California State Board of Pharmacy
2720 Gateway Oaks Drive, Suite 100
Sacramento, CA 95833
Phone: (916) 518-3100 Fax: (916) 574-8618
www.pharmacy.ca.gov

Enforcement and Compounding Committee Report

Maria Serpa, Licensee Member, Chair
Jignesh Patel, Licensee Member, Vice-Chair
Renee Barker, Licensee Member
Indira Cameron-Banks, Public Member
Seung Oh, Licensee Member, President
Ricardo Sanchez, Public Member

During the meeting members will receive a summary of the Committee's work at its January 23, 2023, February 15, 2023, March 23, 2023, and April 13, 2023, meetings as well as updates for discussion and action.

a. Summary of Presentations on US Pharmacopeia (USP) General Chapters including:

1. **USP Chapter 825 Regarding Radiopharmaceuticals**
2. **USP Chapter 795 Pharmaceutical Compounding – Nonsterile Preparations**
3. **USP Chapter 797 Pharmaceutical Compounding – Sterile Preparations**
4. **USP Chapter 800 Hazardous Drugs – Handling in Healthcare Settings**

USP Chapter 825 provides standards for the preparation, compounding, dispensing, and repackaging of radiopharmaceuticals, including all sterile radioactive material that must maintain sterility through manipulations prior to administration. Consist with action taken by the USP Compounding Expert Committee, USP Chapter 825 shall become official on November 1, 2023. USP has published FAQ's on the Chapter available on its website.

USP Chapter 795 provides standards for compounding nonsterile medications to help ensure patient benefit and reduce risks such as contamination, infection, or incorrect dosing. Consist with action taken by the USP Compounding Expert Committee, USP Chapter 795 shall become official on November 1, 2023. To assist with implementation, USP has published FAQs on the Chapter available on its website and information on adding flavor to conventionally manufactured nonsterile products.

USP Chapter 797 provides standards for compounding sterile medications to help ensure patient benefit and reduce risks such as contamination, infection, or incorrect dosing. Consist with action taken by the USP Compounding Expert Committee, USP Chapter 797 shall become official on November 1, 2023. To assist with implementation, USP has published FAQs on the Chapter available on its website. A copy of the USP 797 FAQ

dated November 1, 2022, is included in the attachments. USP's website indicates that to help ensure clarity and consistency, the sterile compounding FAQs are being revised. The Board recommends licensees check with the USP website for updates.

USP Chapter 800 provides standards for safe handling of hazardous drugs to minimize the risk of exposure to healthcare personnel, patients and the environment. Consist with action taken by the USP Compounding Expert Committee, USP Chapter 800 shall become compendial on November 1, 2023. To assist with implementation, USP has published FAQs on the Chapter available on its website.

A copy of the slides for the presentations on the various chapters is provided in **Attachment 1**. A copy of the November 1, 2022, USP <797> FAQs related to sterile compounding is also provided.

b. Discussion, Consideration and Possible Action on Proposed Changes to Regulations as follows:

1. Proposed Addition to Title 16, California Code of Regulations Section 1738-1738.14 Regulations Related to Radiopharmaceuticals and Repeal of Sections 1708.3 – 1708.5
2. Amend Title 16 Article 4.5 and Repeal and Replace existing Sections 1735 - 1735.8 and Adopt New Titles and Sections 1735 – 1735.14 Related to Pharmaceutical Compounding of Nonsterile Preparations
3. Repeal Article 7.5 & and Sections 1751-1751.10 and add new Article 4.6 Add New Titles and Sections 1736-1736.21. Related to Pharmaceutical Compounding of Sterile Preparations
4. Add New Article 4.7 and Add New Titles and Sections 1737-1737.18 Related to Handling Hazardous Drugs

Relevant California Law

BPC Section 4126.8 incorporates the compounding chapters of the current United States Pharmacopeia-National Formulary into statute and authority for the Board to impose additional standards for compounding drug preparations.

Article 7.5, Business and Professions Code (BPC) Sections 4127-4127.8 establish many of the statutory requirements for compounding sterile drug products, including:

- BPC section 4127 which generally provides that a pharmacy that compounds sterile drug products shall possess a sterile compounding pharmacy license as provided in this article and the Board shall adopt regulations to establish policies, guidelines, and procedures to implement. Further, the Board shall review any formal revision to General Chapter 797 of the United States Pharmacopeia and The National Formulary (USP–NF), relating to the compounding of sterile preparations, not later than 90 days after the revision becomes official, to

determine whether amendments are necessary for the regulations adopted by the board pursuant to subdivision (b).

BPC section 4341 provides authority for the Board to institute any action or actions as may be provided by law and that, in its discretion, are necessary, to prevent the sale of pharmaceutical preparations and drugs that do not conform to the standard and tests as to quality and strength, provided in the latest edition of the United States Pharmacopeia or the National Formulary, or that violate any provision of the Sherman Food, Drug, and Cosmetic Act.

Background

In anticipation of the upcoming November 1, 2023, compendial dates for several USP Chapters, the Enforcement and Compounding Committee has met on several occasions to consider the new or revised USP Chapters and the Board's related regulations to determine, in the interest of patient safety, where changes are appropriate.

As part of the Committee's January 2023 meeting an overview of federal requirements for compounding was provided. The presentation provided summary information of some of the federal laws and guidance governing compounding. As part of the overview, attendees were reminded that Section 503A exemptions do not provide an exemption from all areas for the Food, Drug and Cosmetic Act.

Following the overview, as part of the Committee's process at each meeting, members received an overview of the standards established in each chapter followed by discussion on draft regulation language. The process used by the Committee allowed for member discussion on each provision established in the respective sections followed by an opportunity for public comment for each section. In addition to public comment received during the meeting, members also considered written comments received in advance of the Committee meetings. During each of the meetings, after considering input, members made changes to the language where it deemed appropriate.

In each meeting, members and stakeholders were reminded that the proposed regulations would not restate federal law or USP standards. During discussions attendees were also reminded, that as required by Business and Professions Code section 4126.8, USP standards establish the minimum requirements for the respective chapters. The Board **cannot** pursue regulations that would include a lesser standard than those established within the USP Chapters. However, the Board does have authority to impose additional standards.

For Member Consideration and Discussion

During the meeting members will have the opportunity to consider draft regulation language reviewed by the committee. The specific regulation text is proposed to be included in four separate articles:

1. Article 4.5 Related to Nonsterile Compounding

2. Article 4.5 Related to Sterile Compounding
3. Article 4.6 Related to Hazardous Drugs
4. Article 4.7 Relation to Radiopharmaceuticals

Following the committee discussion, consistent with the committee's direction, the Committee Chair worked with staff to review the regulation language for each of the articles to ensure consistency of language where appropriate across the various articles

The regulation text of each of the respective articles as proposed is provided in Attachment 2 detailed below. It is recommended that during the meeting members consider each of the articles individually and ensure consensus among members followed by public comment. After consideration of all of the articles is complete, if the Board believes the regulation language is ready for approval, a motion to initiate the rulemaking process would be appropriate. It is important to note that the proposed regulations must be moved in a single rulemaking package as the chapters relate to one another. Given that the November 1, 2023, compendial is eminent, action by the Board is necessary to ensure licensee have a clear understanding of the Board's expectation. Should the Board believe the language is ready, the following motion could be used to facilitate initiation of the formal rulemaking process:

Possible Motion
Approve the proposed regulatory text as proposed to amend article 4.5 related to nonsterile compounding and the regulation language as proposed, add article 4.6 related to sterile compounding and the text as proposed, add article 4.7 related to hazardous drugs and the regulation text as proposed, and add article 4.8 related to radiopharmaceuticals and the regulation text as proposed. Further, repeal article 7.5 related to sterile compounding and repeal sections 1708.3, 1708.4 and 1708.5 related to radioactive drugs. Direct staff to submit the text to the Director of the Department of Consumer Affairs and the Business, Consumer Services and Housing Agency for review and if no adverse comments are received, authorize the executive officer to take all steps necessary to initiate the rulemaking process. Authorize the Enforcement Committee Chair and Executive Officer to make any nonsubstantive changes or clarifying changes necessary consistent with the Board's policy. If no adverse comments are received during the 45-day comment period and no hearing is requested, authorize the Executive Officer to take all necessary steps to complete the rulemaking and adopt the proposed regulations as noticed.

Attachment 2 includes several items**:**

- 2a Article 4.5 draft regulation text related to nonsterile compounding
- 2b comments received related to nonsterile compounding, including any comments received after the Committee's discussion
- 2c Article 4.6 draft regulation text related to sterile compounding
- 2d comments received related to sterile compounding, including any comments received after the Committee's discussion
- 2e Article 4.7 draft regulation text related to hazardous drugs

- 2f comments received related to the handling of hazardous drugs, include any comments received after the Committee's discussion
- 2g Article 4.8 draft regulation text related to radiopharmaceuticals

Committee meeting minutes are available that include summaries of the discussions for the following proposed regulations:

January 23, 2023 – Article 4.8 Radiopharmaceuticals
February 15, 2023 – Article 4.5 Nonsterile Compounding
March 23, 2023 – Article 4.6 Sterile Compounding

c. Discussion and Consideration of Draft Statutory Proposal to Amend Business and Professions Code Sections 4081 and 4105

Relevant Law

Business and Professions Code section 4081 generally provides that all records of manufacture and of sale and disposition shall at all times during business hours be open to inspection.

Business and Professions Code section 4105 generally provides that all records of acquisition and disposition shall be maintained in a readily retrievable form. Further, this section requires that when requested by an authorized officer of the law, an entity licensed by the board shall provide the board with the requested records within three business days of the time the request was made and provides provisions to request an extension.

Background

During the January 2023 Committee Meeting, members considered a recommendation from staff to amend BPC Sections 4081 and 4105 to address challenges staff are experiencing when requesting records to evaluate for compliance with pharmacy operations including staffing requirements and quota prohibitions. As was discussed during the January 2023 meeting, staff are experiences resistance to records requests for information necessary to evaluate for compliance.

Members discussed the challenges with completing timely investigations when records are not provided timely and noted that changes offered by staff appeared consistent with the policy of the legislature and supported the recommendations offered. At the conclusion of the discussion, the committee requested that staff develop statutory language for consideration at a future meeting.

Summary of Committee Discussion

During the meeting members considered draft statutory language consistent with the Committee's prior discussion. Committee members spoke in support of the language. In response to public comment, members requested that staff consider if the language could be updated to remove a requirement to maintain paper copies of records where an electronic copy is maintained.

During the Board Meeting, members will receive an update from staff regarding the electronic records provision as requested.

Committee Recommendation: Recommend approval of the proposed amendments to 4081 and 4105 as presented and allow for further amendment to the language to incorporate electronic records if appropriate.

Attachment 3 includes a copy of the language for consideration.

d. Discussion and Consideration of Proposal to Amend Title 16, California Code of Regulation Sections related to Compounding of Nonsterile and Sterile Preparations for Dispensing by Veterinarians for Animal Patients

Relevant Law

CCR Section 1732.5 (c) defines a "reasonable quantity" that may be furnished to a prescriber for office use. This section further provides that a reasonable quantity means an amount of compounded preparation that is sufficient for administration or application to a patient solely in the prescriber's office or furnishing of not more than a 120-hour supply for veterinary medical practices as specified.

Background

Over the past several meetings, the committee has considered proposed changes to regulations related to nonsterile and sterile preparations. While reviewing the proposed changes, the proposed language related to "reasonable quantity" did not recommend any changes to provisions for a pharmacy to compound a preparation for veterinarians to furnish not more than 120-hour supply for a veterinary patient. During the meeting, members received comments requesting that the timeframe be extended from 120-hour supply (five days) to a seven-day supply.

Subsequent to the discussion, the Board received correspondence from the California Veterinary Association (CVMA) requesting reconsideration. Staff notes that included in the correspondence are survey results from their members regarding availability of medications for their patients. The survey questions appear to combine issues related to FDA-approved drugs and compounded preparations (including potential drug shortages - - an issuing facing all health care providers). It also appears based on some of the information provided, that some pharmacies and veterinarian practices may be using compounded drug products in lieu of commercially available products as a cost saving measure. This is a violation of Federal law.

Summary of Committee Discussion

During the meeting members were advised that the issue was placed on the agenda to allow members the opportunity to further consider the supplemental information submitted by CVMA. After consideration the committee determined that the following changes are recommended:

1. Extend the current 120-hour for non-sterile preparations to a seven-day supply.
2. Extend the current 120-hour supply for sterile ophthalmic preparations to allow for up to a 28-day supply if the topical ophthalmic preparation is compounded in compliance with USP 797 Section 14.5, Multi-Dose CSPs.

Subsequent to the meeting, consistent with the direction of the committee, the language in proposed section 1735.1(e) and proposed section 1736.1(d) were amended to reflect the committee's direction. The language was considered as part of the prior agenda item. **Attachment 4** includes a copy of the CVMA letter.

e. <u>Review and Discussion of Enforcement Statistics</u>

Since July 1, 2022, the Board has received 2,725 complaints and has closed 2,380 investigations. The Board has issued 141 letters of admonishment, 766 citations with or without a fine, and referred 181 cases to the Office of the Attorney General. The Board has secured 6 interim suspension orders, 3 automatic suspension orders, and been granted 8 Penal Code 23 restrictions. Further, the Board has revoked 40 licenses, accepted the disciplinary surrender of 45 licenses, denied 6 applications, and imposed other levels of discipline against 7 licensees and/or applicants. A copy of the current statistics is provided in **Attachment 5**.

As of April 1, 2023, the Board had 1,389 field investigations pending. Below is a breakdown providing more detail in the various investigation process:

	Apr. 1, 2022		Jul. 1, 2022		Oct. 1, 2022		Jan. 1, 2023		Apr. 1, 2023	
	Vol.	Avg. Days	Vol.	Avg. Days	Vol.	Avg. Days	Vol.	Avg. Days	Vol.	Avg. Days
Awaiting Assignment	43	6	24	6	110	6	80	12	116	6
Cases Under Investigation	738	122	793	118	749	125	853	129	874	138
Pending Supervisor Review	173	30	171	39	223	46	199	85	146	22
Pending Second Level Review	94	56	97	58	205	36	226	55	245	35
Awaiting Final Closure	50	15	127	10	113	42	92	35	8	43

Attachment 1

UNITED STATES PHARMACOPEIA (USP)

GENERAL CHAPTER <825>

RADIOPHARMACEUTICALS—PREPARATION, COMPOUNDING, DISPENSING, AND REPACKAGING

OFFICIAL ON 12/1/20
COMPENDIAL ON 11/1/23

PRESENTATION ADAPTED WITH PERMISSION FROM PAUL B. MAHAN, RPH., BCNP
HTTPS://PHARMACY.CA.GOV/MEETINGS/MINUTES/2019/19_JUN_CMPD_MIN.PDF

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GLOSSARY

- **Compounding:** combining, mixing, pooling, or otherwise altering (excluding preparation with minor deviations) of a conventionally manufactured radiopharmaceutical or synthesizing/formulating a radiopharmaceutical from bulk drug substances and radionuclides.
- **Dispensing:** manipulation or labeling of a radiopharmaceutical to render it in its final form for administration
- **Preparation:** combining a conventionally manufactured kit with a conventionally manufactured radionuclide following manufacturer's recommended instructions. Mixing, reconstituting, combining, diluting, or repackaging of a radiopharmaceutical, or other such acts, performed in accordance with directions contained in the FDA-approved labeling.

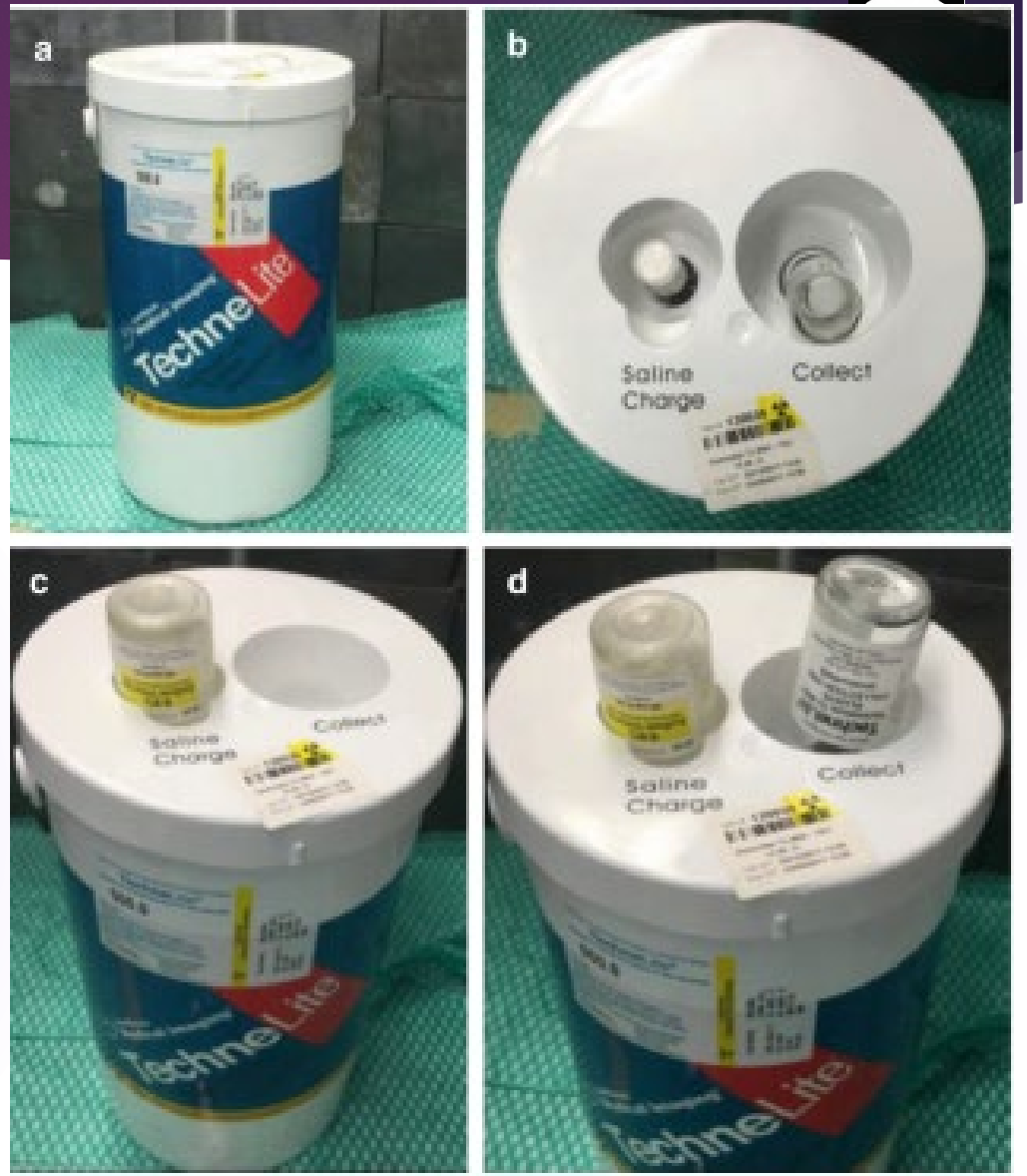
GLOSSARY

- **Preparing with minor deviations:** preparing a conventionally manufactured kit with a conventionally manufactured radionuclide with volume, and/or radioactivity, and/or step-by-step deviations from the manufacturers recommended labeling while ensuring that the final preparation maintains appropriate radiochemical and radionuclidic purity for the entirety of the BUD.
- **Radiopharmaceutical** (radiopharmaceutical preparation/ radioactive drug)**:** Finished dosage that contains a radioactive substance in association with one or more other ingredients and that is intended to diagnose, stage a disease, monitor treatment, or provide therapy.

GLOSSARY

- **Repackaging:** removing a conventionally manufactured radiopharmaceutical from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product. Repackaging also includes the act of placing the contents of multiple containers (e.g., vials) of the same finished drug product into one container, as long as the container does not include other ingredients
- **Segregated radiopharmaceutical processing area (SRPA): A** designated, unclassified space, area, or room with a defined (by facility procedures) perimeter that contains a PEC. An SRPA is only suitable for radiopharmaceutical preparation (with and without minor deviations), dispensing, and repackaging. If the SRPA is used to elute radionuclide generators it must have ISO Class 8 particle count non-viable particle count air quality.

Generator



https://nuclear.pharmacy.purdue.edu/what.php
https://med.uth.edu/radiology/wp-content/uploads/sites/9/2017/09/Nuclear-Lab-2-Generator.pdf

Generator

Figure 1

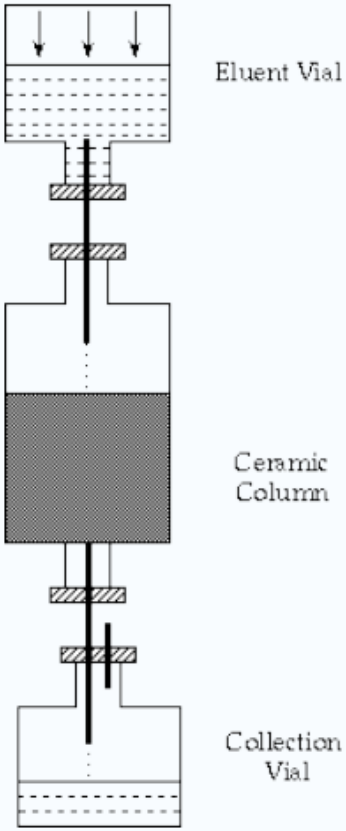


Figure 2

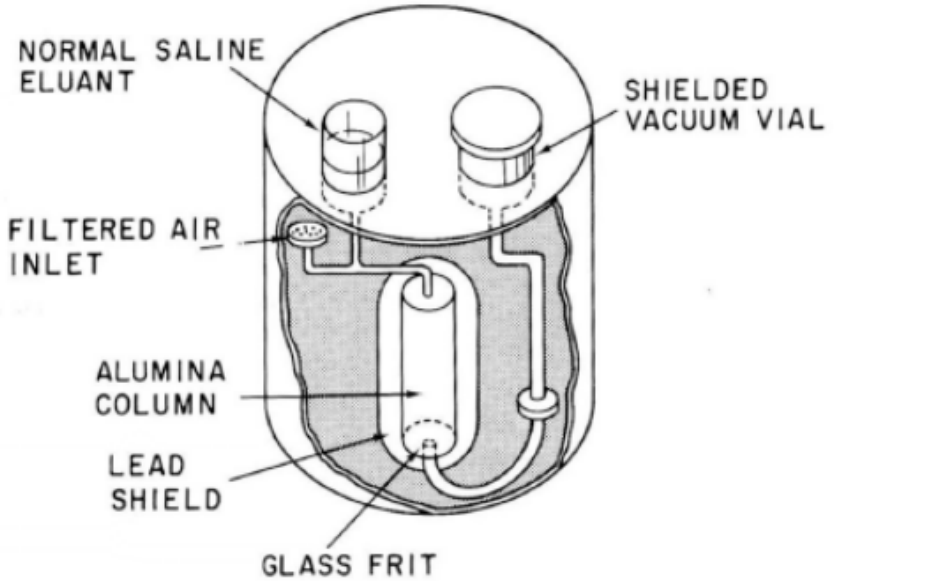


Fig. 7-5. Cross-sectional drawing of a ^{99}Mo-^{99m}Tc generator. (Courtesy of the Society of Nuclear Medicine and Thomas R. Gnau.)

https://nuclear.pharmacy.purdue.edu/what.php
https://med.uth.edu/radiology/wp-content/uploads/sites/9/2017/09/Nuclear-Lab-2-Generator.pdf

PEC

Conventionally Manufactured Kits

https://nuclear.pharmacy.purdue.edu/what.php
https://med.uth.edu/radiology/wp-content/uploads/sites/9/2017/09/Nuclear-Lab-2-Generator.pdf

Preparation

https://nuclear.pharmacy.purdue.edu/what.php
https://med.uth.edu/radiology/wp-content/uploads/sites/9/2017/09/Nuclear-Lab-2-Generator.pdf

Dispensing

https://nuclear.pharmacy.purdue.edu/what.php
https://med.uth.edu/radiology/wp-content/uploads/sites/9/2017/09/Nuclear-Lab-2-Generator.pdf

1. INTRODUCTION

- Intended to provide uniform **minimum** standards for the preparation, compounding, dispensing, and repackaging of radiopharmaceuticals for humans and animals that occur as part of state-licensed activities
- Radiopharmaceuticals are:
  - Radioactive materials (RAMs) falling under the control of the US Nuclear Regulatory Commission (NRC) or NRC-contracted agreement state agency.
  - Prescription drugs falling under the control of the US FDA for manufacturing and marketing.
  - Regulated by other federal authorities (e.g., Department of Transportation)

1.1 NONSTERILE RADIOPHARMACEUTICALS
1.2 STERILE RADIOPHARMACEUTICALS

- Nonsterile prepared or compounded preparations, must comply with applicable identity, quality, and purity standards, as described in manufacturer labeling, *USP* monographs, or other appropriate sources
- Sterile prepared or compounded preparations, must comply with applicable identity, quality, and purity standards.

2. RADIATION SAFETY CONSIDERATIONS

- Must handle meeting the radiation regulatory agency requirements for worker safety.
- Involves licensing commitments to keep all exposure levels for the workers involved as low as reasonably achievable (ALARA) practices. **Principles of radiation safety involve time, distance, shielding, and contamination control.**
- Radiation exposure:
  - **Time**: increase exposure time = increased risk, move quickly
  - **Distance**: increased distance = decreased risk, special tools
  - **Shielding:** increased shielding = decreased risk, special tools and equipment
- Radiation detection and measuring devices are necessary

2. RADIATION SAFETY CONSIDERATIONS

https://nuclear.pharmacy.purdue.edu/what.php
https://med.uth.edu/radiology/wp-content/uploads/sites/9/2017/09/Nuclear-Lab-2-Generator.pdf

2.4 RADIATION CONTAMINATION CONTROL

- Radiation contamination (e.g., spills, drips, sprays, volatility) is an important concern for radiation protection.
  - Disposable absorbent pads
    - In an ISO Class 5 PEC, must be clean and low-lint.
  - Vertical air flow, not horizontal, in a PEC is used to control contamination.
- Require measurement with a suitable radiation measuring device (e.g., dose calibrator).
- Individuals must wear body and extremity dosimeters (e.g., a ring worn on a finger) for long-term monitoring of personnel radiation exposure.
  - Body dosimeter should be worn underneath the gown.
  - Extremity dosimeter must be worn underneath gloves and must not interfere with proper fit of gloves.

MeasuRing Dosimeter

- Individually calibrated
- Available in four sizes

Ultra Rings

- Strong hard plastic construction
- Available in three sizes

Flex Rings

- Soft plastic construction with velcro closure straps

Fingertip Dosimeter

- Comfortable design
- Individually calibrated

4. PERSONNEL QUALIFICATIONS, TRAINING AND HYGIENE

- Personnel
  - must be trained to work with radiopharmaceuticals per the policies and standard operating procedures (SOPs) authorized by an ANP or AU physician.
  - must follow these policies and SOPs
- As appropriate, this should include bloodborne pathogens training.

Authorized nuclear pharmacists (ANPs) and authorized user (AU) physicians

4.1 ASEPTIC QUALIFICATIONS

- Qualifications may be conducted at a different site if all SOPs are identical for the applicable job function.
- **Gloved Fingertip And Thumb Sampling**
  - Garbing competency required for personnel that enter and perform tasks in the ISO-5 PEC
  - Successful completion:
    - initial zero cfu
    - after media-fill testing is defined as ≤3 cfu
- **Media-Fill Testing**
  - all personnel who prepare, compound, dispense, and repackage sterile radiopharmaceuticals.
  - reflective of the actual manipulations to be carried out
  - must simulate the most challenging and stressful conditions to be encountered

4.2 RE-EVALUATION, RETRAINING AND REQUALIFICATION

- **Visual observation:** initially, and every 12 months
- **Gloved fingertip and thumb sampling**: 3 times initially, and then every 12 months (with media-fill testing)
- **Media-fill testing:** After initial qualification, conduct a media-fill test of all personnel engaged in sterile radiopharmaceutical processing at least every 12 months
- **Cleaning and disinfecting**: every 12 months or with change(s) in cleaning and disinfecting SOPs
- **>6month pause in sterile processing**: requalified in all core competencies before resuming duties
- **Sterile compounding using a nonsterile drug substance or components:** requalified in all core competencies every 6 months.

4.5 Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area

- Do not bring electronic devices that are not necessary for compounding
- Before entering:
  - Remove outer garments, all cosmetics; all hand, wrist, and other exposed jewelry
  - Remove visible debris from underneath fingernails under warm running water
  - Wash hands and arms up the elbows with soap and water for at least 30 s and then dry hands using low-lint towels.
  - Don garb: shoe covers, head/hair/facial hair covers, face mask
- While inside:
  - Periodically apply sterile 70% IPA to gloves
  - Routinely inspect gloves for holes, punctures, contamination, or tears.
  - Avoid touch contamination
- When leaving:
  - Gowns may be used for the shift if maintained in the classified area or the SRPA

5.1 FACILITY DESIGN AND ENVIRONMENTAL CONTROLS

- Classified areas and SRPA maintained at a temperature of 25° or cooler
- Temperature and humidity must be monitored in the classified areas each day that it is used, either manually or by a continuous recording device
- Free-standing humidifiers/ dehumidifiers and air conditioners must not be used within the classified area or SRPA.
- Temperature and humidity devices must be verified for accuracy at least every 12 months or as required by the manufacturer
- PEC must be located in secondary engineering control (SEC),
  - ISO-classified buffer room with ante-room
  - Segregated radiopharmaceutical processing area (SRPA):

5.1 FACILITY DESIGN AND ENVIRONMENTAL CONTROLS

- ISO-classified buffer room with ante-room:
  - separated from surrounding unclassified areas with fixed walls and doors
  - Air supplied introduced through HEPA filters in the ceiling
  - Returns low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate.
  - Smoke study of the PEC must be repeated whenever a change to the placement of the PEC within the area is made.
  - Equipped with a pressure-differential monitoring system.
  - Ante-room must have a line of demarcation to separate the clean side from the less clean side.
    - Entered through the less clean side, and the clean side is the area closest to the buffer area.
    - Garb must be worn prior to crossing the line of demarcation.

5.1 FACILITY DESIGN AND ENVIRONMENTAL CONTROLS

- Segregated radiopharmaceutical processing area (SRPA):
  - Unclassified area
    - may be perform only sterile radiopharmaceutical preparation, preparation with minor deviations, dispensing, and repackaging
  - If ISO Class 8; storage and elution of non-direct infusion radionuclide generators (e.g., Tc-99m).
  - Located away from unsealed windows, doors that connect to the outdoors, and traffic flow which may adversely affect the air quality in the PEC.
  - Visible perimeter must establish the boundaries of the SRPA.
  - Access restricted to authorized personnel and required materials.
  - not located adjacent to environmental control challenges

5.1 FACILITY DESIGN AND ENVIRONMENTAL CONTROLS

- PEC:
  - certified to meet ISO Class 5 or better conditions
  - designed to minimize microbial contamination
  - located out of traffic patterns and away from area air currents that could disrupt the intended airflow patterns inside the PEC.
  - to prepare, prepare with minor deviations, dispense, or repackage sterile radiopharmaceuticals the ISO Class 5 PEC may be placed in an unclassified SRPA.
  - to compound sterile radiopharmaceuticals, must be located within an ISO Class 7 or better buffer area with an ISO Class 8 or better ante-room.
  - Dynamic airflow smoke pattern test: initially, and at least every 6 months

5.2 Creating Areas to Achieve Easily Cleanable Conditions

- Classified areas:
  - Surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified area must be smooth, impervious, free from cracks and crevices, and non-shedding
  - Junctures must be sealed to eliminate cracks and crevices.
  - Walls must be constructed of/or covered with a durable material and the integrity of the surface must be maintained.
  - Floors must include coving to the sidewall or the juncture between the floor and wall must be caulked.
  - Exterior lens surface of ceiling light fixtures must be smooth, mounted flush, and sealed.
  - Penetrations through the ceiling or walls must be sealed

5.3 Water Sources

- Buffer area must not contain plumbed water sources [e.g., sink(s), eyewash(es), shower(s), or floor drain(s)].
- Ante-room must not contain floor drain(s).
- SRPA, the sink must be accessible but located at least 1 m from the PEC and generators, if present.
  - sink must not be located inside the perimeter of the SRPA

5.7 Environmental Controls

- Must comply with conditions specified in RAM license and regulations, RAM license conditions may supersede the following requirements for environmental controls described in this section
- May be both positive and negative air pressure within the facility;
  - positive pressure to minimize the potential of microbial contamination in sterile drug preparation areas, > 0.02-inch water column
  - negative pressure to minimize potential radioactive contamination from volatile or airborne radiopharmaceuticals., RAM license will define
- In classified area:
  - Pressure monitoring device must be used to continuously monitor the pressure differential
  - Results from the pressure monitoring system must be reviewed and documented at least daily on days the area is used.
  - Devices must be tested for accuracy and required performance at least every 6 months.

6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

6.1 General Monitoring Requirements

- Air and surface monitoring:
  - All classified spaces
  - During actual or simulated dynamic operating conditions
  - Results and the corrective actions must be documented, and records must be readily retrievable as required by jurisdictional laws and regulations
  - Performed with:
    - Certification of new facilities and equipment
    - After any modification of facilities or equipment
    - In response to identified problems
    - In response to identified trends
    - In response to changes that could impact the controlled area environments

6.2 Monitoring Air Quality for Viable Airborne Particulates

- **Viable air sampling**:
  - Volumetric impaction device sampling
  - Classified areas during dynamic operating or simulated
  - Initially and least every 6 months
- Exceed Action Levels:
  - must be investigated
  - corrective action must be taken
  - attempt must be made to identify any microorganism

ISO Class	Air Sampling Action Levels [cfu/m^3 (1000 L) of air per plate]
5	>1
7	>10
8	>100

6.3 Monitoring Surfaces for Viable Particles

- **Surface sampling**
  - all classified areas
  - at least monthly
- Exceed the Action Levels:
  - must be investigated
  - corrective action must be taken.
  - an attempt must be made to identify any microorganism

ISO Class	Surface Sampling Action Levels (cfu/device or swab)
5	>3
7	>5
8	>50

7. Cleaning and Disinfecting

Site	Cleaning	Disinfecting	Sporicidal
PEC / equipment in PEC	Prior to daily sterile processing	Following cleaning	Monthly
Surfaces of sink(s)	Daily	Daily	Monthly
Hot-Cell interior	Daily	Daily	Monthly
Hot-Cell PEC and equip. in PEC	Prior to daily sterile processing	Following cleaning	Monthly
Work surfaces outside PEC	Daily	Daily	Monthly
Ceilings	Monthly	Monthly	Monthly
Walls/doors & fixtures	Monthly	Monthly	Monthly
Floor(s)	Daily	Daily	Monthly
Storage shelving and bins	Monthly	Monthly	Monthly

8. Assigning BUD
Sterility BUD

Table 7.Preparation Conditions for Sterile Radiopharmaceuticals

Manipulation	PEC	SEC	BUD (h)
Dispensing, repackaging, preparation with and without minor deviations	ISO Class 5	SRPA	12
Radionuclide generator storage/elution (e.g. Tc-99m)	-	SRPA with ISO Class 8 total airborne particle count	12
Radionuclide generator storage/elution (e.g. Tc 99m)	-	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation with and without minor deviations	ISO Class 5	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation with and without minor deviations and compounding using sterile components	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	96
Dispensing, repackaging, preparation with and without minor deviations and compounding using a nonsterile component and performing sterilization procedure (w/o sterility testing)	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	24
Radiolabeled blood components (e.g. radiolabeled leukocytes)	ISO Class 5 BSC	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	6 h after the blood sample is obtained

9. Documentation

- Applicable records (hard-copy or electronic), must be maintained for all activities involved in repackaging, preparing, preparing with minor deviations, compounding, and dispensing radiopharmaceuticals.
- Master Formulation Record (MFR)
  - Required only for a preparation with minor deviations or compounding

10.2 Preparation with Minor Deviations

- **Examples:**
  - Altering the quantity of radioactivity or volume added to the vial
  - Changes in step-by-step operations (e.g., dilute Tc-99m sodium pertechnetate after rather than before addition to the vial)
  - Using alternative devices or equipment (e.g., a heating block rather than a hot water bath, using a different sized needle, different shielding materials)
  - Using QC test methods other than those described in the product labeling (e.g., radiochemical purity)
  - Filtering Tc-99m sulfur colloid

10.3 Preparation of Radiolabeled Blood Components

- Must be administered as soon as possible **but no later than 6 hours after blood sample is obtained from the patient or blood bank.**
- Blood sample may present a risk to the individual performing the preparation as well as cross-contamination to other blood samples or other non-blood related radiopharmaceuticals.

11.1 Compounding Nonsterile Radiopharmaceuticals

- **Compounding** combining, mixing, diluting, pooling, reconstituting or otherwise altering a drug or bulk drug substance other than as provided by the manufacturer's package insert to create a nonsterile radiopharmaceutical.
- Areas designated for nonsterile compounding must be cleaned and uncluttered and separated from areas designated for sterile radiopharmaceuticals.
- The placement of equipment and materials must take into account a design that prevents cross-contamination.
- BUD:
  - must be validated, taking into account the stability of the ingredients, any intermediate containers, the final container, and the storage conditions.
  - cannot be extended past the labeled expiration date of any component in the compound.

