CALIFORNIA HOSPITAL ASSOCIATION

Providing Leadership in Health Policy and Advocacy

July 18, 2016

Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane, Rm.1061
Rockville, MD 20852

Subject: FDA Draft Compounding Guidances – Hospital and Health System Compounding Under the Federal Food, Drug and Cosmetic Act, FDA-2016-D-0271; Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act, FDA-2016-D-0269 and Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act, FDA-2016-D-0238

Dear Commissioner Califf,

On behalf of more than 400 member hospitals and health systems, the California Hospital Association (CHA) appreciates the opportunity to comment on three proposed FDA draft compounding guidance documents released on April 15, 2016. CHA believes the FDA — along with state regulators, including boards of pharmacy — plays an important role in ensuring high quality, safe and timely medications are provided to patients in all settings, including the hospital and health system setting. In addition, we believe development of a federal regulatory framework that compliments state efforts is essential to ensuring that all hospitals have access to essential sterile and non-sterile compounded medications. FDA is an important partner in this process, and we look forward to collaborating with other stakeholders to ensure that a federal framework balances patient safety with the need for timely access to medication, without creating inappropriate regulatory barriers to providing care.

California has a longstanding history of exceptional pharmaceutical practices driven by a proactive, multidisciplinary, evidenced-based approach between hospitals and health systems and the California State Board of Pharmacy (BoP). There are 485 licensed hospital pharmacies, many of them also licensed for sterile compounding, and eight licensed centralized hospital packaging pharmacies (CHPP), which provide compounded drug products to multiple sites from a central hospital location; an additional nine hospitals/health systems are actively applying for central hospital packaging licensing. The state has long embraced a three-pronged framework for purchasing and processing of sterile and non-sterile compounded products through hospital pharmacies, central fill pharmacies and 503B manufacturers.

Patients are requiring more frequent use of compounded medications which, if not manufactured correctly, increases risk of medication error and patient harm. Health care reform and recent catastrophic events involving national and regional sterile compounding pharmacies have caused hospitals to reconsider their available options. Many struggle to balance the costs associated with purchasing products versus preparing them. Many hospitals and health systems have smaller, less suitable pharmaceutical physical plant space to compound the needed quantities of sterile products rapidly in an effective manner; purchasing from 503B manufacturers, while an important component, can only provide a portion of compounded drugs.

California hospital/health system pharmacies recognized the benefits of hospital pharmacy compounding and established CHPP's as an adjunct to their existing hospital compounding framework. In 2012, the

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state passed AB 377[1], enabling hospitals and health systems to obtain a CHPP) license so they may prepare and compound unit dose drugs to inpatients for one or more hospitals provided the hospitals are under common ownership and located within a 75-mile radius of each other. The CHPP legislation was enacted with the support of the California BoP along with hospitals and health systems, when many across the state were proactively addressing strategic opportunities to improve their pharmaceutical operations' efficiency and effectiveness. The BoP supported this licensing process, which emphasized the highest quality and safety standards in compounding management and distribution. Together, hospitals and health systems and the BoP play a significant role in ensuring the safest and highest quality supply of sterile and non-sterile compounded medications and do so with a comprehensive framework composed of hospital compounding pharmacies, CHPP's and 503B manufacturers

California hospitals are positioning themselves to provide state of the art hospital pharmacy compounding services as a means to ensure the production of accurate and safe sterile compounded medications. This service's numerous benefits including:

- Minimizing the impact of drug shortages through batching as unit dose products
- Standardizing production to improve medication safety efficiently
- Minimizing the use of manually-applied auxiliary labels
- Decreasing outsourcing and dependence upon third party vendors
- Deploying quality assurance principles of USP 797 and USP 800
- Staffing with consistent and well-trained individuals whose primary focus is pharmacy compounding and production

The compounding pharmacies, particularly the CHPP's achieve higher production consistency and reliability than multiple smaller pharmacies in different locations with different facility accommodations and equipment. Automation can be more easily accommodated in a standalone space, along with easier shipping and receiving processes than those that serve an entire hospital system. Similar medication packaging and processes across the individual hospital facilities within a health system ensure medication administration accuracy and consistency by providers at the bedside.

