APhA
American Pharmacists Association

March 17, 2022

Brenda Jensen, Chair
Compounding (CMP) Expert Committee Roster
12601 Twinbrook Parkway
Rockville, Maryland 20852

[Submitted electronically to: CompoundingSL@usp.org]

Dear Chair Jensen:

The American Pharmacists Association (APhA) is pleased to submit comments on Proposed Revisions to <797> Pharmaceutical Compounding – Sterile Preparations.

APhA is the only organization advancing the entire pharmacy profession. Our expert staff, and strong volunteer leadership, including many experienced pharmacists, allow us to deliver vital leadership to help pharmacists, pharmaceutical scientists, student pharmacists and pharmacy technicians find success and satisfaction in their work, while advocating for changes that benefit them, their patients and their communities.

APhA appreciates USP's significant public outreach to open a dialogue with pharmacists, other health care professionals, and regulators to discuss the proposed revisions and respond to stakeholder concerns. We agree the safety and efficacy of all prescription drugs, whether commercially manufactured, prepared or compounded, is paramount to the protection of public health. The standards set forth in the proposed revision to Chapter <797> on sterile compounding are of great interest to APhA and our members and we offer the following recommendations developed with input from our members, including feedback from our APhA Academy of Pharmacy Practice and Management (APhA-APPM) Compounding Pharmacy Special Interest Group (SIG), consisting of over 5,000 members, and Nuclear Pharmacy Practice SIG, consisting of over 2,200 members.

Where APhA's comments refers to a cost or burden imposed by a requirement, that "cost," or burden could result in a higher charge to the patient, or a decision by the compounder not to proceed with that particular compound. Increased "cost," results in a portion of the patient population choosing not to fill the prescription, and likewise the impact of a burden that a

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compounding pharmacy determines it cannot take on will also deprive the patient of the medication prescribed.

Major edits to the chapter include:

APhA is strongly supportive of the following statements in the revised chapter to avoid confusion regarding the applicability of <797> to radiopharmaceuticals.

"12. Remove specific information related to radiopharmaceuticals as CSPs and add cross-references to *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩."

1.1 Scope

"Sterile radiopharmaceuticals: Compounding of radiopharmaceuticals is not required to meet the standards of this chapter as they are subject to the requirements in *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩."

APhA has been a strong advocate for clear and effective USP public standards for radiopharmaceuticals that meet patient and practitioner needs for today and in the future and supports USP <825> which clearly delineates the differences between the activities performed by nuclear pharmacists.

2.3 Competency Testing in Aseptic Manipulation

There is no scientific justification to support requiring media fill testing every 6 months for those who oversee compounding of the facility. Accordingly, APhA recommends the following changes:

"For personnel compounding Category 1 and Category 2 CSPs, the aseptic manipulation competency must occur initially and at least every ~~6~~ 12 months thereafter. A single media fill at this frequency demonstrates competency for those who oversee compounding of the facility at the organization."

Additional persons involved in compounding oversight and checking of products do not in many cases ever have to go into cleanrooms spaces or compound themselves. Compounding facilities may even have staff who are amply competent to check product but may have physical

disabilities that preclude their ability to do a media fill and would prevent them from compounding. A didactic background can make that person competent to oversee compounding operations. Annual didactic competencies should cover aseptic technique and compounding procedures for these staff.

APhA recommends adding the following language:

"Personnel exclusively involved in oversight or checking of CSPs but do not peform any compounding themselves must do initial training on sterile compounding and appropriate garbing but are not required to do media fills or gloved fingertip testing at the regular frequency necessary for staff who perform compounding."

Box 4. Hand Sanitizing Procedures

The revision fails to indicate anatomical variation of staff, some of whom may need more or less hand sanitizer to sanitize hands. There is a lack of information regarding manufacturer recommendations specific to pharmacy areas (e.g., guidance for surgical personnel and staff caring for high-risk patients, but not specific guidance for staff performing sterile compounding).

APhA recommends the following updates:

- "~~Apply an alcohol-based hand sanitizer to dry skin following the manufacturer's instructions for the volume of product to use.~~
- Apply an adequate volume of an alcohol-based hand sanitizer to one hand and rub hands together, covering all surfaces of hands and fingers, until hands are dry."

14.4 Additional Requirements for Category 3 CSPs - Table 12: BUD Limits for Category 3 CSPs

The number of samples of a batch to be tested for sterility has been debated for the last 70+ years.[1] Previously, pharmacies could extend CSPs up to 180-day BUDs (at room temperature storage, with sterility testing) using published or unpublished stability studies, or performing potency over time testing.

[1] Bowman, FW. The sterility testing of pharmaceuticals. J. Phurrn. Sci. 58(l 1). 1301-1308 (1969). and Bryce, DM. Tests for the sterility of pharmaceutical preparations. J. Pharrn. Pharmacol. 8, 561-572 (1956).

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Generally, a Category 2 CSP may be assigned a 30 day CRT BUD if aseptically processed and sterility testing performed and passed. However, under the proposed BUD limitations in <797>, to provide a patient with a sterile compound that has a 30-day usable shelf life, a compounder would need to:

- Store the sterile preparation frozen;
- Terminally sterilize and store the preparation in the refrigerator, or;
- Perform a $30,000+ stability study on the preparation.

It is also unrealistic that USP has imposed particular storage conditions for preparations that have undergone a stability study. If the stability study was done performed using forced degradation (increased temperature usually 40 C) and shows that the preparation has stability at room temperature for 365 days, that is a scientifically sound, justifiable BUD.

