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Lauren Roth
Associate Commissioner for Policy
U.S. Department of Health and Human Services
Food and Drug Administration
Submitted electronically to http://www.regulations.gov

Re: Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Draft Guidance for Industry

Dear Ms. Roth:

On behalf of our over 220 members, the Children's Hospital Association appreciates the opportunity to comment on the Food and Drug Administration's (FDA or agency) Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), draft guidance for industry (draft guidance). Although all hospitals rely on compounding, children's hospitals must compound at approximately double the rate of traditional academic medical centers. Consequently, children's hospitals are particularly sensitive to changes in compounding requirements. This greater dependence on compounding is due to the unique nature of our patients: Commercially available drug products generally target the adult population, which is the larger segment of healthcare; young children, for example, aren't able to swallow oral pills; and weight based IV medications must be compounded down to smaller dosages to safely treat children. While we appreciate the agency's intent to provide clarity regarding existing compounding requirements, we are concerned that the agency's preference for outsourcing facilities and some of the proposed policy updates may inadvertently jeopardize the safety of pediatric patients. We detail our specific concerns below.

Hospital and health system compounding serves a vital function and cannot be replaced by outsourcing facilities

While outsourcing facilities are one source of compounded drugs, they are not a substitute or replacement for hospital and health system compounding. Outsourcing facilities are sometimes unable —or unwilling —to compound certain drugs or compound them in the formulation necessary for pediatric patients. In those instances, hospital and health system compounding is the safest, and most reliable, mechanism for children to receive the necessary medication.

We are concerned that the draft guidance's preference for outsourcing facilities may have unintended negative consequences on pediatric patient safety. Instead of assuming that outsourcing facilities should be the default source for compounded drugs, we urge the agency to recognize the vital and necessary role that hospital and health system compounding serves in the delivery of health care. If children's hospitals are discouraged or prohibited from compounding drugs that are not reliably available from outsourcing facilities, it may negatively impact the health outcomes of our child patients.

State laws may limit access to outsourcing facility compounded drugs

Unlike commercially available drug products where the pharmaceutical manufacturers will either be licensed in every state or use a wholesaler partner to distribute their products nationally, outsourcing facilities have a more limited distribution capability. Existing variations in state licensure or registration requirements can limit outsourcing facilities' ability to distribute drug products in certain states. This can create challenges for children's hospitals trying to obtain certain products that may be

generally available in the market, but not otherwise permitted in their states. Children's hospitals in these jurisdictions must compound their own products to ensure their patients can have reliable access to the necessary medication.

Children's hospitals cannot switch to outsourcing facilities unless multiple consistent suppliers are available

Patient safety concerns often force hospitals and health systems to compound their own drugs even if there is one outsourcing facility offering a desired product. Although outsourcing facilities can be an appropriate solution in certain circumstances, children's hospitals cannot rely on a single outsourcing facility because it can be inconsistent at delivering ordered quantities, forcing providers to scramble to procure alternatives on short notice. Outsourcing facilities may also terminate a particular product without sufficient advance notice to providers. Children's hospitals must have consistent expectations of product to safely provide care, which the outsourcing facilities have not been able to reliably satisfy. For this reason, many hospitals will not use outsourced products unless multiple suppliers are available. Currently, for certain drugs there is a limited duplication of offerings as each outsourcing facility develops and maintains its own catalogue. Without multiple suppliers to ensure consistent delivery of essential compounded products, children's hospitals must continue to maintain their own compounding.

Outsourcing facilities do not have a reliable supply of non-sterile pediatric offerings

Finally, while much of the draft guidance is focused on sterile compounding, the proposed policy is equally constraining for non-sterile compounding. Although outsourcing facilities are described as the preferred option in the draft guidance, these facilities rarely have significant non-sterile offerings, including much of what pediatric hospitals need. One example is the oral sildenafil suspension. If there is a shortage of the drug, children's hospitals must compound on their own as the drug would not be available through outsourcing facilities. The FD&C Act, as amended by the Compounding Quality Act (Title I of the Drug Quality and Security Act), does not even allow for exclusively non-sterile outsourcing facilities, thus few have entered this space.

