff, as well as ensuring sufficient volume to enable technicians and other staff to remain competent and develop consistent, standardized repetitive processes. These benefits both increase the efficiency of the health system and make it safer by reducing the likelihood of errors.

Concerns About 24-hour Use Requirement. The FDA has proposed a two-part, risk-based compliance policy that outlines several circumstances under which the agency does not intend to take enforcement action against a hospital or health system pharmacy that compounds and distributes drug products without first receiving individual patients' orders or prescriptions. The AHA supports the FDA's intention to use its enforcement discretion as long as the compounded drug products are administered only to patients within the hospital or health system and compounded in accordance with all other applicable FDA requirements.

However, we have serious concerns about a component of this risk-based compliance policy that would require compounded drug products to be used or discarded within 24 hours of transfer out of the pharmacy. While we agree that that compounded products should be subject to reasonable limitations to ensure quality and safety, requiring compounded drug products to be administered or discarded within 24 hours of their transfer out of the pharmacy is inconsistent with the science-based standards of the United States Pharmacopeia (USP); furthermore, such a policy is wasteful and will exacerbate drug shortages.

The AHA instead recommends that the FDA allow hospitals and health systems to use the established beyond-use date (BUD) timeframes that comply with the USP Chapters 797 and 795. A BUD is the date or time after which administration of a compounded sterile product must not be initiated. USP Chapter 797 describes the procedures and requirements for compounding sterile preparations. It focuses on ensuring that compounding pharmacies provide the conditions and institute practices to prevent harm to patients from microbial, chemical or physical contamination; excessive bacterial endotoxins; variations in product strength; or poor-quality ingredients. Chapter 795 addresses the compounding of nonsterile pharmaceuticals by explaining what constitutes good compounding practice and establishing guidelines that minimize the likelihood of error or cross contamination.

We believe that limiting the distribution of non-patient-specific sterile compounded drugs in hospitals and health systems based on these BUDs addresses the FDA's concerns regarding the risk, quality and quantity of compounded products. The USP chapters rely on scientific evidence to support their BUD requirements, while the 24-hour limitation lacks a clear evidence-based foundation. As described in the USP chapters, the BUD is determined from the date or time the preparation is compounded, and both the stability

of the components and the sterility limits must be taken into consideration when determining BUDs. Specifically, the BUD must be the shorter of the sterility dating or chemical stability dating. Therefore, consistent with the FDA's objective, adopting the USP BUD timeframes would limit the amount of a compounded drug that could be created and distributed without a prescription and would ensure its timely use.

Such an approach also would promote consistency and alignment across different standards. By following the BUDs put forward by USP, the FDA would preserve the States' Boards of Pharmacy oversight of hospital and health system compliance with the USP standards. It also would align with requirements established by the Joint Commission and the Centers for Medicare & Medicaid Services, both of which explicitly require hospitals' and health systems' compliance with the relevant USP chapters on compounding. In fact, CMS' "Survey Protocol, Regulations and Interpretive Guidelines for Hospitals" State Operations Manual notes, "all compounding of medications used or dispensed by the hospital must be performed consistent with standards of practice equivalent to or more stringent than those described in the compounding-related chapters in the United States Pharmacopeia and the National Formulary (USP-NF) published by the USP, which are recognized as authoritative guidance regarding minimum standards of safe practice applicable to both sterile and non-sterile compounding."

Enforcement discretion will not eliminate the challenge of conflicting standards. Hospitals and health systems will continue to be required to comply with two different standards: the FDA's 24-hour limitation standard and the USP BUD timeframes adopted by state boards of pharmacy and other oversight bodies. This will cause confusion for hospitals that want to continue to provide centralized compounding and distribution of non-patient-specific products to other parts of the hospital or health system. To avoid confusion and promote geographic and regulatory harmonization, we urge the FDA to replace the 24-hour limitation with the USP BUDs.

Moreover, the 24-hour limitation risks unintended-but-likely negative consequences. Specifically, this policy could exacerbate drug shortages, especially in the context of the current supply chain issues facing the U.S. due to the COVID-19 public health emergency (PHE). Prior to the PHE, hospitals already were experiencing shortages of key injectable drugs. Subsequently, the surge in demand for critical care and other drugs due to large numbers of critically ill patients with COVID-19 and disruptions in the supply chain have worsened drug shortages. Throughout the pandemic, hospitals' and health systems' compounding pharmacies have played an important role in mitigating these shortages. Adding a requirement to use or discard compounded drug products within 24 hours of transfer out of the pharmacy will increase waste, further exacerbating already-existing challenges from shortages.

Under the FDA's guidance, hospitals will be forced to discard compounded drug products that were stored in refrigerators in units outside of the pharmacy for more than

24 hours, even if they are still within the product's USP-determined BUD. This could have a significant negative impact on patient care during times of sustained drug shortages, particularly for critically needed drugs for patients in the emergency department, intensive care unit and operating rooms.