APhA is concerned that these options could have significant negative impact on patient access and medication quality. **Accordingly, APhA requests USP maintain the current standard of extending CSPs up to 180-day BUDs (at room temperature storage, with sterility testing) using published or unpublished stability studies until addressing the following concerns:**

- Colder storage temperatures could present quality and/or administration problems;
- Crystallization/precipitation formation in sterile solutions;
- Adverse patient reactions to the administration of cold injectables and ophthalmics;
- Terminal sterilization may not be possible (degrade) for drugs or packaging that are heat sensitive, possibly creating deleterious compounds; and
- Stability study expense may be cost prohibitive for some compounders to perform and drive-up medication costs for compounds that do undergo stability testing.

APhA also recommends USP establish the ability to share stability data between pharmacies, or "published studies performed by pharmacies," that can be utilized, given the following conditions for Category 3:

- With every stability study that a pharmacy publishes, pharmacies publish what their environmental monitoring protocol is, their gowning, their cleaning schedules/agents, under what conditions the preparations were made exactly (in a LAFW, CAI, BSC etc.) as all of this has an impact on the sterility of the final preparation.
- With the sharing of stability studies, pharmacies should show a "state of control" over their facility with a certain level of sterility and quality assurance.

14.5 Multiple-dose - non-preserved, aqueous ophthalmic CSPs

In 14.5, Multiple-dose CSPs, there's a disparity in BUD standards for Multiple-dose, non-preserved, aqueous ophthalmic CSPs and the standards for Category 1, 2 and 3 aseptically processed CSPs. While pharmacists understand that there is a risk for contamination with ophthalmic dosage forms if the patient touches the tip of the dropper bottle to the infected eye, the same inherent risk of contamination is virtually the same for any CSP being handled and re-used multiple times.

For example, each time a multiple-dose CSP dosage form is punctured there is a chance that it will not be disinfected with a sterile alcohol wipe and contain microbial contamination on the stopper, which could then be transferred into the CSP. Yet, Category 2 CSPs, stored at refrigerated temperatures can be assigned a 10-day BUD. The contention here is that the dosage form should not necessarily dictate the BUD based on the risk of contamination because the risk of contamination for aqueous, non-preserved CSPs is the same, regardless of dosage form. A multiple dose ophthalmics, with proper patient education, should be able to follow the same standards for BUD assignments that are outlined in Tables 10. (BUD Limits for Category 1 CSPs) and 11. (BUD Limits for Category 2 CSPs).

In addition, this can be restrictive and more costly to patients. It may also affect patient access to these types of CSPs altogether as pharmacies may stop preparing them based on the restrictions with beyond use dating.

15.1 Use of Conventionally Manufactured Single-Dose Containers

It should be first acknowledged that there has been a change in the store period for conventionally manufactured single dose containers from 6 hours to 12 hours. However, it should also be noted that there's been a change in language regarding the use of "technologies" and the potential for stifling of innovation and significant cost savings with the language in this revision.

In previous versions of USP Chapter <797>, regarding the use of technologies USP has stated, "To achieve the above five conditions and practices, this chapter provides minimum practice and quality standards for CSPs of drugs and nutrients based on current scientific information

and best sterile compounding practices. The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein."

In the most recent revision, a significant caveat has been added to the wording regarding the use of technologies, "The alternative technologies, techniques, or materials must not be used to modify requirements outlined in this chapter (e.g., extending beyond-use dates, the amount of time a single-dose or multiple-dose container may be used, compounding in alternative environments)."

While the exact reasoning for why this wording was added by the CEC, there is a significant and specific case study for making exceptions to extend beyond use dating based on scientifically proven rationale. The use of closed-system transfer devices (CSTDs) are traditionally used as devices for containment of hazardous drugs. However, it has been studied that not only do they prevent hazardous drugs from escaping and exposing personnel, but they are also able to prevent contamination from infiltrating the vial it is attached to.[2]

APhA believes this verbiage stifles innovation. Given the current language proposed in this revision regarding the use of technology, it is a step backward rather than advancing the industry forward into a future that should be embracing logical, safer technologies that benefit the patient and the overall cost of healthcare.

16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions

APhA requests clarification if a stock solution is prepared and given a 9-day BUD refrigerated, and 4 days later is used to compound final doses, the BUD would no longer be 5 days if kept refrigerated but could be shortened if the final CSP is stored at room temperature.

APhA recommends the following language updates:

"The component CSP may be used for sterile compounding for up to 12h or its assigned BUD, whichever is shorter, and any remainder must be discarded. Component CSPs or stock solutions may be given BUDs consistent with those in Section 14 of this chapter until they are first used to prepare other preparations, at which point a 12-hour BUD must be applied to the component CSP or stock solution.

[2] See, J Oncol Pract 2012;8[4]:e45-e49; Am J Pharm Benefits 2011;3[1]:9-16; Am J Pharm Benefits 2011;3[6]:311-328; J Hematol Oncol Pharm 2016;6[2]:46-50).

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The final CSP produced from the component CSP should have a BUD of no longer than the BUD assigned to the component CSP, or shorter if the storage conditions change warranting a shorter BUD in accordance with section 14 of the Chapter. "

If you have any questions or require additional information, please contact Michael Baxter, Senior Director of Regulatory Policy, at mbaxter@aphanet.org. We look forward to continuing to work with you on USP Chapter <797> and other USP standards.

Sincerely,

Ilisa BG Bernstein, PharmD, JD, FAPhA
Senior Vice President, Pharmacy Practice and Government Affairs

cc: Brian Serumaga, PhD. Senior Manager, Personalized Medicines–Healthcare Quality Standards