Hospital/health system compounding pharmacies are vital to California hospitals and health systems now and in the future. CHA and its hospitals, health systems and pharmacists, agree with the FDA's intent to provide guidance with essential parameters for quality and safety. However, CHA offers specific guidance below to uphold these elements and enhance quality and patient safety standards for compounded drug administration.

I. Hospital and Health System Compounding Under the Federal Food, Drug, a Cosmetic Act, Guidance for Industry, FDA-2016-D0271

CHA urges FDA to delete the 1-mile radius requirement as criteria for medication distribution by a hospital or health system. California's expansive land mass and advanced health care reform measures have incentivized hospitals towards mergers and consolidation activity among multiple facilities across extensive local, regional and statewide territory. The proposed 1-mile radius is irrational. Determining that any health system distributing outside the 1-mile radius is automatically a large manufacturer is restrictive, arbitrary and an unreasonable distinction between a hospital-based compounding pharmacy and a large manufacturing distributor that does not manufacture per specific

[1] Added Article 7.6, commencing with 4128 to chapter 9 of Division 2 of the California Business and Professions Code.

patient prescription. Rather, the key criteria that should be used in the FDA guidelines for 503A facilities are facility, patient prescription and evidence-based — not mileage-based.

Further, there is no supporting evidence for a specific mileage requirement for hospital/ health system compounding subject to 503A compounding. While California CHPP regulations established a 75-mile radius, this distance was based on an approximate distance of a proposed CHPP several years ago — not on any evidence-based rationale or foreseeable future California CHPP model. California's present CHPPs have distribution distances varying between fewer than 5 miles to more than 70 miles. In addition, many of California hospital/health system campuses extend beyond a one mile radius and, as with the CHPP, the 1-mile radius restriction would have a negative impact on quality of care, forcing hospitals/health systems back to older less sophisticated systems, compromising patient care.

More importantly, the 1-mile limit will significantly affect hospitals that utilize health system compounding resources to support themselves, limiting access and increasing potential for sterile compounding being performed in less than optimal facilities. This practice would increase the risk of medication errors and contamination of sterile products only to patients within its own system facilities under common ownership, — that distribution is driven by patient-specific prescription or order, not geographic mileage boundaries.

CHA recommends FDA retain its facility and patient-specific prescriptions requirements and consider an alternative to replace the 1-mile geographic requirement —specifically, evidence-based criteria found in USP 797, USP 800, and USP 71. CHA recommends the use of safety and quality requirements in lieu of the 1-mile radius requirement, including USP 797, 800 and 71 as evidence-based practice requirements for processing and handling of non-hazardous and hazardous sterile compounding medications. USP 797 and USP 800 ensure compounding pharmacies provide the conditions and practices to prevent harm to patients and staff. Limiting non-patient specific compounding in hospitals and health systems based on USP 797 and USP 800 would address two of FDA's concerns with non-patient specific compounding in a hospital/health system 503A facility, by limiting the amount of product that could be created and used within a timely manner. State boards of pharmacy would retain responsibility for oversight of hospital/health system compliance, along with augmented oversight by Joint Commission accreditation and CMS conditions of participation which focus heavily on USP compliance, freeing FDA to focus on the 503B program oversight.

USP 71 refers to the specific practices that prevent harm to the patient from microbial, chemical or physical contamination; excessive bacterial endotoxins; and variations in product strength or poor quality ingredients. These evidence-based practices assure quality and patient safety regardless of geographic distances.

