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Patrizia Cavazzoni, M.D.
Director, Center for Drug Evaluation and Research
Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
(*sent via www.regulations.gov*)

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– Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Draft Guidance for Industry; Availability.

Dear Director Cavazzoni:

The Federation of American Hospitals (FAH) is the national representative of more than 1,000 leading tax-paying hospitals and health systems throughout the United States. FAH members provide patients and communities with access to high-quality, affordable care in both urban and rural areas across 46 states, plus Washington, D.C and Puerto Rico. Our members include teaching, acute, inpatient rehabilitation, behavioral health, and long-term care hospitals and provide a wide range of inpatient, ambulatory, post-acute, emergency, children's, and cancer services. These tax-paying hospitals account for nearly 20 percent of U.S. hospitals and serve their communities proudly while providing high-quality health care to their patients.

The FAH appreciates the opportunity to comment on the U.S. Food and Drug Administration's (FDA) revised draft hospital and health system compounding guidance published on October 7, 2021. The FAH thanks FDA for its efforts to develop a compounding regulatory framework that balances safety with patient and clinician access to essential compounded medications, and also recognizes the different distribution models in hospital and health system pharmacies.

FDA is an important partner in ensuring that pharmacists and the patients they serve can access safe and high-quality compounded medications. We commend FDA for developing guidance that attempts to address the unique care delivery models within hospitals and health systems, which differ significantly from pharmaceutical manufacturers and traditional community pharmacy models, while maintaining appropriate patient safety. Although the FAH is generally supportive of the risk-based enforcement approach, to assist the agency in finalizing a workable regulatory framework, we offer the following suggestions to strengthen the guidance and harmonize it with other existing regulations:

Harmonizing FDA Regulation with Existing Hospital and Health System Regulations Will Ease Compliance While Ensuring Safety

As noted, we support FDA's efforts to structure the compounding regulatory framework to reduce barriers to care in inpatient settings or at alternate sites of acute care (e.g., outpatient clinics, ambulatory surgical centers, etc.). Tailoring compounding regulations to clinical settings decreases the chances of creating unintended access limitations, while still allowing FDA and clinicians to protect patient health and safety. However, as noted in our comments on the 2016 draft guidance, hospitals and health systems face overlapping federal, state, and local regulations. To the greatest extent possible, we urge FDA to revise its guidance to harmonize with other regulations, particularly the CMS conditions of participation. Specifically, we urge the following changes to the draft guidance:

- **FDA Compounding Definition:** FDA's working definition of compounding is different than the commonly understood definition of the term as used in hospitals and health systems. A consistent understanding of the definition of compounding would help FDA, hospitals and health systems, pharmacists, and other stakeholders to develop and implement a workable compounding framework.

  In practice, hospital pharmacists consider "compounding" to be the practice defined by the United States Pharmacopeia (USP), meaning any manipulation of a sterile product, including extemporaneously reconstituting and diluting injectable medications for administration to individual patients according to manufacturers' instructions in approved labeling. Over time, minor deviations from product labeling regarding preparation have evolved to improve product performance and/or safety. In many cases, the product labeling is not updated after approval to reflect these changes. At minimum, we urge FDA to clarify that product preparation with minor deviations from product insert or product labeling instructions would not immediately qualify as FDA compounding.

- **24-Hour Use or Disposal Requirement:** As noted in our 2016 comments on the original draft guidance, although the FAH agrees that non-patient-specific compounding must be subject to reasonable limitations, FDA's limitation on non-patient specific compounding should be evidence-based. **We applaud the agency for removing the**

one-mile radius geographic limitation from the guidance, but we remain concerned that the proposed 24-hour use or disposal requirement is arbitrary and not aligned with other hospital and health system regulation.

The FAH urges FDA to adopt an alternative approach that would align with existing regulation and care delivery models but still provide limits on non-patient-specific compounding in hospitals and health systems. Specifically, we urge the agency to replace the 24-hour requirement with the USP <797> beyond-use dating (BUD) requirements. While we recognize that these standards are specific to sterile products, we believe they could also be reasonably imposed on non-sterile products as well. USP <797> delineates 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. Further, in order to meet <797> standards, all personnel involved in sterile compounding must undergo specific training and testing.

Instituting a <797> time-based standard would better align FDA's requirements with other existing hospital and health system regulations. As evidenced by the CMS and The Joint Commission standards, the traditional community pharmacy dispensing model (i.e., where the patient presents a prescription for a compounded drug, and the pharmacist then compounds pursuant to that prescription while the patient waits) does not fit hospital and health system practice. Acutely ill or injured patients should not have to wait for their compounded drugs. As proposed, the 24-hour use or disposal requirement would result in significant unnecessary product waste and access problems related to additional Pyxis and automated dispensing cabinet (ADC) refills that are in direct contravention of CMS and The Joint Commission care and quality standards, making simultaneous compliance with both difficult. However, keying compounding limitations to USP <797> would solve the compliance problem and ensure that FDA regulation harmonizes with other evidence-based regulations.

