AGENDA

Florida Board of Pharmacy
Compounding Committee Meeting

August 7, 2018 – 8:00 a.m.

*Rosen Plaza Hotel * 9700 International Drive, Orlando, FL 32818 * (407)996-9700*

Committee Members:
Mark Mikhael, PharmD
Richard Montgomery, BPharm, MBA
Blanca Rivera, BPharm, MBA
David Wright, BPharm

Board Staff
C. Erica White, MBA, JD - Executive Director
Shay Marcelus, JD – Prog. Operations Admin.

Board Counsel:
David Flynn, Assistant Attorney General
Lawrence Harris, Assistant Attorney General

Note: Participants in this public meeting should be aware that these proceedings are being recorded.

1. **Call to Order**

2. **Review of July 25, 2018 Minutes**

3. **Draft Revisions to USP Chapter 795**
   - Copy of letter sent to USP regarding proposed revisions to Chapter 795

4. **Lyophilization**

5. **Student Compounding**

4. **Old Business**

5. **New Business**

6. **Public Comment**

7. **Adjourn**

TAB #3

FLORIDA BOARD OF PHARMACY

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July 27, 2018

United States Pharmacopeia Convention
12601 Twinbrook Parkway
Rockville, MD 20852-1790

Re: Public Comment – Proposed Revisions to USP 795

To Whom It May Concern:

The Florida Board of Pharmacy appreciates the opportunity to provide comment on the proposed revisions to USP-NF Chapter 795 (USP 795). The Board's primary concern with the proposed revisions to USP 795 is that new standards will inhibit the fundamentals of the profession of pharmacy.

Our general position is that many of the proposed revisions inhibit what we consider to be the "practice of pharmacy". Specifically, we observe that a majority of new proposed regulations are geared toward Current Good Manufacturing Practices (CGMP) or mass production, and not toward what the Board would consider the "practice of pharmacy" and non-sterile compounding. As a Board, we believe that many of the proposed revisions within the USP 795 rewrite are overreaching and unnecessarily onerous to the profession of pharmacy:

Proposed Revision #1: USP Ch. 795 should be further revised to tailor the nonsterile compounding requirements to the category of compounding being performed (i.e. simple, moderate, complex) in a facility.

Comment: The Board's position is that not all compounding is created equally; therefore, compounding should be viewed in different categories based on the risk to the public. There should be an understanding of risk and the risk management associated with simple compounding versus the other types of compounding. USP should continue to differentiate requirements for the various types of nonsterile compounded products.

Proposed Revision #2: Introduction and Scope - Definition of Nonsterile Compounding (lines 1-11)

Comment: The term "alteration" is not clearly defined and should be clarified. Under the proposed revision, if a pharmacist splits a tablet for a patient for ease of use, then they have "altered" the tablet. The definition of nonsterile compounding should be updated to clarify that nonsterile compounding does not include pill splitting activities.

Proposed Revision #3: Affected Personnel and Settings (lines 41 – 58)
Comment: The proposed revision goes beyond the intent of what should be required. The Board's recommendations to consider are:

(1) The responsible person does not have to be on site where the compounding is performed;

(2) Any responsibility for a designated person should only be required for the complex compounding, not simple compounding;

(3) The proposed language should not be applicable to all compounding, and any required training needs to be specific to the job functions being performed; and

(4) There is already someone in the pharmacy, the Prescription Department Manager, who is responsible for the functions of the pharmacy; therefore, there is no need for an additional person to perform management functions.

Proposed Revision #4: Training Requirements (lines 62-116)
Comment: Appropriate training needs to be done based on the job functions performed, and it is the responsibility of the facility to ensure that staff is trained appropriately before those job functions are performed. The Board would like to see additional guidance or direction regarding what an approved training program would be, or an outline of what would be contained in an approved training program.

Proposed Revision #5: Personal Hygiene and Garbing (lines 157-163)
Comment: The proposed language does not conform to the standard of practice for the profession of pharmacy. There should be a differentiated process for simple compounds and procedures along with streamlined procedures implemented for simple non-sterile products that do not go to the level proposed by these revisions.

