APhA
American Pharmacists Association

March 23, 2023

Maria Serpa, Licensee Member, Chair
Enforcement and Compounding Committee
California State Board of Pharmacy
2720 Gateway Oaks Drive, Suite 100
Sacramento, CA 95833

RE: Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations

Dear Ms. Serpa:

The American Pharmacists Association's (APhA) Academy of Pharmacy Practice and Management (APPM) Compounding Special Interest Group (SIG) appreciates the opportunity to comment on the California State Board of Pharmacy Enforcement and Compounding Committee's consideration of "Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations)."

APhA is the largest association of pharmacists in the United States representing the entire pharmacy profession. APhA represents pharmacists in all practice settings, including community pharmacies, hospitals, long-term care facilities, specialty pharmacies, community health centers, physician offices, ambulatory clinics, managed care organizations, hospice settings, and government facilities. The APhA-APPM Compounding SIG represents over 5,000 compounding pharmacists and focuses on education, communication, collaboration, advocacy, and sharing of ideas in compounding pharmacy practice.

We also support the comments submitted from the California Pharmacists Association (CPhA).

APhA-APPM's Compounding SIG submits the underlying comments regarding the following specific proposed provisions:

1736 Sterile Compounding Definitions

(d) "Essentially a copy" of a commercially available drug product means all preparations that are comparable in active ingredients to commercially available drug products, except that it does not include any preparations in which there has been a change, made for an identified individual patient, which produces for that patient a clinically significant difference, as determined by a prescribing practitioner, between that compounded preparation and the comparable commercially available drug product.

The phrase comparable in active ingredients is too broad and could encompass all dosage forms of a single active ingredient. For example, because a progesterone oral capsule exists then this could be read as preventing the compounding of progesterone troches or creams because they have comparable active ingredients. We suggest considering criteria such as the same active ingredient, same route of administration, and strength within 10%.

1736.1 Sterile Compounding Scope

The term CNSP is used in this section as opposed to CSP.

1736.1 Sterile Compounding Scope (d)(1)(A)

(d)(1)(A) (A) that drug product appears on an ASHP (American Society of Health-System Pharmacists) or FDA list of drugs that are in short supply at the time of compounding and at the time of dispense

We support the use of this language as it relates to compounding for human patients. However, this language is problematic for compounding for animal patients as these are not lists related to animal drugs. The FDA does have an animal drug shortage list, however, it is limited by the fact that the FDA does not have statutory authority to compel manufacturers of animal drugs to report shortages. We suggest that compounders of animal drugs be able to document their wholesaler being out of a product as evidence of a shortage.

1736.1(d)(3)
(3) Is made with a component for which a conventionally manufactured sterile product is available and appropriate for the intended CSP.

While starting from a conventionally manufactured sterile product has distinct advantages related to sterility, endotoxin content, and others one must also consider the effect on the compounding process. Requiring that some of the ingredients be sourced from conventionally manufactured sterile products and others having to come from nonsterile starting ingredients introduces changes to the process of compounding the CSP. These changes to the process can cause additional and unnecessary manipulations that may introduce contamination into the medications. There are examples of 503B facilities that used only conventionally manufactured sterile products who were later shut down by consent decree from the FDA due to the processes used and not the products. We recommend that compounders be able to determine the appropriate process for preparing the needed medications including the use of sterile or nonsterile starting materials for the process that will be utilized accompanied by appropriate quality control measures.

1736.3(b)
(b) The pharmacist overseeing compounding shall not allow personnel to enter the compounding area with non-removable piercings that increase the risk of contamination of CSP.

Piercings that are visible and can interfere with the garbing should not be worn. However, we are concerned about issues that could be presented by needing to ensure that nonvisible piercings are removed. Piercings that are not visible are unlikely to interfere with garbing.

1736.4 Facilities and Engineering Controls

(f) No CSP shall be compounded if the compounding environment fails to meet criteria specified in the law or the facilities SOPs.

Typically, Boards of Pharmacy have not required a pharmacy to cease compounding operations if an environmental parameter (like a pressure differential) was out-of-spec, but rather the pharmacy must revert to the most limited beyond-use-dates. Under the new USP <797> chapter, the beyond-use-date in this situation could be classified as Category 1, rather than Category 2. This is an important distinction for patient care to continue. If you can compound in a segregated compounding area for a sterile preparation, then it would seem applicable to revert to Category 1 beyond-use-dates rather than eliminate patient care. This is likely to be applicable to hospital and health systems most commonly.

1736.7 Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas and Sterile 70% IPA

(b) Reusable cleaning supplies shall not be stored within 1 meter of the PEC.