The proposed prescription requirement for hospital and health system pharmacies other than outsourcing facilities may impede the delivery of health care services and inadvertently cause patient harm

Section 503A of the FD&C Act describes the conditions that must be satisfied for drugs compounded by a licensed pharmacist in a State licensed pharmacy or Federal facility to be exempt from certain requirements of the FD&C Act. One of the conditions that must be met is that the drug is compounded either "(1) after the receipt of a valid prescription order for an identified individual patient or (2) in limited quantities before the receipt of a valid prescription … if based on a history of the compounder receiving orders for the compounding of the drug product and in the context of certain established relationships."

The draft guidance describes a two-part compliance policy regarding the prescription requirement. In Part 1, the agency explains that it does not intend to take action with respect to the prescription requirement in section 503A of the FD&C Act if the facility meets certain circumstances:

1. The compounded drug products are administered only to patients within the hospital or health system.
2. The compounded drug products are used or discarded within 24 hours of transfer out of the pharmacy.
3. The drug products are compounded in accordance with all other applicable requirements of the FD&C Act and FDA regulations.

If a hospital or health system does not compound drugs within the limited circumstances described in Part 1, the draft guidance identifies in Part 2 certain risk-based factors the agency will consider in prioritizing its compliance and enforcement resources:

- Evidence of poor compounding practices or lack of sterility assurance.
- Non-patient-specific compounded drug products not for emergency uses.
- Routine, large amounts of non-patient-specific compounded drug products.
- Routine interstate distribution of large amounts of non-patient-specific compounded drug products.
- No procedures to obtain non-patient-specific compounded drug products from an outsourcing facility.

The 24-hour requirement under Part 1 is not empirically justified and may inadvertently contribute to patient harm

We are concerned that limiting hospital compounded products to only 24 hours may increase patient harm. Given the lack of consistent availability of products from outsourcing facilities, limiting products compounded in the hospital pharmacy to 24 hours of stability will lead to more compounding at the bedside. In the pharmacy setting, hospitals have consistent processes for double-checks, compounding records, barcode scanning in compounding and other procedures to enhance the safety of the products. Reducing the products pharmacies can provide to nurses and practitioners at the bedside will result in more bedside compounding by staff with less training in potentially more stressful situations.

The FDA also provides no empirical justification for the 24-hour limit in the draft guidance. In the absence of empirical data to the contrary, facilities should be permitted to use beyond-use dates in accordance with state licensure, United States Pharmacopeia standards or other established stability and sterility testing recommendations. This is particularly relevant for non-sterile products, which usually have considerably longer beyond-use dates than sterile products. Using a 24-hour standard for both sterile and non-sterile products is inconsistent with accepted industry practice.

Finally, we wish to highlight that the time a drug is transferred out of the pharmacy is not an event routinely recorded in hospital practice. Hospitals record the time a product is compounded or otherwise prepared, followed by the time it is administered. The act of transfer, in and of itself, does not modify the integrity of the product. We urge the agency to revise the draft guidance such that any policy should be based on the time a drug is compounded, not the time it leaves the pharmacy.

The emergency use risk-based factor under Part 2 is impractically burdensome and may jeopardize the health of our patients

There are situations where a need for a compounded drug is urgent —meaning treatment is needed within the hour —but not emergent. To ensure timely patient access and best outcomes, children's hospitals prepare certain medication in advance and utilize local storage to promote safety and minimize delays. A non-exhaustive list of examples includes parenteral nutrition, which should be administered in the first hour of life; umbilical catheters that need to be promptly installed to maintain arterial patency, which require a dilute heparin solution that is not commercially available; and use of opioid and non-opioid medications to treat neonatal absence syndrome, which occurs when a newborn withdraws from certain drugs it was exposed to in the womb. Syringes of these medications are commonly stored in automated dispensing cabinets to be readily available when a need arises. If the accessibility of these medications decreases as a result of the draft guidance, it may jeopardize the safety and wellbeing of pediatric patients.

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We thank you for the opportunity to provide comments and look forward to continuing to work with you to improve the delivery of children's health care. Please contact Steven Chen at steven.chen@childrenshospitals.org should you need more information.

Sincerely,

Aimee C. Ossman
Vice President, Policy Analysis