11.2 Sterile Compounding

- Must be performed using aseptic technique
- Must be performed in an ISO 5 PEC.
- Must not be performed for any radiopharmaceutical(s) that has been withdrawn from the market
- Must not be essentially copies of marketed FDA-approved radiopharmaceuticals.
- Personnel must consider all possible interactions between the components.
- In some cases, this may require systematic quality control testing over time to validate the appropriateness of a particular BUD.
- "Kit-splitting" or "fractionation" is splitting of kits is compounding

12.1 Dispensing and Radioassay

- Dispensing can take place from single-dose or multi-dose containers of prepared, prepared with minor deviations, compounded, or manufactured radiopharmaceuticals.
- Dispensing may involve needle changes, affixing a sterile cap, or dilution (e.g., adding 0.9% sodium chloride injection) in the final container.
- Except for an unopened manufacturer container, the final dose or ordered amount must be radio assayed (i.e., in a dose calibrator).
  - The measured activity should be mathematically corrected for radioactive decay to the time of scheduled administration (calibration time)

12.2 Labeling

- The labeling falls under the jurisdiction of numerous regulatory agencies
- The **inner** container must be labeled with the following:
  - Standard radiation symbol
  - The words "Caution—Radioactive Material"
  - For all therapeutic and blood-products, the patient name/identifier
  - Radionuclide and chemical form (generic name)
  - Radioactivity at the date and time of calibration
- The **outer** shielding must be labeled with the following:
  - Standard radiation symbol
  - The words "Caution—Radioactive Material"
  - For all therapeutic and blood-products, the patient name/identifier
  - Radionuclide and chemical form (generic name)
  - Radioactivity at the date and time of calibration
  - Volume or number of units dispensed (e.g., 2 capsules), as applicable
  - Product expiration or BUD (see Table 7), as applicable, and any special storage and handling instructions for non-immediate use (e.g., refrigeration, resuspension)
  - Route of administration

13. Repackaging

- **Repackaging**
  - removing a conventionally manufactured radiopharmaceutical(s) from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product.
  - act of placing the contents of multiple containers of the same finished drug product into one container, as long as the container does not include other ingredients.
- must be radio assayed (i.e., in a dose calibrator).
- The inner container should be labeled with the following:
  - Standard radiation symbol
  - The words "Caution—Radioactive Material"
  - The radionuclide and chemical form (generic name)
  - Radioactivity with units at time of calibration and the calibration time
- The outer shielding should be labeled with the following:
  - Standard radiation symbol
  - The words "Caution—Radioactive Material"
  - The radionuclide and chemical form (generic name)
  - Radioactivity with units at time of calibration and the calibration time
  - Volume, or number of units (e.g., capsules), as applicable
  - Product expiration or BUD (see Table 7), as applicable
  - Special storage and handling instructions

14. Quality Assurance and Quality Control

- **Quality assurance (QA):** system of procedures, activities, and oversight that ensures that radiopharmaceutical processing consistently meets quality standards
- **Quality control (QC):** sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the radiopharmaceutical(s)
- A facility's QA and QC programs must be formally established and documented in SOPs that ensure all aspects of the handling of radiopharmaceuticals are conducted in accordance with this chapter and applicable federal, state, and local laws and regulations.

Questions??

Committee Meeting USP <795>

Updated

BY: SUPERVISING INSPECTOR PEG PANELLA-SPANGLER FEBRUARY 15, 2023

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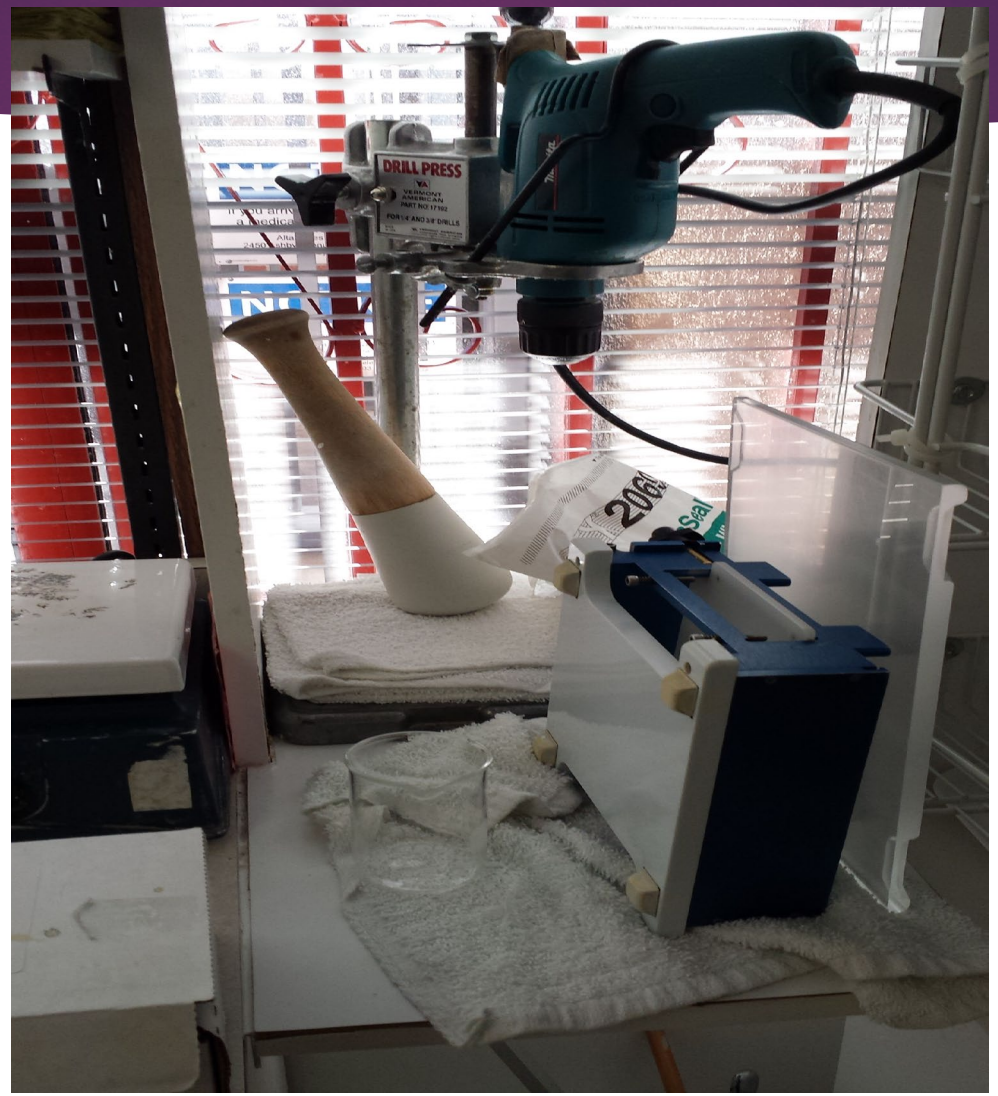

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Overview: Sections

1) INTRODUCTION AND SCOPE
2) PERSONNEL TRAINING AND EVALUATION
3) PERSONAL HYGIENE AND GARBING
4) BUILDINGS AND FACILITIES
5) CLEANING AND SANITIZING
6) EQUIPMENT AND COMPONENTS
7) MASTER FORMULATION AND COMPOUNDING RECORDS
8) RELEASE INSPECTIONS AND TESTING
9) LABELING
10) ESTABLISHING BEYOND-USE DATES (BUD)
11) SOPS
12) QUALITY ASSURANCE AND QUALITY CONTROL
13) CNSP PACKAGING AND TRANSPORTING
14) DOCUMENTATION

Section 1. Introduction And Scope

- Scope Added information on types of Compounded Nonsterile Preparations (CNSP) for humans and animals
- Removed handling of hazardous drugs and added references to General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings.
- Affected Personnel and Settings Added roles and responsibility of the designated person
  - Designated person (DP) = one or more individual responsible and accountable for the performance and operation of the facility and personnel: Must have an SOP describing
  - All places where CNSPS are prepared, not limited to pharmacies

Section 2. Personnel Training and Evaluation

- All personnel who compound or have direct oversight must be trained, demonstrate knowledge and competency prior to performing independently, and must undergo annual refresher training.
- Designated person is responsible for implementing a training program and evaluating competency. This must be documented and retained.
  - Should monitor and observe compounding activities
  - Must take immediate corrective action if deficient practices are observed as described in SOPs
  - The designated person or an assigned trainer may perform training and observation
  - Upon completion of training, the designated person or trainer must document successful completion of training and competency assessments
  - Sole compounders must document training and demonstrate competency

Section 2. Personnel Training and Evaluation Updated

- Proficiency must be demonstrated in at least the following core competencies:
  - Hand hygiene
  - Garbing
  - *Cleaning and sanitizing*
  - *Handling and transporting components and CNSPs*
  - *Measuring and mixing*
  - *Proper use of equipment and devices selected to compound CNSPs*
  - *Documentation of the compounding process (e.g., Master Formulation Records and Compounding Records)*

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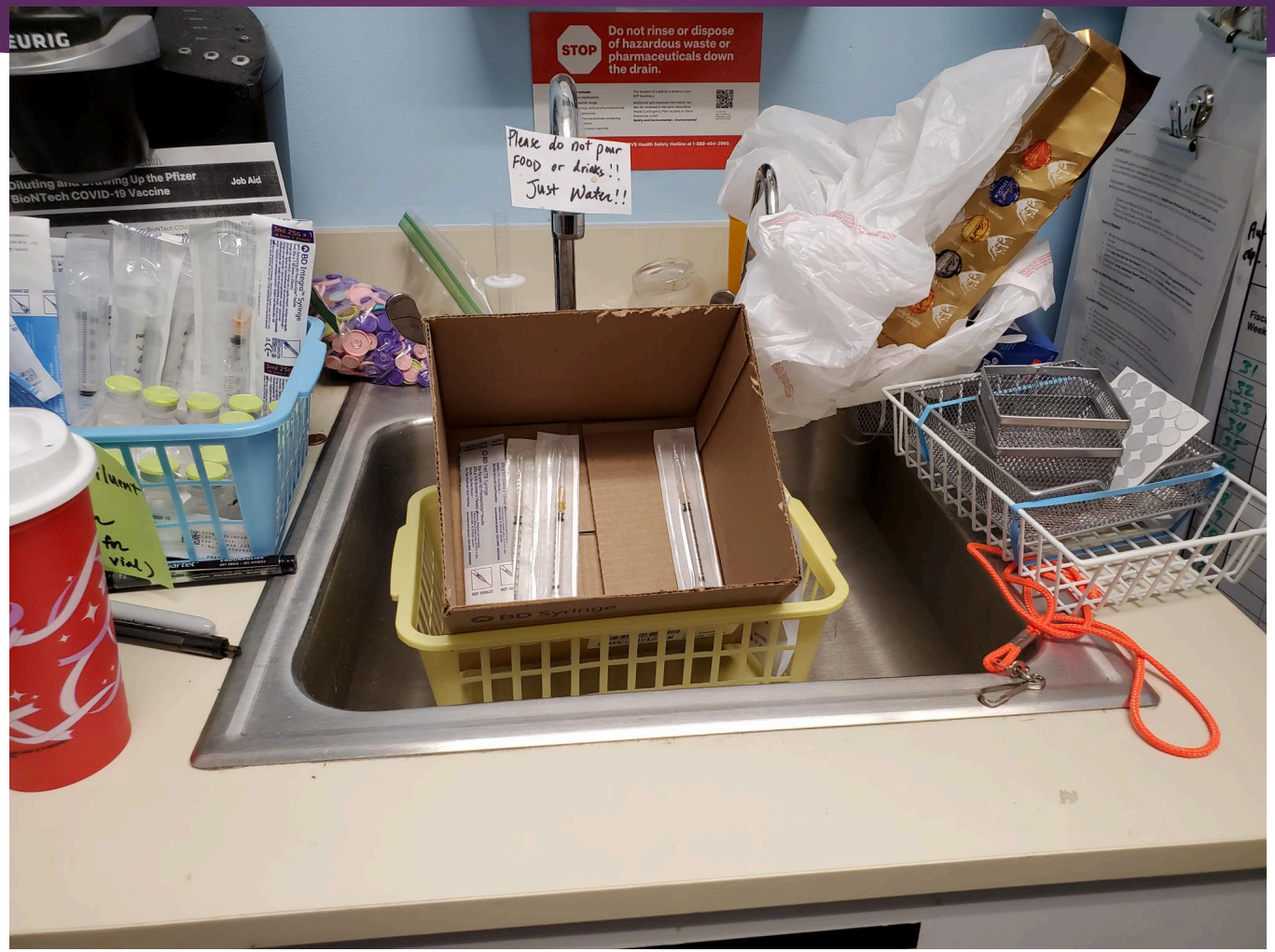

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Section 3. Personal Hygiene And Garbing

- Compounding personnel must maintain appropriate personal hygiene, evaluate risk of potential contaminating conditions and report to the DP, who will evaluate if the personnel should be excluded from compounding
- Before entering a designated compounding area, compounding staff must remove any items that are not easily cleanable and that might interfere with garbing. At a minimum, personnel must:
  - Remove personal outer garments
  - Remove all hand, wrist, and other exposed jewelry or piercing that can interfere with the effectiveness of the garb or hand hygiene
  - Remove headphones and earphones
  - The designated person may permit accommodations provided the quality of the environment and the CNS will not be affected.

Section 3. Personal Hygiene And Garbing

- Hand Hygiene, the use of alcohol-based hand rub alone is not sufficient
  - Wash hands with soap and water for at least 30 seconds
  - Dry hands with disposable towels or wipers
  - Allow hands and forearms to dry thoroughly before donning gloves
- Gloves must be inspected for punctures tears or holes and replaced
- Gloves should be wiped or replaced before beginning a CNSP with different components

Section 3. Personal Hygiene And Garbing

- Other garb requirements are determined by the facility. It should be worn as needed to protect personnel or prevent contamination
  - Garb must be stored to prevent contamination (e.g., away from sinks to avoid splashing onto garb).
  - Visibly soiled garb or garb with tears or punctures must be changed immediately
  - May reuse gown for one shift if not soiled and retained in the compounding area.
  - Gloves, shoe covers, hair covers, facial hair covers, face masks, or head coverings, may not be reused and must be replaced with new ones
  - Non-disposable garb such as goggles should be cleaned with 70% IPA before re-use

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Section 4. Buildings And Facilities

- Designated compounding area is required:
  - Be specifically designated for non-sterile compounding (SOP, LOD).
  - Cannot be used for other activities during nonsterile compounding
  - Areas used to compound hazardous CNSPs must not be used for compounding nonhazardous CNSPs.
  - Have surfaces resistant to damage from cleaners and sanitizing agents and arranged in a way to prevent cross contamination form other areas.
  - Should not be carpeted.
  - Maintained in a clean, orderly, and sanitary condition, and in a good state of repair.

Section 4. Buildings And Facilities

- Facilities:
  - A source of hot and cold water and an easily accessible sink must be available for compounding.
    - The plumbing system must be free of defects.
    - Should use purified water, distilled water or RO water to rinse equipment and utensils
  - All components, equipment, and containers must be stored off the floor and in a manner that will prevent contamination and permit inspection and cleaning of the compounding and storage area.
  - Storage area temperature must be monitored daily when open and results must be store or logged and retrievable.

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Section 5. Cleaning And Sanitizing

- **Cleaning and Sanitizing**
- All surfaces must be cleaned and sanitized:
  - On a regular basis and as specified in the chapter
  - Before compounding if compounding does not occur daily
  - After a spill or if visibly soiled
- When cleaning and sanitizing are separate steps, cleaning comes first
- Effectiveness, compatibility and residue must be considered when selecting agents
- Both cleaning and sanitizing must be documented.

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Section 6. Equipment, Supplies And Components

- **Equipment and Supplies**
  - Must be suitable for the type of compounding process
  - Must be stored in a manner to minimize the risk of contamination
  - Must be located to facilitate their use, maintenance and cleaning
  - Must be cleaned after compounding
  - Maybe dedicated or disposable
  - Must be inspected prior to use
    - If appropriate verify for accuracy as recommended by the manufacturer or at least every 12 months, whichever is more frequent
- Surfaces that contact components must not
  - Be reactive, additive or sorptive
  - Alter the quality of the CNSP

Section 6. Equipment, Supplies And Components

- If weighing, measuring or manipulating components which may become airborne, you must evaluate if a closed system measuring device is required
- Closed system measuring devices include
  - Biological Safety Cabinets (BSC)
  - Containment ventilated enclosures
- BSCs and CVEs must be
  - Certified every 12 months or/and directed by the manufacturer and all applicable laws and regulations

Section 6. Equipment, Supplies And Components

- **Component Selection**
  - Active Pharmaceutical Ingredients (APIs)
    - Must comply with the USP-NF Monograph if there is one
    - Certificate of Analysis must show compliance with specifications
  - For compounding in the US, must be sourced from an FDA registered facility
  - For compounding outside the US, must be sourced from a facility which complies with local laws and regulations

- **Active pharmaceutical ingredient (API):** Any substance or mixture of substances intended to be used in the compounding of a preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body.

Section 6. Equipment, Supplies And Components

- **All components other than the APIs**
  - Should have a COA which verifies it meets the USP-NF monograph and any additional specifications
- Compounding in the US
  - Should be manufactured by an FDA registered facility
  - If it cannot be obtained from an FDA facility, the designated person must select a suitable component for the intended use
- For compounding outside the US, must comply with the local laws and regulations

Section 7. Master Formulation And Compounding Records

- **Master Formulation Records (MFR)**
  - A MFR must be created for each unique formulation of a CNSP
  - Any changes or alterations to the MFR must be approved and documented according to the facilities SOPs
  - CNSPs must be prepared according to the MFR
  - The preparation information is documented on a compounding record (CR)

Section 7. Master Formulation And Compounding Records

- **Master Formulation record must include at least the following:**
  - Name, strength or activity, and dosage form of the CNSP
  - Identities and amounts of all components; if applicable, relevant characteristics of components (e.g., particle size, salt form, purity grade, solubility)
  - Container closure system(s)
  - Complete instructions for preparing the CNSP including equipment, supplies, and description of compounding steps
  - Physical description of the final CNSP
  - Beyond-use date (BUD) and storage requirements

Section 7. Master Formulation And Compounding Records

- **Master Formulation record must include at least the following:**
  - Reference source to support the assigned BUD
  - If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of the API(s)
  - Labeling requirements (e.g., shake well)
  - Quality control (QC) procedures (e.g., pH testing, visual inspection) and expected results
  - Other information needed to describe the compounding process and ensure repeatability (e.g., adjusting pH, temperature)

Section 7. Master Formulation And Compounding Records

- **A Compounding Record must:**
  - Be created for all CNSPs
  - Be reviewed for completeness before the CNSP is release
  - Name or other unique identifier of person completing the review and date of the review
  - Permit traceability of all components in case of a recall or quality issue
- A MFR may be used as the basis for a compounding record

Section 7. Master Formulation And Compounding Records

- **A CR must include at least the following:**
  - Name, strength or activity, and dosage form of the CNSP
  - Date—or date and time—of preparation of the CNSP
  - Assigned internal identification number (e.g., prescription, order, or lot number)
  - A method to identify the individuals involved in the compounding process and individuals verifying the final CNSP
  - Name, vendor or manufacturer, lot number, and expiration date of each component

Section 7. Master Formulation And Compounding Records

- **A CR must include at least the following:**
  - Weight or measurement of each component
  - Total quantity of the CNSP compounded
  - Assigned beyond-use date (BUD) and storage requirements
  - If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of the API(s)
  - Physical description of the final CNSP
  - Results of quality control procedures (e.g., pH testing and visual inspection)
  - MFR reference for the CNSP

Section 8. Release Inspections and Testing

- Elements of release inspection must include:
  - Physical appearance is as expected.
    - Checked for certain characteristics (e.g., emulsions must be checked for phase separation
  - CNSP and labeling match compounding records
  - Inspection of container–closure integrity (e.g., checking for leakage, cracks in the container, or improper seals)
- All checks and inspections, and any other tests necessary to ensure the quality of the CNSP (e.g., pH, assays), must be detailed in the facility's SOPs and the MFR and completed before release, and documented as completed.
- Defective CNSPS must be immediately discarded or marked and segregated to prevent release or dispensing

Why USP Chapter 795 and Regulations

Section 9. Labeling Updated

- **Label: A display of written, printed, or graphic matter on the immediate container of any article and must contain.**
  - Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
  - Active ingredient(s), and their amount(s), activity(ies), or concentration(s)
  - Storage conditions if other than controlled room temperature
  - BUD
  - Dosage form
  - Total amount or volume if it is not obvious from the container

Section 9. Labeling Updated

- **Labeling on the CNSP should display:**
  - Route of administration
  - Indication that the preparation is compounded
  - Any applicable special handling instructions
  - Any applicable warning statements
  - Compounding facility name if the CNSP is to be sent outside of the facility or healthcare system in which it was compounded

Section 10. Establishing Beyond-Use Dates

- Expiration Date = applies to conventionally manufactured drug products
- Beyond use date (BUD) = the date or time beyond which a CNSP must be discarded (not used). The date or time is determined from the date or time when the preparation was compounded.
- Parameters to consider when establishing a BUD
  - Chemical and physical stability of the API and other added components
  - Compatibility of container-closure system
  - Degradation of container-closure system
  - Potential for microbial proliferation
  - Significant deviations from essential compounding steps and procedures;
- If there is a *USP–NF* compounded preparation monograph for the CNSP, the BUD specified in the monograph must be used, unless a shorter BUD is required.

Section 10. Establishing Beyond-Use Dates - Corrected

- Maximum BUD by Type of Preparation in the **absence** of CNSP-Specific Stability Information.
- Must be in a packaged in tight, light-resistant containers.

Type of Preparation	BUDs	Storage Temperature
Non-preserved aqueous dosage $A_w \geq 0.6$	14d	Refrigerator
Preserved aqueous dosage forms $A_w \geq 0.6$	35d	Controlled room temperature
Oral liquids (nonaqueous) $A_w < 0.6$	90d	Controlled room temperature
Nonaqueous dosage forms $A_w < 0.6$	180	Controlled room temperature

12-22

Aw= water activity

Section 10. Establishing Beyond-Use Dates

- Extension of the BUD:
  - Max 180 day with a stability study (published or unpublished) using a stability-indicating assay for the specific API, CNSP, and container–closure that will be used
  - Aqueous CNSP must first be tested for antimicrobial effectiveness at the end of the proposed BUD
  - BUD must not exceed the BUD specified in the monograph.
- CNSPs requiring a shorter BUD:
  - Cannot be extended past the expiration date or BUD of any component in the CNSP
  - APIs or ingredients known to be susceptible to decomposition

Why USP Chapter 795 and Regulations

Section 11: Standard Operating Procedures

- Facilities preparing CNSPs must:
  - Develop SOPs on all aspects of the compounding operation
- All personnel who conduct or oversee compounding
  - Must be trained on the facility's SOPs
  - Are responsible for ensuring that facility SOPs are followed
- One or more persons must be designated to ensure SOPS are fully implemented
- The designated person(s) must ensure follow-up occurs if problems, deviations or errors are identified

Why USP Chapter 795 and Regulations

Section 12. Quality Assurance and Quality Control

- Quality assurance (QA): A system of procedures, activities and oversight which ensures the compounding process consistently meets quality standards
- Quality control (QC): The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CNSP.
- Must have a formal, written QA and QC program that establishes a system of adherence to procedures, prevention and detection of errors and other quality problems, and appropriate corrective actions when needed. The SOPs must describe the roles, duties and training of the personnel responsible for each aspect of the QA Program.
- The overall QA and QC program must be reviewed at least once every 12 months by the designated person, results of review must be documented, and action taken as necessary

Section 12. Quality Assurance and Quality Control

- **Notification About and Recall of Dispensed CNSPs**
- Facility must have an SOP and procedures in place to
  - Determine when a recall must be initiated, investigate and document the reason
  - Recall any unused product and quarantine remaining stock
  - Investigate if other lots are affected and recall if necessary
  - Determine the severity of the problem and urgency for implementation
  - Determine the distribution of any affected CNSP
  - Identify patients who have received the CNSP
  - Report the recall to the appropriate regulatory bodies as required

Section 12. Quality Assurance and Quality Control

- **Complaint Handling and Adverse Event Reporting**
  - Facilities must develop and implement SOPs for receiving, acknowledging and handling complaints and adverse event reports
  - Must designate one or more persons to be responsible for handling complaints and adverse event reports
  - Adverse events must be reported in accordance with the facilities SOPs and all laws and regulations. If there is suspected patient harm, the patients and providers potentially affect must be informed.
  - Complaints may include:
    - Concerns or reports on the quality and labeling of a CNSP
    - Possible adverse reactions to a CNSP

Section 12. Quality Assurance and Quality Control

- **Complaint Handling**
- The designated person must ensure that each complaint is reviewed to determine if a complaint indicates a potential quality problem
  - Must initiate and complete a thorough investigation into the cause of a quality problem
  - Must consider whether the quality problem extends to other CNSPs
  - Must implement corrective action, if necessary, for all potentially affected CNSPs
- Consider whether to
  - Initiate a recall of affected/potentially affected CNSPs
  - Cease non-sterile compounding under all underlying problems have been corrected

Section 13: CNSP Packaging and Transporting

- **Packaging and Transporting of CNSPS:**
  - Personnel should select and use packaging materials that will maintain the physical and chemical integrity and stability of the CNSPs
  - SOPs must describe the packaging of CNSPs
  - Packaging materials must simultaneously protect:
    - CNSPS from damage, leakage, contamination and degradation
    - Personnel from exposure
  - If transporting CNSPs, the facility must have SOPs that describe:
    - The mode of transportation
    - Any special handling instructions
    - Whether temperature monitoring devices are needed

Section 14. Documentation Updated

- All facilities where CNSPs are prepared must have and maintain written or electronic documentation to demonstrate compliance with this chapter.
- Must include, but is not limited to, the following:
  - Personnel training, competency assessments, and qualification records including corrective actions for any failures
  - Equipment records (e.g., calibration, verification, and maintenance reports)
  - COAs and all documentation required for components not conventionally manufactured
  - Receipt of components
  - SOPs, MFRs, and CRs
  - Release inspection and testing records
  - Information related to complaints and adverse events including corrective actions taken
  - Results of investigations and corrective actions

Section 14. Documentation - Updated

- **Documentation required cont'd:**
  - Records of cleaning and sanitizing the designated area
  - Temperature logs
  - Accommodations to personnel compounding CNSPs
  - Any required routine review (e.g., yearly review of QA/Q, yearly review of chemical hazard and disposal information)
- Records must be legible and stored in a manner that prevents their deterioration and/or loss
- All required CR for a particular CNSP must be readily retrievable for at least 2 years after preparation or as required by applicable regulatory bodies.

Questions?

UNITED STATES PHARMACOPEIA (USP)

GENERAL CHAPTER <797> PHARMACEUTICAL COMPOUNDING – STERILE PREPARATIONS

COMPENDIAL ON 11/1/23

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USP <797> Overview: Sections

1. Introduction and Scope
2. Personnel Training and Evaluation
3. Personal Hygiene and Garbing
4. Facilities and Engineering Controls
5. Certification and Recertification
6. Microbiological Air and Surface Monitoring
7. Cleaning, Disinfecting and applying sporicidal disinfectants and sterile 70% IPA
8. Introducing items into the SEC and PEC
9. Equipment, Supplies, and Components
10. Sterilization and Depyrogenation

USP <797> Overview: Sections

11. Master Formulation (MF) and Compounding Record (CR)
12. Release Inspections and Testing
13. Labeling
14. Establishing Beyond-Use Dates
15. Use of Conventionally Manufactured Products as Components
16. Use of CSPs As Components
17. Standard Operating Procedures (SOP)
18. Quality Assurance and Quality Control
19. CSP Storage, Handling, Storage, Packaging, Shipping, And Transport
20. Documentation
21. Compounding Allergenic Extracts

USP <797>
Section 1. Introduction and Scope

- This chapter describes the minimum standards to be followed when preparing compounded sterile human and animal drugs.
- Applies to all persons who prepare compounded sterile preparations (CSP) and to all places where CSPs are made for humans or animals.
- Any person entering a sterile compounding area, whether preparing a CSP or not, must meet the requirements in section 3. Personal Hygiene and Garbing
- The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose
  - Validation of Alternative Microbiological Methods ⟨1223⟩
  - Validation of Compendial Procedures ⟨1225 ⟩

USP <797>
Section 1. Introduction and Scope

- **Compounding** is the process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile preparation.
- **Administration** means the direct application of a sterile product or preparation to a single patient by injecting, infusing, or otherwise providing a sterile product or CSP in its final form.
  - It is out of the scope of this chapter
- Proprietary bag and vial systems:
  - Docking and activation in accordance with the manufacturer's instructions for immediate administration to an individual patient is not considered compounding.
  - Docking for future activation and administration is considered compounding.

USP <797>
Section 1. Introduction and Scope

Immediate-Use CSPs

- 7 conditions are met **and**
  - 1) Aseptic techniques, processes, and procedures are followed, and written SOPs are in place
  - 2) Personnel are trained and demonstrate competency in aseptic processes
  - 3) Performed in accordance with evidence-based information for physical and chemical compatibility of the drugs
  - 4) Involves not more than 3 different sterile products
  - 5) Unused starting component from a single-dose container must be discarded after preparation is complete.
  - 6) Administration begins within 4 hrs or discarded
  - 7) No labeling requirement when administered by the preparer.
- For direct and immediate administration
- Not subject to the requirements for Category 1, Category 2, or Category 3 CSPs

USP <797>
Section 1. Introduction and Scope

- Category is based on the conditions under which CSPs are made, the probability for microbial growth during storage, and the time period within which they must be used.
- All Categories can use sterile starting ingredients or nonsterile starting ingredients.
- **Cleanroom suite:** A classified area that consists of both an anteroom and buffer room.

USP <797>
Section 1. Introduction and Scope

Category 1(CAT 1):

- PECs may be placed in an unclassified segregated compounding area (SCA)
- Beyond use date (BUD):
  - Controlled Room Temperature (CRT): < 12 hours
  - Refrigerated: < 24 hours

Category 2 (CAT 2):

- PECs must be placed in clean room suite
- BUD: (Table 13 in section 14)
  - CRT: > 12 hours
  - refrigerated > 24 hours

USP <797>
Section 1. Introduction and Scope

Category 3 (CAT 3):

- PECs must be placed in clean room suite
- Undergo end product testing
- Increased requirements on staff and facility
- Max 250 units per batch
- BUD: (Table 14 in section 14)
  - Max: 180 days

USP <797> Section 2. Personnel Training and Evaluation

- Personnel who compound or have direct oversight of compounding must be initially trained and qualified by demonstrating knowledge and competency before being allowed to perform independently.
- Written training program:
  - Describes the required training
  - Describes the frequency of training
  - Describes the process for evaluating the performance of individuals.
  - Equips personnel with the appropriate knowledge
  - Trains personnel in the required skills necessary to perform their assigned tasks,
- Training and evaluation must be documented

USP <797> Section 2. Personnel Training and Evaluation

Demonstrating Knowledge and competency of core skills: Every 12 months

- Hand hygiene
- Garbing
- Cleaning and disinfection
- Calculations, measuring, and mixing
- Aseptic technique
- Achieving and/or maintaining sterility and apyrogenicity
- Use of equipment
- Documentation of the compounding process (MFR and CR)
- Principles of HEPA-filtered unidirectional airflow within the ISO Class 5 area
- Proper use of PECs
- Principles of movement of materials and personnel within the compounding area

Only one person compounds:

- Must document they have obtained training and demonstrated competency,
- Must comply with the other requirements of this chapter.

USP <797> Section 2. Personnel Training and Evaluation

Gloved fingertip and thumb sampling (GFT):

- Evaluates a compounder's competency in correctly performing hand hygiene and garbing.
- Initial Training and Competency: gloved fingertip and thumb sampling
  - No fewer than 3 separate times (full garbing process)
    - After garbing but before IPA
  - Must be performed on donned sterile gloves in the classified area or SCA.
  - Action level ≥1cfu as a total from both hands.

USP <797> Section 2. Personnel Training and Evaluation

Gloved fingertip and thumb sampling (GFTT):

- Ongoing Training and Competency: :
  - Must be performed on donned sterile gloves inside of an ISO 5 PEC.
  - CAT 1 & 2 every 6 months after completing the media-fill test.
  - CAT 3 every 3 months after completing the media-fill test.
  - Direct oversight every 12 months after completing the media-fill test
  - Action level >3 cfu as a total from both hands.

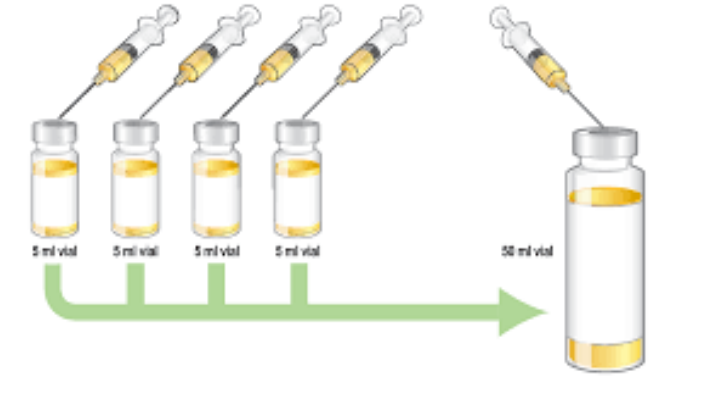
USP <797>
Section 2. Personnel Training and Evaluation

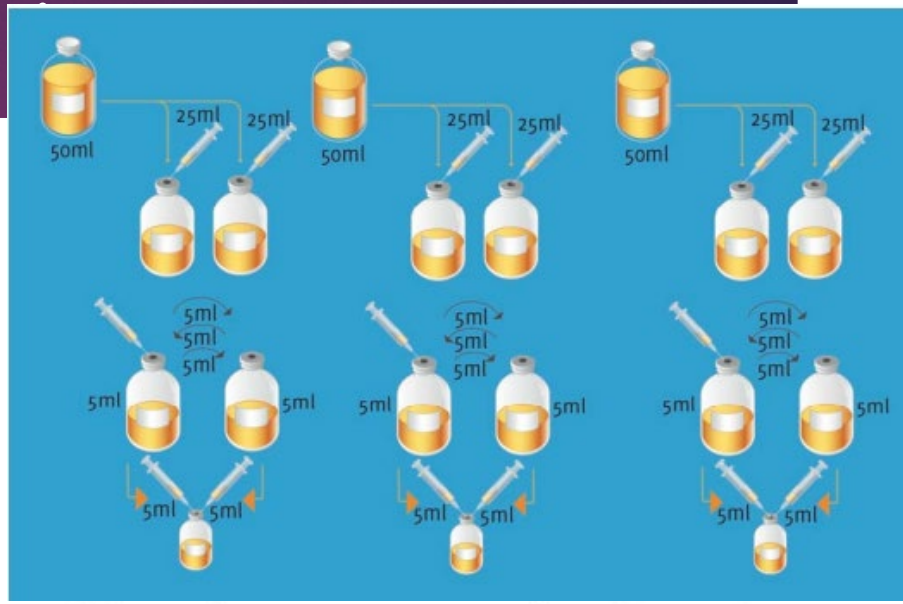
USP <797> Section 2. Personnel Training and Evaluation

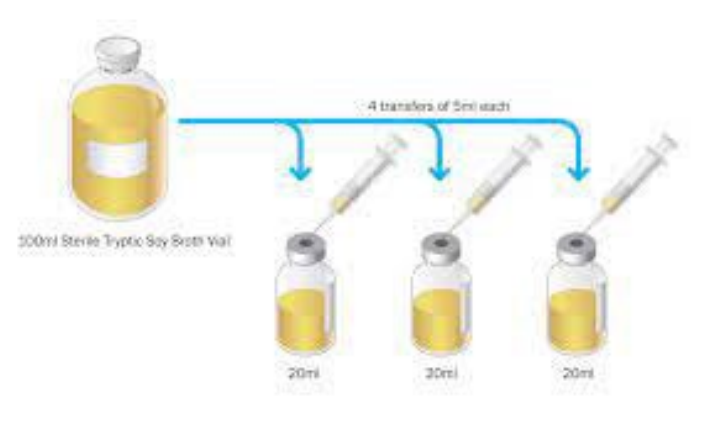
Media-fill test:

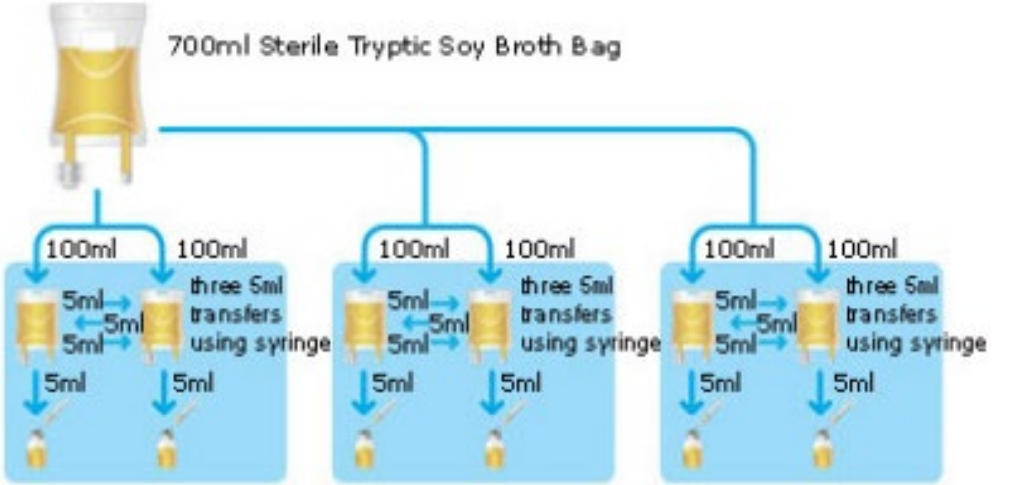
- Simulate the most difficult and challenging aseptic compounding procedures encountered and must capture elements that could potentially affect the sterility of the CSP including but not limited to:
  - Factors associated with the length of process (operator fatigue, quality of equipment)
  - Number of aseptic additions or transfers
  - Number, type, and complexity of manipulations
  - Number of personnel in the buffer room or SCA
- Immediately following the media-fill test, GFT must be performed inside of an ISO Class 5 PEC.

USP <797>
Section 2. Personnel Training and Evalua









USP <797> Section 2. Personnel Training and Evaluation

Aspect Manipulation: Visual observation, media-fill testing, followed by a GFT on both hands, and surface sampling of the direct compounding area.

- Initial Training and Competency: before compounding
- Ongoing Training and Competency:
  - CAT 1 & 2 every 6 months
  - CAT 3 every 3 months
  - Direct oversight only every 12 months

USP <797>
Section 3. Personal Hygiene and Garbing

Personnel Preparation

- Before entering the compounding area:
  - Remove personal outer garments.
  - Remove all cosmetics (including eyelashes)
  - Remove all hand, wrist, and other exposed jewelry including piercings that could interfere with the effectiveness of garbing.
  - No ear buds or headphones.
  - No electronic devices that are not necessary
  - Keep nails clean and neatly trimmed to minimize particle shedding and avoid glove punctures. Nail polish, artificial nails, and extenders must not be worn.
  - Wipe eyeglasses

USP <797> Section 3. Personal Hygiene and Garbing

Hand Hygiene:

- Must be performed before entering a compounding area
- Brushes must not be used for hand hygiene (skin irritation)
- Hand driers must not be used (air turbulence and contamination)
- Hands must be sanitized with alcohol-based hand rub before donning sterile gloves.