Proposed Revision #6: Buildings and Facilities (lines 166-189)
Comment: These provisions are not necessary for simple compounding processes. This is both impractical and unnecessary in the vast majority of pharmacy settings. If a pharmacy is engaging in patient specific compounds, and not doing them in bulk, these requirements create an undue burden on many pharmacies unnecessarily.

Proposed Revision #7: Cleaning and Sanitizing (lines 205-214)
Comment: Similar to previous concerns, we would ask USP to consider a differentiated process for simple non-sterile compounds to limit the impact to the practice of pharmacy while still maintaining patient safety standards.

Proposed Revision #8: Equipment and Components / Component Handling and Storage (lines 232-241, line 333)
Comment: The Board would suggest that this language be worded more broadly to state that the equipment and components should be left up to the discretion of the facility in ensuring a procedure and process which not only protects the operator, but also protects the integrity of the final product.

Proposed Revision #9: SOPs and Master Formulation and Compounding Records (lines 387-388) *Comment: The requirement to maintain a Master Formulation Record should be optional – not required. The Board would be in support of a Master Formulation Record, but what is currently identified in the USP 795 revision is extremely burdensome to most pharmacies. The language relating to the record should only be identified for complex compounds, and only be pertinent to the information needed for the compound itself. Additionally, the language regarding the Release Testing is overbroad.*

Proposed Revision #10: Labeling (lines 426-468, specifically line 455)
Comment: Use of the Beyond Use Date (BUD) in lieu of expiration date is concerning and can cause confusion for the patient; therefore, the labeling requirement should reference an "expiration date" for the prepared prescription.

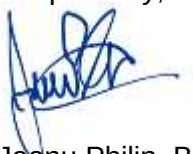
Proposed Revision #11: Establishing a BUD for a CNSP (lines 470-590, and specifically lines 523 and 535)
Comment: The Board is not in support of the requirement of establishing a mandatory BUD requirement and would not be in favor of predetermined BUDs. Should USP continue to require the use of BUDs for CNSP's, the day the product is compounded should be "0" instead of "1". The Board also discussed that there is no basis for reducing the expiration from 180 to 90 days.

Proposed Revision #12: CNSP Handling, Packaging Storage and Transport (lines 647-654)
Comment: The board believes these provisions to be impractical considering in most community pharmacy settings the compounded space will likely be open air to the entire facility.

Proposed Revision #13: Documentation (line 713)
Comment: The board proposes that USP utilize a differentiated approach between simple non-sterile compounds and others. The board believes documentation requirements should be varied based on the type of compounding taking place and this approach would not be practical in the standard, traditional drug store.

Thank you for allowing this opportunity for the Florida Board to provide our observations, comments, and concerns regarding the USP 795 rewrite. Our primary concern as can be seen throughout the comments is the lack of differentiation between simple non-sterile compounded products and all other compounded products. The proposed revisions will create barriers to patient care and inhibit what we consider to be the "practice of pharmacy". We observe that a majority of new proposed revision standards are geared toward Current Good Manufacturing Practices (CGMP) or mass production, and not toward what the Board would consider to be the "practice of pharmacy" and non-sterile compounding. We ask USP to reconsider their current revisions to ensure the traditional practice of pharmacy is not hindered with little to no patient safety enhancements.

Respectfully,



Jeenu Philip, BPharm
Chair

TAB #4

Proposed new section. Draft not for dissemination.

64B16-27-797**64B16-27.797 The Standards of Practice for Compounding Sterile Products.** The purpose of this section is to assure positive patient outcomes through the provision of standards for 1) pharmaceutical care; 2) the preparation, labeling, and distribution of sterile pharmaceuticals by pharmacies, pursuant to or in anticipation of a prescription drug order; and 3) product quality and characteristics. These standards are intended to apply to all sterile pharmaceuticals, notwithstanding the location of the patient (e.g., home, hospital, nursing home, hospice, doctor's office, or ambulatory infusion center).