Limiting non-patient-specific compounding in hospitals and health systems based on USP <797> BUD standards also makes sense from the risk and quality perspective. Using a BUD standard would address two of FDA's primary concerns with non-patient-specific compounding in hospitals and health systems. It would limit the amount of product that could be created, and it would ensure that that product is used in a timely fashion. As intended by Quality System Assessment, state Boards of Pharmacy would retain responsibility for oversight of hospital and health system compliance with <797> standards, freeing FDA to focus on the 503B program. This state Board oversight would be augmented and backstopped by TJC accreditation surveys and CMS reviews that concentrate heavily on USP <797> compliance.

An arbitrary 24-hour beyond use date assignment once a compounded medication leaves the pharmacy as proposed, would promote compounding at the bedside in non-sterile settings by clinicians that are not as practiced in compounding – potentially leading to patient harm and care quality challenges. It also would intensify labor challenges in already stressed hospitals with staffing shortages. Additionally, it would exacerbate the

risk of medication errors by adding unnecessary challenges, and constitutes a huge economic burden to use more costly mechanisms and vendors. Hospitals and health systems compound drug products daily in order to care for patients. While the majority are patient specific, there is certainly a fair amount of anticipatory compounding, as allowed per other FDA guidance, based on historical data and anticipated need. The USP beyond use date, as allowed by USP Chapter <797>, allows for hospitals and health systems to promote economies of scale with the lean personnel and resources on-site. We strongly advocate that the FDA substitute the 24-hour requirement with USP Beyond-Use-Dating in order to implement a standard that is already in place and ensure patient access and safety.

Finally, we urge FDA to further clarify what it considers "transfer" out of the pharmacy. Our understanding from the recent listening session and from the guidance itself is that transfer would include loading into Pyxis machines and ADCs. If that is the case, this definition directly conflicts with some state Boards of Pharmacy requirements that explicitly consider Pyxis and ADCs to be under a pharmacy department's control. 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 requirement. We urge FDA to harmonize its definition of "transfer out of a pharmacy" with state definitions that explicitly include Pyxis and ADCs within a hospital or health system's pharmacy department control.

Supporting the Development and Expansion of a Robust 503B Market

The development of a robust 503B marketplace is needed and FAH considers 503Bs essential to a strong supply chain. However, we remain concerned that, at present, 503Bs do not have the capacity to meet all system needs in real-time. Unfortunately, hospitals and health systems continue to encounter significant wait times and longer turn-around times when purchasing from 503Bs that suggests 503Bs are already straining to meet demand. Outsourcing facilities typically make large batches of compounded drugs and are not equipped to provide tailor-made products to hospitals and health systems and they are limited in what they can produce. Due to the nature of certain medications (e.g., timing, risk level), hospitals and health systems may not be able to ensure medication access by purchasing from a 503B outsourcing facility. As a result, hospitals and health systems compound products to meet their own unique patient needs and do so in quantities significantly below a 503B's volume. If the Draft Guidance document is finalized, as is, and hospitals and health systems are forced to utilize outsourcers (503B Compounding Pharmacies) for the majority of anticipatory drug compounds, the existing 503Bs will not be meet the demand, and the safety of our most vulnerable – the patients in our hospitals – will be greatly affected.

The FAH does not object to considering the lack of policies and procedures for purchasing from a 503B a risk factor for hospitals and health systems who do not meet FDA's proposed three-pronged safe harbor. However, we strongly encourage the agency to provide more detail about its expectations for such policies and procedures. Specifically, does the agency anticipate that hospitals/health systems will have a policy in place for procuring non-

patient-specific compounds that fall outside of the safe harbor from a 503B, or does it expect to see a purchase contract in place with a 503B for those products?

Further, to remove lingering quality concerns related to 503B purchases, we recommend that FDA create a system for updating 483 reports. At present, the reports are posted without any detail regarding subsequent amelioration or correction of deficiencies. These standing reports can contribute to reluctance by hospitals and health systems to rely on 503Bs because the hospital or health system remains solely responsible for medication quality under CMS and Joint Commission standards. Additionally, if FDA hopes to see more hospitals register as 503Bs, it should consider creating 503B guidance specific to those sites. The very small number of hospitals registered as 503Bs is a strong indicator of the barriers that remain to successful 503B registration and compliance for these organizations.

Additional Recommendations

The FAH appreciates the FDA's willingness to engage with stakeholders as the agency finalizes its compounding framework. While the November 17th telephonic listening session was helpful, we urge the agency to consider convening additional listening sessions in the near future. We would welcome the opportunity to convene members who can provide the agency with frontline accounts regarding hospital compounding operations, as well as ongoing difficulties/issues with 503B purchasing and registration.