USP <797> Section 3. Personal Hygiene and Garbing

Garbing Requirements CAT 1/2:

- Low-lint garment with sleeves that fit snugly around the wrists and an enclosed neck
  - May be reused for a shift
- Low-lint covers for shoes
- Low-lint cover for head that covers the hair and ears, and if applicable, cover for facial hair
- Low-lint face mask
- Sterile powder-free gloves
  - must be donned in a classified room or SCA
- If using a RABS (CAI or CACI), sterile gloves must be worn over the gloves attached to the RABS sleeve.

USP <797> Section 3. Personal Hygiene and Garbing

Garbing Requirements CAT 3: additive to CAT 1/2

- Do not allow any exposed skin in the buffer room (i.e., face and neck must be covered).
- Low-lint outer garb must be sterile,
- Disposable garbing items must not be reused
- Laundered garb must not be reused without being laundered and resterilized with a validated cycle.
- SOPs must describe disinfection procedures for reusable equipment.

USP <797>
Section 3. Personal Hygiene and Garbing

USP <797> Section 4. Facilities and Engineering Controls

Design requirement to maintain air quality

- Anteroom:
  - ISO 8 into a positive-pressure buffer room
  - ISO 7 into a negative-pressure buffer room
- Buffer room at least ISO 7

Facility design and Environmental Controls

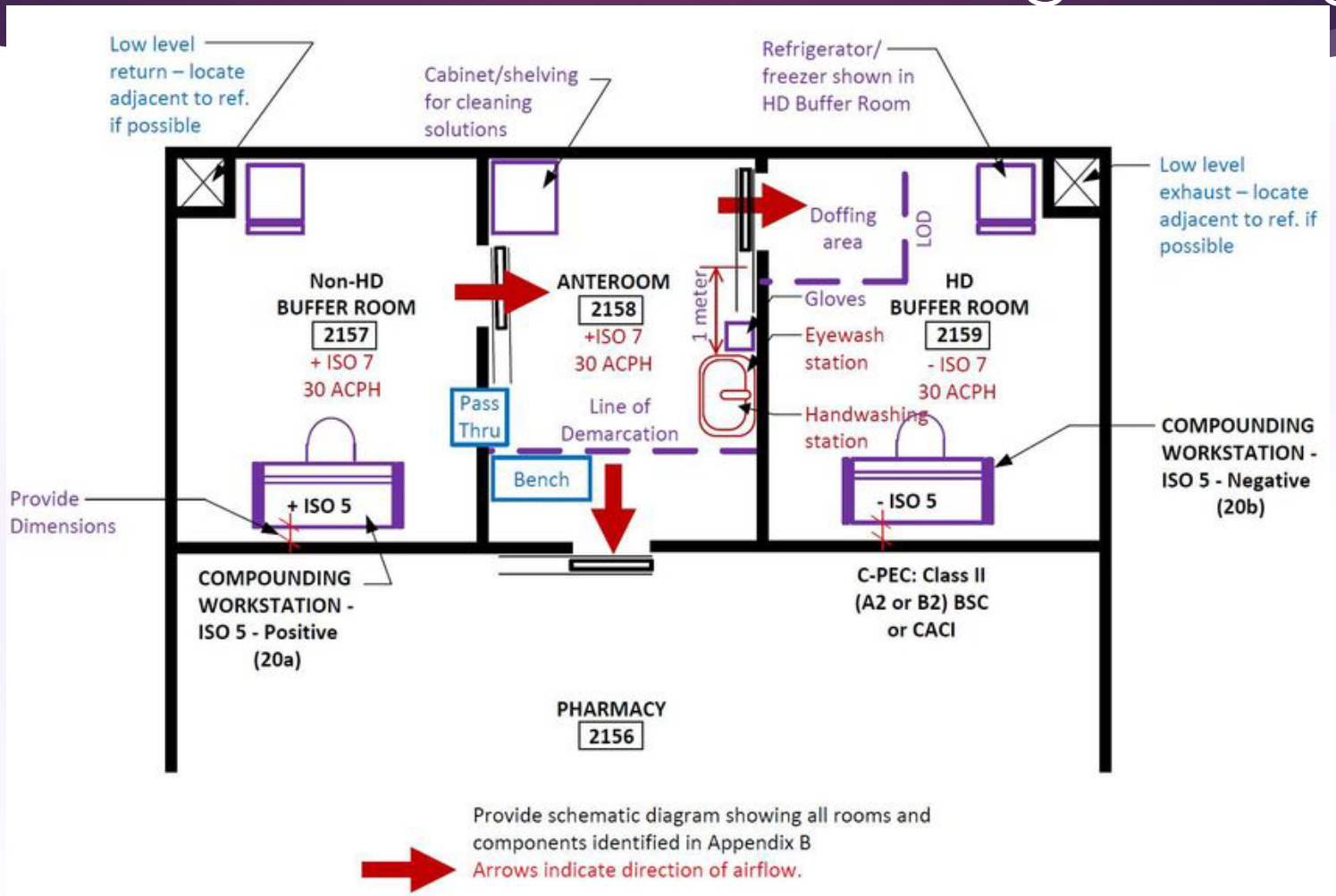
- Temperature and Humidity monitored each day when compounding takes place.

USP <797> Section 4. Facilities and Engineering Controls

Cleanroom suite:

- Fixed walls and doors
- Pressure –differential monitoring systems must continuously monitor the pressure differentials.
- All surfaces must be smooth, impervious, free from cracks and crevices, and nonshedding
- Air supplied via HEPA filters located in the ceilings
- Air returns must be low on the wall or have a smoke study
- Line of demarcation in the ante-room (clean and dirty sides)
- Pass-through chamber must never have both doors open at the same time
- No tacky surfaces
- All junctures must be sealed
- Sterile and non-sterile PEC 1 meter apart (4.2.6)
- Buffer room must not contain plumbed water sources
- Anteroom must not contain floor drain(s)
- Should: Temperature of 20° (68 F) or cooler and a relative humidity below 60%

USP <797>
Section 4. Facilities and Engineering



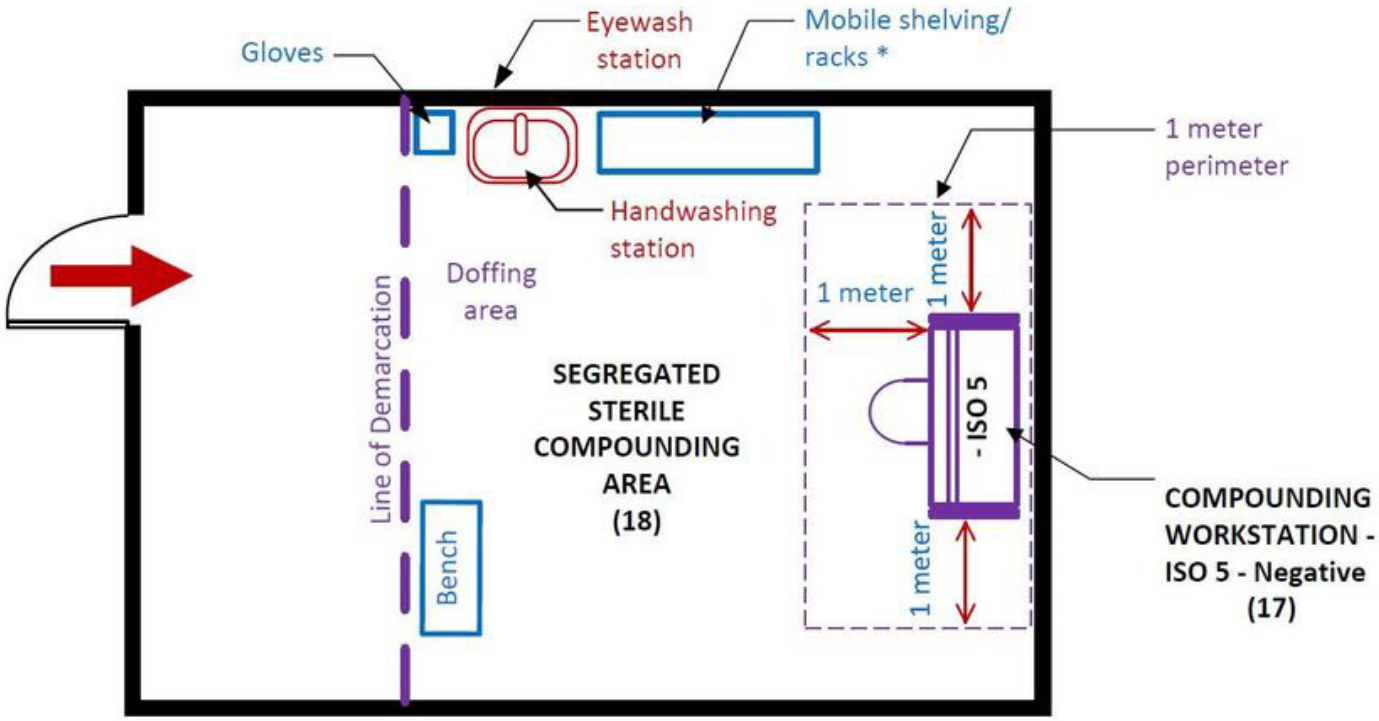
USP <797>

USP <797> Section 4. Facilities and Engineering Controls

Segregated Compounding Areas (SCA):

- Must be located away from:
  - Unsealed windows, doors that connect to the outdoors, and traffic flow.
  - Environmental control challenges (restrooms, warehouses, cafeterias, etc.)
- Sink at least 1 meter from the PEC

USP <797>
Section 4. Facilities and Engineering Controls



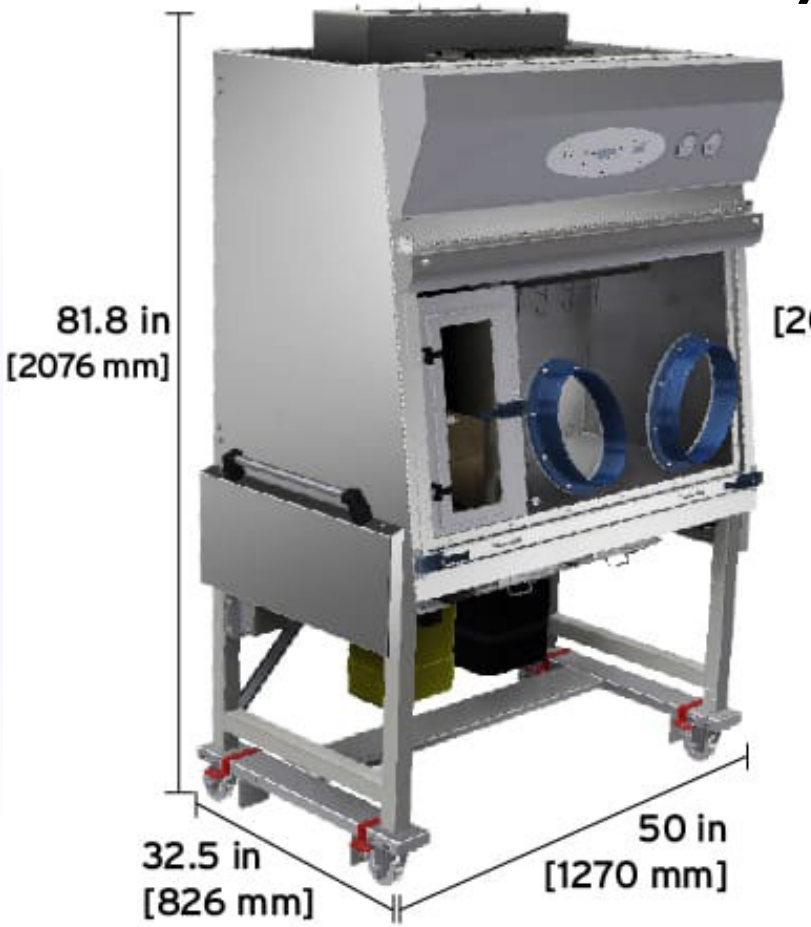
* Other equipment/furniture shown for reference only.
Arrows indicate direction of airflow.

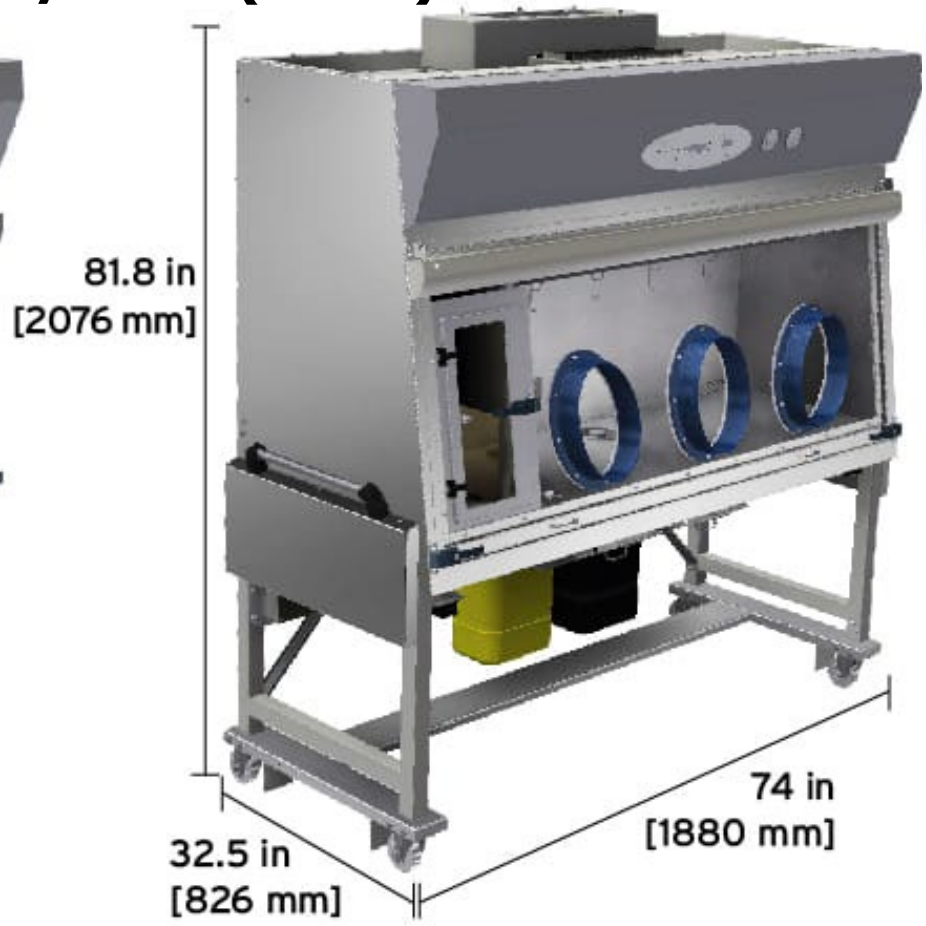
USP <797> Section 4. Facilities and Engineering Controls

- **Restricted-access barrier system (RABS):** enclosure that provides HEPA-filtered ISO Class 5 unidirectional air that allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations.
  - Compounding aseptic containment isolator (CACI): A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for the compounding of sterile HDs.
  - Compounding aseptic isolator (CAI): A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for compounding of sterile non-HDs.
- **Pharmaceutical isolator**: An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air operated at a continuously higher pressure than its surrounding environment and Is decontaminated using an automated system. It uses only decontaminated interfaces or Rapid transfer ports for materials transfer.

USP <797>
Section 4. Facilities and Engineering Controls

Restricted-access barrier system (RABS):





USP <797>
Section 4. Facilities and Engineering Controls

Pharmaceutical isolator:

USP <797> Section 4. Facilities and Engineering Controls

Air exchange per hour (ACPH) Requirements

- As tested under dynamic conditions:
  - Unclassified SCA; No requirement
  - ISO Class 7 room(s); ≥ 30 ACPH (at least 15 from HVAC)
  - ISO Class 8 room(s); ≥ 20 ACPH(at least 15 from HVAC)
- If PEC is used for any ACPH it must never be off

USP <797> Section 4. Facilities and Engineering Controls

CAT 2/3 from nonsterile component

- Presterilization procedures, weighing and mixing, must be completed: (section 4.2.6)
  - ISO Class 8 or better environment
  - In single-use containment glove bags, containment ventilated enclosures (CVEs), BSCs, or CACIs

USP <797> Section 5. CERTIFICATION AND RECERTIFICATION

- Where: all classified areas
- When: Initially, every 6 months and when changes to the area could affect airflow or air quality
- What:
  - Airflow testing air velocity, the room air exchange rate, and the room pressure differential
  - HEPA filter integrity testing
  - Total particle count testing
    - Under dynamic operating conditions (# of staff documented)
  - Dynamic airflow smoke pattern test each PEC
    - Under dynamic operating conditions (# of staff documented)

USP <797> Section 6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

- What:
  - Viable impact volumetric airborne particulate sampling (viable air):
    - CAT 1/2: Initially and Every 6 months
    - CAT 3: 30 days before start and monthly
  - Monitoring surfaces for Viable Particles (viable surface):
    - Includes Pass-though
    - CAT 1/2: Initially and monthly
    - CAT 3: initially, weekly and in the PEC at the end of each batch

USP <797>
Section 6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

- Where: all classified areas
- When:
  - Certification of new facilities and equipment
  - After any servicing of facilities or equipment
  - In response to identified problems (failed sterility test)
  - In response to identified trends (failed GFT or media fill, repeated observations of air or surface contamination)
  - In response to changes that could impact the sterile compounding environment (new cleaning agent)
  - Every 6 months and when changes to the area that could affect airflow or air quality
- How: Under dynamic operating conditions

USP <797>
Section 6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

- What: action levels

Action Levels		
ISO Class	Air	Surface
5	>1	>3
7	>10	>5
8	>100	>50

- The incubator must be placed in a location outside of the sterile compounding area.

USP <797> Section 7. CLEANING, DISINFECTING, AND APPLYING SPORICIDAL DISINFECTANTS AND STERILE 70% IPA

- Edited Table 10

Site	Cleaning	Disinfecting	Sporicidal
PEC	Equipment and all interior surfaces of the PEC: * daily * surface contamination	Equipment and all interior surfaces of the PEC: * daily * surface contamination	Cat 1/2: Monthly Cat 3: Weekly
Removable work tray of the PEC,	Work surface of the tray: *daily All surfaces and the area underneath the work tray: *monthly	Work surface of the tray: *daily All surfaces and the area underneath the work tray: *monthly	*monthly
Pass-through	*daily	*daily	Cat 1/2: Monthly Cat 3: Weekly
Work surface(s) outside PEC	*daily	*daily	
Floors	*daily	*daily	
Walls, doors, door frames, Celling, shelving, bins, equipment outside the PEC	*monthly	*monthly	*monthly

*daily on days when compounding occurs

USP <797> Section 8. INTRODUCING ITEMS INTO THE SEC AND PEC

- Into the SEC:
  - Wipe with a sporicidal disinfectant, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers by personnel wearing gloves.
- Into the PEC:
  - Wipe with sterile 70% IPA using sterile low-lint wipers and allowed to dry before use
- Critical Sites within the PEC:
  - Wipe with sterile 70% IPA in the PEC and allowed to dry.

USP <797> Section 9. Equipment, Supplies, and Components

- **Equipment**:
  - Follow SOPs for the calibration, maintenance, cleaning, and use of the equipment based on the manufacturer's recommendations
  - An accuracy assessment before the first use and again each day the equipment is used to compound CSPs.
  - Maintain a daily record of the accuracy measurements on the days the equipment is in use.
- **Supplies**:
  - Supplies in direct contact with the CSP must be sterile and depyrogenated

USP <797> Section 9. Equipment, Supplies, and Components

- **Component Selection**:
  - Conventionally manufactured sterile products should be used when available and appropriate
  - Must be evaluated for suitability for use in sterile drug preparation.
  - Components labeled with "not for pharmaceutical use", "not for injectable use", "not for human use" or an equivalent statement must not be used to compound for these purposes
- **Active Pharmaceutical Ingredient (API):**
  - Must comply with the criteria in the USP–NF monograph, if one exists
  - Must have a COA
  - Must be manufactured by an FDA-registered facility

USP <797> Section 9. Equipment, Supplies, and Components

- **Components other than API**:
  - Comply with the criteria in the USP–NF monograph, if one exists
  - Accompanied by documentation (COA)
  - Should be manufactured by an FDA-registered facility
  - When CSPs are used they are of the correct identity, appropriate quality, within expiry date and have been stored under appropriate conditions.
  - Handled and stored in a manner that prevents contamination, mix-ups, and deterioration.
  - Must monitor temperature in the area(s) where components are stored at least once daily.

USP <797> Section 10. Sterilization and Depyrogenation

- **Terminal Sterilization** is preferred, unless CSP or container cannot tolerate
  - Dry heat
  - Steam autoclaving
  - Irradiation
- **Aseptic Preparation** Compounding with only sterile ingredients
  - Sterilization by filtration (not for a suspension or emulsion)).

USP <797> Section 10. Sterilization and Depyrogenation

- **Dry heat depyrogenation**:
  - Cycle must be established initially and verified annually using endotoxin challenge vials (ECVs) to demonstrate that the cycle is capable of achieving a ≥3-log reduction in endotoxins (USP ⟨85⟩)
  - Not thermostable depyrogenated with multiple rinses with sterile, nonpyrogenic water (e.g., Sterile Water for Injection or Sterile Water for Irrigation) and then thoroughly drained or dried immediately before use in compounding.

USP <797> Section 10. Sterilization and Depyrogenation

- **Sterilization by Filtration:**
  - Filters must be sterile, depyrogenated, have a nominal pore size of 0.22 µm or smaller, and appropriate for pharmaceutical use.
  - Filters are chemically and physically compatible with all ingredients in the CSP;
  - Filters are chemically stable at the pressure and temperature conditions that will be used; and
  - Filters have enough capacity to filter the required volumes.

USP <797> Section 10. Sterilization and Depyrogenation

- **Sterilization by Steam Heat**:
  - Preferred method for terminal sterilization of aqueous CSPs in their final, sealed container closure system.
  - Not an option if moisture, pressure, or the temperatures used would degrade the CSP
  - Immediately before filling containers that will be steam sterilized, solutions must be passed through a filter with a nominal pore size of not larger than 1.2 µm for removal of particulate matter.
  - Must be able to generate steam internally
  - Effectiveness must be verified and documented with each sterilization run or load by using appropriate biological indicators (spores of Geobacillus stearothermophilus)
  - calibrated data recorder or chart must be used to monitor each cycle and to examine for cycle irregularities
  - Date, run, and load numbers of the steam sterilizer used to sterilize a CSP must be documented in the CR.

USP <797> Section 10. Sterilization and Depyrogenation

- **Sterilization by Dry Heat:**
  - Must be equipped with temperature controls and a timer.
  - Data recorder or chart must be used to monitor each cycle and the data must be reviewed to identify cycle irregularities (e.g., deviations in temperature or exposure time).
  - The date, run, and load numbers of the dry heat oven used to sterilize a CSP must be documented in the CR

USP <797>
Section 11. Master Formulation and Compounding Records

- Master Formulation Record (MFR); required if:
  - CSP prepared in a batch for > 1 patient
  - CSPs prepared from nonsterile ingredient(s)

Box 9. Master Formulation Records

An MFR must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Identities and amounts of all ingredients; if applicable, relevant characteristics of components (e.g., particle size, salt form, purity grade, solubility)
- Type and size of container closure system(s)
- Complete instructions for preparing the CSP, including equipment, supplies, a description of the compounding steps, and any special precautions
- Physical description of the final CSP
- BUD and storage requirements
- Reference source to support the stability of the CSP
- Quality control (QC) procedures (e.g., pH testing, filter integrity testing)
- Other information as needed to describe the compounding process and ensure repeatability (e.g., adjusting pH and tonicity; sterilization method, such as steam, dry heat, irradiation, or filter)

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USP <797>
Section 11. Master Formulation and Compounding Records

- Compounding Record (CR) required for **all CSPs**
  - Except immediate-use for one patient
  - May be in the form of prescription or medication order, compounding log, or label
  - May be stored electronically (must be retrievable)

USP <797>
Section 11. Master Formulation and Compounding Records

CRs must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Date and time of preparation of the CSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- A method to identify the individuals involved in the compounding process and individuals verifying the final CSP
- Name of each component
- Vendor, lot number, and expiration date for each component for CSPs prepared for more than one patient and for CSPs prepared from nonsterile ingredient(s)
- Weight or volume of each component
- Strength or activity of each component
- Total quantity compounded
- Final yield (e.g., quantity, containers, number of units)
- Assigned BUD and storage requirements
- Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing)

If applicable, the CR must also include:

- MFR reference for the CSP
- Calculations made to determine and verify quantities and/or concentrations of components

USP <797>
Section 12. RELEASE INSPECTIONS AND TESTING

- **Visual Inspection** at the completion of compounding, before release and dispensing
  - Physical appearance
    - particulate, color, leaks, ect.
  - Label and prescription match
  - Container closure integrity
- Defects must be investigated

USP <797> Section 12. RELEASE INSPECTIONS AND TESTING

- **Sterility Testing** (CAT 2 as required, CAT 3)
  - Units to be tested:
    - 1- 39 CSPs in batch: 10% of CSPs round up
    - > 40 CSPs in batch, follow USP<71>, Table 3
    - Max of 250 final yield units (requiring sterility testing)
  - According to USP <71>
    - Method Suitability Test must be performed
    - A validated alternative method <1223>, noninferior
  - Failure must prompt an investigation

USP <797> Section 12. RELEASE INSPECTIONS AND TESTING

- **Bacterial Endotoxin Testing**
  - Injectables only (included implantable)
  - Complaint with USP <85> limit
  - Required for:
    - CAT 2:
      - Nonsterile component(s) and assigned a BUD that requires sterility testing
    - CAT 3:
      - From nonsterile component(s)

USP <797>
Section 13. LABELING

- **Label:** immediate container
  - Assigned internal identification number
  - Active ingredient(s) and their amount(s), activity(ies), or concentration(s)
  - Storage conditions if other than controlled room temperature
  - BUD
  - Dosage form
  - Total amount or volume if it is not obvious
  - SDV or MDV
- **Labeling:**
  - Route(s) of administration
  - Special handling instructions
  - Warning statements
  - Facility name and contact information

USP <797> Section 14. Establishing Beyond-Use Dates

- **Beyond-use date (BUD):** Either the date or hour and date after which a CSP must not be used, or administration must not begin.
  - Determined from the date/time that preparation of the CSP is initiated.
  - Based primarily on factors that affect the achievement and maintenance of sterility,
- Table limits are based on the risk of microbial contamination or not achieving and maintaining sterility despite implementation of the requirements in This chapter.

USP <797> Section 14. Establishing Beyond-Use Dates

- **Beyond-use date (BUD):**
  - Terminal sterilization > aseptic processing
  - Conventionally manufactured sterile > one or more nonsterile starting component(s).
  - Sterility testing results are within acceptable limits > no sterility testing
  - Freezer > refrigerator > room temp
  - Must not exceed the shortest remaining expiration date starting components
  - For CSPs prepared from one or more compounded components, the BUD should generally not exceed the shortest BUD of any of the individual compounded components

USP <797> Section 14. Establishing Beyond-Use Dates

Table 12. BUD Limits for Category 1 CSPs[a]

Storage Conditions	
Controlled Room Temperature (20°–25°)	**Refrigerator (2°–8°)**
≤12 h	≤24 h

[a] A shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

USP <797> Section 14. Establishing Beyond-Use Dates

Table 13. BUD Limits for Category 2 CSPs[a]

Preparation Characteristics		Storage Conditions		
Compounding Method	**Sterility Testing Performed and Passed**	**Controlled Room Temperature (20°–25°)**	**Refrigerator (2°–8°)**	**Freezer (–25° to –10°)**
Aseptically processed CSPs	No	Prepared from one or more nonsterile starting component(s): 1 day	Prepared from one or more nonsterile starting component(s): 4 days	Prepared from one or more nonsterile starting component(s): 45 days
		Prepared from only sterile starting components: 4 days	Prepared from only sterile starting components: 10 days	Prepared from only sterile starting components: 45 days
	Yes	30 days	45 days	60 days
Terminally sterilized CSPs	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

[a] A shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

USP <797> Section 14. Establishing Beyond-Use Dates

- **CAT 3:**
  - Increased facility and personnel requirements
- Stability requirement;
  - Supported by stability data.
  - Prepared according to the exact formulation from the stability data
  - Packaged and stored in container closure system (CCS) used in the study.
  - Analytical method must be validated
- Release testing:
  - Sterility tested and meets requirements of ⟨71⟩ or a validated alternative method

USP <797> Section 14. Establishing Beyond-Use Dates

Table 14: BUD Limits for Category 3 CSPs[a]

Preparation Characteristics	Storage Conditions		
Compounding Method	**Controlled Room Temperature (20°–25°)**	**Refrigerator (2°–8°)**	**Freezer (−25° to −10°)**
Aseptically processed, sterility tested, and passing all applicable tests for Category 3 CSPs	60 days	90 days	120 days
Terminally sterilized, sterility tested, and passing all applicable tests for Category 3 CSPs	90 days	120 days	180 days

[a] A shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table.

USP <797> Section 14. Establishing Beyond-Use Dates

- **Multiple-Dose CSPs**
  - Must be prepared as a CAT 2/3
  - Aqueous CSP must pass antimicrobial effectiveness testing, USP ⟨51⟩
  - Once entered or punctured must not be used for longer than the assigned BUD or 28 days if supported by antimicrobial effectiveness testing results whichever is shorter.
  - CCS used must be evaluated for and conform to container closure integrity, USP ⟨1207⟩
- Multiple-dose, non preserved, aqueous topical, and topical ophthalmic, CSPs: (section 14.5)
  - Antimicrobial Effectiveness Testing ⟨51⟩ not required if
    - Prepared as a CAT 2/3
    - For use by a single patient
    - Labeled once opened, discarded after 24 h at room temperature and/or after 72 h when stored under refrigeration

USP <797>
Section 15. USE OF CONVENTIONALLY MANUFACTURED PRODUCTS AS COMPONENTS

- Conventionally Manufactured Product must be used by:

Type of Container	Time to use
Single-Dose Vial	Entered in ISO Class 5 = 12 hrs
Ampule	Immediately only
Multiple-Dose Containers	28 days or per manufacture
Pharmacy Bulk Package	Per manufacture, must be entered in ISO class 5

USP <797>
Section 16. Use of CSPs As Components

- Multiple-dose CSPs:
  - Must have antimicrobial effectiveness testing
  - Must be stored properly
  - Once enter must not be used longer than BUD of 28 days
    - In-use time will not limit the BUD of final CSP
- Single-dose CSPs and compounded stock solutions:
  - Must be entered in ISO class 5 can be used for up to 12 hrs.
    - In-use time will not limit the BUD of final CSP
  - Must be stored properly

USP <797> Section 18. Quality Assurance and Quality Control

- **QA:** a system of procedures, activities, and oversight that ensures the compounding process consistently meets quality standards.
- **QC:** is the sampling, testing, and documentation of results that, taken together, ensure specifications have been met before release of the CSP.
- Must be formally established and documented in the facility's SOPs
- Must be reviewed every 12 months

USP <797> Section 18. Quality Assurance and Quality Control

- Notification About and Recall of Out-of-Specification Dispensed:
- Before results of release testing known
  - Must be able to:
    - Immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., sterility, strength, purity, bacterial endotoxin, or other quality attributes)
    - Recall any unused dispensed CSPs and quarantine any stock remaining in the pharmacy
    - Investigate if other lots are affected and recall if necessary
- An SOP must contain:
  - Procedures to determine the severity of the problem and the urgency for implementation and completion of the recall
  - Procedures to determine the distribution of any affected CSP, including the date and quantity of distribution
  - Procedures to identify patients who have received the CSP
  - Procedures for disposal and documentation of the recalled CSP
  - Procedures to investigate and document the reason for failure

USP <797> Section 18. Quality Assurance and Quality Control

- Complaint handling:
  - Designated person must review all complaints
  - All potential quality problem but be investigated
- Adverse Event Reporting:
  - Must be reported

USP <797>
Section 19. CSP Handling, Storage, Packaging, Shipping and Transport

- Packaging
  - Packaging materials should protect CSPs from damage, leakage, contamination, degradation, and adsorption.
  - Appropriate shipping containers and packaging materials must be selected.
- Shipping and Transporting
  - Must select modes of transport that are expected to deliver properly packed CSPs in an undamaged, sterile and stable condition.
  - Consider exposure to heat, cold, light, physical shaking.
  - If special handling is required, instructions must be included on the exterior of the container.

USP <797>
Section 20. Documentation

- Personnel training, competency assessments, and qualification records including corrective actions for any failures
- Certification reports, including corrective actions for any failures
- Environmental air and surface monitoring procedures and results
- Equipment records (calibration, verification, maintenance)
- Receipt of components
- SOPs, MFRs, and CR
- Release testing records
- Information related to complaints and adverse events
- Results of investigations and corrective actions

Questions?

United States Pharmacopeia (USP)
Chapter <800> Hazardous Drugs—Handling in Healthcare Settings

COMPENDIAL ON 11/1/2023

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USP <800> Overview: Sections

1. Introduction and Scope
2. List of Hazardous Drugs
3. Types of Exposure
4. Responsibilities of Personnel Handling Hazardous Drugs
5. Facilities and Engineering Controls
6. Environmental Quality and Control
7. Personal Protective Equipment
8. Hazard Communication Program
9. Personnel Training

USP <800> Overview: Sections

10. Receiving
11. Labeling, Packaging, Transport, and Disposal
12. Dispensing Final Dosage Forms
13. Compounding
14. Administering
15. Deactivating, Decontaminating, Cleaning and Disinfecting
16. Spill Control
17. Documentation and Standard Operating Procedures
18. Medical Surveillance

Section 1. Introduction and Scope

- This chapter describes practice and quality standards for handling hazardous drugs (HDs) to promote patient safety, worker safety, and environmental protection.
- Handling HDs includes, but is not limited to, the receipt, storage, compounding, dispensing, administration, and disposal of sterile and nonsterile products and preparations.
- This chapter applies to all healthcare personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs.

Section 1. Introduction and Scope

- Entities that handle HDs must incorporate the standards in this chapter into their occupational safety plan which must, at a minimum, include:
  - A list of HDs
  - Facility and engineering controls
  - Competent personnel
  - Safe work practices
  - Proper use of appropriate Personal Protective Equipment (PPE)
  - Policies for HD waste segregation and disposal

Section 2. List of Hazardous Drugs

- The National Institute for Occupational Safety and Health (NIOSH) maintains a list of antineoplastic and other HDs used in healthcare.
- For the purposes of this chapter, the term antineoplastic only refers to antineoplastic drugs included in Table 1 of the most current NIOSH List.
- Must maintain a list of HDs, which must include any items on the current NIOSH list that the entity handles.
- The entity's list must be reviewed at least every 12 months.
- Whenever a new agent or dosage form is used, it should be reviewed against the entity's list.

NIOSH

- NIOSH is a division of Center for Disease Control and Prevention (CDC)
- Maintains a list of antineoplastic and other hazardous drugs in Healthcare Settings:
  - 2004, 2010, 2012, 2014, 2016
  - The most current list – *2016 List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings*
  - NIOSH proposed an updated list on May 1, 2020, for public comment, which is not yet official.

NIOSH

- HD is a drug identified as hazardous or potentially hazardous by NIOSH
- Exhibit one or more of the following six characteristics in humans or animals: (Criteria)
  - Carcinogenicity
  - Teratogenicity or developmental toxicity
  - Reproductive toxicity in humans
  - Organ toxicity at low doses in humans or animals
  - Genotoxicity
  - New drugs that mimic existing HDs drugs in structure or toxicity

NIOSH

Table 1: Antineoplastic drugs

- Meet one or more of the NIOSH criteria for a hazardous drug.
- Many of these drugs are cytotoxic
- Represent an occupational hazard to healthcare workers and should *always* be handled with use of recommended engineering controls and personal protective equipment (PPE), regardless of their formulation.

NIOSH

Table 2. Non-antineoplastic drugs that meet one or more of the NIOSH criteria for a hazardous drug

- Some of these drugs may represent an occupational hazard to males or females who are actively trying to conceive, women who are pregnant or may become pregnant, and women who are breast feeding, because they may be present in breast milk.
- Unopened, intact tablets and capsules may not pose the same degree of occupational exposure risk as injectable drugs, which usually require extensive preparation.

NIOSH

Table 3.Non-antineoplastic drugs that primarily have adverse reproductive effects

- NIOSH criteria for reproductive hazards.
- Represent a potential occupational hazard to males or females who are actively trying to conceive, women who are pregnant or may become pregnant, and women who are breast feeding, as they may be present in breast milk.
- Unopened, intact tablets and capsules may not pose the same degree of occupational risk as injectable drugs that usually require extensive preparation.

NIOSH

Table 4

- Drugs that were deleted from the 2014 NIOSH hazardous drug list for the 2016 update; however, there are no deletions to report.

Table 5

- Provides general guidance for some of the possible scenarios that may be encountered in healthcare settings where hazardous drugs are handled.

Section 2. List of Hazardous Drugs

Box 1: Containment Requirements

- Drugs on the NIOSH list that must follow the requirements in this chapter include:
  - Any HD API
  - Any antineoplastic requiring HD manipulation
- Drugs on the NIOSH list that do not have to follow all the containment requirements of this chapter if an assessment of risk is performed and implemented include:
  - Final dosage forms of compounded HD preparations and conventionally manufactured HD products, including antineoplastic dosage forms that do not require any further manipulation other than counting or repackaging (unless required by the manufacturer)
- For dosage forms of other HDs on the NIOSH list, the entity may perform an assessment of risk to determine alternative containment strategies and/work practices

Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the compounding of a drug preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body.