(1) Adoption of the United States Pharmacopeia: Beginning on October 1, 2014, all sterile compounding shall be performed in accordance with the minimum practice and quality standards of the following chapters of the United States Pharmacopeia (USP):

(a) Chapter 797, Pharmaceutical Compounding-Sterile Preparations;

(b) Chapter 71, Sterility Tests;

(c) Chapter 85, Bacterial Endotoxins Test;

(d) Chapter 731, Loss on Drying.

All referenced chapters of the USP, in subsection (1) are specifically referring to the United States Pharmacopeia, 36th revision, Second Supplement, which is hereby incorporated and adopted by reference with the effective chapter dates of December 1, 2013. A subscription to all relevant chapters is available for purchase at www.uspnf.com. The Board has determined that posting the incorporated material on the Internet would constitute a violation of federal copyright law. At the time of adoption, the copyrighted incorporated material will be available for public inspection and examination, but may not be copied, at the Department of Health, 4052 Bald Cypress Way, Tallahassee, Florida 32399-3254 and at the Department of State, Administrative Code and Register Section, Room 701, The Capitol, Tallahassee, Florida 32399-0250.

(2) Minimum Standards: The minimum practice and quality standards of the USP are adopted as the minimum standards to be followed when sterile products are compounded. However, nothing in this rule shall be construed to prevent the compounding of sterile products in accordance with standards that exceed the USP.

(3) Current Good Manufacturing Practices: The Board deems that this rule is complied with for any sterile products that are compounded in strict accordance with Current Good Manufacturing Practices per 21 U.S.C. § 351 (2012), adopted and incorporated herein by reference, available at https://www.flrules.org/gateway/reference.asp?NO=Ref-04436 and 21 C.F.R. Parts 210 and 211 (2013), adopted and incorporated herein by reference, available at http://www.flrules.org/Gateway/reference.asp?No=Ref-04437.

(4) Specific Exceptions to the United States Pharmacopeia:

(a) Although the USP requires the donning of gloves prior to entry into the clean-room, all required donning of gloves can be performed after entry into the clean-room to avoid contamination of the gloves from the door handle or access device leading into the clean-room.

(b) USP Chapter 797 requires that: "When closed-system vial-transfer devices (CSTDs) (i.e., vial-transfer systems that allow no venting or exposure of hazardous substance to the environment) are used, they shall be used within an ISO Class 5 (see Table 1) environment of a BSC or CACI. The use of the CSTD is preferred because of their inherent closed system process. In facilities that prepare a low volume of hazardous drugs, the use of two tiers of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room) is acceptable." For purpose of said provision, a "low volume of hazardous drugs" is defined as less than 40 doses per month.

(c) USP Chapter 797 provides as follows in the "Facility Design and Environmental Controls" section: "An ISO Class 7 (see Table 1) buffer area and ante-area supplied with HEPA-filtered air shall receive an ACPH of not less than 30. The PEC is a good augmentation to generating air changes in the air supply of an area but cannot be the sole source of HEPA-filtered air. If the area has an ISO Class 5 (see Table 1) recirculating devise, a minimum of 15 ACPHs through the area supply HEPA filters is adequate, providing the combined ACPH is not less than 30. More air changes may be required, depending on the number of personnel and processes. HEPA-filtered supply air shall be introduced at the ceiling, and returns should be mounted low on the wall, creating a general top-down dilution of area air with HEPA-filtered make-up air. Ceiling-mounted returns are not recommended." Notwithstanding the quoted provision, pharmacies that meet the standards set forth in the section quotes as of the effective date of this rule are not required to change the location of supply air or return filters or ducts so long as the ISO standards are maintained.

(5) (a) The Board finds that the production of sterile compounded products prepared with a process that includes the lyophilization of the sterile product may not be adequately regulated under the provisions of (1) of this section. The use of lyophilization in the production of drug products has generally been considered a manufacturing process and therefore the standards of USP 797 do not address the use of such process in pharmacies.

(b) To provide standards for the safe production of sterile compounds as described in (a) in pharmacies the board finds that such products shall be prepared according to Current Good Manufacturing Practices as described by (3) of this section.

Lyophilization

Lyophilization Process:

- A process of removing water (solvent) from liquid formulation to increase the stability of the material (dosage form).