We also offer specific line recommendations in Attachment A beginning on page 6 of this letter.

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FAH appreciates the opportunity to comment on the FDA guidance on compounding in hospitals and health systems. As described in detail above, we are concerned that the guidance does not reflect patient care needs and could exacerbate drug shortages by creating waste with the 24-hour use limit. We urge FDA to engage with hospital and health system pharmacists and caregivers to better understand the impact of its proposed guidance and instead use scientifically based standards set by USP and other FDA guidance.

FAH stands ready to work with FDA to ensure safe medication availability and use in hospitals. If you have any questions, please contact me or a member of my staff at 202-624-1534.

Sincerely,

Attachment A: Line-specific recommendations and comments

Lines 241-295: Recommend removal of this section. See comments on line 404-end below for rationale.

Lines 355-56: "…use or discarded within 24 hours post transfer out of the PHARMACY". If this is literal, to mean the four walls of the "room(s)" housing the "Pharmacy Department" proper, then this statement doesn't only limit transfer outside of the hospital building/campus to an off-site department of the hospital, such as a provider-based emergency department, but also limits the ability to transfer compounded drug products to nursing units within the hospital itself. This would include starter/vanilla TPNs in the NICU for the urgent administration of amino acids post birth of a premature infant or cardioplegic solution in the operating room. Many other scenarios exist, including the misoprostol manipulation for laboring patients. Specifically, we urge the agency to replace the 24-hour requirement with the USP <797> beyond-use dating (BUD) requirements. USP Chapter <797>, as mentioned in our letter, assesses scenarios based on environment and applied risk. The draft "Policy" statement within the Draft Guidance document not only promotes waste, but also aggravates drug shortage scenarios and conservation mechanisms (primary shortage, but also environmental challenges (e.g., hurricanes, floods)]. An assigned 24-hour beyond use date once a compounded medication leaves the pharmacy, intensifies the labor challenges in the already stressed staffing shortages currently in existence. Additionally, it exacerbates the risk of medication errors by adding on unnecessary challenges, and constitutes a huge economic burden to use more costly mechanisms and vendors. Hospitals and health systems compound drug products daily in order to care for patients.

The limited 24-hour beyond use date suggested in the Draft Guidance document will greatly affect off-site departments of the hospital, as pharmacy staff are not on site daily, but as required by state law. Again, this will be burdensome to the already stressed staff and will affect patient care. Additionally, in the case of a natural disaster, or an emergency, pharmacy staff will be unable to travel to the site in question to restock compounds post the 24-hour limit. This, again, will greatly affect patient care.

Line 373: USP Chapter <797> does not require 100% skin coverage. Suggest substituting USP <797> requirements based on the compounding risk level (i.e., Category I, II, or III).

Lines 378-379: The phrase "emergency situations" is extremely strong language. It is unreasonable to expect patients to be in dire needs or in an emergent situation before a non-patient specific compounded product can be utilized. Anticipatory compounding, as allowed by other FDA Guidance documents, should be allowed to limit actual "emergencies". This phrase is too limiting. Suggest revision to a phrase more in tune with high-quality patient care practices.

Line 383: The phrase "large total number of compounded products" is not defined. What does "large total number" mean? This is subjective.

Line 387: Interstate distribution: The guidance language creates challenges for markets that cross state borders, such as Kansas City, Cincinnati, Washington, D.C., etc. The phrase "large

amounts" is not defined. Again, this is subjective and ignores hospital systems operating in multistate markets.

Line 394: Hospital/health-systems have policies defining use of Outsourcing Pharmacies and those which are vetted/approved for use. Is the intent of the guidance document to force hospitals/health systems to become a 503B Compounding Pharmacy in order to provide real-time patient care, even when they are not distributing compounded products outside of their system? Patient care should always be the top priority, not use of 503B outsourcers.

Line 404-end: Section B. Essential Copy section. This section does not fit the overall tone of the Guidance document. Recommend removal of this section as an FDA Guidance Document related to 503A Compounders and Essential Copies already exists. Most hospitals/health-systems provide 503A compounding as allowed by the Food, Drug, and Cosmetic Act (FD&C Act), including anticipatory compounding. The FDA definition of an essential copy does not include products that are explicitly compounded per package insert, regardless of if a product is manufactured by a conventional manufacturer. Operationalization of this section would be burdensome and difficult for hospitals/health-systems. Documentation is not defined – how would a hospital/health-system document and maintain records? The guidance (lines 416-418) requires a statement that "indicates that the compounded drug product will be administered only to patients for whom the change produces a significant difference from the commercially available drug product. "Significant difference" is not defined and is subjective. Again, recommend removal of this section.