In addition, the FDA proposed facility component ("healthcare facilities that are owned and controlled by the same entity that owns and controls the hospital pharmacy") and the patient prescription requirement ("the drug products are only administered within the healthcare facilities to patients within the healthcare facilities, pursuant to a patient specific prescription or order"[2]) explicitly differ from 503B facilities that manufacture non- patient specific prescriptions. More importantly, these two factors imply patient responsibility and distinguish hospital and health system pharmacies from community and 503B pharmacies in that the hospital/health system retains authority for patient care outcomes and traceability of the compounded drug. FDA's terminology related to "common control" in its proposed facility component may need further definition, as multiple types of ownership configurations occur in

[2] Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act, Guidance for Industry, April 2016, page 5

hospital/health systems and alternative care settings. These sites can include assistance to smaller rural and critical access hospitals, along with support of ambulatory and surgical care settings, which may imply variable definitions of "common control." CHA supports a definition of "common control" that reflects the various relationships but maintains that compounded medications distributed to alternative settings of care are obtained and administered only pursuant to a physician's specific prescription or order.

CHA suggests that FDA adopt an expanded version of the definition of health system used in section 506F of the Federal Food, Drug and Cosmetic Act. Section 506F defines a health system as "a collection of hospitals that are owned and operated by the same entity and that share access to data bases with drug order information for their patients." However, because health systems often include other types of health care facilities that could benefit from access to high quality and safety sterile compounded drugs prepared by a system's centralized compounding pharmacy, we suggest a more expansive definition that includes not only hospitals but also other health system facilities, such as provider-based infusion centers, ambulatory surgical centers and other health care facilities that are owned and operated by the same entity.

While FDA suggests 503B manufacturers may fill the void should compounding services be needed outside a 1-mile radius, CHA is concerned that, while providing essential services, 503B facilities do not presently have the capacity to meet hospital compounding needs. Outsourcing facilities make larger batches of compounded drugs and are not equipped to provide specific products to hospitals and health systems. They also are limited in what they can provide and often times experience delays and shortages. As a result, hospitals compound products to meet their own unique needs in quantities significantly below 503B manufacturers' volume capabilities.

Using the outlined safety and quality standards would ensure standardization and consistency with other state and federal standards and regulations, including California compounding and CHPP regulations, and would prevent disruption to the present highly successful CHPP pharmacy configurations with advanced centralized compounding operations staffed by the most experienced pharmacy personnel. Reverting to antiquated systems for today's compounding in less sophisticated spaces would be resource intensive and would increase the risk of adverse drug events and patient injury. The 1-mile radius requirement could actually compromise patient health and safety as hospital pharmacies move towards increasing safeguards and updated facilities.

II. Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act, Guidance for Industry, FDA-2016-D-0269

California hospital and health system licensed compounding pharmacies are staffed with dedicated, fully trained personnel that provide sterile, non-sterile and repackaged unit dose medications for their hospitals/health systems. All of the medications are dispensed or administered with an appropriately licensed prescriber's order or prescription. Compounded medication that is prepared in batches and stocked for anticipatory compounding are assigned appropriate beyond-use-dates based on reliable, published stability studies and end-product testing that includes sterility, potency, endotoxin, pH and particulate matter tests. All sterile batched –prepared compounded medications that have extended use dating beyond USP 797 are quarantined and tested according to USP 797 and USP 71 standards before release for dispensing and administration. All compounding and repackaging activities are thoroughly documented and standardized, and include a review by staff to provide consistency and improve safety. All compounded preparations and repackaged medications are only dispensed to patients within the respective hospital/health system in quantities and timing parameters under USP 797 and USP 71.

Although the turn-over for batch prepared (anticipatory) compounded preparation is usually within 30 days, some preparations may have a longer shelf life because they are emergent drugs — including hydralazine a vasodilator used to prevent stroke secondary to hypertension, and norepinephrine, a cardiovascular support agent used for sepsis — that need to be stocked and ready for immediate use 24 hours a day, seven days a week, but may only be used once or twice in a six-month period. The supply is usually only enough for one to two patients and is tested according to USP 797 and USP 71 standards, assuring sterility and potency throughout the beyond-use -date and storage.