3 Stages of Lyophilization:

- Freezing
- Primary Drying (Sublimation)
- Secondary Drying (Desorption)

FREEZING RATE:

- The freezing rate can alter the ice crystal size, which can affect the flow of water vapor through the dried layer during processing

Impact of Freezing Rate:

- A slow freezing rate leads to larger ice crystals.
  This results in faster primary drying rate.
- A fast freezing rate leads to smaller ice crystals.
  This results in a slower primary drying rate

Primary Drying (Sublimation)

- The purpose of primary drying is to remove all the ice (water) that has been frozen as pure water (unbound)
- This is most of the water in the matrix
- Water goes directly from solid to gas phase

For freeze drying to happen:

- Must manipulate conditions of pressure (vacuum) and temperature to convert solid ice directly to a vapor.
- Cannot pass through water state; product irreversibly liquifies!
- Also need to condense the water vapor back into ice on the condenser.

Where does the water go?

- As the water vapor flows from the vial to the chamber, and the chamber to the condenser, it passes over the condenser surface.
- Vapor to solid phase (ice)
- The condenser must be maintained at a temperature low enough to condense water vapor, at the pressure level existing in the condenser.

Thermal Analysis

- Characterization of the bulk material is essential for freeze-drying.
- To start primary drying, the material must be solid (frozen), so we must know the temperature below which this occurs.
- The only way to determine this is by low temperature thermal analysis of the bulk material.

Why are Thermal Properties Important?

- During primary drying, removal of free (unbound) water (solvent) occurs

  aka Sublimation (solid to vapor phase)

- Thermal properties indicate the temperature at which the frozen matrix starts to soften (melt); above this temperature, the water is no longer frozen (solid); therefore, above this temperature, sublimation cannot occur

The Result??

- If a product is inadequately frozen, or dried at a product temperature in primary drying that is above the critical processing parameters, the product may have:
- Poor appearance
- Melt back or collapse
- High residual moisture
- Poor stability

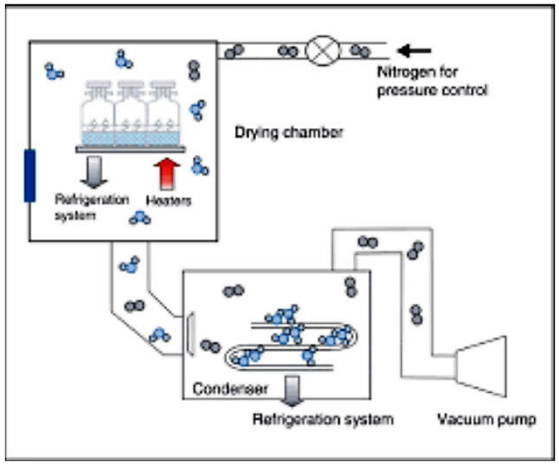
What about Sterility?

- The drug solution is sterilized and put into vials that are partially stoppered and NOT sealed prior to transfer to the lyophilizer. As a result, the contents of the vials are subject to contamination until they are actually sealed.
- The entire transfer from the fill area to the lyophilizer MUST be conducted in ISO 5 laminar flow air that has been proven, with smoke studies, to maintain laminarity.
- The fill AND transfer process must be validated with media fills

Sterilizing the Lyophilizer

- The lyophilizer must be sterilized before the partially stoppered vials are placed in the unit.
- The lyophilizer chamber, the nitrogen gas lines to the chamber, the path to the condenser and the condenser and lines must be sterilized to protect the product from contamination.
- Sterilization of both the lyophilizer and the nitrogen system must be validated with biological indicators.

Diagram of lyophilizer



The Importance of Fill Volumes

- A major concern with the filling operation is assurance of fill volumes. A low fill volume would represent a sub-potent vial and an overfill a super-potent vial.
- Unlike a liquid fill, this will not be readily apparent in a lyophilized product.

Conclusion

- Lyophilization is a **complex** manufacturing process that requires:

- Product specific cycle development to ensure conformance to specifications
- Validation of the aseptic fills and transfer to the lyophilizer
- Validation of the sterilization of the lyophilizer
- Assurance of fill volumes and stability studies to ensure that the products meet all acceptance criteria for potency, stability and sterility.