Section 2. List of Hazardous Drugs

- If an assessment of risk (AOR) is not performed, all HDs must be handled with all containment strategies defined in this chapter.
- If an AOR is performed:
  - Must document what alternative containment strategies and/or work practices are being employed for specific dosage forms to minimize occupational exposure
  - Must be reviewed at least every 12 months and the review documented.
- The assessment of risk must, at a minimum, consider the following:
  - Type of HD (e.g., antineoplastic, non-antineoplastic, reproductive risk only)
  - Dosage form
  - Risk of exposure
  - Packaging
  - Any manipulation that might be required

Section 3. Types of Exposure

Table 1. Examples of Potential Opportunities of Exposure Based on Activity

Activity	Potential Opportunity of Exposure
Receipt	• Contacting HD residues present on drug containers, individual dosage units, outer containers, work surfaces, or floors
Dispensing	• Counting or repackaging tablets and capsules
Compounding and other manipulations	• Crushing or splitting tablets or opening capsules • Pouring oral or topical liquids from one container to another • Weighing or mixing components • Constituting or reconstituting powdered or lyophilized HDs • Withdrawing or diluting injectable HDs from parenteral containers • Expelling air or HDs from syringes • Contacting HD residue present on PPE or other garments • Deactivating, decontaminating, cleaning, and disinfecting areas contaminated with or suspected to be contaminated with HDs • Maintenance activities for potentially contaminated equipment and devices
Administration	• Generating aerosols during administration of HDs by various routes (e.g., injection, irrigation, oral, inhalation, or topical application) • Performing certain specialized procedures (e.g., intraoperative intraperitoneal injection or bladder instillation) • Priming an IV administration set
Patient-care activities	• Handling body fluids (e.g., urine, feces, sweat, or vomit) or body-fluid-contaminated clothing, dressings, linens, and other materials
Spills	• Spill generation, management, and disposal
Transport	• Moving HDs within a healthcare setting
Waste	• Collection and disposal of hazardous waste and trace contaminated waste

Section 4. Responsibilities of Personnel Handling Hazardous Drugs

- Designated person who is qualified and trained to be responsible for:
  - Developing and implementing appropriate procedures;
  - Overseeing compliance with this chapter and other applicable laws, regulations, and standards;
  - Ensuring competency of personnel;
  - Ensuring environmental control of the storage and compounding areas.
- Thoroughly understands:
  - Rationale for risk-prevention policies,
  - Risks to themselves and others,
  - Risks of noncompliance that may compromise safety,
  - The responsibility to report potentially hazardous situations to the management team.
- Responsible for the oversight of monitoring the facility and maintaining reports of testing/sampling performed in facilities and acting on the results.

Section 5. Facilities and Engineering Controls

- HDs must be handled under conditions that promote patient safety, worker safety, and environmental protection.
- Signs designating the hazard must be prominently displayed before the entrance to the HD handling areas.
- Access to areas where HDs are handled must be restricted to authorized personnel to protect persons not involved in HD handling.
  - HD handling areas must be located away from breakrooms and refreshment areas for personnel, patients, or visitors to reduce risk of exposure.
- Designated areas must be available for:
  - Receipt and unpacking
  - Storage of HDs
  - Nonsterile HD compounding
  - Sterile HD compounding

Section 5. Facilities and Engineering Controls
5.1 Receipt/Unpacking

- Antineoplastic HDs and all HD APIs must be unpacked in an area that is:
  - Neutral/normal or negative pressure relative to the surrounding areas.
- HDs must not be unpacked in:
  - Sterile compounding areas
  - Positive pressure areas

Section 5. Facilities and Engineering Controls
5.2 Storage

- Storage of HDs:
  - Stored in a manner to prevent spillage/breakage if falls
  - Not on floor
- Antineoplastic HDs (requiring manipulation) and all HD APIs:
  - Stored separately from non-HDs
  - Stored in an externally ventilated, negative-pressure room with at least 12 air changes per hour (ACPH).
  - Refrigerated antineoplastic HDs:
    - Stored in a dedicated refrigerator in a negative pressure area with at least 12 ACPH.
- Non-antineoplastic, reproductive risk only, and final dosage forms of antineoplastic HDs:
  - May be stored with other inventory.

Section 5. Facilities and Engineering Controls
5.2 Storage

- Can sterile and nonsterile HDs be stored together?
  - Yes
  - However, HDs used for nonsterile compounding should not be stored in areas designated for sterile compounding (to minimize traffic flow)

Section 5. Facilities and Engineering Controls
5.3 Compounding (Engineering Controls)

- **Containment primary engineering control (C-PEC)**
  - Ventilated device to minimize worker and environmental HD exposure
    - Must operate continuously if it supplies some or all of the negative pressure in the C-SEC or if it is used for sterile compounding.
- **Containment secondary engineering control (C-SEC)**
  - The room in which the C-PEC is placed, which must be (for sterile/nonsterile compounding):
    - Externally vented (doesn't have to be vented through HEPA filtration)
    - Physically separated (a different room from other areas)
    - Have an appropriate air exchange (ACPH)
    - Have a negative pressure **between** 0.01 and 0.03 inches of water column relative to all adjacent areas.

Section 5. Facilities and Engineering Controls
5.3 Compounding (Engineering Controls)

- **Supplemental engineering controls:**
  - Closed-system drug-transfer device (CSTD) are adjunct controls to offer additional levels of protection.
- In addition:
  - Sink must be available for hand washing.
  - An eyewash station must be readily available.
  - Water sources and drains must be located at least 1 meter away from the C-PEC.

Section 5. Facilities and Engineering Controls
5.3 Compounding (Engineering Controls)

- For entities that compound both nonsterile and sterile HDs:
  - C-PECs must be placed in separate rooms, unless C-PECs used for nonsterile compounding are sufficiently effective that the room can continuously maintain ISO 7 classification throughout the nonsterile compounding activity.
  - If in the same room, they must be placed at least 1 meter apart and particle-generating activity must not be performed when sterile compounding is in process.

Section 5. Facilities and Engineering Controls
5.3.1 Nonsterile Compounding

- Must also follow the standards in USP <795>
- C-PEC is not required if manipulations are limited to handling of final dosage forms (e.g., counting or repackaging of tablets and capsules) that do not produce particles, aerosols, or gasses.
- C-SEC surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the nonsterile compounding area must be smooth, impervious, free from cracks and crevices, and non-shedding.

Table 2. Engineering Controls for Nonsterile HD Compounding

C-PEC	C-SEC Requirements
• Externally vented (preferred) or redundant–HEPA filtered in series • Examples: CVE, Class I or II BSC, CACI	• Externally vented • 12 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas

Section 5. Facilities and Engineering Controls
5.3.1 Nonsterile Compounding

- Can C-PEC used for sterile compounding be used for nonsterile HD compounding?
  - Yes (occasionally)
  - Must be decontaminated, cleaned, and disinfected before resuming sterile compounding

Section 5. Facilities and Engineering Controls

5.3.2 Sterile Compounding

- Must also follow the standards in USP <797>

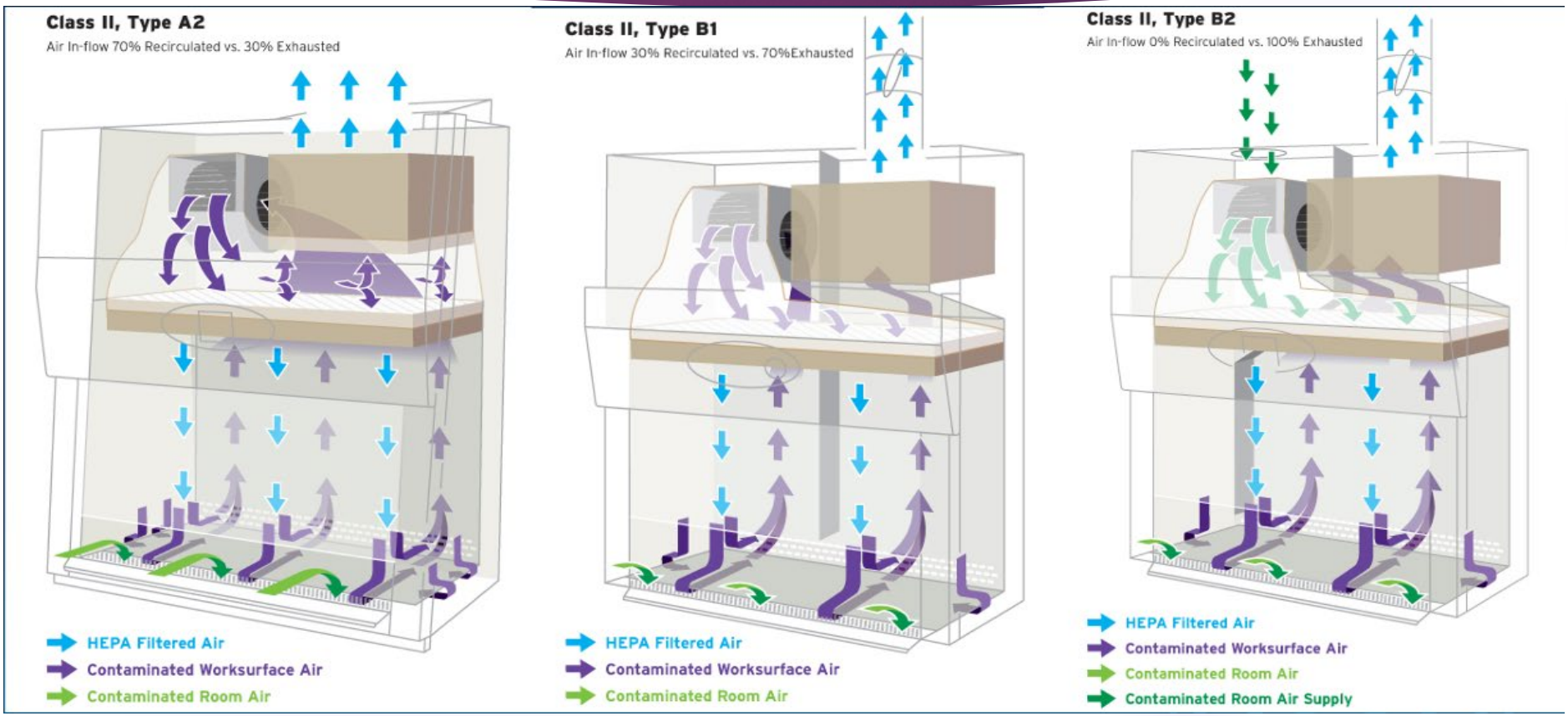
Table 3. Engineering Controls for Sterile HD Compounding

Configuration	C-PEC	C-SEC	Maximum BUD
ISO Class 7 buffer room with an ISO Class 7 ante-room	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 30 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in ⟨797⟩
Unclassified C-SCA	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 12 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in ⟨797⟩ for CSPs prepared in a segregated compounding area

Section 5. Facilities and Engineering Controls
5.3.2 Sterile Compounding

- Can a C-PEC used for compounding HDs be used for compounding non-HD?
  - Must not be used for the preparation of a non-HD unless:
    - Non-HD is placed into a protective outer wrapper during removal from the C-PEC and is labeled to require PPE handling precautions.
    - All associated materials and wrappers should be discarded as HD waste because the preparation and associated materials have potentially been contaminated by exposure to HDs.

CLASS II BSCs



https://www.nuaire.com/how-class-two-bsc-work

Section 5. Facilities and Engineering Controls
5.3.2 Sterile Compounding

- **C-SEC: (Cleanroom)**
  - Externally vented
  - Fixed walls
  - Minimum of 30 ACPH of HEPA-filtered supply air
  - Air quality of ISO Class 7 or better
  - Negative pressure **between** 0.01 and 0.03 inches of water column relative to all adjacent areas
- **C-SEC (Anteroom)**
  - Fixed walls
  - Minimum of 30 ACPH of HEPA-filtered supply air
  - Positive pressure of at **least** 0.02 inches of water column relative to all adjacent unclassified areas
  - Air quality of ISO Class 7 or better
  - Hand-washing sink **must** be placed in the ante-room at least 1 meter from the entrance to the HD buffer room

Section 5. Facilities and Engineering Controls
5.3.2 Sterile Compounding

- IF HD buffer room entered through the positive-pressure non-HD buffer room, the following is also required: (**Not a recommended facility design)**
  - Line of demarcation must be defined within the negative-pressure buffer room for donning and doffing PPE.
  - Method to transport HDs, HD CSPs, and HD waste into and out of the negative pressure buffer room to minimize the spread of HD contamination.
    - If using a pass-through chamber (negative pressure buffer area and adjacent space).
      - Must be included in the facility's certification (particles and pressure)
      - Refrigerator pass-through must not be used.

Section 5. Facilities and Engineering Controls
5.3.2 Sterile Compounding

- Containment Segregated Compounding Area (C-SCA)must have:
  - Fixed walls
  - Negative pressure **between** 0.01 and 0.03 inches of water column relative to all adjacent areas,
  - 12 ACPH
  - Externally vented
  - Hand-washing sink must be placed at least 1 meter from C-PEC
    - Either inside the C-SCA or directly outside the C-SCA.

Section 5. Facilities and Engineering Controls
5.4 Containment Supplemental Engineering Controls

- **Closed-system drug-transfer device (CSTD):** A drug-transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of HD or vapor concentrations outside the system.
- CSTD:
  - May limit the potential of generating aerosols during compounding.
  - Must not be used as a substitute for a C-PEC when compounding.
  - Should be used when compounding HDs when the dosage form allows.
  - Must be used when administering antineoplastic HDs when the dosage form allows.
  - CSTDs known to be physically or chemically incompatible with a specific HD must not be used for that HD.

Section 5. Facilities and Engineering Controls

5.4 Containment Supplemental Engineering Controls

Photo courtesy of Equashield

https://www.pppmag.com/article/2496

Section 6. Environmental Quality and Control

Environmental wipe sampling for HD surface residue should be performed routinely.

- Surface wipe sampling should include:
  - Interior of the C-PEC and equipment contained in it
  - Pass-through chambers
  - Surfaces in staging or work areas near C-PEC
  - Areas adjacent to C-PECs (floors, staging, and dispensing area)
  - Areas immediately outside the HD buffer room or the C-SCA
  - Patient administration areas
- Common marker HDs that can be assayed include cyclophosphamide, ifosfamide, methotrexate, fluorouracil, and platinum-containing drugs.
  - Example of measurable contamination: cyclophosphamide levels >1.00 ng/cm2,
  - If any measurable contamination is found, the designated person **must** identify, document, and contain the cause of contamination.

Section 7. Personal Protective Equipment

- PPE required for compounding HDs:
  - Chemo Gowns
  - Head cover
  - Hair cover
  - Shoe cover
  - Chemotherapy gloved (two pairs)
- The entity must develop SOPs for PPE based on the risk of exposure and activities performed.
- Appropriate PPE must be worn when handling HDs including during: Receipt, Storage, Transport, Compounding, Administration, Deactivation/decontamination, Cleaning and Disinfecting, Spill control, Waste disposal.

Section 7. Personal Protective Equipment

- **Gloves:**
  - Must meet American Society for Testing and Materials (ASTM) standard D6978
  - Should be worn for handling all HDs
  - Must be powder-free
  - Must be inspected for physical defects before use.
  - For sterile compounding:
    - The outer chemotherapy gloves must be sterile
    - Should be changed every 30 minutes
    - Must be changed when torn, punctured, or contaminated
- **Gowns:**
  - Must be disposable and shown to resist permeability by HDs
  - Must be selected based on the HDs handled
  - Must close in the back (i.e., no open front), be long sleeved, and have closed cuffs that are elastic or knit
  - Must not have seams or closures that could allow HDs to pass through
  - Must be changed per the manufacturer's information for permeation of the gown. If no information - every 2–3 hours or after a spill.
  - Must not be worn to other areas to avoid spreading HD contamination

Section 7. Personal Protective Equipment

- **Head, Hair, Shoe, and Sleeve Covers:**
  - When compounding HDs, a second pair of shoe covers must be donned before entering the C-SEC and doffed when exiting the C-SEC.
  - Shoe covers worn in HD handling areas must not be worn to other areas.
- **Eye and Face Protection:**
  - Must be worn when there is a risk for spills or splashes of HDs or HD waste materials when working outside of a C-PEC.
  - Goggles must be used when eye protection is needed.

Section 7. Personal Protective Equipment

- **Respiratory Protection:**
  - Surgical masks must not be used when respiratory protection is required.
  - For most activities, a fit-tested NIOSH-certified N95 respirator or more is sufficient to protect against airborne particles.
    - No protection against gases and vapors and little protection against direct liquid splashes
  - Appropriate full-facepiece, chemical cartridge-type respirator or powered air-purifying respirator (PAPR) should be worn when there is a risk of respiratory exposure to HDs, including when:
    - Attending to HD spills larger than what can be contained with a spill kit
    - Deactivating, decontaminating, and cleaning underneath the work surface of a C-PEC
    - There is a known or suspected airborne exposure to powders or vapors

Section 7. Personal Protective Equipment

https://www.pppmag.com/article/2253/?search=chemical%20cartridge-type%20respirator

Section 7. Personal Protective Equipment

- **Disposal of Used Personal Protective Equipment**
  - Consider all PPE worn when handling HDs to be contaminated with, at minimum, trace quantities of HDs.
  - All PPE worn during compounding to be disposed of in the proper waste container before leaving the C-SEC.
  - Chemotherapy gloves and sleeve covers worn during compounding must be carefully removed and discarded immediately into a waste container approved for trace contaminated waste inside the C-PEC or contained in a sealable bag for discarding outside the C-PEC.

Section 8. Hazard Communication Program

- Required to establish P&Ps that ensure worker safety during all aspects of HD handling.
- Must develop SOPs to ensure effective training regarding proper labeling, transport, storage, and disposal of the HDs and use of Safety Data Sheets (SDS), based on the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).
- Elements of the hazard communication program plan must include:
  - Written plan that describes how the standard will be implemented
  - All containers of hazardous chemicals must be labeled, tagged, or marked with the identity of the material and appropriate hazard warnings
  - Must have an SDS for each hazardous chemical they use (29 CFR 1910.1200)
  - Must ensure that the SDSs for each hazardous chemical used are readily accessible to personnel during each work shift and when they are in their work areas
  - Personnel who may be exposed to hazardous chemicals when working must be provided information and training before the initial assignment to work with a hazardous chemical, and also whenever the hazard changes
  - Personnel of reproductive capability must confirm in writing that they understand the risks of handling HDs

Section 9. Personnel Training

- Must be trained based on their job functions.
- Must occur before the employee independently handles HDs.
- Competency must be reassessed at least every 12 months.
- Must be trained prior to the introduction of a new HD or new equipment and prior to a new or significant change in process or SOP.
- All training and competency assessment must be documented.
- The training must include at least the following:
  - Overview of entity's list of HDs and their risks
  - Review of the entity's SOPs related to handling of HDs
  - Proper use of PPE
  - Proper use of equipment and devices (e.g., engineering controls)
  - Response to known or suspected HD exposure
  - Spill management
  - Proper disposal of HDs and trace-contaminated materials

Section 10. Receiving

- Should be received from the supplier in impervious plastic to segregate them from other drugs
- Must be delivered to the HD storage area immediately after unpacking.
- PPE, including chemotherapy gloves, must be worn when unpacking HDs.
- A spill kit must be accessible in the receiving area.
- The entity must enforce policies that include a tiered approach, starting with visual examination of the shipping container for signs of damage or breakage (e.g., visible stains from leakage, sounds of broken glass).
- Damaged shipping containers should preferably be transported to a C-PEC designated for nonsterile compounding.
  - Considered spills and must be reported to the designated person and managed.

Section 10. Receiving

Table 4. Summary of Requirements for Receiving and Handling Damaged HD Shipping Containers

If the shipping container appears damaged	• Seal container without opening and contact the supplier • If the unopened package is to be returned to the supplier, enclose the package in an impervious container and label the outer container "Hazardous" • If the supplier declines return, dispose of as hazardous waste
If a damaged shipping container must be opened	• Seal the container in plastic or an impervious container • Transport it to a C-PEC and place on a plastic-backed preparation mat • Open the package and remove undamaged items • Wipe the outside of the undamaged items with a disposable wipe • Enclose the damaged item(s) in an impervious container and label the outer container "Hazardous" • If the supplier declines return, dispose of as hazardous waste • Deactivate, decontaminate, and clean the C-PEC (see *Deactivating, Decontaminating, Cleaning, and Disinfecting*) and discard the mat and cleaning disposables as hazardous waste

Section 11. Labeling, Packaging, Transport and Disposal

Labeling

- HDs identified must be clearly labeled at all times during their transport.
- Personnel must ensure that the labeling processes for compounded preparations do not introduce contamination into the non-HD handling areas.

Packaging

- Must select and use packaging containers and materials that will maintain physical integrity, stability, and sterility (if needed) of the HDs during transport.
- Must protect the HD from damage, leakage, contamination, and degradation, while protecting healthcare workers who transport HDs.
- Must have written SOPs to describe appropriate shipping containers and insulating materials

Transport

- Must be labeled, stored, and handled in accordance with applicable federal, state, and local regulations.
- Must be in containers that minimize the risk of breakage or leakage.
- Must ensure that labels and accessory labeling for the HDs include storage instructions, disposal instructions, and HD category information in a format that is consistent with the carrier's policies

Disposal

- All personnel performing custodial waste removal and cleaning activities must be trained in appropriate procedures
- Disposal of all HD waste, including, but not limited to, unused HDs and trace-contaminated PPE and other materials, must comply with all applicable federal, state, and local regulations.

Section 12. Dispensing Final Dosage Forms

- HDs that do not require any further manipulation, other than counting or repackaging of final dosage forms, may be prepared for dispensing without any further requirements for containment unless required by the manufacturer or if visual indicators of HD exposure hazards are present (e.g., HD dust or leakage).
- Clean equipment should be dedicated for use with HDs and should be decontaminated after every use.
- Tablet and capsule forms of antineoplastic HDs must not be placed in automated counting or packaging machines.

Section 13. Compounding

- Must be compliant with the appropriate USP standards for compounding including <795> and <797>.
- Must be done in proper engineering controls.
- When compounding HD preparations in a C-PEC, a plastic-backed preparation mat should be placed on the work surface of the C-PEC.
  - The mat should be changed immediately if a spill occurs and regularly during use and should be discarded at the end of the daily compounding activity.
  - Equipment for compounding (such as mortars and pestles, and spatulas) must be dedicated for use with HDs.
- Bulk containers of liquid and API HD must be handled carefully to avoid spills.
- APIs or other powdered HDs must be handled in a C-PEC to protect against occupational exposure, especially during particle-generating activities.

Section 14. Administering

- Must be administered safely using protective medical devices and techniques.
  - Protective medical devices: needleless and closed systems.
  - Protective techniques: spiking or priming of IV tubing with a non- HD solution in a C-PEC and crushing tablets in a plastic pouch.
- Appropriate PPE must be worn when administering HDs.
- PPE must be removed and disposed of in a waste container approved for trace contaminated HD waste at the site of drug administration.
- Equipment (such as tubing and needles) and packaging materials must be disposed of properly, such as in HD waste containers, after administration.
- CSTDs must be used for administration of antineoplastic HDs when the dosage form allows. Techniques and ancillary devices that minimize the risk posed by open systems must be used when administering HDs through certain routes.
- If HD dosage forms do require manipulation such as crushing tablet(s) or opening capsule(s) for a single dose, personnel **must** don appropriate PPE and use a plastic pouch to contain any dust or particles generated.

Section 15. Deactivating, Decontaminating, Cleaning, and Disinfecting

- All areas where HDs are handled and all reusable equipment and devices must be deactivated, decontaminated, and cleaned.
  - Sterile compounding areas and devices must be subsequently disinfected.
- P&Ps for cleaning must include procedures, agents used, dilutions (if used), frequency, and documentation requirements.
- Appropriate PPE:
  - Resistant to the cleaning agents used
  - Two pairs of chemotherapy gloves
  - Impermeable disposable gowns
  - Eye protection and face shields must if splashing is likely
  - Respiratory protection must be used, if warranted
- Agents used for deactivation, decontamination, and cleaning should be applied through the use of wipes wetted with appropriate solution.
- All disposable materials must be discarded to meet EPA regulations and the entity's policies.
- Perform cleaning in areas that are sufficiently ventilated.

Section 15. Deactivating, Decontaminating, Cleaning, and Disinfecting

Table 5. Cleaning Steps

Cleaning Step	Purpose	Example Agents
Deactivation	Render compound inert or inactive	As listed in the HD labeling or other agents which may incorporate Environmental Protection Agency (EPA)-registered oxidizers (e.g., peroxide formulations, sodium hypochlorite, etc.)
Decontamination	Remove HD residue	Materials that have been validated to be effective for HD decontamination, or through other materials proven to be effective through testing, which may include alcohol, water, peroxide, or sodium hypochlorite
Cleaning	Remove organic and inorganic material	Germicidal detergent

Section 15. Deactivating, Decontaminating, Cleaning, and Disinfecting

Deactivation

- Renders a compound inert or inactive.
- Residue must be removed by decontaminating the surface.
- There is no one proven method for deactivating all compounds. (EPA-registered oxidizing agents that are appropriate for the intended use)

Decontamination

- Inactivating, neutralizing, or physically removing HD residue and transferring it to absorbent, disposable materials (e.g., wipes, pads, or towels) appropriate to the area being cleaned.
- The work surface of the C-PEC must be decontaminated between compounding of different HDs.
- The C-PEC must be decontaminated at least daily, any time a spill occurs, before and after certification, any time voluntary interruption occurs, and if the ventilation tool is moved.
  - areas under the work tray must be deactivated, decontaminated, and cleaned at least monthly

Cleaning

- A process that results in the removal of contaminants (e.g., soil, microbial contamination, HD residue) from objects and surfaces using water, detergents, surfactants, solvents, and/or other chemicals.
- Cleaning agents used on compounding equipment should not introduce microbial contamination.

Disinfection

- A process of inhibiting or destroying microorganisms.
- Must be done for areas intended to be sterile, including the sterile compounding areas.

Section 16. Spill Control

SPILL CONTROL

- Personnel must receive proper training in spill management and the use of PPE and NIOSH-certified respirators.
- Spills must be contained and cleaned immediately by qualified personnel with appropriate PPE.
- Qualified personnel must be available at all times while HDs are being handled.
- Signs must be available for restricting access to the spill area.
- Spill kits must be readily available in all areas where HDs are handled.
- All spill materials must be disposed of as hazardous waste.
- The circumstances and management of spills must be documented.
- Personnel potentially exposed during the spill or spill clean up or who have direct skin or eye contact with HDs require immediate evaluation.
- Non-employees exposed to an HD spill should follow entity policy, which may include reporting to the designated emergency service for initial evaluation and completion of an incident report or exposure form.
- SOPs must:
  - Be developed to prevent spills and to direct the clean up of HD spills.
  - Address the size and scope of the spill and specify who is responsible for spill management and the type of PPE required.
  - Address the location of spill kits and clean-up materials as well as the capacity of the spill kit.

Section 17. Documentation and Standard Operating Procedures

- SOPs must be reviewed (and documented) at least every 12 months
- SOPs should include:
  - Hazard communication program
  - Occupational safety program
  - Designation of HD areas
  - Receipt
  - Storage
  - Compounding
  - Use and maintenance of proper engineering controls
  - Hand hygiene and use of PPE based on activity
  - Deactivation, decontamination, cleaning, and disinfection
  - Dispensing
  - Transport
  - Administering
  - Environmental monitoring
  - Disposal
  - Spill control
  - Medical surveillance
- Personnel who transport, compound, or administer HDs must document their training according to OSHA standards (OSHA Standard 1910.120) and other applicable laws and regulations.

Section 18. Medical Surveillance

- Medical surveillance is part of a comprehensive exposure control program complementing engineering controls, safe work processes, and use of PPE. Healthcare workers who handle HDs as a regular part of their job assignment should be enrolled in a medical surveillance program.

Questions

Questions

<797> FAQs

November 1, 2022

General

1. Where can I find FAQs and other information on USP Compounding Standards?

For FAQs on USP Compounding Standards, please see below:

- General Chapter <795> *Pharmaceutical Compounding—Nonsterile Preparations*
- General Chapter <797> *Pharmaceutical Compounding—Sterile Preparations*
- General Chapter <800> *Hazardous Drugs—Handling in Healthcare Settings*
- General Chapter <825> *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging*
- Compounded Preparation Monographs (CPMs)

2. Where can I find information about how to interpret and apply General Chapters?

The *General Notices and Requirements* describe the basic assumptions, definitions, and default conditions for the interpretation and application of *USP–NF* content. For example, Section *2.30. Legal Recognition* describes the legal recognition of USP and NF. Section *3.10.30 Applicability of Standards to the Practice of Compounding* describes when USP compounding practice standards are or are not applicable.

Introduction and Scope

3. What is the definition of sterile compounding?

For purposes of General Chapter <797>, sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile medication. However, administration and preparation per the manufacturer's approved labeling are out of the scope of the chapter as described in *1.2 Administration* and *1.4 Preparation Per Approved Labeling*, respectively.

4. To whom do the standards in General Chapter <797> apply?

This chapter applies to all persons who prepare compounded sterile preparations (CSPs) and all places where CSPs are prepared for human and animal patients. This includes, but is not limited to, pharmacists, technicians, nurses, physicians, veterinarians, dentists, naturopaths, and chiropractors in all places including, but not limited to, hospitals and other healthcare institutions, medical and surgical patient treatment sites, infusion facilities, pharmacies, and physicians' or veterinarian practice sites. Any person entering a sterile compounding area, whether preparing a CSP or not, must meet the requirements in *3. Personal Hygiene and Garbing*.

Please note, compounding of sterile hazardous drugs (HDs) must additionally comply with General Chapter <800> *Hazardous Drugs—Handling in Healthcare Settings*.

5. What is considered a compounding facility? Are there requirements that have to be met in order to be considered a compounding facility?

The requirements of the chapter apply to all places where CSPs are prepared for human and animal patients. Additionally, there may be local or federal requirements that must be met.

6. How do I know what are requirements versus recommendations in the chapter?

Generally, requirements in a General Chapter are conveyed by use of the term "must". Recommendations are conveyed by use of the terms "should" and "may".

7. What does "official date" mean?

The USP "official date" indicates the date by which affected users are expected to meet the requirements of a particular standard. Ensuring compliance with the requirements of these standards is the responsibility of the applicable regulatory jurisdiction. USP has no role in enforcement. All text in the United States Pharmacopeia (USP) or National Formulary (NF) that has reached its official date is "official text." Although all text of the *USP–NF* that has reached its official date is "official text," not all official text states requirements with which compendial users must comply. Some official text is intended to assist or guide compendial users or to serve informational purposes.

8. When do the revisions to General Chapter <797> become official?

The revision of <797> published on November 1, 2022, will become "official" on November 1, 2023. The "official date" indicates the date by which affected users are expected to meet the requirements of a particular standard. However, ensuring compliance with the requirements of these standards is the responsibility of the applicable regulatory jurisdiction. Regulatory bodies such as state boards of pharmacy may have a different official date. USP has no role in enforcement.

9. Are the temperatures in the chapter expressed in degrees Fahrenheit or Celsius?

Unless otherwise specified, all temperatures in the *USP–NF* are expressed in degrees centigrade (Celsius) (see also *General Notices 8.180 Temperatures*).

10. Who can be the designated person(s)?

The designated person is one or more individuals assigned by the facility to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of compounded sterile preparations (CSPs). Facilities must determine whether they have one or more designated person(s), select the designated person(s), and determine how to allocate responsibility if there is more than one designated person. The designated person(s) can delegate activities to an assigned trainer provided that is described in the organization's policies.

11. Why were the categories of low-risk, medium-risk, and high-risk CSPs renamed?

In the 2015 proposed revision of *USP* <797>, it was first introduced to change the compounded sterile preparation (CSP) categories from a three-termed format of low-risk, medium-risk, and high-risk to a two-termed format of Category 1 and Category 2. This change was to avoid inaccurately conferring a level of risk to a particular CSP without consideration for all factors that influence the quality of that CSP. Renaming the CSP categories as Category 1 and Category 2, distinguished primarily by the conditions under which they are made and the time within which they are used, is intended to be a neutral designation. The 2021 proposed revision of *USP* <797> added Category 3 which allows compounders who are willing to add additional quality assurance requirements, the ability to assign BUDs longer than Category 2 BUDs.

12. What are Category 3 CSPs?

Category 3 describes CSPs made in a compounding facility that meets additional quality assurance requirements. Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14*, if compounded in accordance with all applicable requirements for Category 3 CSPs in <797>. Category 3 CSPs undergo sterility testing, supplemented by endotoxin testing when applicable, and have more requirements than Category 2 CSPs for personnel qualification, use of sterile garb, use of sporicidal disinfectants, frequencies for environmental monitoring, and determining stability.

13. Does docking and activation of a proprietary bag and vial system for immediate administration in accordance with the manufacturer's labeling instructions have to occur under ISO 5 conditions?

No. Docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for *immediate* administration to an individual patient is not considered compounding and may be performed outside of an ISO Class 5 environment.

14. When does the chapter apply for docking a proprietary bag and vial system?

Docking of the proprietary bag and vial systems for f*uture activation* and administration is considered compounding and must be performed in an ISO Class 5 environment in accordance with <797>, with the exception of *14. Establishing Beyond-Use Dates*. BUDs for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

15. Am I required to keep proprietary bags and vials which have been docked for future activation in a classified cleanroom?

The chapter does not address storage of the docked proprietary bag and vial system, nor does the chapter require it to be stored in a cleanroom suite. The chapter states that docking of the proprietary bag and vial systems for future activation and administration is considered compounding and must be performed in accordance with this chapter, with the exception of *14. Establishing Beyond-Use Dates*. Users should refer to the manufacturer's labeling for storage recommendations.

16. Does the chapter apply for repackaging of a conventionally manufactured sterile product?

Yes, repackaging of a sterile product or preparation from its original container into another container must be performed in accordance with the requirements in this chapter.

17. Is administration out of the scope of the chapter?

Yes. The intent of the chapter is to establish minimum standards for practitioners when compounding sterile products in order to minimize harm, including death, to human and animal patients. The scope of the chapter is intended to ensure a CSP maintains its integrity up until the time when administration begins. Standard precautions such as the Centers for Disease Control and Prevention's (CDC's) safe injection practices apply to administration (see *1.2 Administration*).

18. Does a conventionally manufactured sterile product prepared for administration to a single patient in accordance with manufacturer's approved labeling outside of ISO Class 5 conditions have to be administered within 4 hours of reconstitution or mixing if it meets all the conditions in *1.4 Preparation Per Approved Labeling*?

No. When all of the conditions in *1.4 Preparation Per Approved Labeling* are met, the storage information in the manufacturer's approved labeling may be followed.

19. What is the appropriate BUD to assign when preparing a conventionally manufactured sterile product for administration?

Preparation of a single dose of a conventionally manufactured sterile product in accordance with the approved labeling that includes information about the diluent to be used, the resultant strength, storage time, and container closure system is not considered compounding and these preparations are not subject to the BUD limits in the chapter. The BUD provided in the approved labeling may be assigned to these preparations when the labeling contains the required information mentioned above. (See *1.4 Preparation per Approved Labeling*).

20. Is withdrawing a dose from a container of a conventionally manufactured sterile product or spiking an IV bag, without any further manipulation, for immediate administration to a patient considered compounding?

No, withdrawing a dose from a container or spiking an IV bag of a conventionally manufactured sterile product without any further manipulation is considered administration rather than compounding and is out of the scope of <797>. If the dose is further mixed with another product, it would be considered compounding and subject to the requirements of <797>.

21. Is spiking IV fluids (taking IV spikes and putting them into a bag; putting a set into an IV bag) considered compounding?

No, a facility's policies and procedures regarding spiking IV fluids is outside the scope of the chapter.

22. When compounding immediate-use CSPs, may more than three individual containers of a sterile product be used?

The immediate-use CSPs provision states that the preparation must not involve more than 3 different sterile products. Two or more of the same sterile components (product) may be used as long as there are not more than three different sterile components (products). For example, two vials of the same component (drug product) are reconstituted using two vials of *Sterile Water for Injection* (component products) and added to a single component product intravenous diluent bag such as NS or D5W. As another example, when the CSP requires combining 4 vials of the same component (drug product) into a single component product intravenous bag of diluent, only 2 different sterile components (products) are used to prepare the CSP. Both examples may be considered immediate- use as long as the criteria listed in *1.3 Immediate-Use CSPs* are met.

23. Are COVID-19 vaccines limited by the 4-hour immediate-use BUD or can the BUD from the manufacturer be used?

As long as the approved labeling or supplemental materials provided by the product's manufacturer includes information for the diluent, the resultant strength, the container closure system, and storage time, then this would be considered *1.4 Preparation Per Approved Labeling* and is not considered compounding.

24. Can a single-dose container be used to prepare doses for more than one patient when compounding an immediate-use CSP?

No. One of the conditions of the immediate-use CSP provision specifies that any unused starting components from a single-dose container must be discarded after preparation for the individual patient is complete. Single-dose containers must not be used for more than 1 patient when used for preparing immediate-use CSPs.

25. Why does the immediate-use CSP provision allow for administration to begin within 4 hours following the start of the preparation?

The immediate-use CSP provision was revised to allow up to 4 hours for beginning administration to balance the need for ensuring CSP quality with timely access to medication in a variety of healthcare settings. The allowance of up to 4 hours was based on the 4-to-6-hour lag phase of microbial growth, during which potential bacterial cells are adjusting to their environment and change very little, and they do not immediately start reproducing.[1] In the event bacterial cells were inadvertently introduced into a CSP during compounding, replication is unlikely and therefore there is a window of time in which a CSP can be held prior to administration.

[1] References:

- Daquigan N et al. Early recovery of *Salmonella* from food using a 6-hour non-selective pre-enrichment and reformulation of tetrathionate broth. *Front Microbiol*. 2016;7:2103.
- Jarvis, Basil. *Statistical Aspects of the Microbiological Examination of Foods, Third Edition*. Academic Press, 2016.
- Ryan, Kenneth et al. *Sherris Medical Microbiology, Sixth Edition*. McGraw-Hill Education, 2014.
- Wang J et al. A novel approach to predict the growth of *Staphylococcus aureus* on rice cake. *Front Microbiol*. 2017;8:1140.

26. Is it considered compounding if the steps used to prepare a single dose of a conventionally manufactured product are different from the directions contained in the manufacturer's approved labeling?

Yes. Any compounding (e.g., mixing, reconstituting) that is not performed according to the manufacturer's approved labeling is considered sterile compounding and is subject to the requirements in the chapter.

27. What information is needed to meet the requirements of Section *1.4 Preparation Per Approved Labeling?*

The approved labeling or supplemental materials provided by the product's manufacturer, including information for the diluent, the resultant strength, the container closure system, and storage time.

28. Does the chapter address compounded radiopharmaceutical dosage forms?

No. Compounding of radiopharmaceuticals is not required to meet the standards of this chapter as they are subject to the requirements in General Chapter <825> *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging*.

29. Do pharmaceutical manufacturers have to comply with <797>?

No. Manufacturers must comply with FDA's current good manufacturing practices (CGMP) and/or laws and regulations of the applicable regulatory jurisdiction.

30. What is the difference between compounding and what is described in *1.4 Preparation Per Approved Labeling*?

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer if the product is prepared as a single dose for an individual patient and the approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

31. Where may Category 1 CSPs be prepared?

Category 1 CSPs must be prepared in a primary engineering control (PEC) that may be placed in an unclassified segregated compounding area (SCA) or a cleanroom suite.