The 30-day limit is an understandable goal, but should not be a mandate because of the need for anticipatory compounding for acutely ill or injured patients who should not wait for the administration of medications, as outlined in CMS[3] and TJC guidelines[4]. Aligning compounding beyond-use dates with USP 797 and USP 71 valid sterility requirements is a more appropriate requirement that aligns with existing hospital and health system regulations for safe and effective care of acutely ill patients.

III. Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act, FDA-2016-D-0238

CHA believes the three-pronged framework for purchasing and processing of sterile and non-sterile compounded products through hospital pharmacies, CHPPs and 503B manufacturers is critical to successful administration and distribution of compounded medications and essential to realizing DSQA's goals[5]. All agree that 503B manufacturers are vital to the process; however, with continued sophistication of many of the CHPP's pharmacies, some are considering registering as outsourcing facilities.

To encourage participation in 503B programmatic development, CHA urges FDA to provide more clarity of the term "facility." FDA draft Facility Definition Guidance defines "facility," for the purposes of 503B, to include "all activities, equipment, appurtenances, and materials part of such a facility if they are related to human drug compounding under the supervision of the facility's management at the same street address, or in the same building, or in buildings located in close proximity to one another." It is unclear whether FDA would consider buildings that are on a hospital campus to be the same geographic location or in "close proximity" to one another. Hospitals and health systems must use 503A facilities to meet

[3] **CMS** Interpretive guidelines, Compounding includes: "Preparation of drugs or devices **in anticipation of prescription drug orders** based on routine, regularly observed prescribing patterns"; **"Medications must be available for administration to patients** when needed, including when the pharmacy is not open. Methods to accomplish this when the pharmacy is not open could include, but are not limited to, one or more of the following: automated dispensing units outside the pharmacy, night cabinets, contracted services after hours via telepharmacy contracting, on-call pharmacists, etc."; [The medication distribution system may include] Use of a **"floor stock system (i.e.; storage of pharmaceutical and over-the-counter drugs on the patient care unit),**" as long as the drugs are secured and controlled [emphasis added]

[4] **TJC,** "Hospital leaders, in conjunction with members of the medical staff and licensed independent practitioners, decide which emergency medications and their associated supplies **will be readily accessible in patient care areas based on the population served**; **Emergency medications and their associated supplies are readily accessible in patient care areas.** (See also PC.03.01.01, EP 8); Whenever possible, emergency medications are available in **unit-dose, age-specific, and ready-to-administer forms" [emphasis added].**

[5] **DQSA-The Drug Quality and Security Act (H.R. 3204)** creates a uniform, national standard for tracing pharmaceuticals through the supply chain. The bill ensures the safety of drugs for patients and the immediate preemption provision eliminates the burdensome patchwork of state pedigree laws. Wholesale distributors can start conducting business the same way in all 50 states.

urgent patient care and clinician needs, since some 503A compounded medications cannot be compounded in accordance with 503B Current Good Manufacturing Practices' requirements. If this definition is read to mean that anything produced on the same campus as a 503B facility would need to meet 503B standards, then 503A compounding would be prohibited — which would be contraindicated and prevent potential 503B development. CHA suggests that the FDA rethink its expansive definition of "facility." Hospitals and health systems cannot be expected to abandon existing facilities to qualify for 503B status. 503B "facility" requirements should be flexible enough to work within the existing three-pronged framework.

In conclusion, California hospitals and the California BoP work collaboratively to uphold continuous quality improvement measures to assure the highest standards of quality care and patient safety. Hospitals and health systems are deploying centralized packaging pharmacies due to more reliable production and distribution capability with highly educated pharmacists and staff as well as centralized, standardized practices that will enhance compounded medication safety measures. CHA appreciates the opportunity to respond and looks forward to working with FDA to ensure that final guidance provides workable solutions to meet our patients' needs. If you have additional questions, please contact me at akeefe@calhospital.org or (202) 488-4688 or BJ Bartleson, vice president, nursing and clinical services, at bbartleson@calhospital.org or (916) 552-7537.

Sincerely:

/s/
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