TO: State Boards of Pharmacy

FROM: Scott Brunner, CAE
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SUBJECT: *U.S. Pharmacopeia <797> Regulatory Implementation*

As you know, the Compounding Expert Committee (CEC) of the U.S. Pharmacopeia (USP) has introduced revised USP Chapters <795> and <797>, which will become effective November 1, 2023. The new chapters include numerous modifications to compounding standards.

While the CEC can demonstrate that many of the changes instituted under the new chapters will enhance compounding quality and patient safety, that is not true for all of the changes – most notably a couple of restrictions for which the CEC has not enunciated the scientific basis for the restriction or how those restrictions keep patients safer. That not only represents a striking departure from the norm for an independent organization like USP, whose credibility is rooted in its laser-like focus on hard data to document the standards it issues. It also will almost certainly create impediments to patient access to certain compounded sterile preparations.

As state boards of pharmacy make decisions about implementing provisions of the USP compounding chapters, it's essential, then, that they consider the implications of certain unsubstantiated restrictions on patient safety and access in their state.

Below are proposed changes to USP <797> that should not be implemented without thoughtful consideration by boards of pharmacy:

Beyond-use dating (BUDs) and batch size restrictions and increased environmental monitoring.

The new Chapter <797> restricts batch sizes for CSPs to 250 units and curtails beyond-use dating of CSPs based on no substantiable evidence those restrictions enhance patient safety by reducing the risk of contamination.

The number 250 is arbitrary as a batch size limit. In fact, the batch size restriction may actually serve to increase contamination. By reducing the batch size to 250 units in the new chapter, some compounders will now need to prepare multiple batches instead of fewer larger batches, increasing the number of manipulations for components and traffic into and inside the cleanroom. Increasing manipulations and activity create more potential opportunities for contamination and may increase operator fatigue which may lead to poor aseptic technique. Moreover, limiting batch size – which will require more batches – increases costs associated with preparing these medications including testing cost per batch and the quantity of consumables used in the compounding lab. This will ultimately result in higher costs for patients.

Based on the explanation provided in the *BUD Scientific Rationale for the 2021 Proposed Revisions to <797>* the CEC has created this batch size limit primarily based on the number of containers required for sterility testing per USP <71>. The requirements of USP <71> are that 10

units from a CSP batch be tested for sterility for batch sizes ranging from 100 units to 500 units. It appears the CEC has determined that this long-standing minimum sample size of 10 units per 500 found in USP <71> is no longer appropriate to detect microbial contamination of sterile medications, and that a more appropriate minimum ratio to sample is 10 units per 250 units produced. While simple math demonstrates the percentage of units from a batch tested doubles when 10 samples are tested out of 250 vs out of 500 (4% of the batch is tested vs 2%), the CEC has provided no data or evidence to demonstrate the *necessity* to double the percentage of units tested per batch, no statistical evidence or data to support how or if doubling the percentage of units tested per batch will increase the probability of detecting a contaminated sample, and has provided no data, evidence, or explanation as to why limiting the batch size, rather than increasing the minimum number of required samples to 4% *regardless of batch size*, is the only allowable way to increase the probability of detecting contamination within a CSP batch.

Additionally, restrictions on beyond-use dating to less than 180 days – with no scientific basis for the restriction – will require compounders to compound CSP more frequently to meet patient need, increasing the number of batches, In addition, shorter BUDs will mean that patients must get refills more frequently, introducing not merely inconvenience to the equation but the increased risk that a patient may not remain adherent to their physician-prescribed therapy.

The CEC itself is acknowledging the need for CSPs to be assigned a BUD of up to 180 days, but in doing so is misrepresenting the proposed <797> as allowing Category 3 CSPs *in general* to be assigned a BUD of up to 180 days, when in fact the proposed <797> only allows one type of Category 3 CSP – a terminally sterilized Category 3 CSP stored frozen – a maximum BUD of 180 days. The need in the healthcare system for CSPs with extended BUDs up to 180 days goes beyond just terminally sterilized CSPs stored frozen, it is a need that applies to aseptically processed CSPs and CSPs stored refrigerated and at room temperature as well.

In addition, some 503a pharmacies have introduced automation into their compounding practice. Reducing human intervention with automation, only to increase it with these restrictions, raises contamination risk.

The batch size and BUD restrictions introduced in the new Chapter <797>, while no doubt well intentioned, have not been supported by scientific data and in fact introduce greater contamination risk into the preparation of CSP. That's why we urge boards of pharmacy to consider carefully whether to adopt these restrictions in the new Chapter <797>.

RECOMMENDATION. Boards of pharmacy should consider rejecting the new USP <797. beyond-use dating and batch size restrictions in favor of the previous USP <797> requirements. Requiring compounders to create a solid contamination control strategy and stability program including environmental monitoring sampling when warranted will eliminate many of the concerns that precipitated USP's concern on this matter in the first place.

Ultimately, adopting USP<797> in its entirety without careful consideration of the practical and patient-facing implications of certain of its provisions risks introducing greater risk and cost into the sterile compounding process. We urge boards to think carefully through the implications of the particular provisions discussed here.

We appreciate your attention to this important matter. If APC may be helpful to you on this or any other issue related to pharmacy compounding, please contact us at savannah@a4pc.org.