Some pharmacy practices utilize tools for cleaning, disinfecting, or applying a sporicidal agent that is a stainless steel tool on which presterilized pads are added to. Is it not possible to store this stainless steel tool within one meter of the PEC?

1736.8 Introducing Items into the SEC and PEC

SOPs shall specify the process and products to be used on any equipment and other items entering from an unclassified area into the clean side of the ante-room, entering a PEC, and entering the SCA. These SOPs will define at a minimum, what product is to be used, the dwell time required, and how dwell time will be monitored and documented.

We are confused as to why items would be moved from an unclassified area directly into the clean of the ante-room. Typical movement would be from the unclassified area to the dirty side of the ante-room, to the clean side of the ante-room, then to the buffer room, and then to the primary engineering control. Is the intent here to ensure that SOPs exist for staging products and that the appropriate contact time is used for the disinfectant or sporicidal product is utilized?

1736.9 Equipment, Supplies, and Components

(d) All components used to compound a CSP shall be manufactured by an FDA-registered facility and suitable for use in sterile pharmaceuticals. A Certificate of Analysis (COA) which includes the compendial name, the grade of the material and the applicable compendial designations on the COA must be received and evaluated prior to use.

It is our understanding that not all excipients can come from FDA-registered manufacturers. This is not a stipulation found in section 503A of the FDCA. Under federal law, active ingredients are required to come from FDA-registered manufacturers.

(e) If a bulk drug substance, or API, is used to compound a CSP, it shall comply with a USP drug monograph, be the active substance of an FDA approved drug, or be listed in CFR List of Bulk Drug Substances That Can Be Used To Compound Drug Products, 21 CFR 216, unless authorized by a public health official in an emergency use situation for a patient-specific compounded sterile preparation.

This portion of the regulation is not needed as it is repeating federal law criteria under section 503A. This is also problematic for animal compounding as this is not a set of criteria applied to compounding for animals under federal law.

1736.10 Sterilization and Depyrogenation

(a) Dry heat depyrogenation shall be done in compliance with USP Chapter 1228.1, Dry Heat Depyrogenation.

USP General Notices 3.1 states "Applicable general chapters" means general chapters numbered below 1000 or above 2000 that are made applicable to an article through reference in *General Notices*, a monograph, or another applicable general chapter numbered below 1000." "General chapters numbered 1000 to 1999 are for informational purposes only. They contain no mandatory tests, assays, or other requirements applicable to any official article, regardless of citation in a general chapter numbered below 1000, a monograph, or these *General Notices*." While these chapters are

helpful and valuable for compounders to be aware of for their practices, they are not intended by USP to be applicable.

1736.12 Release Inspections and Testing

(c) Injectable CSP's made from nonsterile components regardless of Category, must be tested to ensure that they do not contain excessive bacterial endotoxins, as established in Chapter 85. Results must be reviewed and documented in the compounding record prior to release.

In the revisions to 797 a Category 2 CSP that is prepared from one or more nonsterile ingredients that are aseptically processed, and not sterility tested has a limited BUD. At room temperature 1 day or 4 days when refrigerated. Requiring that these CSPs be tested for endotoxin content will mean that they cannot be prepared for more immediate patient needs as they will either be unable or highly unlikely to be tested fast enough by appropriately qualified laboratories.

1736.15 Use of Conventionally Manufactured Products as Components

(b) A single-dose container entered or punctured inside of an ISO class 5 area must be discarded within 12 hours.

For clarity, would this indicate that the container is expected to be kept in the ISO 5 classified area after being punctured?

1736.16 Use of CSPS as Components

A compounded stock solution intended for use in a CSP must comply with all provisions of this article including Category 1, Category 2, and Category 3.

As written it would seem that the stock solution would need to comply with all 3 Categories which does not seem possible. Perhaps the intent is that the compounded stock solution comply with all the requirements of the Category under which it was compounded. If this is the case then changing "and" to "or" between Category 2 and Category 3 could reflect this.

1736.17 Standard Operating Procedures (SOPs)

USP 1163 compliance required.

As mentioned above, we are concerned that the way in which USP Chapters above 1000 are referenced will establish them as enforceable. USP's General notices state that chapters numbered 1000 to 2000 are intended to be informationally only.

Thank you for the opportunity to submit comments on behalf of the APhA-APPM Compounding SIG. If you have any questions or require additional information, please contact APhA at mbaxter@aphanet.org.

Sincerely,

Michael Baxter

Michael Baxter
Acting Head of Government Affairs