32. What qualifications must a designated person have?

This must be determined by the facility's SOPs. Some states and accreditation organizations have more specific guidance.

33. Is the use of technology other than what is listed in the chapter allowed?

The introduction and scope section outlines the use of technologies, techniques, materials, and procedures not specifically covered by the chapter, as it would be impossible for this chapter to address all of the current technology on the market and potential for new technology coming to market in upcoming years after release of the finalized chapter. It is important that the technology that is being used as indicated in the manufacturers approval documentation or if it is being used for a different intended purpose that it is validated for that purpose. This ensures that any use of technology does not bypass any safety requirements within the chapter itself and meets or exceeds those requirements. *USP* chapters <1223> and <1225> can assist compounders in this validation process.

34. What is USP's position on drug vial optimization (DVO)?

USP <797> does not address drug vial optimization (DVO). The organization would need to determine if the process used is noninferior to the requirements of the chapter.

35. Will there be any future USP guidance on the use of technology in compounding?

The Compounding Expert Committee will consider the development of future resources or a standard related to the use of technology in compounding. The introduction and scope section of <797> outlines the use of technologies, techniques, materials, and procedures not specifically covered by the chapter, as it would be impossible for this chapter to address all of the current technology on the market and potential for new technology coming to market in upcoming years after release of the finalized chapter. It is important that the technology that is being used as indicated in the manufacturers approval documentation or if it is being used for a different intended purpose that it is validated for that purpose. This ensures that any use of technology does not bypass any safety requirements within the chapter itself and meets or exceeds those requirements. *USP* chapters <1223> and <1225> can assist compounders in this validation process.

36. If a device (e.g., a repeater pump) has undergone validation by the FDA, is the compounder required to verify the volumetric accuracy each day of use?

Yes. Before using automated compounding devices or other similar equipment, compounding personnel must conduct an accuracy assessment before the first use and again each day the equipment is used to compound CSPs.

37. Are albumin, IVIG, etc., included as part of "blood-derived and other biological materials" in Section *1.1.2*?

No. These commercial products have been processed by the manufacturer to be sterile. Blood or biological materials derived directly from a patient are not sterile.

38. Do facilities have to change their standard operating procedures (SOPs) and practices for immediate-use from 1 h to 4 h?

No, facilities may choose to maintain the 1-hour limit for administration of immediate-use CSPs, however increasing the time to 4 hours would be considered acceptable.

39. Can immediate-use CSPs be made in a batch for more than one patient?

Compounders can prepare multiple doses of immediate-use CSPs intended for use in one or more patients in a single batch as long as the conditions in Section *1.3* are met.

40. What does "directly administered" mean in *1.3 Immediate-Use CSPs*?

"Directly administered" refers to the dose being prepared and then immediately administered by the person who prepared it, or administration is witnessed by the person who prepared it. In a situation where a CSP may be prepared for direct and immediate administration there is risk involved if a CSP is unlabeled and the person who compounded it is not administering or present for the administration.

41. What are the training and competency assessment requirements for personnel who only prepare immediate-use CSPs?

Training and competency assessment requirements are determined by the specific tasks performed and the facility's SOPs, and must include aseptic processes to minimize the potential for contact with nonsterile surface surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products or CSPs.

42. How often does the training and competency of personnel who perform immediate-use products need to be performed?

Section *1.3 Immediate-Use CSPs* requires that personnel are trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs. No specific frequency is identified for training and competency of personnel who perform compounding of immediate-use CSPs.

43. Is the use of dispensing pins allowed per <797>?

The chapter does not address the use of specific disposable supply items other than to say supplies in direct contact with the CSP must be sterile and depyrogenated. It is the responsibility of the facility to determine the appropriateness of specific items, including dispensing pins.

Personnel Training and Evaluation

44. Section *2.1 Demonstrating Knowledge and Competency of Core Skills* states that personnel must complete training and be able to demonstrate knowledge of principles initially and at least every 12 months. Does this mean that each person needs written or electronic testing on each of the listed topics in addition to competency testing?

The written training program must describe the required training and the process for evaluating the performance of personnel, but personnel must both demonstrate knowledge of principles and competency of skill for performing sterile manipulations and achieving and maintaining appropriate environmental conditions as applicable to their assigned job functions.

45. Must cleaning staff or personnel who restock the cleanroom undergo the same training as compounders?

Personnel who only perform restocking or cleaning and disinfecting duties outside of the primary engineering control (PEC) must be initially trained and demonstrate competency in maintaining the quality of the environment in which they are performing their assigned task. At a minimum, these personnel must meet the requirements for personal hygiene and garbing that are described in *3. Personal Hygiene and Garbing*. Facility SOPs must outline what initial and ongoing training is required.

46. Must vendors and certifiers be trained before entering the cleanroom?

Section *1.1.3* specifies that any person entering a sterile compounding area, whether preparing a CSP or not, must meet the requirements in *3. Personal Hygiene and Garbing*. Facility SOPs must outline specific requirements.

47. Do supervising pharmacists that do not compound have to undergo training and evaluation?

Yes. The following must be included:

1. **Core skills:** <797> requires that personnel who do not compound, but supervise compounding personnel, have to be trained and demonstrate competency initially and at least every 12 months as outlined in Section *2.1 Demonstrating Knowledge and Competency of Core Skills*.
2. **Garbing Competency:** Initially and at least every 12 months.
3. **Aseptic Manipulation Competency:** Personnel who have direct oversight of compounding must complete an aseptic manipulation competency evaluation at least every 12 months. The evaluation should correspond to the type of activities of the personnel they oversee but does not require the same quantities.

48. Compounding independently is mentioned multiple times. Does that mean someone can compound for patients before passing testing as long as they are observed? Is this left entirely to SOPs?

Before beginning any compounding (independently or with supervision), personnel must successfully complete the initial garbing competency. Additionally, all personnel entering a compounding area must abide by *3. Personal Hygiene and Garbing*. The process of developing competency requires practice. Each compounding facility must develop a written training program that outlines what is permitted.

49. How many gloved fingertip and thumb sampling tests and media-fill tests must be done initially and subsequently?

In the revised chapter gloved fingertip and thumb samplings are taken during both the aseptic manipulation competency (i.e., immediately after media-fills) and the garbing competency evaluation (i.e., after garbing and gloving). The complete garbing competency evaluation, including gloved fingertip and thumb sampling, must be successfully completed no fewer than 3 separate times initially, and only 1 time on subsequent evaluations. All aseptic manipulation competency evaluations, including media-fill and gloved fingertip and thumb sampling after media-fill, must be successfully completed 1 time for the initial and 1 time for all subsequent evaluations.

50. What is the purpose of the increased frequency of the garbing competency?

Personal hygiene and garbing are essential to maintain microbial control of the environment. Most microorganisms detected in cleanrooms are transferred from individuals. Preparation of compounded sterile preparations by personnel who lack proper training and competency may result in increased contamination risk and potentially poor outcomes for patients. Preventing contamination by ensuring personnel are trained and competent is more impactful than detecting contamination through sampling methods.

51. Is documentation of gloved fingertip and thumb sampling and media-fill testing only required when results exceed action levels?

No. All results of the evaluations must be documented and maintained to provide a record and long-term assessment of personnel competency. Documentation must at a minimum include the name of the person evaluated, evaluation date/time, media and components used including the manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

52. If compounding personnel fail media-fill testing or gloved fingertip and thumb sampling, are they required to stop compounding until corrective action and reevaluation have been completed?

General Chapter <797> chapter does not require compounding personnel to cease compounding, however, the facility must evaluate the cause of failure and determine appropriate corrective actions. The results of the evaluation and corrective action must be documented, and the documentation must be maintained to provide a record and long-term assessment of personnel competency. General Chapter <797> describes gloved fingertip and thumb sampling and media-fill testing in Sections *2.2 Demonstrating Competency in Garbing* and *Hand Hygiene* and *2.3 Competency Testing in Aseptic Manipulation*, and required documentation in *20. Documentation*.

53. Why are incubation conditions different for media-fill testing, gloved fingertip and thumb sampling, and environmental air and surface sampling?

Environmental air and surface samples and gloved fingertip and thumb samples are incubated at a high temperature 30°–35° for no less than 48 h and then a low temperature 20°–25° for no less than 5 additional days. Incubation at a lower temperature first may compromise recovery of Gram-positive cocci which are often associated with humans. The incubation conditions are consistent with General Chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*. Media-fill test samples are incubated for a longer period, 7 days each at two temperatures, 20°–25° and 30°–35° to detect a broad spectrum of microorganisms. The order of the incubation temperatures must be described in the facility's SOPs.

54. Why must a higher incubation temperature be used first for gloved fingertip and thumb sampling, and environmental air and surface sampling?

Incubating gloved fingertip and thumb samples, and environmental air and surface samples at a higher incubation temperature first helps recover bacteria first. Incubation at a lower temperature first may compromise recovery of Gram-positive cocci which are often associated with humans.

55. If the controlled room temperature is 20-25°, can the samples be incubated without an incubator?

No. Samples must be incubated in an incubator

56. Do the three initial gloved fingertip tests need to be done on the same day?

Not necessarily. The organization can determine the interval for the three initial gloved fingertip tests. In any case, these need to be three separate instances of hand hygiene, garbing, and the gloved fingertip test. Garbing once and completing three sets of gloved fingertip tests does not meet the requirement for the initial testing. The 3 successful completions must be in succession—failure of any of the 3 initial garbing competency evaluations requires repeat testing until personnel successfully complete 3 evaluations in a row.

57. Are personnel who only prepare immediate-use CSPs required to perform media-fill testing?

No, but the facility's SOPs must determine how their competency will be evaluated. When specific conditions in <797> are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 CSPs. Personnel must be trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs. The competency should include appropriate preparation (e.g., hand washing, cleaning the area that will be used) and technique that is evaluated and approved by a qualified individual.

58. Can gloved fingertip testing be done more frequently than what is in the chapter?

The chapter provides minimum compounding standards. Compounders can implement more frequent sampling if they deem it appropriate for their facility.

59. Media used for media-fill test doesn't filter easily and personnel may need to use additional filters for the media-fill test than used for the actual batch. Is this acceptable?

Yes. Additional filters may be used as necessary for the media-fill test. Using a pre-filter may help maximize the volume of the sterilizing filter. A filter integrity test (e.g., bubble point test) must be performed on all sterilizing filters used during media-fill testing.

60. Does the ongoing garbing competency include gloved fingertip and thumb sampling (GFT) after the visual observation of garbing?

Yes. Performing GFT after the visual observation of garbing ensures personnel can don sterile gloves without contaminating them.

61. Describe how to appropriately handle and store samples for media-fill testing, including the right temperature.

All samples must be incubated for 7 days each at two temperatures, 20°–25° and 30°–35°, to detect a broad spectrum of microorganisms. The order of the incubation temperatures must be described in the facility's SOPs. If sending samples to the laboratory for incubation, samples must be sent as soon as possible (e.g., within 24 h) for the most accurate results. Samples must be protected from damage as well as temperature and humidity extremes during transit. Refer to <1117> *Microbiological Best Laboratory Practices* for additional information.

62. How many personnel are allowed in the buffer room or SCA during media-fill testing?

Media-fill testing must simulate the most difficult and challenging aseptic compounding procedures encountered by the person, and it must capture all elements that could potentially affect the sterility of the CSP. The chapter does not specify the exact number of personnel in the buffer room or SCA, but it must simulate the conditions encountered by the compounder.

Personal Hygiene and Garbing

63. What is the order and location of garbing?

General Chapter <797> does not specify the order and location of garbing. The order and location of donning and doffing each article of required garb would depend on the type of garb used (e.g., sterile gowns) and the placement of the sink (e.g., if the sink is located inside or outside of the anteroom). The garbing order, location, and donning/doffing each article of required garb must be determined by the facility and documented in the facility's SOP. For example, if a sink is located outside of the anteroom, a facility's garbing policies and procedures may indicate that certain garb would be donned outside of the anteroom to more easily transition into hand hygiene procedures. Garb must be donned and doffed in an order that reduces the risk of contamination. Please note, sterile gloves must be donned in a classified room or SCA. Skin must not be exposed inside the ISO Class 5 PEC (e.g., gloves must not be donned or doffed inside the ISO Class 5 PEC exposing bare hands).

64. Can donning and doffing activities by different personnel occur in the same room at the same time?

The chapter recommends (but does not require) that donning and doffing not occur in the anteroom or the segregated compounding area (SCA) at the same time. Personnel must be aware of activity in the room to ensure that the integrity of garb is not compromised. For example, if one person is performing hand hygiene while another is donning a gown, personnel must consider the risk of contaminating the gown (e.g., from potential splashing).

65. What are examples of methods to cover jewelry that cannot be removed?

Examples of jewelry that cannot be removed are dermal piercings (also known as a microdermal piercing), which is a piercing that is held in place with a dermal anchor that is installed underneath the skin. Facilities must determine the appropriate method for covering dermal piercings to minimize the risk of contaminating the CSP and the environment. For example, depending on the location of the piercing, an adhesive bandage or head cover may be used to cover the jewelry.

66. Are wedding rings permitted to be worn under sterile gloves?

The chapter requires removing all hand jewelry that could interfere with the effectiveness of garbing or otherwise increase the risk of contamination of the CSP. Wedding rings may potentially compromise the integrity of the glove (e.g., tearing) and prevent adequate hand hygiene.

67. Are eyelash extensions allowed in the cleanroom?

No. Cosmetics are not permitted.

68. What accommodations can the designated person allow with regards to garbing in the cleanroom?

The designated person(s) may permit accommodations to personnel preparation as long as the quality of the CSP and environment will not be affected. Accommodations must be documented.

69. Must the accommodation to personnel preparation be documented each time or just once?

The accommodation must be documented per the facility's SOPs and *20. Documentation*.

70. Are 3 pairs of gloves required for using a compounding aseptic isolator (CAI) or compounding aseptic containment isolator (CACI)?

No, if using a CAI or CACI, the chapter recommends disposable gloves to be worn inside gloves attached to the restricted-access barrier system (RABS) sleeves. However, the chapter requires sterile gloves to be worn over the gloves attached to the RABS sleeves. The use of disposable gloves inside of gloves attached to the RABS sleeve is intended to maintain the cleanliness of the gloves attached to the RABS sleeve which may collect sweat or other touch contaminants. Sterile gloves outside of the gauntlet gloves help minimize the risk of contamination to the environment and the CSP.

71. If I am compounding Category 1 CSPs in an SCA, do I have to wear the same garb as when compounding Category 2 CSPs in a cleanroom suite?

Yes. Minimum garbing requirements are not stratified based on facility design. The chapter lists the minimum garbing requirements to protect the CSP and the environment. Sterile gloves are required for preparing CSPs inside an ISO Class 5 PEC.

72. Can gowns be re-used?

Yes. If compounding Category 1 and Category 2 CSPs, gowns used for nonhazardous compounding may be reused within the same shift by the same person if the gown is maintained in a classified area or adjacent to, or within, the SCA in a manner that prevents contamination. Garb must be replaced immediately if it becomes visibly soiled or if its integrity is compromised. Additionally, gowns and other garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing).

73. Regarding Section *3.1*, gum-chewing and mints are considered food. Why can't compounders have anything in their mouths or put anything in their mouths while in the cleanroom suite?

It is too easy to want to blow bubbles or move gum and candy around in the mouth that could spew additional wet into the mask and contaminate it. The candy or gum can also fall out of the mouth, out of the mask and onto a hood counter or floor and contaminate the area.

74. Why is the use of brushes not allowed for hand hygiene?

The practice of using a brush to scrub hands in hand-antisepsis can damage skin of personnel and result in an increase of bacteria shed from the hands. The CDC recommended discontinuing the use of the brushes and the brush side of scrub/sponge brushes in 2002. See the CDC Guideline for Hand Hygiene in Health-Care Settings, Morbidity and Mortality Weekly Report, October 25, 2002, 51(RR16); 1-44.

75. Where should I garb when preparing Category 1 CSPs in an SCA?

Sections *3.2* and *3.3* outline the requirements for hand hygiene and garbing for Category 1. The order of hand washing and garbing depends on the placement of the sink, is determined by the facility, and is documented in the facility's SOPs.

An example garbing procedure in a facility that has a sink in the SCA is as follows:

1. The compounder enters the SCA and dons head, face, and shoe covers in an order determined by the facility and documented in the facility's SOPs.
2. The compounder washes their hands then dons a gown.
3. The compounder applies alcohol-based hand rub to all surfaces of hands and fingers and allows hands to dry thoroughly then dons sterile gloves.

76. When sterile garb is required, does the equipment, such as goggles or PAPRs, need to be sterile as well?

No. Sterile garb is limited to powder-free gloves when compounding Category 1, 2, and 3 CSPs, and low-lint garb when compounding Category 3 CSPs. Facilities must have an SOP describing the disinfection procedures for reusable equipment.

77. For which categories must the facility's SOPs describe disinfection procedures for reusing goggles, respirators, and other reusable equipment?

For Category 1, 2, and 3 CSPs, the facility's SOPs must describe disinfection procedures for reusing goggles, respirators, and other reusable equipment.

78. When must laundering be performed with a validated cycle?

For facilities that compound Category 3 CSPs, laundered sterile garb must not be reused without being laundered and resterilized with a validated cycle. The facility's SOPs must describe this process.

79. When should I apply sterile 70% IPA to gloves?

Application of sterile 70% IPA to gloves must occur immediately before compounding (e.g., before entering the ISO Class 5 PEC) and regularly throughout the compounding process.

80. Do conditions such as dandruff, eczema, or psoriasis exclude someone from compounding CSPs?

These are all conditions that could cause someone to be at higher risk for contaminating a CSP or the environment so they must be reported to the designated person(s). The designated person(s) is responsible for evaluating the situation and making a decision on whether the affected person must be excluded from working in compounding areas until the condition is resolved.

Facilities and Engineering Controls

81. Why must the HEPA filter be located in the ceiling of the buffer and anterooms?

Placement of HEPA filters in the ceiling eliminates the potential for post-filtration contamination of the air stream. Air distribution systems with duct-mounted HEPA filters are susceptible to introduction of unfiltered air into the airstream after the air is filtered. HEPA filter placement in the ventilation duct is difficult to leak test and susceptible to contamination, especially in the event of water leakage or other breaches. Ceiling mounted filters help facilitate testing and servicing.

82. Why are CAIs and CACIs required to be placed in an ISO Class 7 buffer room with an ISO Class 8 anteroom for preparing Category 2 CSPs?

The PEC must be located in a controlled environment for preparing Category 2 CSPs to minimize the risk of contamination. Movement of materials in and out of the RABS (e.g., CAI or CACI) in unclassified air carries a higher risk of contamination. Placement of the RABS in a classified area mitigates the risk of inadvertent contamination of CSPs with the longer BUDs that are permitted for Category 2 CSPs.

83. Does the integrated vertical laminar flow zone (IVLFZ) require 100% HEPA filter coverage in the ceiling? Can returns be under the worktable?

In the IVLFZ, unidirectional airflow is created by placing HEPA filters over the entire surface of the worktables and by effective placement of air returns. Strategic location of air returns in addition to full coverage of HEPA filters above the work surface is required. Specific location of the air returns is not specified. Both static and dynamic smoke studies verifying a continuous flow of HEPA-filtered air void of turbulence, dead air zones, and refluxing from the HEPA filters to and across the entire work area and to the air returns must be documented (e.g., with video). [Note—Dynamic airflow smoke pattern tests have shown that it is difficult to achieve this type of design and also achieve and maintain unidirectional airflow under dynamic operating conditions.]

84. Can a containment ventilated enclosure (CVE) be used for presterilization procedures (e.g., weighing, mixing nonsterile components)?

Presterilization procedures must be performed in a single-use containment glove bag, CVI, BSC, or CACI to minimize the risk of airborne contamination.

85. When pass-through chambers are used, do the doors have to be interlocking?

The chapter recommends that pass-through doors be interlocking. However, if a pass-through is used, both doors must never be opened at the same time.

86. How often are visual smoke studies performed (e.g., in rooms where air returns are not located low on the wall)?

Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow. This smoke study along with environmental monitoring must be repeated whenever a change is made to the placement of equipment within the room or any other alteration is performed within the cleanroom suite that affects the quality of the air (e.g., HVAC alterations, change of HEPA filter units). A visual smoke study uses a visible source of smoke, which is neutrally buoyant, to verify an absence of stagnant airflow where particulates can accumulate in ISO Class 7 and ISO Class 8 rooms that do not have unidirectional airflow.

87. What is the difference between a pharmaceutical isolator and a RABS (i.e., a CAI or CACI)?

Unlike RABS, pharmaceutical isolators are different in that they contain 4 major elements: controlled workspace, transfer device, access device, and a decontamination system. A pharmaceutical isolator is equipped with a generator that distributes a sporicidal disinfectant throughout the chamber. If the isolator is used to prepare Category 2 CSPs, it must be placed in an ISO Class 8 or better positive-pressure room. In contrast, if a CAI or CACI is used to prepare Category 2 CSPs, the CAI or CACI must be placed in a cleanroom suite with an ISO Class 7 or better positive-pressure buffer room with an ISO Class 8 or better positive-pressure anteroom.

88. Can Magnehelic gauges be used for monitoring pressure differentials?

Yes, Magnehelic gauges may be used to monitor pressure. The quantitative results from the pressure monitoring device must be reviewed and documented at least daily on the days when compounding is occurring. Users should note that Magnehelic gauges do not warn or alert personnel to events where there is a loss of pressure whereas there are other pressure monitoring systems may have audible or visible alarms.

89. Why are sinks allowed to be placed outside of the anteroom? Does the sink placement in <797> contradict the sink placement requirements in <800>?

In facilities with cleanroom suites, the sink used for hand hygiene may be placed either inside or outside of the anteroom. If the sink is located outside of the anteroom, it must be located in a clean space to minimize the risk of bringing in contaminants into the anteroom. Sinks are permitted outside of the anteroom to offer more flexibility to the cleanroom design and help minimize the risk of contamination from water sources to the classified areas. In facilities preparing hazardous drugs (HDs) in a cleanroom suite, General Chapter <800> requires the sink to be placed in the anteroom at least 1 meter away from the entrance of the HD buffer room to avoid contamination migration into the negative-pressure HD buffer room. There are no conflicts for the sink placement in <797> and <800>. Facilities compounding sterile HDs must meet the requirements in both <797> and <800>.

90. Is an SCA required to be in an enclosed room (i.e., walls and doors)?

No. An SCA is defined as a designated, unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of only Category 1 CSPs.

91. Why do I need a line of demarcation in the anteroom?

The line of demarcation serves to create visible separation between the clean and dirty sides of the anteroom. Distinguishing the "dirty" side of the anteroom from the "clean" side ensures all personnel abide by the garbing and material transfer procedures defined by the sterile compounding organization's SOPs. The line of demarcation signifies the locations where specific contamination control principles are implemented to aid in decreasing the number of particles introduced into the buffer room. The facility may choose where the line of demarcation is located. Please note, the anteroom is entered through the dirty side, and the clean side is the area closest to the buffer room (see Section *4.2 Facility Design and Environmental Controls*). Facilities may also utilize a design with two physically separate anterooms, one clean and one dirty.

92. Can presterilization procedures (e.g., weighing) be performed in an unclassified environment?

Yes. Presterilization procedures can be performed in unclassified environments for Category 1 CSPs. For Category 2 and Category 3 CSPs, presterilization procedures must be completed in an ISO Class 8 or better environment (e.g., anteroom or buffer room) wherein the compounder uses a containment device (e.g., single-use containment glove bags, containment ventilated enclosure (CVE), BSC, or CACI) to minimize the risk of airborne contamination.

93. In an SCA, can the sink be in the same area or room?

The sink needs to be accessible to the compounding area. It can be inside the area defined as the SCA but cannot be closer than 1 meter to the PEC. That distance is intended to ensure that splashes do not reach the PEC.

94. How can the garbing location be in a classified area with a sink outside the anteroom?

The order of garbing must be determined by the facility and documented in the facility's SOPs. If hand hygiene is completed outside of a classified area, alcohol-based hand rub must be used prior to donning garb. Hands must also be sanitized with alcohol-based hand rub before donning sterile gloves.

An example garbing procedure in a facility that has a sink outside the anteroom is as follows:

1. The compounder washes their hands in the sink located outside of the anteroom.
2. The compounder enters the anteroom and applies alcohol-based hand rub to all surfaces of hands and fingers and allows hands to dry thoroughly.
3. The compounder dons garb in an order determined by the facility and documented in the facility's SOPs.
4. Before donning sterile gloves, hands are re-sanitized with alcohol-based hand rub and allowed to dry thoroughly.

95. What types of biological safety cabinets (BSCs) are appropriate for compounding?

A BSC is a ventilated cabinet that is typically used for compounding hazardous sterile and nonsterile preparations but may be used to compound nonhazardous sterile and nonsterile preparations as well. BSCs are divided into three general classes (Class I, Class II, and Class III). Class II and Class III BSCs provide an ISO Class 5 environment so are suitable for sterile compounding. Class II BSCs are further divided into types (Type A1, Type A2, Type B1, Type B2, and Type C1). Class I BSCs are suitable for nonsterile compounding only. A BSC used for hazardous drugs must exhaust to the outdoors.

Nonsterile Non-HD	Nonsterile HD	Sterile Non-HD	Sterile HD
Class I, II, or III	Class I, II, III Must exhaust to outdoors	Class II, III	Class II, III Must exhaust to outdoors

96. What are the requirements for temperature and humidity for an SCA?

There are no specific requirements for temperature or humidity in an SCA, but it is reasonable to use the requirements for a cleanroom suite as guidance. However, if drugs or supplies are stored in the SCA, there may be other USP, FDA, or manufacturer/supplier requirements. See *USP* <659> for additional information on storage requirements for drugs.

97. May personnel reach across the perimeter of the SCA to access supplies without actually stepping over the perimeter?

The chapter requires that when personnel exit the compounding area, garb, except for gowns, cannot be reused. At minimum, this would require changing the affected garb (e.g., gloves).

98. May an anteroom be shared between a Category 2 and Category 3 buffer room?

Yes.

99. May an anteroom be shared between an HD and non-HD buffer room?

Yes.

Certification and Recertification

100. Is certification of the compounding area required to be performed using the current Controlled Environment Testing Association (CETA) *Certification Guide for Sterile Compounding Facilities*?

Before a compounding area is used to compound either Category 1, Category 2, or Category 3 CSPs, it must be independently certified using the requirements in this chapter and when applicable, manufacturer specifications. Facilities must determine the appropriate certification guide to use for certifying their compounding area.

101. What is ASHRAE?

The American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) is a professional organization that provides certification (including healthcare facility design) and professional development for engineers in this field.

102. What is CETA?

The Controlled Environment Testing Association is a professional organization for controlled environment certification personnel that provides certification (including Registered Certification Professional – Sterile Compounding Facilities), education, and resources for certification personnel.

103. A facility may have several cleanrooms under the same corporate structure (e.g., within a healthcare system) but state law requirements may require separate licenses for each compounding area. Are personnel that float between the different cleanrooms required to complete training and competency at each location if they are working in the same type of primary and secondary engineering controls?

This is in the purview of the state board of pharmacy and outside the scope of <797>. The chapter requires that each compounding facility develop a written training program that describes the required training, the frequency of training, and the process for evaluating performance. This program must equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks. The facility's SOPs should specify the training required for such tasks, and training and evaluation of personnel must be documented.

104. Regarding 'dynamic operating conditions', what does "the largest number of personnel and highest complexity" mean as it relates to certification of ISO-classified areas?

This refers to testing in a particular ISO-classified area (e.g., ISO Class 5 PEC, ISO Class 7 buffer room). The highest number of personnel that would be expected to work in a PEC and/or SEC should be present and performing the highest complexity of compounding expected including use of compounding equipment and performance of particle-generating activities (e.g., pre-sterilization activities such as weighing and mixing powders). Testing under dynamic operating conditions is required for particle testing of ISO-classified areas, air changes per hour (ACPH) of ISO-classified rooms, and some types of smoke studies.

Microbiological Air and Surface Monitoring

105. Why has the frequency of surface sampling changed?

Surface sampling was previously required "periodically", which was interpreted differently by users (e.g., monthly, quarterly, or biannually). The change requiring minimum frequencies based on the category of CSP the facility compounds is intended to provide an additional measure of control and monitoring in between viable air monitoring and certification requirements. Regular surface sampling provides additional data for trending and allows for monitoring of contamination risks.

106. How many microbiological air and surface samples are required based on the size of classified areas?

Microbiological air and surface testing must be conducted in all classified areas to confirm that the required environment quality is maintained. The microbiological air and surface sampling must be facility-specific and must be described in the facility's SOPs. The chapter does not specify a minimum number of air or surface samples based on the size of the room, however, the International Organization for Standards (ISO) 14644-1:2015(E) Table A.1 – 'Sampling locations related to cleanroom area' states the area of a cleanroom (m^2) and the minimum number of sampling locations to be tested (N_L) that are necessary for certification. Facilities must determine the appropriate number of locations and select the locations of sampling based on their relationship to the activities performed in the area.

107. Do microorganisms need to be identified to the genus level regardless of action level?

No. An attempt must be made to identify any microorganisms recovered to the genus level if the levels measured during sampling exceed the action levels in the chapter.

108. What is the rationale for only requiring an attempt to identify any microorganisms recovered to the genus level if the levels measured during sampling exceed the action levels in the chapter?

In some instances, microorganisms cannot be identified to the genus level because the microorganism is no longer viable, or if a mold, it may not be producing the reproductive structures necessary for identification. In these instances, the genus may not be identified, but the chapter does require than an attempt be made to identify the microorganism to the genus level.

109. Is changing HEPA filters considered "servicing facilities or equipment" for the purposes of requiring microbiological air and surface monitoring?

Yes, changing HEPA filters in the ceiling would require microbiological air and surface sampling because there is potential for unclassified air to enter the cleanroom. Changing HEPA filters in the ISO Class 5 PEC would also require microbiological air and surface sampling to ensure the PEC is operating as expected. Changing prefilters for the ISO-classified rooms and PECs usually would not require additional sampling because the downstream HEPA filter remains intact.

110. If two media samples are collected at a single location, how are the colony-forming units (CFU) counted?

If a facility were to choose to utilize two different media devices for sampling, they would sample each location according to their sampling map using both devices (e.g., TSA and MEA). If each device at one location demonstrates growth, the CFU are counted separately. For example, if a TSA plate grows 5 CFU and the MEA plate at the same location grows 3 CFU, the CFU would be recorded separately as 5 CFU and 3 CFU for the respective plates. The count would NOT be recorded as 8 CFU.

111. Is a self-enclosed robotic device different than a "closed RABS" as used in <1211?>? When should surface sampling occur in a self-enclosed robotic device?

This verbiage "self-enclosed robotic device" was specifically used in <797> as there are robotic enclosures on the market that do not meet the definition of a closed-RABS, whereas some would meet this definition. For self-enclosed robotic devices that meet the definition of closed-RABS, it would be detrimental to the air quality inside the device to surface sample at the completion of each batch. Therefore, the requirement for these specific devices is to be conducted at least once daily at the end of compounding operations. This is generally when the device is opened for cleaning and disinfecting.

112. May settle plates be used in place of an impaction air sampler for viable air sampling?

No. An impaction air sampler must be used to collect 1 cubic meter or 1000 L of air from each classified area.

113. When should samples be submitted by certifiers to the laboratory after collection?

If the certifier is sending samples to the laboratory for incubation and identification, samples must be sent as soon as possible (e.g., within 24 h) for the most accurate results. Samples must be protected from damage as well as temperature and humidity extremes during transit. Refer to <1117> *Microbiological Best Laboratory Practices* for additional information.

114. Describe the process and action levels associated with testing of pass-through chambers.

For entities compounding Category 1 and Category 2 CSPs, each pass-through chamber must have surface sampling performed monthly (see <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*). For entities compounding Category 3 CSPs, each pass-through chamber must have surface sampling completed prior to assigning a BUD longer than the limits established in *Table 13*, and at least weekly (see <1116>) on a regularly scheduled basis regardless of the frequency of compounding of Category 3 CSPs.

Neither General Chapter <797> nor <1116> states which ISO classification to correlate with. The facility's SOPs should describe how growth bacteria will be defined. For example, if a pass-through chamber goes between an ISO 7 and an ISO 8 area, the surface sampling growth criteria could be based on either the ISO 7 or ISO 8 limits.

Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA

115. What is the difference between cleaning and disinfecting?

Cleaning is the process of removing substances (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products. Disinfecting is the process of destroying fungi, viruses, and bacteria on inanimate surfaces and objects.

Sporicidal disinfectants are also indicated in the chapter. A sporicidal disinfectant destroys bacterial and fungal spores and is expected to kill all vegetative microorganisms.

116. What is a one-step disinfectant cleaner?

A one-step disinfectant cleaner is a product with an EPA-registered (or equivalent) claim that it can clean and disinfect a nonporous surface in the presence of light to moderate organic soiling without a separate cleaning step.

It is important to note that sterile isopropyl alcohol (IPA) is not a one-step disinfectant cleaner. Sterile IPA is a sanitizing agent which, when used on inanimate surfaces and objects, reduces the number of all forms of microbial life including fungi, viruses, and bacteria.

117. Where can I find examples or sources of EPA-registered one-step disinfectant cleaners?

USP cannot endorse particular products. Users may research one-step disinfectant cleaners or contact cleaning/disinfecting agent manufacturers to get more information on available products.

118. Does *Table 10. Minimum Frequency for Cleaning and Disinfecting Surfaces* and *Applying Sporicidal Disinfectants in Classified Areas and in the SCA* apply to all surfaces in the SCA?

The minimum frequencies in *Table 10* apply to all surfaces within the perimeter of the SCA except the ceiling. Ceilings of the SCA are required to be cleaned, disinfected, and applied with sporicidal disinfectant only when visibly soiled and when surface contamination is known or suspected.

119. Does the equipment inside a PEC need to be cleaned?

Yes, the chapter requires equipment inside of the PEC to be cleaned, disinfected, and a sporicidal disinfectant applied (see *Table 10*).

120. Are cleaning supplies required to be sterile?

Cleaning and disinfecting supplies used in the PEC must be sterile with the exception of tool handles and holders, which must be cleaned and disinfected prior to use in a PEC. The chapter states that all cleaning supplies (e.g., wipers, sponges, and mop heads) with the exception of tool handles and holders must be low lint.

Further, the chapter recommends that wipers, sponges, and mop heads be disposable.

121. Are cleaning agents required to be sterile?

Cleaning, disinfecting, and sporicidal disinfectants used within the PEC must be sterile. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used.

122. Where can I find information about the minimum contact time for the cleaning, disinfecting, and sporicidal disinfectants used?

Refer to the manufacturer's directions or published data for the minimum contact time for the agent used. The minimum contact time may differ depending on the agent used and on the intended purpose. For example, an agent may have a 1-minute contact time to be bactericidal and a 3-minute contact time to be sporicidal.

123. Does the chapter require a separate cleaning and disinfecting step in addition to applying a sporicidal disinfectant?

The chapter requires cleaning and disinfecting of the compounding areas. These steps can be combined if an EPA-registered one-step disinfectant is used. One-step disinfectants have been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step. Sporicidal disinfectants must be used at least monthly. Some EPA-registered disinfectant cleaners may also have sporicidal properties. If the sporicidal disinfectant is an EPA-registered (or equivalent) one-step disinfectant sporicidal cleaner, separate cleaning and disinfecting steps are not required.

124. Is a biological safety cabinet the only PEC that has a removable work surface tray?

No. CAIs, CACIs, and some laminar airflow workbenches (LAFWs) have removable work trays.

125. Do cleaners and disinfectants have to be EPA-registered?

In the U.S., yes. Disinfectants are registered with the EPA in the USA, and depending on the international location, registered with entities with an equivalent jurisdiction in that nation

126. Can containers of sterile supplies (such as bottles of sterile alcohol and containers of sterile saturated wipers) be used for more than one compounding session?

Yes, as long as they remain in the intended area once opened. This needs to be defined by the organization's policies, based on information provided by the manufacturer/supplier. Sterile solutions and supplies are used to avoid introducing spores or other contamination into the cleanroom. For example, a packet of saturated sterile alcohol wipers opened in the ISO 5 PEC can remain in the PEC until depleted, unless the packet is contaminated. A bottle of sterile alcohol can remain open and used in the ISO 7 cleanroom until depleted, unless contaminated.

127. Once opened, how long may a cleaning and disinfecting agent or package of sterile wipers be used?

Once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.

128. Are personnel that only clean and disinfect ISO 7 and ISO 8 areas, but not ISO 5 areas, required to wear sterile gloves?

Any person entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared must be properly garbed including sterile gloves.

129. If an IV bag has tubing attached in one hood and compounding is done in a second hood, does the IV bag need to be wiped with sterile 70% IPA before bringing into the second hood?

Yes. Just before any item is introduced into the PEC, it must be wiped with sterile 70% IPA using sterile low-lint wipers and allowed to dry before use.

130. Do personnel have to wipe gloves with sterile 70% IPA every time their hands enter the ISO Class 5 PEC even if not touching contaminated surfaces (e.g., throwing out trash without touching trash can or grabbing a supply that was disinfected for them prior to touching)?

Application of sterile 70% IPA to gloves must occur immediately before compounding and regularly throughout the compounding process. The facility SOPs should describe this process. For example, gloves might be wiped with sterile 70% alcohol before beginning to stage items into the hood then re-wiped before beginning compounding, after handling trash, when retrieving items outside the hood, etc. Handling trash or retrieving a supply item outside the hood could contaminate gloves so they should be re-wiped with sterile 70% alcohol after performing these tasks.

Equipment, Supplies, and Components

131. Why are active pharmaceutical ingredients (APIs) required to be obtained from an FDA-registered facility and components other than APIs only recommended to be obtained from an FDA-registered facility?

The Federal Food, Drug, and Cosmetic Act requires compounded preparations to be prepared from bulk drug substances that are obtained from FDA-registered facilities. The Expert Committee recognizes that there may be some components other than APIs that cannot be obtained from an FDA-registered facility, thus, it is a recommendation that these components be obtained from an FDA-registered facility.

132. How often do I need to calibrate my temperature monitoring equipment or verify its accuracy?

Section *9.3.4 Component handling and storage* states that all monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer. For example, if the manufacturer specifies to calibrate every 2 years, then that would be the correct interval. If a manufacturer does not specify the calibration interval, then it must occur at least every 12 months.

133. Does API refer to conventionally manufactured drug products?

The term "API" refers to any substance or mixture of substances intended to be used in the compounding of a preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body. Also referred to as *Bulk drug substance*. A conventionally manufactured drug product is not an API but is typically manufactured from an API(s).