Implementation of this new standard also will cause delays in access to critical compounded sterile products used in patient care. We are particularly concerned that the 24-hour limitation will prevent hospitals from stocking products in automated dispensing cabinets (ADCs) and Pyxis machines in hospital units, which are needed for immediate retrieval and administration. This especially poses a risk for patient care in the emergency department, operating rooms and intensive care units, where medications must be immediately available to prevent harm.

As previously stated, the AHA recommends that the FDA replace the 24-hour limitation with BUDs. If, however, the FDA declines to do so, to prevent any confusion, we request that the FDA clarify the meaning of "transfer out of the pharmacy" in the context of the 24-hour limitation. In this letter, we assume that the FDA literally means the movement of compounded product outside of a pharmacy's four walls within which the compounded sterile product was prepared. However, it could also be interpreted as movement outside of the physical hospital building in which the pharmacy is located. Additionally, we remain unclear as to whether transferring product from one hospital pharmacy to another on the same campus or within the same system would trigger the 24-hour limitation. These distinctions make a difference in terms of compliance with the FDA's policy. **At the very least, to avoid the possible delays in access to critical compounded products, as described in the previous paragraph, we urge the FDA to consider ADCs and Pyxis machines to be part of the compounding pharmacy and therefore not subject to the 24-hour limitation.** Their use has become the standard of care in hospitals and health systems as they are essential to providing timely and high quality patient care and securing the storage of medications. In fact, some state Boards of Pharmacy requirements explicitly consider ADCs and Pyxis machines to be under a pharmacy department's direct control. Finally, we urge the FDA to clarify that a compounded product is not required to be discarded within 24 hours if it does not leave the pharmacy.

<u>Hospitals and Health Systems Cannot Solely Rely on Outsourcing Facilities</u>. Throughout the updated draft guidance, the FDA encourages hospitals and health systems with a need for compounded drug products to obtain such products from 503B outsourcing facilities.[1] However, while hospitals and health systems can and do obtain many products from outsourcing facilities, they cannot be relied upon exclusively for all of the compounding needs of hospitals and health systems. For instance, the nation's

[1] Outsourcing facilities, defined in Section 503B of the FD&C Act, are compounders that may send prescription drugs to health care facilities without obtaining prescriptions for identified individual patients. However, they must comply with several of the same FD&C Act requirements as drug manufacturers, including CGMP, and are subject to a risk-based FDA inspection schedule.

existing, currently registered outsourcing facilities do not have the capacity to serve all the nation's hospitals. This is evidenced by hospitals' reports of long waits and turnaround times for the 503B compounded products that they require on short notice. Hospitals report that it can take several days to receive products ordered from an outsourcing facility.

Furthermore, outsourcing facilities do not produce all the specialized compounded products hospitals need for patient care. They typically make large batches of compounded drugs and are thus not equipped to provide small amounts of tailor-made products to hospitals and health systems. Also, when a drug is in shortage, outsourcing facilities often cannot provide the needed product. By contrast, hospitals and health systems have processes in place to help stretch the supply of compounded drugs that are in short supply.

Finally, although outsourcing facilities are required to comply with several of the same FD&C Act requirements as drug manufacturers, while remaining subject to a risk-based FDA inspection schedule, there is some ambiguity about whether they are able to maintain these required quality and safety standards. That is, according to the FDA's website, 74% of the 72 FDA-registered outsourcing facilities have been issued an FDA Form 483 by the agency. A 483 is issued at the conclusion of an inspection when an investigator has observed conditions that may constitute violations of the FD&C Act, which may indicate the sub-standard preparation of compounded drug products by the facility. Hospitals and health systems have difficulty interpreting these inspection reports. Specifically, these reports offer little context or insight into the level of risk associated with various findings. Further, although the 483s are posted, information regarding the outsourcing facility's response is not made public nor are the reports ever cleared or reconciled. Information related to an outsourcing facility's response to a 483, particularly any quality improvements undertaken, could considerably reduce hospital or health system concerns associated with purchasing product from a 503B outsourcing facility. Furthermore, the use of outsourcing facilities can oftentimes be associated with increased costs to health systems, the impact of which has the potential to exacerbate rising health care costs due the increased acuity of patients, labor shortages, increasing cost of pharmaceuticals and supply chain shortages.

Therefore, given the many factors at play, hospitals and health systems cannot exclusively rely on 503B outsourcing facilities for all their compounding needs. Conversely, our recommended use of BUD standards fit within current delivery models and adequately control non-patient-specific compounding volume while concurrently safeguarding patients' access and limiting adverse operations impact.

We appreciate your consideration of these issues. Please contact me if you have questions or feel free to have a member of your team contact Roslyne Schulman, the AHA's director for policy, at rschulman@aha.org.

Sincerely,

/s/

Stacey Hughes
Executive Vice President
Government Relations and Public Policy