134. If a CSP is stored outside of the pharmacy, do we need to monitor and document temperature readings for nursing unit floor refrigerators or remote-access Pyxis refrigerators?

Once a CSP is dispensed, you should handle this as you would any other medication (manufactured or compounded). Temperature storage conditions in healthcare facilities such as hospitals have requirements from other regulators and accreditors concerning maintaining and documenting temperatures of medication storage areas. Generally, this requires at least daily monitoring and documentation.

135. "All monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer." Does this statement apply to humidity sensors, pressure monitors, and thermostats?

Yes. Those are examples of monitoring equipment

136. Do we need a certificate of quality for each lot of sterile empty bags we use? <797> states "Each lot of commercially available sterile, depyrogenated containers and container closure systems must be accompanied by a COA or other documentation showing conformance with established specifications (i.e., sterility and depyrogenation requirements)."

Sterile empty bags obtained from suppliers are described as such in the product labeling. The lot number is traceable back to the manufacturer/supplier if any concerns would be identified.

Sterilization and Depyrogenation

137. What is the difference between aseptic processing and terminal sterilization?

USP General Chapter <1229> *Sterilization of Compendial Articles* summarizes the common requirements for sterilization process: design, development, validation, and process control. *USP* <1229.4> *Sterilizing Filtration of Liquids* states, "Sterilization processes are divided broadly into two categories: destruction of microorganisms, and their physical removal from the material to be sterilized. Terminal sterilization (e.g., autoclaving) is an example of the former, and sterilizing filtration is an example of the latter."

Aseptic processing includes either 1) compounding with only sterile starting ingredient(s), or 2) compounding with nonsterile ingredient(s) followed by sterilization by filtration. Filtration sterilization is not terminal sterilization because it is not a lethal process of microbial destruction.

Terminal sterilization includes compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization with a lethal process intended to achieve a probability of a nonsterile unit (PNSU) of 10^{-6} (e.g., steam, dry heat, irradiation).

138. Can stoppered and crimped empty vials be sterilized using steam heat?

Sealed containers must be able to generate steam internally to be sterilized by steam heat. Stoppered and crimped empty vials must contain a small amount of sterile water to generate steam (see also <1229> *Sterilization of Compendial Articles*).

139. Why is a prefiltration step with a filter of a pore size of 1.2 µm required before sterilization procedures?

A prefiltration step with a filter of a pore size of 1.2 µm removes particulate matter in the solution before sterilization. This is only required if CSPs are known to contain excessive particulate matter, which may also be an indication that the formulation may be problematic and therefore the formulation and the process should be assessed and modified if necessary.

140. What is the PNSU for CSPs sterilized by filtration?

A PNSU value cannot be applied to CSPs that are sterilized by filtration because sterilization by filtration is not terminal sterilization.

141. Is a biological indicator required for each sterilization cycle using steam or dry heat?

Yes, the effectiveness of the steam and dry heat sterilization method must be verified and documented with each run or load using an appropriate biological indicator.

142. Why does the chapter continue to exclude terminal filtration container systems from its definition of terminal sterilization?

Filtration-based methods of sterilization are not considered to be a method of terminal sterilization because they are not a lethal process of microbial destruction.

Each method of sterilization must take into consideration the container closure system that holds the compounded preparation. Since there are many container closure systems and methods of terminal sterilization, it becomes a complex matrix that is specific to the container closure system and the method of sterilization. The permutations are too numerous to include in the chapter.

143. What is depyrogenation?

Pyrogens are organic compounds that are soluble in water and not removed by filtration or steam sterilization. They are endotoxins; lipo-polysaccharides produced by Gram-negative bacteria. Depyrogenation is the destruction or elimination of endotoxins (i.e., pyrogens). There are several methods that can be used to accomplish depyrogenation.

Master Formulation and Compounding Records

144. Do I need a master formulation record (MFR) for repackaged conventionally manufactured components?

Repackaging conventionally manufactured components is within the scope of the chapter. General Chapter <797> requires a master formulation record for CSPs created for more than 1 patient and for CSPs prepared from nonsterile ingredients. If the CSP is created for more than 1 patient, such as repackaging several units, a master formulation record is required.

145. Are master formulation records required for patient-specific CSPs?

A master formulation record must be created for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s). If the CSP is only for a single patient and does not contain nonsterile ingredients, a master formulation record is not required.

146. When is a compounding record needed for immediate-use CSPs?

If the immediate-use CSPs are prepared in a batch and are intended for use in more than one patient, then a compounding record as described in Section *11.2 Creating Compounding Records* is required.

147. Does a change in any of the information listed in MFR requirement *Box 9* when compounding the same drug require an entirely new MFR, or can an MFR be created to contain the differences?

Any change to the process, ingredients, or packaging specified in an MFR are to be noted on a compounding record. The MFR is not changed.

If a preparation is made repeatedly that has differences in process, ingredients, or packaging, consideration should be given to creating a new MFR for that version of the preparation. Otherwise, all changes are to be noted on a compounding record.

148. Where does the documentation of compounding occur (in process, in the buffer room, outside of classified areas)?

The master formulation record would be established prior to compounding a CSP, usually outside of the cleanroom suite. The compounding record should be initiated before the components of the CSP are assembled. When documented on paper, this is usually performed outside of the cleanroom suite. Depending on your work practices, final sign-off on the CR would be done in the most appropriate area. While labels need to be available for placement on the completed CSP in the buffer room, exposure of paper records should be minimized in the buffer room. Those organizations with workflow technology that supports completion of the CR in the buffer room will likely have a different process than those with only manual records.

Release Inspections and Testing

149. What is required to be documented for the visual inspection of the CSP and the container closure system?

All CSPs must be visually inspected to determine whether the physical appearance of the CSP is as expected. The master formulation record must list specific requirements for a particular CSP. Examples of visible quality characteristics might include discoloration, visible particulates, or cloudiness. Examples of visual inspection of the container closure system might include checking for leakage, cracks in the container, or improper seals.

150. Why should CSPs administered epidurally have the same endotoxin limit as that of intrathecally administered CSPs?

CSPs delivered by implanted pumps may be administered over a long period of time and may be compounded from nonsterile components. Bacterial endotoxin testing helps ensure that CSPs do not contain excessive bacterial endotoxins. Although <797> refers to General Chapter <85> *Bacterial Endotoxins Test* for calculating endotoxin limits for the appropriate route of administration, <85> does not address products administered epidurally or administered directly into the central nervous system. Compounders should be aware that endotoxin testing is also important for CSPs administered epidurally due to the close proximity of the epidural and intrathecal spaces.

151. Do all Category 2 CSPs need to undergo bacterial endotoxins testing?

No. General Chapter <797> Section *12.3 Bacterial Endotoxins Testing* requires Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing per *Table 13* to undergo bacterial endotoxins testing. For example, ophthalmic compounded preparations are not required to undergo bacterial endotoxins testing because they are not Category 2 injectable CSPs. Category 2 injectable CSPs made from one or more nonsterile component(s) and assigned a BUD that does not require sterility testing are recommended to be tested for bacterial endotoxins.

152. How is the endotoxin limit of CSPs for non-human species determined?

Endotoxin limits for non-human species are calculated as described in *USP* <85> based on the largest recommended dose and weight (or average weight for more than a single animal) of the target animal species unless a different limit is scientifically supported. The formula to calculate endotoxin limit is: K/M where K = the threshold pyrogenic limit for the dosage form (expressed as EU or endotoxin units), and where M = the largest dose/patient or per species average weight in kg per hour. K has been defined by route of administration as follows: injections = 5 EU/kg, radiopharmaceutical injections = 175 EU/dose, intrathecal injections = 0.2 EU/kg, and radiopharmaceutical intrathecal injections = 14 EU/dose. To calculate the endotoxin limit for compounded morphine sulfate 50 mg/ml injection in a 5 kg cat, the following calculations are performed. The maximum dose of morphine sulfate in cats is 0.25 mg/kg. K = 5 EU/kg/hr (as defined for injections) M = 0.25 mg x 5 kg x 1hr = 1.25 mg/kg/hr K/M = 5 EU/kg/hr / 1.25 mg/kg/hr = 4 EU/mg.

The average representative weights for non-human species can be found here: https://www.fda.gov/media/102469/download.

153. Why is there a maximum batch size of 250 units for CSPs requiring sterility testing?

Sterile compounding within 503A facilities is largely a manual process. The chapter sets a minimum standard for quality assurance that encompasses a wide variety of practice sites. These quality assurance parameters are not intended for outsourcing facilities or pharmaceutical manufacturers, as they were created to accommodate the equipment and processes normally performed by 503A facilities. The risk of contaminating a CSP is likely to increase as the batch size increases, especially for a manual process. For example, equipment limitations (such as the size of a PEC) may only permit a portion of a large batch to be packaged in one continuous process. If 25 units are packaged in one continuous process, a batch of 250 units would require repeating this process 10 times. A batch of 1000 units would require repeating this process 40 times. Smaller batches reduce the potential for operator error due to fatigue. To help ensure sterility assurance, batch size is limited to 250 final dosage units for CSPs that require sterility testing. Sterility testing does not guarantee that an entire batch is sterile, only the units tested. The possibility of detecting a contaminated preparation is about 10% for batch sizes between 10 and 100 but drops to about 4% for a batch size of 250 and only 2% for a batch size of 500.

154. Why is there not a batch size limit in <71> *Sterility Tests*?

USP General Chapter <71> *Sterility Tests* falls under the Microbiology Expert Committee and was created for facilities that follow current good manufacturing practices (CGMP). Following CGMP requires a level of quality assurance significantly higher than what is required by 503A facilities who follow <797>. Modifications have been made in <797> to require a fewer number of test samples with batch sizes 1 to 39 units and to limit batch size to 250 final dosage units. Other aspects of <71>, including method suitability, number of units to be tested (for batch sizes 40 to 250), and quantity per unit tested, are required.

155. Do I have to wait for the results of the sterility tests before releasing the CSP?

Sterility testing is not required for Category 1 CSPs. Category 2 and Category 3 CSPs that require sterility testing may be administered or dispensed prior to receiving the results of release testing (including sterility testing).

In order to do this, the facility must have procedures in place to:

- Immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., sterility, strength, purity, bacterial endotoxin, or other quality attributes)
- Recall any unused dispensed CSPs and quarantine any stock remaining in the pharmacy
- Investigate if other lots are affected and recall if necessary

An SOP for recall of out-of-specification dispensed CSPs must contain:

- Procedures to determine the severity of the problem and the urgency for implementation and completion of the recall
- Procedures to determine the distribution of any affected CSP, including the date and quantity of distribution
- Procedures to identify patients who have received the CSP
- Procedures for disposal and documentation of the recalled CSP
- Procedures to investigate and document the reason for failure

156. <797> states, "When a CSP will not be released or dispensed on the day of preparation, a visual inspection must be conducted immediately before it is released or dispensed to make sure that the CSP does not exhibit any defects such as precipitation, cloudiness, or leakage, which could develop during storage." Would this prohibit stocking CSPs on the floors in automated dispensing cabinets (i.e., Pyxis) to no more than a 24-hour supply?

No, releasing a CSP to the floor is similar to dispensing to a patient so a second check is not required by a pharmacist. Nurses should be educated to check all types of sterile preparations – manufactured, from a registered outsourcer, prepared by pharmacy, or those that they activate or mix – prior to administration to a patient.

157. Why is bacterial endotoxin testing required for Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing and Category 3 injectable CSPs compounded from one or more nonsterile component(s)?

The purpose of the bacterial endotoxins test is to ensure the source material does not contain excessive endotoxins and ensure any mitigation steps that were performed are adequate. Bacterial endotoxins entering patients' bloodstreams in sufficient concentrations can cause harmful effects such as fever and septic shock and can be fatal in the most severe cases.

Establishing Beyond-Use Dates

158. What is the difference between the beyond-use date (BUD) and "hang time" (e.g., administration time, infusion time)?

The BUD is the date, or the hour and date, after which the CSP must not be used. BUDs apply to CSPs and are not intended to limit the time during which a CSP is administered (e.g., infused). "Hang time" is often used to refer to the amount of time during which a CSP or conventionally manufactured product (e.g., pre-mix, large volume parenteral solution) may be infused before which either the tubing or the medication must be changed. General Chapter <797> does not address administration time (e.g., hang time).

159. Can a CSP be administered beyond the assigned BUD?

Administration cannot begin past the assigned BUD; however, it is not intended to limit administration that began before the BUD lapsed (see 14*.1 Terminology*). For example:

- An intravenous preparation begins 1 hour before the BUD lapses; however, it is scheduled to continue infusing for a total of 2 hours. The BUD is not intended to limit the dose from being completed.
- An ophthalmic preparation is scheduled to be given once daily for 14 days; however, the BUD will lapse in 10 days. The medication can continue to be administered up until the assigned BUD in 10 days, beyond which the preparation must not be used and must be discarded.

160. After the CSP has begun to infuse, does it need to be taken down and discarded after the BUD is met?

No. Administration must begin before the BUD. The administration process is outside the scope of <797>. Standard precautions such as the Centers for Disease Control and Prevention (CDC) safe injection practices apply to administration. See <800> for additional recommendations for the administration of hazardous drugs.

161. How does the storage condition affect the BUD of a CSP? What is the relationship between storage temperature and BUDs?

Generally, longer BUDs are permitted for CSPs stored in colder conditions than for CSPs stored at controlled room temperature as colder temperatures have been shown to slow the growth of most microorganisms.

Temperature affects chemical reaction rates; thus, storage at higher temperatures will accelerate degradation and reduce a BUD. The accepted rule of thumb is reaction rates increase two-fold for every 10 degree increase in temperature. This means that 1 year storage at 30 °C is equivalent to approximately 6 months at 40 °C and approximately 3 months at 50 °C. Correlating this concept to a refrigerated product (stored at 5 °C) estimates the BUD to be one-fourth at room temperature (25 °C). The exact mechanism of degradation and rate of reaction will determine the actual difference, which can only be determined through a stability evaluation over time.

162. Are BUDs cumulative?

No, BUDs must not be additive. The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage condition.

For example, a CSP that is assigned a BUD based on storage at room temperature cannot subsequently be refrigerated or frozen in order to extend the original BUD assigned. Likewise, the BUD of a frozen CSP must not be extended based on storage at room temperature when it is thawed.

163. Can the BUDs of Category 2 CSPs be extended beyond those in *Table 13. BUD Limits for Category 2 CSPs*?

The chapter states that BUDs for Category 2 CSPs must be established in accordance with *Table 13*. However, if there is a compounded preparation monograph for a particular CSP formulation, that BUD may be assigned if the CSP is prepared according to the monograph and all monograph requirements are met (e.g., Specific Tests). *General Notices 3.10* states that where the requirements of a monograph differ from the requirements in an applicable general chapter, the monograph requirements apply and supersede the general chapter.

Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14*, if compounded in accordance with all applicable requirements for Category 3 CSPs.

BUDs must be assigned conservatively and must take into account factors such as validated stability-indicating analytical methods and testing for sterility, endotoxins, container closure integrity, and particulate matter.

164. Why is the BUD for aseptically prepared Category 2 CSPs using only sterile ingredients 4 days when stored at controlled room temperature?

The previous version of <797> specified a storage time of 48 hours and 30 hours at controlled room temperature for low- and medium-risk level CSPs, respectively. The longer BUD in the revised chapter is based on a risk-based approach to balance the need for quality CSPs and to facilitate patient access. Further, the revised chapter contains additional requirements (e.g., facility and engineering controls and surface sampling) to help mitigate risks of inadvertent contamination.

165. Is mixing MVI vial 1 and vial 2 compounding? What is the BUD?

No. Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer. Refer to the approved labeling for use of MVI once mixed.

166. If the compounding facility meets the requirements for compounding Category 3 CSPs, can a CSP still be given a Category 2 BUD to avoid sterility testing that particular CSP?

Yes. The chapter does not prohibit a compounder from assigning a shorter BUD than is specified in the BUD Limits tables (*Table 14* for Category 3 CSPs). As these are BUD limits, they are the date and time after which a CSP must not be used, stored, or transported, and a BUD shorter than the limit may be assigned to a CSP.

167. What is an example of a CSP requiring a shorter BUD based on stability and sterility?

Shorter BUDs must be assigned when the CSP's stability and/or sterility is less than the hours or days established in BUD limits for each CSP Category. For example, per guidelines, parenteral nutrition compounded as a total nutrient admixture (TNA) at a final concentration of amino acid > 4%, monohydrated dextrose > 10%, and lipid injectable emulsion > 2% are more likely to remain stable for up to 30 hours at room temperature or for 9 days refrigerated followed by 24 hours at room temperature.

168. Are there special considerations for CSPs that contain lipid emulsions?

Manufacturer recommendations regarding administration times and filtering must be followed for CSPs containing lipid emulsions. Some lipid-containing products should not exceed an administration hang time exceeding 12 hours and many require the use of a 1.2-micron filter.

169. Do Category 3 CSP BUDs have to be based on published stability studies?

The USP Compounding Expert Committee has compiled the Stability Study Reference Document posted here to help compounders understand when a stability study is suitable for assigning Category 3 BUDs to CSPs. While every CSP must meet release testing requirements for each batch to ensure sterility, evidence to prove the physicochemical stability of a CSP may be obtained from any stability-indicating assay method study, either published or unpublished, and does not have to be repeated for each batch as long as the formula, procedures, and container closure systems in the study are exactly the same for the CSP being prepared.

170. Describe when <51> testing is necessary

An aqueous multiple-dose CSP must pass antimicrobial effectiveness testing in accordance with <51> *Antimicrobial Effectiveness Testing*.

171. Is <51> testing required for stock solutions?

No. When a CSP stock solution is used as a component to compound additional CSPs, the original CSP stock solution must be entered or punctured in ISO Class 5 or cleaner air and must be stored under the conditions upon which its BUD is based (e.g., refrigerator or controlled room temperature). The CSP stock solution may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded.

172. Must antimicrobial effectiveness testing results be provided by an FDA-registered facility?

The compounder may rely on antimicrobial effectiveness testing 1) conducted (or contracted for) once for each formulation in the particular container closure system in which it will be packaged or 2) results from an FDA-registered facility or published in peer-reviewed literature sources, provided that the CSP formulation (including any preservative) and container closure system are exactly the same as those tested, unless a bracketing study is performed. Outside of the United States, facilities must comply with the laws and regulations of the applicable regulatory jurisdiction.

173. The conversion from high, medium, and low-risk compounding to Category 1 and Category 2 CSPs means that CSPs previously categorized as low-risk (48 hours at room temperature; 14 days refrigerated), now categorized as Category 2 (4 days room temperature; 10 days refrigerated) would increase the BUD at room temperature but decrease the BUD if refrigerated. Why is that?

The Compounding Expert Committee replaced risk levels with categories based on criteria other than just starting ingredients and number of manipulations. In addition to starting ingredients, BUDs are also based on environmental quality, personnel hygiene and garbing, physicochemical stability, and requirements for release testing.

174. If I only compound Category 3 CSPs occasionally, do I still have to follow the Category 3 requirements at all times?

Yes, if a compounder desires to assign a BUD longer than those allowed in *Tables 12* and *13*, then the requirements outlined in Section *14.4 Additional Requirements for Category 3 CSPs* must be met at all times.

175. What BUD should we use if there is no stability data available for the exact concentration of a CSP?

In this case, the maximum allowable BUD limits in <797> must not be exceeded.

176. May a plastic luer lock vial be stored after access?

No. The container closure system must remain intact in order to store a single-dose container after opening. Opened plastic luer lock vials are treated like ampules and must not be stored for any time period.

177. May a vial that has the septum or metal septum ring removed be stored after access?

No. The container closure system must remain intact in order to store a single-dose container after opening. Vials that have the septum or metal septum ring removed are treated like ampules and must not be stored for any time period.

Use of Conventionally Manufactured Products as Components

178. Is a conventionally manufactured single-dose container required to be stored in an ISO Class 5 PEC in order for it to be allowed to be used for up to 12 hours?

No, opened or punctured conventionally manufactured single-dose containers may be stored outside of an ISO Class 5 PEC. However, the chapter does require that the conventionally manufactured single-dose container be entered or punctured inside of an ISO Class 5 PEC. These containers may be used up to 12 hours after initial entry or puncture provided that the storage requirements (e.g., controlled room temperature, cold temperature) are maintained. Opened single-dose ampules must not be stored for any period of time.

179. Are conventionally manufactured sterile topical ophthalmic products considered multiple-dose containers?

No, <659> *Packaging and Storage Requirements* defines multiple-dose containers as a container closure system that holds a sterile medication for parenteral administration (injection or infusion) that has met antimicrobial effectiveness testing requirements, or is excluded from such testing requirements by FDA regulation. Therefore, the requirement that multiple-dose containers not be used for more than 28 days unless otherwise specified on the labeling does not apply to conventionally manufactured sterile topical products.

180. If the approved labeling of a pharmacy bulk package describes a long storage time (e.g., 14 days), can the pharmacy bulk package be stored and used for that period of time?

Users should carefully review the manufacturer's approved labeling for pharmacy bulk packages. Some approved labeling may provide a storage time based on stability (e.g., 14 days) as well as a shorter time (e.g., 4 hours) based on the risk of microbial contamination. Users must use the shorter storage time specified in the manufacturer's approved labeling. The pharmacy bulk package must be used according to the manufacturer's approved labeling.

Use of CSPs as Components

181. How is the BUD of a CSP affected by pH-modifiers or other stock solutions that are used as components?

For CSPs prepared from one or more compounded components, the BUD should generally not exceed the shortest BUD of any of the individual compounded components. However, there may be acceptable instances when the BUD of the final CSP exceeds the BUD assigned to compounded components (e.g., pH-altering solutions). If the assigned BUD of the final CSP exceeds the BUD of the compounded components, the physical, chemical, and microbiological quality of the final CSP must not be negatively impacted.

182. What is an example of assigning a BUD to compounded stock solutions and their subsequent CSPs?

A compounder wants to reconstitute a conventionally manufactured sterile product and further dilute it to prepare a subsequent CSP (see *16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions*).

- Day 1: a 2-gram single-dose conventionally manufactured container of powder for solution is reconstituted with 8 mL of a conventionally manufactured diluent, yielding 10 mL of 200 mg/mL of drug (CSP-A, original CSP). CSP-A is assigned a BUD of 10 days because it is aseptically processed, has not passed sterility testing, was prepared from only sterile starting components, and will be stored in a refrigerator (see *Table 13*).

- Day 3: CSP-A is entered or punctured in an ISO Class 5 PEC, where 10 mL of CSP-A solution is further diluted with 40 mL of diluent, yielding 50 mL solution of 40 mg/mL of drug (CSP-B, a finished CSP). CSP-B is aseptically processed, has not passed sterility testing, was prepared from only sterile starting components, and will be stored in a refrigerator. The BUD of a CSP prepared from one or more compounded components may not exceed the shortest BUD of any of the individual starting components. Therefore, the assigned BUD for CSP-B will be 7 days (10 days minus the 3 lapsed days of CSP-A), because that is the shortest BUD of all of its individual components.

- Additionally, CSP-A must be used within 12 hours of initial entry/puncture or its originally assigned BUD, whichever is shorter, and the remainder must be discarded.

183. What BUD must be assigned to Category 2 or Category 3 CSPs made using a CSP stock solution?

The BUD assigned to a CSP, whether compounded from conventionally manufactured components or from compounded stock solutions, follows the same standards in Section *14. Establishing Beyond-Use Dates*. The one difference found in Section *14.3 Establishing a BUD for a CSP,* is that the BUD of CSPs made from compounded components may, at times, exceed the BUD of compounded components. For example, if a compounded pH-altering solution with a short BUD is used to compound a CSP, the resulting CSP would likely have greater stability, and thus a longer BUD than the pH-altering solution. Another example would be a Category 2 CSP that was not sterility tested and used to make a Category 3 CSP that will be sterilized and sterility tested. If the physical, chemical, and microbiological stability is not negatively impacted, the BUD of the resulting CSP may exceed that of the component. This exception does not exist for commercially available components. It is important to note that the BUD of the final CSP should not be further restricted by the time limits for entering or puncturing components found in Sections *15* and *16*.

184. Once punctured, can a CSP or conventionally manufactured product still be used for the length of its BUD?

Compounders may utilize both conventionally manufactured and compounded components. The chapter specifies the time in which each of these components can be stored and used after first entered. This is often called in-use time, although this term is not used in the chapter. The BUD is not the same as in-use time. A multiple-dose vial may have a BUD of 60 days but must still be discarded no later 28 days after first puncture.

185. The chapter states, "After a multiple-dose CSP is initially entered or punctured, the multiple-dose CSP must not be used for longer than the assigned BUD or 28 days, whichever is shorter. This time limit for entering or puncturing is not intended to restrict the BUD of the final CSP." Can you clarify what the last sentence means?

Each component, whether conventionally manufactured or compounded, must have a time limit for entering or puncturing after first use. For example, a conventionally manufactured multiple-dose vial may not be used after 28 days of first puncture. This 28-day time limit for use is not the same as the BUD of the component and is not intended to restrict the BUD of the resulting CSP. If a CSP is prepared from a multiple-dose vial either 1 day or 10 days after first puncture, the BUD of the resulting CSP would remain the same. For example, let's assume a conventionally manufactured multiple-dose vial with a one-year expiration date is used to compound a CSP with a 60-day BUD. The multiple-dose vial component may be punctured on day 1 to make the CSP and a BUD of 60 days would be given. Now, 27 days later the same multiple-dose vial component is punctured to make the CSP, and still, a 60-day BUD is assigned. In this instance, the time limit for entering or puncturing the MDV component does not further restrict the CSP being compounded.

186. Please provide guidance as to the appropriate BUD for a reconstituted single-dose vial. For example, a reconstituted vial of daptomycin is stable for 2 days in the refrigerator. Can this vial be saved and reused for multiple preparations if kept in the refrigerator?

See Section *15* of <797> which describes the different types of components that could be part of a CSP. When using a single-dose vial, <797> says: "If a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12-h period are maintained." Using the example listed, you could maintain the punctured single-dose vial inside the ISO 5 PEC (as long as the manufacturer's information supports that long a time), but you could not move it between the PEC and the refrigerator for use on multiple patients. You would be able to use it for more than one dose or more than one patient if it remained in the PEC and was stable for up to 12 hours.

Quality Assurance and Quality Control

187. What does "the overall QA and QC program" entail?

A quality assurance program is guided by written procedures that define responsibilities and practices that ensure compounded preparations are produced with quality attributes appropriate to meet the needs of patients and healthcare professionals. The authority and responsibility for the quality assurance program should be clearly defined and implemented and should include at least the following nine separate but integrated components: (1) training; (2) standard operating procedures (SOPs); (3) documentation; (4) verification; (5) testing; (6) cleaning, disinfecting, and safety; (7) containers, packaging, repackaging, labeling, and storage; (8) outsourcing, if used; and (9) responsible personnel.

CSP Handling, Storage, Packaging, Shipping, and Transport

188. <797> states that the temperature in the storage area must be monitored each day, either manually or by a continuous recording device. ("The results of the temperature readings must be documented in a temperature log per facility SOPs or stored in the continuous temperature recording device and must be retrievable.") Does this mean that it would be acceptable to record temperatures on Monday if closed on weekends?

Yes.

189. Do all personnel who "touch" a CSP need to have training?

Yes, but not all personnel require the same training. <797> is specific about training for compounding, but leaves requirements for other personnel up to the organization. Personnel who receive sterile products and preparations, enter orders but do not compound or check CSP preparation, clean compounding areas, transport CSPs, or other activities must have documented competence as defined by the organization.

See related question in Personnel Training and Evaluation.

Compounding Allergenic Extracts

190. What are allergenic extracts?

Allergenic extracts are biological substances used for the diagnosisand/or treatment of allergic diseases such as allergic rhinitis, allergic sinusitis, allergic conjunctivitis, bee venom allergy, and food allergy. Allergenic extract prescription sets are combinations of licensed allergenic extracts which would be mixed and diluted to provide subcutaneous immunotherapy to an individual patient, even though these allergenic extract combinations are not specified in the approved biological license application (BLA) for the licensed biological products.

191. Does *21. Compounding Allergenic Extracts* apply to physician and pharmacy settings?

Yes, the provisions in *21. Compounding Allergenic Extracts* apply regardless of where the allergenic extract is compounded when:

1. The compounding process involves transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances, and
2. Manipulations are limited to penetrating stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile vials.

192. Why are the BUDs for compounded allergenic extracts longer than those required for Category 1 and Category 2 CSPs?

Because of certain characteristics of allergenic extracts and allergy practice (e.g., preservative systems and risk of anaphylaxis), preparation of allergenic extract for individual patient prescription sets is not subject to the requirements in this chapter that are applicable to other sterile CSPs. Further, FDA provides additional information for preparation of allergenic extracts in the FDA Guidance for Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application.

193. Does gloved fingertip and thumb sampling need to occur after media-fill testing for personnel who compound allergenic extracts?

No. Unlike personnel training for other CSPs, the goal of gloved fingertip and thumb sampling for personnel who compound allergenic extracts is to evaluate hand hygiene and garbing but not aseptic technique, due to the nature of the CSPs they compound. Therefore, personnel perform gloved fingertip and thumb sampling three times initially before compounding; thereafter gloved fingertip and thumb sampling is performed immediately after donning gloves at least once every 12 months. The action level for these samples is anything greater than 0 CFU per each hand.

194. Can allergenic extracts be prepared for immediate-use?

Yes.

195. Can this section apply for vials that are made for multiple patients?

No. Compounding allergenic extracts is per individual patient prescription set only.

Attachment 2a

Article 4.5 draft regulation text

related to nonsterile compounding

Title 16. Board of Pharmacy
Proposed Regulation

Proposed changes to the current regulation language are shown by ~~strikethrough~~ for deleted language and underline for added language.

Amend title of Article 4.5 and Repeal sections 1735, 1735.1, 1735.3, 1735.4, 1735.5, 1735.6, 1735.7, and 1735.8 of Article 4.5, adopt a new title for and amend section 1735.2, adopt new titles and sections 1735, 1735.1, 1735.3, 1735.4, 1735.5, 1735.6, 1735.7, 1735.8, 1735.9, 1735.10, 1735.11, 1735.12, 1735.13, and 1735.14 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

Article 4.5 Nonsterile Compounding ~~in Pharmacies~~
~~1735. Compounding in Licensed Pharmacies~~
~~(a) "Compounding" means any of the following activities occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist, pursuant to a prescription:~~

(1) ~~Altering the dosage form or delivery system of a drug~~
~~(2) Altering the strength of a drug~~
~~(3) Combining components or active ingredients~~
~~(4) Preparing a compounded drug preparation from chemicals or bulk drug substances~~

~~(b) "Compounding" does not include reconstitution of a drug pursuant to a manufacturer's direction(s), nor does it include the sole act of tablet splitting or crushing, capsule opening, or the addition of flavoring agent(s) to enhance palatability.~~

~~(c) The parameters and requirements stated by Article 4.5 (Section 1735 et seq.) apply to all compounding practices. Additional parameters and requirements applicable solely to sterile compounding are stated by Article 7 (Section 1751 et seq.).~~
~~Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052,and 4127, Business and Professions Code.~~

1735. Compounding Definitions.

In addition to the definitions contained in United States Pharmacopeia (USP) General Chapter 795 titled *Pharmaceutical Compounding – Nonsterile Preparations* "USP Chapter 795" for the purposes of this article, the following definitions apply to this article and supplement the definitions provided in USP Chapter 795.

(a) "Approved labeling" means the Food and Drug Administration's (FDA) approved labeling in accordance with sections 201.56 and 201.57 of title 21, Code of Federal Regulations that contains FDA approved information for the diluent, the resultant strength, the container closure system, and storage time.

(b) "Essentially a copy" of a commercially available drug product means all preparations that include the same API(s) as the 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.

(c) Designated person(s) means one or more individuals assigned by the pharmacist-in-charge to be responsible and accountable for the performance and operation of the facility and personnel as related to the preparation of the compounded nonsterile preparations ("CNSP") for the purposes of this article). Nothing in this definition allows for the designated person to exceed the scope of their issued license. When the designated person is not a pharmacist, the Pharmacist-in-Charge (PIC) must review all practices related to the operations of the facility that require professional judgement.

(d) "Diluent" means a liquid with no pharmacological activity used in reconstitution, such as purified water or sterile water for injection.

(e) "Integrity" means retention of strength until the beyond use date provided on the label when the preparation is stored and handled according to the label directions.

(f) "Quality" means the absence of harmful levels of contaminants, including filth, putrid, or decomposed substances, or the absence of active ingredients other than those listed on the label, or the absence of inactive ingredients other than those listed on the master formulation record as specified in USP Chapter 795.

(g) "Repackaging" means the act of removing a product or preparation from its original primary container and placing it into another primary container, usually of smaller size without further manipulation, when the act is not done pursuant to a prescription.

(i) "Strength" means amount of active ingredient per unit of a compounded drug preparation.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

~~1735.1. Compounding Definitions~~

~~(a) "Ante-area" means an area with ISO Class 8 or better air quality where personnel hand hygiene and garbing procedures, staging of components, and other high-particulate-generating activities are performed, that is adjacent to the area designated for sterile compounding. It is a transition area that begins the systematic reduction of particles, prevents large fluctuations in air temperature and pressures in the cleanroom, and maintains air flows from clean to dirty areas. ISO Class 7 or better air quality is required for ante-areas providing air to a negative pressure room.~~

~~(b) "Beyond use date" means the date, or date and time, after which administration of a compounded drug preparation shall not begin, the preparation shall not be dispensed, and the preparation shall not be stored (other than for quarantine purposes).~~

~~(c) "Biological Safety Cabinet (BSC)" means a ventilated cabinet for compounding sterile drug preparations, having an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection. Where hazardous drugs are prepared, the exhaust air from the biological safety cabinet shall be appropriately removed by properly designed external building exhausting. This external exhaust should be dedicated to one BSC or CACI.~~

~~d) "Bulk drug substance" means any substance that, when used in the preparation of a compounded drug preparation, processing, or packaging of a drug, is an active ingredient or a finished dosage form of the drug, but the term does not include any intermediate used in the synthesis of such substances.~~

~~e) "Cleanroom or clean area or buffer area" means a room or area with HEPA-filtered air that provides ISO Class 7 or better air quality where the primary engineering control (PEC) is physically located.~~

> ~~1) For nonhazardous compounding a positive pressure differential of 0.02-to 0.05-inch water column relative to all adjacent spaces is required.~~
> ~~2) For hazardous compounding at least 30 air changes per hour of HEPA-filtered supply air and a negative pressure of between 0.01 to 0.03 inches of water column relative to all adjacent spaces is required.~~

~~(f) "Compounding Aseptic Containment Isolator (CACI)" means a unidirectional HEPA-filtered airflow compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where hazardous drugs are prepared, the~~

~~exhaust air from the isolator shall be appropriately removed by properly designed external building exhaust. This external exhaust should be dedicated to one BSC or CACI. Air within the CACI shall not be recirculated nor turbulent.~~

~~(g) "Compounding Aseptic Isolator (CAI)" means a form of isolator specifically designed for nonhazardous compounding of pharmaceutical ingredients or preparations while bathed with unidirectional HEPA-filtered air. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless the air has first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Air within the CAI shall not be recirculated nor turbulent.~~

~~h) "Controlled cold temperature" means 2 degrees to 8 degrees C (35 degrees to 46 degrees F).~~

~~(i) "Controlled freezer temperature" means -25 degrees to -10 degrees C (-13 degrees to 14 degrees F) or at a range otherwise specified by the pharmaceutical manufacturer(s) for that product.~~

~~(j) "Controlled room temperature" means 20 degrees to 25 degrees C (68 degrees to 77 degrees F).~~

~~(k) "Copy or essentially a copy" of a commercially available drug product includes 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.~~

~~(l) "Daily" means occurring every day the pharmacy is operating, except when daily monitoring of refrigerator and freezer temperature are required, then daily means every 24 hours.~~

~~m) "Displacement airflow method" means a concept which utilizes a low pressure differential high airflow principle to maintain segregation from the adjacent ante-area by means of specific pressure differentials. This principle of displacement airflow shall require an air velocity of 40 ft per minute or more, from floor to ceiling and wall to wall, from the clean area across the line of demarcation into the ante-area. The displacement concept may not be used to maintain clean area requirements for sterile compounds which originate from any ingredient that was at any time non-~~

~~sterile, regardless of intervening sterilization of the ingredient, or for hazardous compounds.~~

~~(n) "Dosage unit" means a quantity sufficient for one administration to one patient.~~

~~(o) "Equipment" means items that must be calibrated, maintained or periodically certified.~~

~~p) "First air" means the air exiting the HEPA filter in a unidirectional air stream that is essentially particle free.~~

~~(q) "Gloved fingertip sampling" means a process whereby compounding personnel lightly press each fingertip and thumb of each hand onto appropriate growth media, which are then incubated at a temperature and for a time period conducive to multiplication of microorganisms, and then examined for growth of microorganisms.~~

~~r) "Hazardous" means all anti-neoplastic agents identified by the National Institute for Occupational Safety and Health (NIOSH) as meeting the criteria for a hazardous drug and any other drugs, compounds, or materials identified as hazardous by the pharmacist-in-charge.~~

~~(s) "Integrity" means retention of potency until the beyond use date provided on the label, so long as the preparation is stored and handled according to the label directions.~~

~~(t) "Lot" means one or more compounded drug preparation(s) prepared during one uninterrupted continuous cycle of compounding from one or more common active ingredient(s).~~

~~(u) "Media-fill test" means a test used to measure the efficacy of compounding personnel in aseptic techniques whereby compounding procedures are mimicked using a growth-based media and then the resulting preparation is evaluated for sterility. The media-fill test must mimic the most complex compounding procedures performed by the pharmacy.~~

~~(v) "Non-sterile-to-sterile batch" means any compounded drug preparation containing two (2) or more dosage units with any ingredient that was at any time non-sterile, regardless of intervening sterilization of that ingredient.~~

~~(w) "Parenteral" means a preparation of drugs administered in a manner other than through the digestive tract. It does not (x) "Personal protective equipment" means clothing or devices that protect the employee from exposure to compounding ingredients and/or potential toxins and minimize the contamination of compounded~~

~~preparations. These include shoe covers, head and facial hair covers, face masks, gowns, and gloves.~~

~~y) "Potency" means active ingredient strength within +/-10% (or the range specified in USP37NF32, 37th Revision, Through 2nd Supplement Effective December 1, 2014) of the labeled amount. Sterile injectable products compounded solely from commercially manufactured sterile pharmaceutical products in a health care facility licensed under section 1250 of the Health and Safety Code are exempt from this definition. For those exempt, the range shall be calculated and defined in the master formula.~~

~~(z) "Preparation" means a drug or nutrient compounded in a licensed pharmacy; the preparation may or may not be sterile.~~

~~aa) "Prescriber's office" or "prescriber office" means an office or suite of offices in which a prescriber regularly sees patients for outpatient diagnosis and treatment. This definition does not include any hospital, pharmacy, or other facility, whether or not separately licensed, that may be affiliated with, adjacent to, or co-owned by, the prescriber's practice environment.~~

~~ab) "Primary Engineering Control (PEC)" means a device that provides an ISO Class 5 or better environment through the use of non-turbulent, unidirectional HEPA-filtered first air for compounding sterile preparations. Examples of PEC devices include, but are not limited to, laminar airflow workbenches, biological safety cabinets, sterile compounding automated robots, compounding aseptic isolators, and compounding aseptic containment isolators.~~

~~ac) "Process validation" means demonstrating that when a process is repeated within specified limits, the process will consistently produce preparations complying with predetermined requirements. If any aspect of the process is changed, the process would need to be revalidated.~~

~~(ad) "Product" means a commercially manufactured drug or nutrient evaluated for safety and efficacy by the FDA.~~

~~(ae) "Quality" means the absence of harmful levels of contaminants, including filth, putrid, or decomposed substances, the absence of active ingredients other than those listed on the label, and the absence of inactive ingredients other than those listed on the master formula document.~~

~~(af) "Segregated sterile compounding area" means a designated space for sterile-to-sterile compounding where a PEC is located within either a demarcated area (at least three foot perimeter) or in a separate room. Such area or room shall not contain and shall be void of activities and materials that are extraneous to sterile compounding.~~

~~The segregated sterile compounding area shall not be in a location that has unsealed windows or doors that connect to the outdoors, in a location with high traffic flow, or in a location that is adjacent to construction sites, warehouses, or food preparation. The segregated sterile compounding area shall not have a sink, other than an emergency eye-washing station, located within three feet of a PEC. The segregated sterile compounding area shall be restricted to preparation of sterile-to-sterile compounded preparations. include topical, sublingual, rectal or buccal routes of administration.~~

~~(1) The BUD of a sterile drug preparation made in a segregated sterile compounding area is limited to 12 hours or less as defined by section 1751.8(d).~~
~~(2) When the PEC in the segregated sterile compounding area is a CAI or a CACI and the documentation provided by the manufacturer shows it meets the requirements listed in section 1751.4(f)(1)-(3), the assigned BUD shall comply with section 1751.8(a-b) or (d).~~
~~(ag) "Strength" means amount of active ingredient per unit of a compounded drug preparation~~
~~Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.~~

1735.1. Introduction and Scope

In addition to the standards in the USP Chapter 795, the preparation of CNSP shall meet the following requirements of this article.

(a) For the purposes of this article, nonsterile compounding occurs, by or under the supervision of a licensed pharmacist, pursuant to a patient specific prescription, unless otherwise specified in this article.

(b) Repackaging of a conventionally manufactured drug product shall be not considered compounding but must be compliant with USP Chapter 1178, *Good Repackaging Practices*.

(c) Reconstitution of a conventionally manufactured drug product in accordance with directions that have not been Food and Drug Administration (FDA) approved in accordance with 21 U.S.C.A Section 355 is considered compounding and this article applies.

(d) Notwithstanding subdivision (a), a limited quantity of CNSP may be prepared and stored in advance of receipt of a patient specific prescription document where, and solely in such quantity, as is necessary to ensure continuity of care individual patients based on a documented history of prescriptions for those patient populations.

(e) A reasonable quantity of a compounded drug preparation may be furnished to a veterinary office for use by the veterinarian that is sufficient:

(1) for administration or application to veterinary patients solely in the veterinarian's office
(2) for furnishing of not more than 7-day supply, as fairly estimated by the prescriber and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing;

(f) In addition to prohibitions and requirements for compounding established in federal law, no CNSP shall be prepared that:

(1) Is essentially a copy of one or more commercially available drug products, unless:

(A) the drug product appears on an ASHP (American Society of Health-System Pharmacists) or FDA Drug Shortages Database that are in short supply at the time of compounding and at the time of dispense, or

(B) the compounding produces a clinically significant difference of the medical need of an identified individual patient, as determined:

(1) by the prescribing practitioner,

(2) the compounding pharmacist, and

(3) the dispensing pharmacist(s).

(C)) Documentation describing the conditions in (1)(A) & (1) (B) is maintained in a readily retrievable format

(2) Is made with any component not suitable for use in a CNSP for the intended patient population, unless allowable under Animal Medicinal Drug Use Clarification Action of 1994 (AMDUCA).

(g) Prior to allowing any CNSP to be compounded within a pharmacy, the pharmacist-in-charge shall complete a self-assessment consistent with the requirements established in section 1715.

(g) In addition to the provisions provided in Section 1707.2, consultation shall be provided to the patient and/or patient's agent concerning proper use, storage, handling and disposal of the CNSP and related supplies furnished.

(h) CNSPs with human whole blood or human whole blood derivatives shall be prepared in compliance with Health and Safety Code section 1602.5.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4105, 4126.8 and 4169, 4301, 4306.5 and 4332 of the Business and Profession Code.

~~1735.2. Compounding Limitations and Requirements; Self-Assessment~~

~~(a) Except as specified in (b) and (c), no drug preparation shall be compounded prior to receipt by a pharmacy of a valid prescription for an individual patient where the prescriber has approved use of a compounded drug preparation either orally or in writing. Where approval is given orally, that approval shall be noted on the prescription prior to compounding.~~

~~(b) A pharmacy may prepare and store a limited quantity of a compounded drug preparation in advance of receipt of a patient-specific prescription where and solely in such quantity as is necessary to ensure continuity of care for an identified population of patients of the pharmacy based on a documented history of prescriptions for that patient population.~~

~~(4) That the pharmacist has a credible basis for concluding it is a reasonable quantity for office use considering the intended use of the compounded medication and the nature of the prescriber's practice; and~~
~~(5) With regard to any individual prescriber to whom the pharmacy furnishes, and with regard to all prescribers to whom the pharmacy furnishes, is an amount which the pharmacy is capable of compounding in compliance with pharmaceutical standards for integrity, potency, quality and strength of the compounded drug preparation; and~~
~~(6) Does not exceed an amount the pharmacy can reasonably and safely compound.~~

~~(d) No pharmacy or pharmacist shall compound a drug preparation that:~~

~~(1) Is classified by the FDA as demonstrably difficult to compound;~~
~~(2) Appears on an FDA list of drugs that have been withdrawn or removed from the market~~
~~because such drugs or components of such drugs have been found to be unsafe or not effective; or~~
~~(3) Is a copy or essentially a copy of one or more commercially available drug products, unless 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, and the compounding of that drug preparation is justified by a specific, documented medical need made known to the pharmacist prior to compounding. The pharmacy shall retain a copy of the documentation of the shortage and the specific medical need in the pharmacy records for three years from the date of receipt of the documentation.~~

~~(e) A drug preparation shall not be compounded until the pharmacy has first prepared a written master formula document that includes at least the following elements:~~

~~(1) Active ingredients to be used.~~
~~(2) Equipment to be used.~~
~~(3) The maximum allowable beyond use date for the preparation, and the rationale or reference source justifying its determination.~~
~~(4) Inactive ingredients to be used.~~
~~(5) Specific and essential compounding steps used to prepare the drug.~~
~~(6) Quality reviews required at each step in preparation of the drug.~~
~~(7) Post-compounding process or procedures required, if any.~~
~~(8) Instructions for storage and handling of the compounded drug preparation.~~

~~(f) Where a pharmacy does not routinely compound a particular drug preparation, the master formula record for that preparation may be recorded on the prescription document itself.~~

~~(g) The pharmacist performing or supervising compounding is responsible for the integrity, potency, quality, and labeled strength of a compounded drug preparation until the beyond use date indicated on the label, so long as label instructions for storage and handling are followed after the preparation is dispensed.~~

~~(h) All chemicals, bulk drug substances, drug products, and other components used for drug compounding shall be stored and used according to compendia and other applicable requirements to maintain their integrity, potency, quality, and labeled strength.~~

~~(i) Every compounded drug preparation shall be given beyond use date representing the date or date and time beyond which the compounded drug preparation should not be used, stored, transported or administered, and determined based on the professional judgment of the pharmacist performing or supervising the compounding.~~

~~(1) For non-sterile compounded drug preparation(s), the beyond use date shall not exceed any of the following:~~
~~(A) the shortest expiration date or beyond use date of any ingredient in the compounded drug preparation,~~
~~(B) the chemical stability of any one ingredient in the compounded drug preparation;~~
~~(C) the chemical stability of the combination of all ingredients in the compounded drug preparation,~~
~~(D) for non-aqueous formulations, 180 days or an extended date established by the pharmacist's research, analysis, and documentation,~~

~~(E) for water-containing oral formulations, 14 days or an extended date established by the pharmacist's research, analysis, and documentation, and~~

~~(F) for water-containing topical/dermal and mucosal liquid and semisolid formulations, 30 days or an extended date established by the pharmacist's research, analysis, and documentation.~~

~~(G) A pharmacist, using his or her professional judgment may establish an extended date as provided in (D), (E), and (F), if the pharmacist researches by consulting and applying drug-specific and general stability documentation and literature; analyzes such documentation and literature as well as the other factors set forth in this subdivision, and maintains documentation of the research, analysis and conclusion. The factors the pharmacist must analyze include:~~

~~(i) the nature of the drug and its degradation mechanism,~~

~~(ii) the dosage form and its components,~~

~~(iii) the potential for microbial proliferation in the preparation,~~

~~(iv) the container in which it is packaged,~~

~~(v) the expected storage conditions, and~~

~~(vi) the intended duration of therapy.~~

~~Documentation of the pharmacist's research and analysis supporting an extension must be maintained in a readily retrievable format as part of the master formula.~~

~~(2) For sterile compounded drug preparations, the beyond use date shall not exceed any of the following:~~

~~(A) The shortest expiration date or beyond use date of any ingredient in the sterile compounded drug product preparation,~~

~~(B) The chemical stability of any one ingredient in the sterile compounded drug preparation,~~

~~(C) The chemical stability of the combination of all ingredients in the sterile compounded drug preparation, and~~

~~(D) The beyond use date assigned for sterility in section 1751.8.~~

~~(3) For sterile compounded drug preparations, extension of a beyond use date is only allowable when supported by the following:~~

~~(A) Method Suitability Test,~~

~~(B) Container Closure Integrity Test, and~~

~~(C) Stability Studies~~

~~(4) In addition to the requirements of paragraph three (3), the drugs or compounded drug preparations tested and studied shall be identical in ingredients, specific and essential compounding steps, quality reviews, and packaging as the finished drug or compounded drug preparation.~~

~~(5) Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist.~~

~~(j) The pharmacist performing or supervising compounding is responsible for the proper preparation, labeling, storage, and delivery of the compounded drug preparation.~~

~~(k) Prior to allowing any drug product preparation to be compounded in a pharmacy, the pharmacist-in-charge shall complete a self-assessment for compounding pharmacies developed by the board (Incorporated by reference is "Community Pharmacy & Hospital Outpatient Pharmacy Compounding Self-Assessment" Form 17M-39 Rev. 02/12.) as required by Section 1715 of Title 16, Division 17, of the California Code of Regulations. That form contains a first section applicable to all compounding, and a second section applicable to sterile injectable compounding. The first section must be completed by the pharmacist-in-charge before any compounding is performed in the pharmacy. The second section must be completed by the pharmacist-in-charge before any sterile compounding is performed in the pharmacy. The applicable sections of the self-assessment shall subsequently be completed before July 1 of each odd-numbered year, within 30 days of the start date of a new pharmacist-in-charge or change of location, and within 30 days of the issuance of a new pharmacy license. The primary purpose of the self-assessment is to promote compliance through self-examination and education.~~

~~(l) Packages of ingredients, both active and inactive, that lack a supplier's expiration date are subject to the following limitations:~~

~~(1) such ingredients cannot be used for any non-sterile compounded drug preparation more than three (3) years after the date of receipt by the pharmacy.~~

~~(2) such ingredients cannot be used for any sterile compounded drug preparation more than~~

~~(1) year after the date of receipt by the pharmacy.~~

~~Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.~~

1735.2. Personnel Training and Evaluation

In addition to the standards in the USP Chapter 795, the preparation of CNSP shall meet the following requirements of this article.

(a) In addition to the training required by USP Chapter 795 training and competencies procedures for all personnel who compound or have direct oversight of personnel performing compounding, verifying, and/or handling a CNSP shall also address the following topics:

(1) Quality assurance and quality control procedures,

(2) Container closure and equipment selection, and

(3) Component selection and handling.

(b) A pharmacist responsible for, or directly supervising, the compounding of CNSPs, shall demonstrate proficiency in skills necessary to ensure the integrity, strength, quality, and labeled strength of a CNSP as described in the facilities SOPs as referenced in section 1735.11.

(c) A "reasonable quantity" that may be furnished to a prescriber for office use by the prescriber as authorized by Business and Professions Code section 4052, subdivision (a)(1), means that amount of compounded drug preparation that:

(1) Is sufficient for administration or application to patients solely in the prescriber's office,-or for furnishing of not more than a 120-hour supply for veterinary medical practices, solely to the prescriber's own veterinary patients seen as part of regular treatment in the prescriber's office, as fairly estimated by the prescriber and documented on the purchase order or other documentation submitted prior to furnishing.

(d) Compounding personnel or persons with direct oversight over personnel performing compounding, who fail any aspect of ongoing training and evaluation shall not be involved in compounding or oversight of the preparation of a CNSP until after successfully passing training and competency in the deficient area(s) as detailed in the facility's SOPs.

(e) Any person assigned to provide the training specified in this section shall have demonstrated competency in the skills in which the person will provide training or observe and measure competency described in the facilities SOPs as referenced in section 1735.11. Documentation must be maintained demonstrating compliance.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301, 4306.5 and 4332 of the Business and Profession Code.

~~1735.3. Recordkeeping of Compounded Drug Preparations~~

~~(a) For each compounded drug preparation, pharmacy records shall include:~~

~~(1) The master formula document.~~

~~(2) A compounding log consisting of a single document containing all of the following:~~

~~(A) Name and Strength of the compounded drug preparation.~~

~~(B) The date the drug preparation was compounded.~~

~~(C) The identity of any pharmacy personnel engaged in compounding the drug preparation.~~

~~(D) The identity of the pharmacist reviewing the final drug preparation.~~

~~(E) The quantity of each ingredient used in compounding the drug preparation.~~

~~F) The manufacturer, expiration date and lot number of each component. If the manufacturer name is demonstrably unavailable, the name of the supplier may be substituted. If the manufacturer does not supply an expiration date for any component, the records shall include the date of receipt of the component in the pharmacy, and the limitations of section 1735.2, subdivision (l) shall apply.~~

~~(i) Exempt from the requirements in this paragraph (1735.3(a)(2)(F)) are sterile — in a single lot for administration within seventy-two (72) hours to a patient in a health care facility licensed under section 1250 of the Health and Safety Code and stored in accordance with standards for "Redispensed CSPs" found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP37-NF32) Through 2nd Supplement (37th Revision, Effective December 1, 2014), hereby incorporated by reference.~~

~~(G) A pharmacy-assigned unique reference or lot number for the compounded drug product preparation.~~

~~H) The beyond use date or beyond use date and time of the final compounded drug, expressed in the compounding document in a standard date and time format.~~

~~I) The final quantity or amount of drug preparation compounded for dispensing.~~

~~(J) Documentation of quality reviews and required post-compounding process and procedures.~~

~~(b) Pharmacies shall maintain records of the proper acquisition, storage, and destruction of chemicals, bulk drug substances, drug products, and components used in compounding.~~

~~(c) Active ingredients shall be obtained from a supplier registered with the Food and Drug Administration (FDA). All other chemicals, bulk drug substances, and drug products used to compound drug preparations shall be obtained, whenever possible, from FDA-registered suppliers. The pharmacy shall acquire and retain certificates of purity or analysis, either written in English or translated into English, for chemicals, bulk drug substances, and drug products used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the FDA. Any certificates of purity or analysis acquired by the pharmacy shall be matched to the corresponding chemical, bulk drug substance, or drug products received.~~

~~(d) Pharmacies shall maintain and retain all records required by this article in the pharmacy in a readily retrievable form for at least three years from the date the record was last in effect. If only recorded and stored electronically, on magnetic~~

~~media, or in any other computerized form, the records shall be maintained as specified by Business and Professions Code section 4070 subsection (c).~~

~~Authority cited: Sections 4005, 4127, and 4169, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.~~

1735.3. Personnel Hygiene and Garbing

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) Prior to admitting any personnel into a compounding area, the supervising pharmacist shall evaluate compounding personnel experiencing any of the following: rashes, recent tattoos or oozing sores, conjunctivitis, active respiratory infection or and other medical conditions to determine if such condition could contaminate a CNSP or the environment ("contaminating conditions"). After such evaluation and determination the supervising pharmacist shall not allow personnel with potentially contaminating conditions to enter the compounding area.

(b) A gown and face mask shall be used whenever a closed system processing device is required.

(c) Disposable garb shall not be shared by staff and shall be discarded after each shift and when soiled. Garb removed during a shift must be maintained in the compounding area.

(d) Gloves shall be wiped or replaced before beginning a CNSP that has different components.

(e) Non-disposable garb shall be cleaned with a germicidal cleaning agent and sanitized with 70% isopropyl alcohol before re-use.

(f) Any garbing accommodations provided by the designated person shall be documented and the record shall include the name of the individual granted the accommodation, date granted and description of the reasons for granting the accommodation. The record shall be retained in accordance with Business and Professions Code section 4081.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

~~1735.4. Labeling of Compounded Drug Preparations~~

~~(a) Each compounded drug preparation shall be affixed with a container label prior to dispensing that contains at least:~~

~~(1) Name of the compounding pharmacy and dispensing pharmacy (if different);~~

~~2) Name (brand or generic) and strength, volume, or weight of each active ingredient. For admixed IV solutions, the intravenous solution utilized shall be included;~~

~~(3) Instructions for storage, handling, and administration. For admixed IV solutions, the rate of infusion shall be included;~~

~~(4) The beyond use date for the drug preparation;~~

~~(5) The date compounded; and~~

~~6) The lot number or pharmacy reference number.~~

~~(b) Any compounded drug preparation dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required under Business and Professions Code section 4076 and California Code of Regulations, title 16, section 1707.5.~~

~~(c) Any compounded drug preparation dispensed to a patient or readied for dispensing to a patient shall also include, on the container label or on a receipt provided to the patient, a statement that the drug has been compounded by the pharmacy.~~

~~(d) Prior to dispensing drug preparations compounded into unit-dose containers that are too small or otherwise impractical for full compliance with subdivisions (a), (b), and (c) shall be labeled with at least the name of the compounding pharmacy and dispensing pharmacy, if different, the name(s) of the active ingredient(s), strength, volume or weight of the preparation, pharmacy reference or lot number, and beyond use date, and shall not be subject to minimum font size requirements. Once dispensed, outer packaging must comply with 1735.4(a) – (c).~~

~~(e) All hazardous agents shall bear a special label which states "Chemotherapy - Dispose of Properly" or "Hazardous – Dispose of Properly."~~

~~Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4076 and 4127, Business and Professions Code.~~

1735.4. Building and Facilities

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) A sink used for compounding or hand hygiene shall not be part of a restroom or water closet.

(b) Purified water, distilled water, or reverse osmosis water shall be used for rinsing equipment and utensils.

(c) No CNSP shall be compounded if it is known, or reasonably should be known, that the compounding environment fails to meet criteria specified in the law or the facilities SOPs

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301, 4306.5 and 4332 of the Business and Profession Code.

~~1735.5. Compounding Policies and Procedures~~

~~(a) Any pharmacy engaged in compounding shall maintain written policies and procedures for compounding that establishes procurement procedures, methodologies for the formulation and compounding of drugs, facilities and equipment cleaning, maintenance, operation, and other standard operating procedures related to compounding. Any material failure to follow the pharmacy's written policies and procedures shall constitute a basis for disciplinary action.~~

~~(b) The policies and procedures shall be reviewed and such review shall be documented on an annual basis by the pharmacist-in-charge. The policies and procedures shall be updated whenever changes in policies and procedures are implemented.~~

~~(c) The policies and procedures shall include at least the following:~~

~~1) Procedures for notifying staff assigned to compounding duties of any changes in policies .~~

~~2) A written plan for recall of a dispensed compounded drug preparation where subsequent demonstrates the potential for adverse effects with continued use. The plan shall ensure that all affected doses can be accounted for during the recall and shall provide steps to identify which patients received the affected lot or compounded drug preparation(s).~~

~~3) Procedures for maintaining, storing, calibrating, cleaning, and disinfecting equipment used in , and for training on these procedures as part of the staff training and competency evaluation process.~~

~~(4) Procedures for evaluating, maintaining, certifying, cleaning, and disinfecting the facility (physical plant) used for compounding, and for training on these procedures as part of the staff training and competency evaluation process.~~

~~(5) Documentation of the methodology used to validate integrity, potency, quality, and labeled strength of compounded drug preparations. The methodology must be appropriate to compounded drug preparations.~~

~~(6) Documentation of the methodology and rationale or reference source used to determine appropriate beyond use dates for compounded drug preparations.~~

~~(7) Dates and signatures reflecting all annual reviews of the policies and procedures by the pharmacist-in-charge.~~

~~8) Dates and signatures accompanying any revisions to the policies and procedures approved by pharmacist-in-charge.~~

~~9) Policies and procedures for storage of compounded drug preparations in the pharmacy and daily documentation of all room, refrigerator, and freezer temperatures within the pharmacy.~~

~~10) Policies and procedures regarding ensuring appropriate functioning of refrigeration devices, refrigeration device temperatures, and actions to take regarding any out of range temperature variations within the pharmacy.~~

~~(11) Policies and procedures for proper garbing when compounding with hazardous products. shall include when to utilize double shoe covers.~~

~~Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4127, and 4301, Business and Professions Code~~

1735.5. Cleaning And Sanitizing

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) In addition to the documentation requirements in USP Chapter 795, the facility's documentation of each occurrence of the cleaning and sanitizing of the compounding area shall include a record of the identity of the person completing the cleaning and sanitizing as well as the product name of the cleaning and sanitizing agents used.

(b) Any cleaning or sanitizing agents used by the facility to meet the requirements in this article shall be used in accordance with manufacturers' specifications.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

~~1735.6. Compounding Facilities and Equipment~~

~~(a) Any pharmacy engaged in compounding shall maintain written documentation regarding the facilities and equipment necessary for safe and accurate compounding of compounded drug preparations. This shall include records of maintenance and cleaning of the facilities and equipment. Where applicable, this shall also include records of certification(s) of facilities or equipment.~~

~~(b) Any equipment used to compound drug preparations shall be stored, used, maintained, and cleaned in accordance with manufacturers' specifications.~~

~~c) Any equipment that weighs, measures, or transfers ingredients used to compound drug preparations for which calibration or adjustment is appropriate shall be calibrated prior to use, on a schedule and by a method determined by the manufacturer's specifications, to ensure accuracy. Documentation of each such calibration shall be recorded in a form which is not alterable and these records of calibration shall be maintained and retained in the pharmacy.~~

~~(d) Any pharmacy engaged in any hazardous drug compounding shall maintain written documentation regarding appropriate cleaning of facilities and equipment to prevent cross-contamination with non-hazardous drugs.~~

~~(e) Hazardous drug compounding shall be completed in an externally exhausted physically separate room with the following requirements:~~

~~(1) Minimum of 30 air changes per hour except that 12 air changes per hour are acceptable for segregated compounding areas with a BSC or CACI when products are assigned a BUD of 12 hours or less or when non sterile products are compounded; and~~

~~2) Maintained at a negative pressure of 0.01 to 0.03 inches of water column relative to all adjacent spaces (rooms, above ceiling, and corridors); and~~

~~(3) A) For sterile compounding, each BSC or CACI shall also be externally exhausted. y~~

~~(B) For nonsterile compounding, a BSC, a CACI, or other containment ventilated enclosure shall be used and shall either use a redundant-HEPA filter in series or be externally exhausted.; For purposes of this paragraph, a containment ventilated enclosure means a full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through high-efficiency particulate air (HEPA) filtration and to prevent their release into the work environment.~~

~~Each PEC in the room shall also be externally vented; and~~

~~4) All surfaces within the room shall be smooth, seamless, impervious, and non-shedding.~~

~~(f) Where compliance with the January 1, 2017 amendments to Article 4.5 or Article 7, requires physical construction or alteration to a facility or physical environment, the board or its designee may grant a waiver of such compliance for a period of time to permit such physical change(s). Application for any waiver shall be made by the licensee in writing, and the request shall identify the provision(s) requiring physical construction or alteration, and the timeline for any such change(s). The board or its designee may grant the waiver when, in its discretion, good cause is demonstrated for such waiver.~~

~~Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052 and 4127, Business and Professions Code.~~

1735.6. Equipment And Components

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) Any equipment used to compound a CNSP shall be used in accordance with the manufacturer's specifications.

(b) Any component used to compound a CNSP shall be used and stored in accordance with all federal laws and regulations and industry standards including the manufacturers' specifications and requirements.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

~~1735.7. Training of Compounding Staff~~

~~(a) A pharmacy engaged in compounding shall maintain documentation demonstrating that personnel involved in compounding have the skills and training required to properly and accurately perform their assigned responsibilities and documentation demonstrating that all personnel involved in compounding are trained in all aspects of policies and procedures. This training shall include but is not limited to support personnel (e.g. institutional environmental services, housekeeping), maintenance staff, supervising pharmacist and all others whose jobs are related to the compounding process.~~

~~(b) The pharmacy shall develop and maintain an ongoing competency evaluation process for pharmacy personnel involved in compounding, and shall maintain documentation of any and all training related to compounding undertaken by pharmacy personnel.~~

~~(c) Pharmacy personnel assigned to compounding duties shall demonstrate knowledge about processes and procedures used in compounding prior to compounding any drug preparation.~~

~~Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052 and 4127, Business and Professions Code~~

1735.7. Master Formulation and Compounding Records

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) A CNSP shall not be compounded until the facility has first prepared a written master formulation record in compliance with USP Chapter 795 and identified in that document the following additional elements:

(1) When a source is referenced to support the assigned beyond-use date (BUD); each source referenced shall be readily retrievable at the time of compounding and shall be maintained for three years from the date each CNSP is dispensed.

(2) Instructions for storage and handling of the CNSP.

(b) Where a facility does not routinely compound a particular drug preparation, the master formulation record for that preparation may be recorded on the prescription document itself. This record shall comply with USP Chapter 795 standards and this section.

(c) A compounding record (CR) shall be a single document. The document shall satisfy the compounding record requirements in USP Chapter 795, as well as the following:

(1) The date and time of preparation. The time of preparation is the time when compounding the CNSP started, which also determines when the assigned BUD starts.(2) The manufacturer, lot number, and expiration date for each component.

(3) The assigned internal identification number shall be unique for each CR.

(4) The total quantity compounded shall include the number of units made and the volume or weight of each unit.

(5) The identity of each person performing the compounding, that has direct oversight of compounding, and pharmacist verifying the final drug preparation.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

~~1735.8. Compounding Quality Assurance~~

~~(a) Any pharmacy engaged in compounding shall maintain, as part of its written policies and procedures, a written quality assurance plan designed to monitor and ensure the integrity, potency, quality, and labeled strength of compounded drug preparations.~~

~~(b) The quality assurance plan shall include written procedures for verification, monitoring, and review of the adequacy of the compounding processes and shall also include written documentation of review of those processes by qualified pharmacy personnel.~~

~~(c) The quality assurance plan shall include written standards for qualitative and quantitative analysis of compounded drug preparations to ensure integrity, potency, quality, and labeled strength, including the frequency of testing. All qualitative and quantitative analysis reports for compounded drug preparations shall be retained by the pharmacy and maintained along with the compounding log and master formula document. The quality assurance plan shall include a schedule for routine testing and analysis of specified compounded drug preparations to ensure integrity, potency, quality, and labeled strength, on at least an annual basis.~~

~~(d) The quality assurance plan shall include a written procedure for scheduled action in the event any compounded drug preparation is ever discovered to be outside minimum standards for integrity, potency, quality, or labeled strength.~~

~~(e) The quality assurance plan shall include a written procedure for responding to out-of-range temperature variations within the pharmacy and within patient care areas of a hospital where furnished drug is returned for redispensing.~~

~~Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052 and 4127, Business and Professions Code.~~

1735.8. Release Inspections and Testing

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

A pharmacist performing or supervising the nonsterile compounding is responsible for the integrity, quality, and labeled strength of a CNSP until the beyond-use date indicated on the label provided the patient or the patient's agent follows the label instructions provided on the CNSP for storage and handling after receiving the CNSP.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4036.5, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

1735.9. Labeling

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) A CNSPs label shall also include the following:

(1) Route of intended administration, and

(2) Name of compounding facility and dispensing facility (if different).

(b) A CNSPs Labeling shall also include:

(1) Any special handling instructions,

(2) Any applicable warning statements, and

(3) Name, address, and phone number of the compounding facility if the CNSP is to be sent outside of the facility or healthcare system in which it was compounded.

(c) Any CNSP dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required by Business and Professions Code section 4076 and section 1707.5.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

1735.10. Establishing Beyond-Use Dates

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) Beyond-use dates (BUDs) assigned with only a date shall expire at 11:59 p.m. on that date.

(b) A CNSP's BUDs shall not exceed:

(1) The chemical and physical stability data of the active pharmaceutical ingredient (API) and any added component in the preparation,

(2) The compatibility and degradation of the container–closure system with the finished preparation (e.g., possible leaching, interactions, and storage conditions),

(3) The shortest remaining expiration date or BUD of any of the starting components, or,

(4) The potential for microbial proliferation in the CNSP.

(c) If a licensee chooses to use antimicrobial effectiveness testing results provided by an current FDA-registered drug establishment or outsourcing facility or published in current peer-reviewed literature sources, the reference (including the raw data and testing method suitability), shall be readily retrievable in accordance with Business and Professions Code section 4081 in its entirety for three years from the last date the CNSP was dispensed.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

1735.11. Standard Operating Procedures (SOPs)

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) The facility's standard operating procedures (SOPs) for nonsterile compounding shall be followed and shall:

(1) Comply with USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding.

(2) In addition to the SOPs required in USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding, SOPs must also be developed to describe the following:

(A) Methods by which the supervising pharmacist will ensure the quality of compounded drug preparations.

(B) Procedures for handling, compounding, and disposal of infectious materials. The written SOPS shall describe the facility protocols for cleanups and spills in conformity with local health jurisdictional standards.

(C) The methods a pharmacist will use to determine and approve the ingredients and the compounding process for each preparation before compounding begins.

(D) The method for complying with any other requirements specifically required to be addressed in the facility's SOPS as described in this article.

(b) The SOPs shall be reviewed on an annual basis by the pharmacist-in-charge. Such review shall be documented by the pharmacist-in-charge consistent with the facility's SOPs. The SOPs shall be updated any time changes are made to compounding processes, facility changes or other changes occur that impact the CNSP. Such SOP changes shall be disseminated to the affected staff prior to implementation.

(c) Failure to follow written SOPs shall constitute a basis for enforcement action.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

1735.12. Quality Assurance And Quality Control

The requirements of this section apply to nonsterile compounding in addition to the standards established in USP Chapter 795.

(a) The quality assurance program shall also comply with section 1711 and the standards contained in USP Chapter 1163, entitled *Quality Assurance in Pharmaceutical Compounding*. In addition, the program shall include in its SOPs the following:

(1) A written procedure for scheduled action, such as a recall, in the event any compounded drug preparation is discovered to be outside the expected standards for integrity, quality, or labeled strength.

(2) A written procedure for responding to out-of-range temperature variations within the medication storage areas where a furnished drug may be returned for furnishing to another patient.

(b) The Board shall be notified in writing within 72 hours of the facility's receipt of a complaint of a potential quality problem or the occurrence of an adverse drug event involving a CNSP.

(c) All complaints related to a potential quality problem with a CNSP and all adverse events shall be reviewed by the pharmacist-in-charge within 72 hours of receipt of the complaint or occurrence of the adverse event. Such review shall be documented and dated as defined in the SOPs.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

1735.13. CNSP Packaging and Transporting

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

There shall be written procedures recorded in the facility's SOPs (as described in Section 1735.11) describing validated processes for storage, shipping containers and transportation of temperature sensitive CNPSs to preserve quality standards for integrity, quality and labeled strength.

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

1735.14. Documentation

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) Records shall be maintain as required by USP Chapter 795 or this article, in a readily retrievable form, for at least three years from the date the record was created or relied upon to meet the requirements of this article. If only recorded and stored electronically, on magnetic media, or in any other computerized form, the records shall be maintained as specified by Business and Professions Code section 4070.

(b) Records created shall be created and maintained in a manner to provide an audit trail for revisions and updates of each record document. Prior versions of each record must be maintained in a readily retrievable format and include the changes to the document, identification of individual who made the change, and the date of each change

Note: Authority cited: Sections 4001.1, 4005, 4057, 4126.8 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4076, 4081, 4105, 4126.8 and 4169, 4301 and 4332 of the Business and Profession Code.

Attachment 2b

Comments received related to nonsterile compounding, including any comments received after the Committee's discussion

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Board of Pharmacy

faegre drinker

faegredrinker.com

Faegre Drinker Biddle & Reath LLP
1500 K Street NW, Suite 1100
Washington, DC 20005
+1 202 230 5000 main
+1 202 842 8465 fax

February 14, 2023

VIA E-MAIL AND OVERNIGHT MAIL

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

Seung Oh, PharmD
Licensee Member, President
California Board of Pharmacy
2720 Gateway Oaks Drive
Suite 100
Sacramento, CA 95833

Re: **Medication Flavoring**

Dear Dr. Serpa and Dr. Oh:

This firm is counsel to FLAVORx, Inc., and we write to you regarding the California Board of Pharmacy's Enforcement and Compounding Committee meeting scheduled for February 15, 2022 where, among other things, the agenda includes a discussion regarding USP Chapter <795> and flavoring of conventionally manufactured nonsterile drug products.

We believe that the California Board of Pharmacy (the "Board") has the clear legal authority to continue its current policy of permitting medication flavoring without requiring adherence to the nonsterile compounding standards set forth in USP Chapter <795>.

Since the first publication of USP Chapter <795> in 2004, USP has asserted that medication flavoring constitutes compounding as defined in Chapter <795>.[1] However, the Board has consistently permitted medication flavoring despite the publication of USP Chapter <795> in 2004 and its subsequent revision in 2014. The Board ratified its position regarding medication flavoring with the promulgation of 16 CCR § 1735(b), which became effective on January 1, 2017:

> **"Compounding" does not include** reconstitution of a drug pursuant to a manufacturer's direction(s), nor does it include the sole act of tablet splitting or crushing, capsule opening, or **the addition of flavoring agent(s) to enhance palatability**.

The regulation at 16 CCR § 1735(b) does not conflict with the statute at Cal.Bus. & Prof.Code § 4126.8. This statute states:

> The compounding of drug preparations by a pharmacy for furnishing, distribution, or use in this state shall be consistent with standards established in the pharmacy compounding chapters of the current version of the United States Pharmacopeia-National Formulary, including relevant testing and quality assurance. **The board**

[1] *See* Adding Flavor to Conventionally Manufactured Nonsterile Products – USP, *available at:* https://storage.pardot.com/323321/1676042053uuJdHazV/USP22_HQS_Compounding_795_Flavoring_V5a.pdf.

> **may adopt regulations to impose additional standards for compounding drug preparations.**[2]

The statute does *not* state that the additional standards adopted by the Board must be stricter that the standards adopted by USP. "Additional standards" may be stricter or less strict than, and/or allow for exemptions from, USP standards. Thus, the Board's regulation at 16 CCR § 1735(b) does not conflict with Cal. Bus. & Prof. Code § 4126.8; rather, the two can be read together to allow the Board to adopt USP Chapter <795> *while also* allowing the Board to adopt its own changes to the standards issued by USP.

In any event, a plain reading of Cal.Bus. & Prof.Code § 4126.8 indicates that it does not encompass medication flavoring in California. The statute states that the "**compounding of drug preparations** by a pharmacy... shall be consistent with standards established in the pharmacy compounding chapters of the current version of the United States Pharmacopeia..."[3] However, Board regulations exempt medication flavoring from 'compounding' and thus, flavoring is outside the scope of this statute as flavoring does not constitute compounding under California regulation.

Finally, even if the Board were to change course and determine that medication flavoring constitutes compounding, the Board still has the authority to exercise its enforcement discretion. USP has no enforcement authority regarding Chapter <795>; rather, the adoption and enforcement of such standards rests solely with the Board.

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[2] Cal.Bus. & Prof.Code § 4126.8.
[3] *Id.* (emphasis added).

Title 16 Board of Pharmacy Proposed Regulations – Sterile Compounding

Institution/Contact	**Cedars-Sinai Medical Center** Department of Pharmacy Services 310-423-5611 Rita Shane, PharmD, Vice President & Chief Pharmacy Officer; rita.shane@cshs.org Vipul Patel, PharmD, Executive Director, Pharmacy & Oncology Services; Vipul.patel@cshs.org

Proposed Language	**Recommendations/Comments**
CCR 1736.2 Personnel Training and Evaluation. subsection (b): Aseptic manipulation competency initial training and competency and ongoing training and competency documentation shall include the Primary Engineering Control (PEC's) type and unique identifier used during the evaluation. Aseptic manipulation competency evaluation and requalification shall be performed using the same procedures, type of equipment, and materials used in compounding drug preparations. Aseptic qualifications from one premises may be used for another premises if all of the following conditions are met: 1. The SOPs are identical 2. The facility designs are identical 3. The PECs are of the same type and sufficiently similar to accommodate the use of the same SOPs describing use and cleaning	**Rationale:** • The new USP 797-chapter requires a significant increase in the frequency of observation, garbing, glove finger testing, media fill and surface sampling. This coupled with the growth in census volumes, complexity of patient diseases requiring IV therapy[1] and the workforce challenges[2,3,] creates significant constraints for hospital pharmacies to complete competency training for each compounding site for all compounding personal. The inability to have staff perform compounding in another licensed site with identical SOPs and PECs would delay patient care and result in potential patient harm • Statement #2 indicating "Facility designs are identical" would further increase the requirements above and associated costs. It is rare and not common that the physical layout of clean rooms or segregated compounding areas are identical. If the intent of the Board is to differentiate the type of room (i.e classified vs non-classified) recommend removing #2 and update #3 to include Secondary Engineering Controls (SEC) are the same type to meet the intent of #2. **Recommendation:** 1. *The SOPs are identical.* ~~2. *The facility designs are identical*~~ 3. *The PECs and SECs are of the same type and sufficiently similar to accommodate the use of the same SOPs describing use and cleaning* References: 1. Drug Shortages List. American Society of Health-System Pharmacy. https://www.ashp.org/drug-shortages/current-shortages/drug-shortages-list?page=CurrentShortages. Accessed March 20, 2023. 2. Pharmacy technician shortage survey findings executive summary. American Society of Health-System Pharmacy. March 2020. Accessed March 20, 2023. 3. Hospitals Scramble as Pharmacy Technician Shortage Persists (ashp.org) https://www.ashp.org/News/2022/05/02/hospitals-scramble-as-pharmacy-technician-shortage-persists. Accessed March 20, 2023.

Title 16 Board of Pharmacy Proposed Regulations – Sterile Compounding

Proposed Language	Recommendations/Comments
CCR 1736.11 Master Formulation and Compounding Records. subsection (c)(3): The manufacturer, lot number, and expiration date shall be recorded for each component for CSPs.	**Rationale:** Current language in CCR 1735.3 states: (F) The manufacturer, expiration date and lot number of each component. If the manufacturer name is demonstrably unavailable, the name of the supplier may be substituted. If the manufacturer does not supply an expiration date for any component, the records shall include the date of receipt of the component in the pharmacy, and the limitations of section 1735.2, subdivision (l) shall apply. (i) Exempt from the requirements in this paragraph (1735.3(a)(2)(F)) are sterile preparations compounded in a single lot for administration within seventy-two (72) hours to a patient in a health care facility licensed under section 1250 of the Health and Safety Code and stored in accordance with standards for "Redispensed CSPs" found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP37-NF32) Through 2nd Supplement (37th Revision, Effective December 1, 2014), hereby incorporated by reference. **Recommendation:** Add back the language above: 1736.11 Master Formulation and Compounding Records, subsection (c)(3): ***The manufacturer, lot number, and expiration date shall be recorded for each component for CSPs.*** *(i) Exempt from the requirements in this paragraph are sterile preparations compounded in a single lot for administration within seventy-two (72) hours to a patient in a health care facility licensed under section 1250 of the Health and Safety Code.*
CCR 1736.1 Sterile Compounding Scope. Subsection (b): CSPs for direct and immediate administration as provided in the Chapter shall only be done in those limited situations where the failure to administer could result in loss of life or intense suffering. Any such compounding shall be only in such quantity as is necessary to meet the immediate need. Documentation for each such CSP shall include identification of the CSP, compounded date and time, number of units, the patient's name and patient's unique identifier and the circumstance causing the immediate need.	**Rationale:** In the instance of a code blue in a hospital, the requirement for additional documentation goes against the very purpose of making a drip to prevent a loss of life. The burden of completing additional documentation while attempting to save a life, could work to the detriment of a patient in an emergent situation. We recommend the board to remove language requiring documentation due to patient safety concerns. **Recommendation:** ***1736.1 Sterile Compounding Scope. Subsection (b)*** *CSPs for direct and immediate administration as provided in the Chapter shall only be done in those limited situations where the failure to administer could result in loss of life or intense suffering. Any such compounding shall be only in such quantity as is necessary to meet the immediate need.* ~~*Documentation for each such CSP shall include identification of the CSP, compounded date and time, number of units, the patient's name and patient's unique identifier and the circumstance causing the immediate need.*~~

Title 16 Board of Pharmacy Proposed Regulations – Sterile Compounding

Proposed Language	Recommendations/Comments
CCR 1736.1 Sterile Compounding Scope. Subsection (d) (1) (A): (d) In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that: (1) Is essentially a copy of one or more commercially available drug products, unless: (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, or	**Rationale:** • The ASHP and FDA drug shortage lists do not always reflect real-time real time drug shortages. Health systems have monitoring strategies in place to track these drug shortages real-time from drug manufacturers or wholesalers before these shortage drugs get added to the ASHP and FDA drug shortage lists. **Recommendation:** Recommend the board to add language regarding recent drug shortages that may not be reflected on the ASHP and FDA lists to ensure that health systems are compliant with requirements. ***1736.1 Sterile Compounding Scope. Subsection (d) (1) (A):*** *(d) In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that:* *(1) Is essentially a copy of one or more commercially available drug products, unless:* *(A) that drug product appears on an ASHP (American Society of Health- System Pharmacists), ~~or~~ FDA list of drugs, or recent drug shortage that has not been added to the aforementioned lists that are in short supply at the time of compounding and at the time of dispense, or*
CCR 1736.11 Master Formulation and Compounding Records subsection (c): A compounding record shall be a single document. The document shall satisfy the requirements of USP Chapter 797, as well as the following: (1) The date and time of preparation. The time of preparation is the time when compounding the CSP started, which also determines when the assigned BUD starts. (2) The assigned internal identification number shall be unique for each compounded drug preparation. (3) The manufacturer, lot number, and expiration date shall be recorded for each component for CSPs. (4) The total quantity compounded shall include the number of units made and either the volume or the weight of each unit. (5) The identity of each person performing the compounding and pharmacist verifying the final drug preparation (6) When applicable, endotoxin level calculations and results.	**Rationale:** • Current documentation practices in Health-System pharmacies include utilizing electronic record keeping systems/software. However, it is not always feasible for the required elements of the electronic records to be pulled from computer software on a single document. **Recommendation:** Recommend the Board of Pharmacy to consider removing the requirement of "single document" to readily retrievable document to satisfy the requirements of USP Chapter 797 ***CCR 1736.11 Master Formulation and Compounding Records subsection (c):*** *A compounding record shall be a readily-available ~~single~~ document. The document shall satisfy the requirements of USP Chapter 797, as well as the following:*

Title 16 Board of Pharmacy Proposed Regulations – Sterile Compounding

Proposed Language	Recommendations/Comments
CCR 1736.13 Labeling subsection (b): (b) Any CSP dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required by Business and Professions Code section 4076 and section 1707.5.	**Rationale:** Currently, a health facility, as defined in Section 1250 of the Health and Safety Codes, are exempt from patient centered label requirements. **Recommendations:** To be consistent with current regulations, recommend adding exemption language to the current proposed language for HSC 1250 (a) licensed facilities as the administration of compounded medications to patients are done by health care personnel authorized to administer medications and not dispensed for outpatient use. ***CCR 1736.13 Labeling subsection (b):*** *(b) Any CSP dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required by Business and Professions Code section 4076 and section 1707.5.* *(i) Exempt from this requirement are health facilities, as defined in Section 1250 of the Health and Safety Code, if the prescriptions are administered by a licensed health care professional. Prescriptions dispensed to a patient in a health facility that will not be administered by a licensed health care professional or that are provided to the patient upon discharge from the facility shall be subject to the requirements of this section and the regulations promulgated pursuant to subdivision (b).*

From: Christian James
To: Damoth, Debbie@DCA
Subject: URGENT: Parents Concern for Flavoring Medication
Date: Friday, April 14, 2023 11:44:03 AM

WARNING: This message was sent from outside the CA Gov network. Do not open attachments unless you know the sender: christianjames728@gmail.com

Greetings,

It has been brought to my attention that the California Board of Pharmacy is thinking about making it almost impossible for pharmacies to flavor medicine in our great state of California. As a mother of two children who require medication to thrive in their day to day life, this is very alarming. Flavoring my children's medication helps ensure that they are able to take medication without a struggle and continue to thrive.

The potential ban of flavoring medications in the State of California could have a detrimental impact on children who need medication, but refuse to take medication due to the flavor that the medication has. No child has been hurt by flavoring. As a parent, I have never once heard another parent that has complained about flavoring. No medication has been rendered inactive by flavoring. Truly the only thing flavoring has done is help children, mine included, take their medicine when they would otherwise struggle.

My daughter has been on medication since she was a year old and without flavoring, we would have struggled for her to take her medicine due to the disgusting flavor it usually has.

I greatly urge the State of California to reconsider these strict regulations put in place on flavoring medicines. By making it EXTREMELY difficult to offer flavoring for children in a regulatory oversight perspective, pharmacies will cease to offer flavoring which in turn will be detrimental to our children in California.

Thank you
Christian Mulkey

From: jmcgop@aol.com
To: Damoth, Debbie@DCA
Subject: Parenting- State Pharmacy Board
Date: Friday, April 14, 2023 9:59:01 AM

WARNING: This message was sent from outside the CA Gov network. Do not open attachments unless you know the sender: jmcgop@aol.com

To Whom It May Concern,

We know children can be fussy and uncooperative when taking medicine. Flavored medication can make it easier for children to take necessary treatments and improve their health.

Please don't take any of the options from our local pharmacies to add flavoring to medicine.

Parenting is hard enough without finding a compounding pharmacy or having parents mix in their flavoring.

Thank you.

Julie Vallante

From: Amy Dellinger
To: Damoth, Debbie@DCA
Subject: Medicine Flavoring - Local Pharmacy
Date: Thursday, April 13, 2023 11:17:14 AM

WARNING: This message was sent from outside the CA Gov network. Do not open attachments unless you know the sender: amy@adellingerevents.com

Ms. Damoth,

Please share my concerns with the California Board of Pharmacy.

Please don't remove my child's ability to choose her medicine flavoring.

When my daughter is not feeling well, I do everything I can to comfort her, make her feel better, and let her pick the flavoring of her medicine so that she takes it all and gets better.

As a parent with a sick child, it is already stressful, and taking away this choice or having me during this period, having to search for a compounding pharmacy, is a heavy burden.

What about the parents who live in our more rural communities, northern California or Central Valley, where there are fewer options?

Why create more difficulties for parents when there isn't an existing problem?

Thank you,

Amy Dellinger

From:	Keller, Jonathan A.
To:	Damoth, Debbie@DCA
Cc:	Baney, Libby
Subject:	Materials for Consideration - Board of Pharmacy April 19-20 Meeting
Date:	Friday, April 14, 2023 12:02:05 PM
Attachments:	NABP Innovations Newsletter_Medication Flavoring Article_Marc_2023.pdf

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WARNING: This message was sent from outside the CA Gov network. Do not open attachments unless you know the sender: jonathan.keller@faegredrinker.com

Dear California Board of Pharmacy:

I am writing to provide the Board of Pharmacy (the "Board") with the attached article regarding medication flavoring that was published in the March 2023 issue of NABP Innovations Newsletter. I understand at the upcoming Board meeting (April 19-20), the Board will review a summary of the Enforcement and Compounding Committee's (the "Committee") recent work that was conducted in 2023. This work may include, among other things, the Committee's recommendation to repeal 16 CCR § 1735 in its current form and adopt new regulations that will change how California views medication flavoring. I submit the attached article to provide the Board with additional information regarding the current status of medication flavoring throughout the United States. Thank you.

Jonathan

Jonathan A. Keller
Counsel
jonathan.keller@faegredrinker.com
Connect: vCard

+1 973 549 7059 direct

Faegre Drinker Biddle & Reath LLP
600 Campus Dr.
Florham Park, New Jersey 07932, USA

March 2023 | Volume 52 | Number 3

INNOVATIONS

CONTINUITY, COLLABORATION

2022

Year in Review

NABP
National Association of Boards of Pharmacy

Something Tastes Different: Is Medication Flavoring Compounding?

Libby Baney, JD
Faegre Drinker Biddle & Reath LLP

Jonathan A. Keller, PharmD, JD, RPh
Faegre Drinker Biddle & Reath LLP

Ryan Shay, MA
Faegre Drinker Biddle & Reath LLP

It is no secret that children do not enjoy taking medication. If you have children, you know what a struggle it can be to get them to take their medicine. Pleading, arguing, and even bribing are all tactics parents employ to get their children to swallow the medicines they so desperately need. Most often, the culprit for these medicine-related meltdowns is taste.

To lessen this challenge, pharmacists have added flavoring to prescription medications, such as bubble gum, for decades. Using specific equipment and training, medication flavoring takes place at more than 40,000 pharmacies each year as a point-of-care service focused on improving the taste and palatability of children's liquid medication. It literally helps to make "the medicine go down."

Like many aspects of pharmacy, flavoring has become more sophisticated over time. Today, typical flavoring agents are independently tested, manufactured in Food and Drug Administration (FDA)-registered facilities, and are chemically inert. There have been no reports in decades, if ever, of patient harm or death from the use of medication flavoring. Further, flavoring medications can now be automated by flavoring machines. In pharmacies that have this specialized equipment, the pharmacist is no longer required to physically add the various sweeteners and flavoring agents; instead, the flavoring process is fully automated and accomplished with the touch of a few buttons.

How Is the Practice of Medication Flavoring Regulated?

It depends. While FDA's definition of "compounding" does not explicitly include flavoring, it is implied. However, the state boards of pharmacy – not FDA – have final say as to the regulation of medication flavoring.

Many state boards of pharmacy have explicitly exempted medication flavoring from the state's definition of drug compounding, thus preventing flavoring from being regulated as compounding. State regulators have observed that the act of flavoring does not rise to the level of traditional compounding in any practical way. Further, several other states have issued guidance indicating that their boards of pharmacy do not consider flavoring to be compounding or regulate it as such. In total, 25 states have a law, regulation, or similar guidance that carves out medication flavoring from traditional compounding requirements. Practically speaking, this means flavoring is permitted in those 25 states without having to comply with United States Pharmacopeia (USP) standards applicable to nonsterile compounding in USP Chapter <795>.

Twenty-four states have not taken a formal stance on medication flavoring, but as a policy, they appear to not regulate flavoring as compounding. Washington State has indicated that medication flavoring constitutes compounding and, as such, flavoring must comply with the requirements applicable to compounded nonsterile preparations.

What Has Changed or – More Accurately – Has Not Changed

In November 2022, USP reiterated its definition of compounding. Specifically, USP issued a guidance document underscoring that its definition of compounding has not changed since General Chapter <795> was originally published in 2004 (and subsequently revised in 2014): nonsterile compounding is defined as combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer package insert, or otherwise altering

a drug or bulk drug substance to create a nonsterile medication.

The USP Guidance included comments specific to flavoring as it relates to compounding: adding components (such as flavors) not stipulated in the labeling to conventionally manufactured products is compounding as defined in <795> and has been within the scope of <795>.

From a substantive standpoint, USP has not changed its position nor its definition of compounding since 2004. However, by issuing a recent guidance document regarding medication flavoring, USP has reiterated its position that flavoring falls within the purview of General Chapter <795>. Simply put, by describing the "adding of components (such as flavors)" under the definition of nonsterile compounding, nonsterile compounding requirements necessarily follow – unless an exemption or other caveat is in place. Therefore, if states were to adopt USP's General Chapter <795> in its entirety, then medication flavoring would be subjected to all of the nonsterile compounding requirements set forth in General Chapter <795>. Proponents of flavoring argue that requiring compliance with General Chapter <795> in order to flavor medicines will lead to pharmacies refusing to offer patients this service because of the additional requirements that pharmacies would need to implement.

Using specific equipment and training, medication flavoring takes place at more than 40,000 pharmacies each year as a point-of-care service focused on improving the taste and palatability of children's liquid medication.

The State of the States – For Now

Half of the states have taken efforts to expressly clarify that medication flavoring does not constitute compounding in their state. Because of this clarification, the act of medication flavoring is not subject to the USP requirements applicable to compounding drugs. The remaining 25 states (Washington State being the one exception), the District of Columbia, and Puerto Rico appear to have an implicit policy whereby the board exercises its enforcement discretion to not enforce USP General Chapter <795> nonsterile compounding standards as they pertain to medication flavoring, thereby allowing pharmacies to flavor medication without having to meet USP's nonsterile compounding requirements. To date, state action on flavoring has been almost unanimously focused on carving out medication flavoring from compounding requirements.

In the states that have not taken an official position on whether medication flavoring constitutes compounding, when USP's revised General Chapter <795> goes into effect on November 1, 2023, it is unclear whether they will use enforcement discretion to allow flavoring to continue outside of compounding pharmacies. Medication flavoring advocates are ringing alarm bells, fearing that this decrease in pharmacy-directed flavoring would decrease medication adherence for children and increase negative health outcomes.

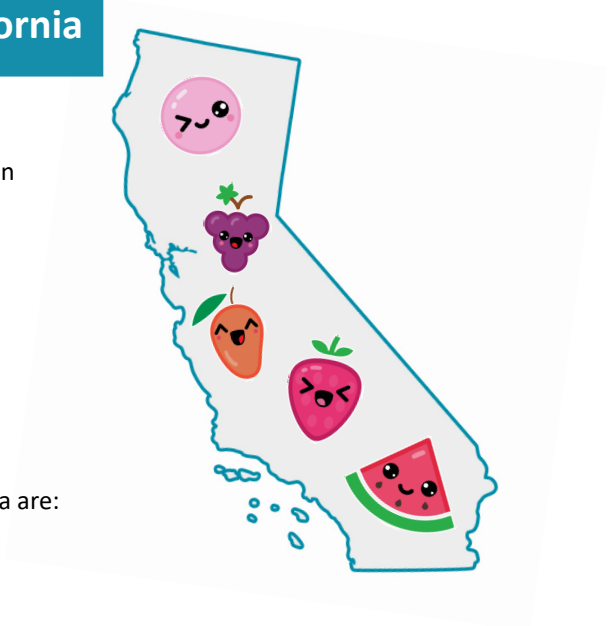
Flavoring in 2023 and Beyond

Noting the lack of any reported patient harms, states with existing exemptions for medication flavoring will likely retain the status quo. What will the remaining states and jurisdictions do? Stay tuned. In all states, it is up to the boards of pharmacy to decide whether non-compounding pharmacies will be able to offer flavored medications. ●

This article was written by Libby Baney, JD; Jonathan A. Keller, PharmD, JD, RPh; and Ryan Shay, MA, with Faegre Drinker Biddle & Reath LLP. Please note, the opinions and views expressed by Faegre Drinker Biddle & Reath do not necessarily reflect the official views, opinions, or policies of NABP or any member board unless expressly stated.

Please Keep California Flavor-Full!

The Medication Flavoring Landscape in California



- 3,000+ pharmacies in California offer flavoring to their customers, primarily for commercially available liquid medications.
- 6 million children under the age of 11 live in California - these children typically take liquid medications when they are sick.
- At least 300,000-500,000 medications are flavored every year in California's pharmacies, depending on the severity of cold/flu season.
- Commonly flavored medications in California's pharmacies include:
  - Amoxicillin
  - Augmentin
  - Cleocin
  - Tamiflu
  - Zithromax
- The most popular medication flavors selected by children in California are:
  - Bubblegum
  - Grape
  - Mango
  - Strawberry
  - Watermelon

Flavoring in Action
Jamie T.
Pharmacy Manager in California

"As we all know clindamycin liquid is not very appeasing to any kid the smell alone is horrendous. We had a young patient needing about 6 bottles to complete her therapy and the mom said she hates taking medication so she was worried about her daughter not taking this antibiotic. I told her we can flavor it and the machine we have marks which flavors work best with the medicine. The mom was very excited and I gave her the options. She asked if we could do a different flavor for each one if possible and I said yes excitedly, I marked each bottle with the recommended flavor from FLAVORx. I told the mom which ones were which she was very happy we were able to help her daughter. I called her 2 days later to see how her daughter was doing and she was almost in tears her daughter loved the grape-ade flavor the best. She was so appreciative of our call. It was all because we have the amazing machine to help guide us and made it super easy to help our patient."

Most, if not all, of us have been there. Whether you hated taking medicine as a child or your children struggle with it now, taste is almost always the reason the medicine won't go down without a fight.

Due to the California Board of Pharmacy's forward-thinking approach, every pharmacy in California has the ability to improve pediatric compliance and make medicine-time easier for children by letting them choose how their medicine will taste.

That's because, since 2014, the California Board of Pharmacy has had the following language on the books:

Article 4.5 Compounding 1735. Compounding in Licensed Pharmacies (b) "Compounding" does not include reconstitution of a drug pursuant to a manufacturer's direction(s), nor does it include the sole act of tablet splitting or crushing, capsule opening, or the addition of flavoring agent(s) to enhance palatability

- **NO ADVERSE EVENTS:**
  Since this language was adopted almost a decade ago, millions of children's medications have been flavored in California's pharmacies with no reported adverse events or incidents of harm. Furthermore, over our 25+ years of operation, we estimate 180 million medications have been flavored using the FLAVORx system across the country, again with **no reported adverse events or incidents of harm.**

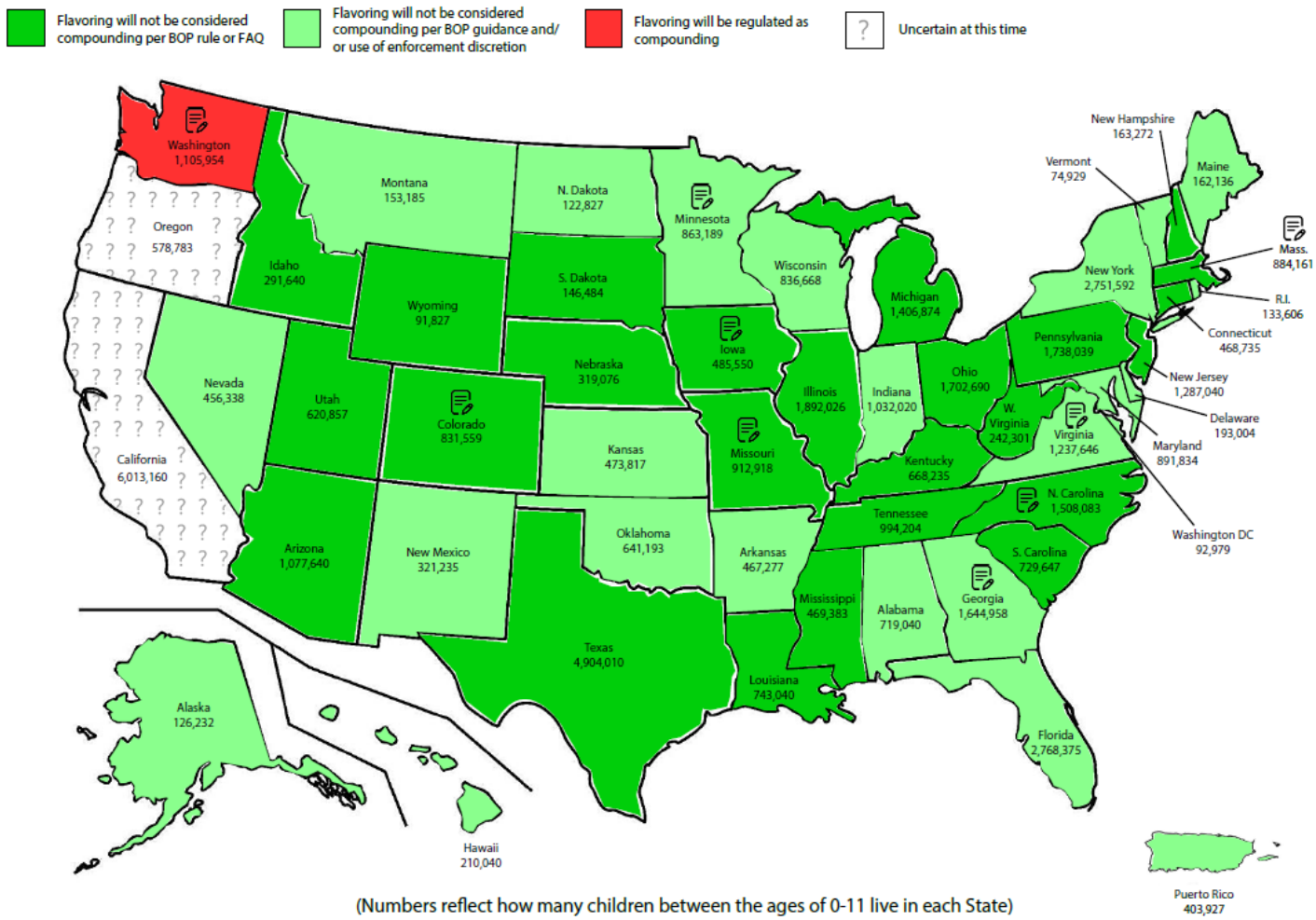
- **IMPACT ON CALIFORNIA KIDS:**
  Should the California Board of Pharmacy change its currently held position on flavoring and begin to regulate this core pharmacy service under new USP 795 non-sterile compounding standards, most pharmacies in California will cease to offer flavoring to their customers. We understand flavoring will not be illegal. But the new regulatory requirements non-compounding pharmacies will be forced to comply with will make it effectively impossible. If this happens, parents in California, many of whom rely on flavoring now, will be forced to resort to home-cooked methods to get the medicine down or, what's even more likely, kids won't take their medicine at all. That would be disastrous for children's health.

- **REQUEST:**
  On behalf of the thousands of pharmacies in California who provide the flavoring service and the millions of children who benefit from it, **we urge the California Board of Pharmacy to stay the course and keep "the addition of flavoring agents" an activity that is not included in compounding.**

It is important to note that there is nothing new about USP's stance on flavoring. This has been USP's position since 2004. The California Board of Pharmacy felt otherwise in 2014, and took the forward-thinking position currently found in Article 4.5 Compounding 1735. By keeping a flavoring carve-out provision in place, the Board is further demonstrating its commitment to protect and promote the safety and health of all Californians.

How Each State Plans to Approach Flavoring

ANTICIPATED **BOARD OF PHARMACY POSITIONS** TOWARDS **FLAVORING** ON NOVEMBER 1, 2023
(STATUS AS OF APRIL 14, 2023)



(Numbers reflect how many children between the ages of 0-11 live in each State)

Data Source: Population Division, U.S. Census Bureau

How Do Medicines Get Flavored with FLAVORx?

For starters, there are three ways kids can get their medicine flavored at the pharmacy.

1. Parents can ask for it.
2. Pharmacists can recommend it.
3. Prescribers can write for it.

Most of the time, it's the pharmacist who recommends flavoring. They know the medications that kids often struggle to take. They also know the kids who often struggle taking medicine.

Once the child or the parent has chosen a preferred flavor, the FLAVORx program kicks in. With FLAVORx, medications can be flavored by hand or by a machine.

Flavoring The Automated Way

If the pharmacy has one of our automated dispensers, the steps are as follows:

Scan the barcode of the medication to be flavored

Confirm the information on the screen is correct

Select the preferred flavor

Press "Dispense"

If reconstitution is required, the machine will dispense water and flavor simultaneously. This process, from scan to bag, takes about 20 seconds.

It's important to note the machine will remove the precise amount of water that is being replaced by flavoring ingredients to keep the concentration of drug per dose the same.

For Example: a 100ml bottle of Cleocin 75mg/5ml Granules, that would normally need 75mls of water to reconstitute, would instead get 72.7ml of water and 2.3ml of flavor ingredients, if the child chose to have it taste like bubblegum instead of...whatever they call that Cleocin flavor (its supposed to be cherry btw).

If the medication does not require reconstitution, the amount of flavor added to liquid medications usually amounts to 3% of a drugs total volume, and never exceeds 5%, so changes to concentration are small and always within acceptable thresholds of variance.

To see a video of the FLAVORx Auto in action, go to www.flavorxauto.com

Flavoring The Manual Way

If a pharmacy does not have one of our machines, the steps are as follows:

Lookup the flavoring recipe using our online tool.

- The pharmacist selects the drug, the volume, and the flavor to get the recipe, which is unique to that drug and flavor.

Following the recipe, the pharmacist adds the quantities of flavor ingredients specified, using calibrated oral syringes to dispense flavor into the medication

This process, along with reconstitution, takes about 2 minutes.

If reconstitution is required, the pharmacist is directed to remove the amount of water that will be replaced by the flavor ingredients. If reconstitution is not required, the pharmacist adds the flavor to the liquid medication. Same as above, the concentration of the medication is either unchanged or negligibly impacted by the addition of flavor. We're talking a couple of drops per dose at the most.

And that is how medicines get flavored with FLAVORx.

From: Vanessa Diaz
To: Damoth, Debbie@DCA
Subject: Keep Allowing Pharmacies to Flavor Medicines
Date: Thursday, April 13, 2023 4:40:52 PM

WARNING: This message was sent from outside the CA Gov network. Do not open attachments unless you know the sender: briteandbubbly@gmail.com

Hello, It has been brought to my attention that the California Board of Pharmacy is thinking about making it almost impossible for pharmacies to flavor medicine in the great state of California. I am a resident in Los Angeles/Sherman Oaks and I am a parent. I don't understand why the California Board of Pharmacy would purposely want to make it harder for parents. Most parents already have a difficult time getting kids to take medicines when they need them to take medicines. Taking away the flavoring of medicines would be a literal nightmare for parents. No child loves the way medicines taste and kids will outright refuse to take medicines they need to take without it. There is no reason to do this and it should not be done! There are better things to worry about like making prescriptions cheaper for people. No child has been hurt, no parents have complained about this, and no medication has been rendered inactive by flavoring. There is literally no reason to do this other than to make parents' lives more difficult than they already are! Do not do this and keep allowing our pharmacies to flavor medications. They are literally a life saver!

Thank you,

Vanessa Diaz
Sherman Oaks, CA

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If reconstitution is required, the machine will dispense water and flavor simultaneously. This process, from scan to bag, takes about 20 seconds.

It's important to note the machine will remove the precise amount of water that is being replaced by flavoring ingredients to keep the concentration of drug per dose the same.

For Example: a 100ml bottle of Cleocin 75mg/5ml Granules, that would normally need 75mls of water to reconstitute, would instead get 72.7ml of water and 2.3ml of flavor ingredients, if the child chose to have it taste like bubblegum instead of...whatever they call that Cleocin flavor (its supposed to be cherry btw).

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And that is how medicines get flavored with FLAVORx.

From:	Acosta, Christine@DCA
To:	Damoth, Debbie@DCA
Cc:	Sodergren, Anne@DCA
Subject:	FW: USP 795 FAQ #44 MFR vs CR for different quantities
Date:	Thursday, March 16, 2023 8:13:23 AM
Attachments:	image001.png image002.png

Thank you,
Christine Acosta PharmD, Supervising Inspector
California State Board of Pharmacy
(619) 818-7255 | FAX (760) 796-4610 | www.pharmacy.ca.gov
Be Aware and Take Care: Talk to your Pharmacist!
Useful links:
2023 law book: **https://pharmacy.ca.gov/laws_regs/lawbook.pdf**

From: Marie Cottman <marie@pacificcompound.com>
Sent: Wednesday, March 15, 2023 7:05 PM
To: Panella-Spangler, Peg@DCA <Peg.Panella-Spangler@dca.ca.gov>; Acosta, Christine@DCA <Christine.Acosta@dca.ca.gov>
Subject: USP 795 FAQ #44 MFR vs CR for different quantities

WARNING: This message was sent from outside the CA Gov network. Do not open attachments unless you know the sender: marie@pacificcompound.com

Dear Inspector Panella-Spangler and Inspector Acosta,

I apologize for not being present at the Compounding and Enforcement Committee meeting in February. I am in the process of reviewing that material.

In reference to USP <795> FAQ #44 relative to Master Formulas, I partook of a USP Virtual Open Forum webinar on November 8th, 2022 where the USP committee specifically addressed this. Based on the response of the Committee, I believe that USP has a typo in FAQ#44; it should state that a new Compounding Record (CR not MFR) must be generated for each different quantity. I acknowledge that this is NOT what the printed material states, but clarification from USP should be acquired as this would be an onerous requirement that would likely cause more compounding errors.

Here is the link to the webinar recording. (https://uspevents.webex.com/recordingservice/sites/uspevents/recording/d83d929b419e103badb18e1b4c569c84/playback)
You will find the question posed to the Committee at 51:50. Gus Bussani (<795> Sub Committee Chair) indicates that clearly a separate CR is required for different quantities, but it wasn't the intent of the Committee to have a separate MFR for each quantity; while Brenda Jensen (Chair of the Compounding Expert Committee) states definitively that an MFR is for every unique entity and "quantities can change. We may need to look at that FAQ to make sure it is clear."

I hope this is helpful to the discussion of USP 795 and the proposed regulations in California. Further, I hope it clarifies and simplifies enforcement for both inspectors and

licensees.

I fully expect that you will reach out to the USP Compounding Committee for further clarification on this matter.

Sincerely,

Marie

Marie Cottman, Pharm.D.
Clinical Pharmacist/ Co-Owner
Pacific Compounding Pharmacy and Consultations
312 Lincoln Center
Stockton, CA 95207
209-474-7271
fax 209-474-7168

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From: thatocmama@yahoo.com
To: Damoth, Debbie@DCA
Subject: Don"t Repeal to California Code of Regulations Article 4.5, Section 1735
Date: Thursday, April 13, 2023 3:59:12 PM

WARNING: This message was sent from outside the CA Gov network. Do not open attachments unless you know the sender: thatocmama@yahoo.com

Debbie,

According to Pfizer "Children are generally more sensitive to sweet and bitter flavors than adults, and an additional 10 percent of kids have elevated taste receptors, which could make a drug that tastes acceptable to the majority of kids taste terrible to a minority of kids."

I am writing to you not only as a parent but as a professional who worked in the drugstore industry. And I spent a few years working for a drug stores like Sav-on and Longs. I worked in the actual pharmacy and filled prescriptions when I was training to be a pharmacy technician. There are so many reasons repealing the California Code of Regulations Article 4.5, Section 1735 is not only wrong, it's unethical.

Foremost, let me state is ultimately the parents' choice whether the medication should be flavored. If you repeal this regulation, you were taking away the choice that only a parent should make. This makes it harder for a parent to give their child medication in a way that is not forceful and traumatic.

It also makes it harder for the pharmacies, and many pharmacies (especially ones that are owned by the actual pharmacist, not a corporation) to keep the customer satisfied. You will hear all the pharmacies complaining that parents are coming back and asking for more medication because their children spit it out. Trust me, I know from experience. How are sick children supposed to get better if they won't swallow their medicine?

What about the impact this will have fiscally (California has the largest economy in the United States that is also the most populated state in the country) on the pharmaceutical companies and the pharmacies themselves? Think of all the medication that will be lost from children refusing to take it or spitting it out?

Can you imagine how difficult a nurse's job is going to be when they're trying to force a child in the hospital to take a medication that they refuse to swallow? Especially when they are trying to force a child to take medication that would've taken three seconds before, which now takes a long time? Trying to get a small child or infant to swallow medication that is bitter and unpalatable is not an effortless task. Could you imagine how much time is being wasted when the nurse could help another patient instead?

When you take away the flavoring you make taking medicine something traumatic,

especially for small children who don't understand the need to take medicine to get a better. We all have seen a child at least once in our lifetime being held down and forced to take medication that they don't want. It is a terrifying, traumatic experience for them. And there's no reason for it. How is it OK to say that parents no longer have the choice to flavor their children's medication?

And as a neurodivergent individual with a chronic medical condition myself, I cannot imagine how cruel that would be especially when the child is terminally ill, has a chronic condition or is neurodivergent and really has no choice but to take medication daily.

I beg of you to reconsider and keep California Code of Regulations Article 4.5, Section 1735 on the books. There is no logical reason for this. And ultimately repealing it will probably end up in a long and drawn out expensive litigation. So what's the point of repealing it to begin with when it's probably going to be overturned in court?

Even if you can take away the flavoring in the pharmacy, they still have plenty of over-the-counter medication is available for children in flavors. So this makes no sense.

Sincerly,

Megan H. Beaver
26371 Paloma apt 113
Foothill Ranch Ca 92610

CALIFORNIA® VETERINARY MEDICAL ASSOCIATION

1400 River Park Drive, Suite 100
Sacramento, CA 95815-4505
916-649-0599
fax 916-646-9156
staff@cvma.net
www.cvma.net

February 6, 2023

Maria D. Serpa, PharmD
Chair, Enforcement and Compounding Committee
California Board of Pharmacy
2720 Gateway Oaks Drive, Suite 100
Sacramento, CA 95833

RE: Comments on Board of Pharmacy Discussion, Consideration and Possible Action on Proposed Changes to Regulations Related to Pharmaceutical Compounding of Nonsterile Preparations

Dear Dr. Serpa:

The California Veterinary Medical Association (CVMA), representing over 7,800 veterinarians, registered veterinary technicians, and veterinary students, would like to ensure that potential changes to California Code of Regulations, Title 16 (16 CCR), section 1735.2(c)(3) do not further harm California's pets, consumers, or the veterinarians who are trying to provide vitally needed medications to their patients.

Now, more than ever, veterinarians are experiencing difficulties in finding and obtaining sources of medications needed to treat patients immediately. The CVMA notified your Board of this growing issue in a letter dated January 19, 2022 (see attached). As stated in that letter, in many instances the pharmaceutical industry falls short of providing FDA-approved medications commonly utilized in veterinary practice. As a result, the veterinary industry relies on compounding pharmacies to provide such medications in order to effectively treat animal patients to alleviate suffering, illness and death. While the recent emergence of 503B outsourcing facilities in California has helped to some degree, only two outsourcers in California currently carry appreciable lines of veterinary products. While some outsourcers advertise sterile compounds for veterinary practice, most of those are chemotherapeutics, which represent a small subset of medications used by veterinarians. Thus, the 503B route is not a complete solution to veterinarians finding medications that they need on hand to help animals in need.

Veterinarians must rely on 503A pharmacies to fill gaps in medication availability, including for medications needed in-house to treat patients. Unlike humans, animals instinctively hide their pain or illness, which results in many of them needing immediate treatment when they come to a veterinary practice. Because so few 503A compounding pharmacies offer veterinary products in California, consumers must often wait several days for a patient-specific prescription to be filled. This is due not only to stringent compounding mandates, but also to delays experienced when trying to locate a pharmacy willing to compound a veterinary medication. It is not uncommon for veterinarians and consumers to wait weeks for an animal patient to receive the medication that it needs pursuant to a patient-specific prescription. And, despite the CVMA's

multiple communications to the Board of Pharmacy over the past decade, this problem has grown worse as a result of regulatory changes that have resulted in an industry shift.

CCR 16 section 1735.2(c)(3) indicates that a 503A compounding pharmacist can prepare in advance, in anticipation of a veterinarian's needs, a supply that is "sufficient for administration or application to patients solely in the prescriber's office, or for furnishing of not more than a 120-hour supply for veterinary medical practices, solely to the prescriber's own veterinary patients seen as part of regular treatment in the prescriber's office, as fairly estimated by the prescriber and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing." At the time that this regulation was instituted, the CVMA met with then BOP Executive Officer Ginny Herold and DAG Joshua Room to discuss the significance of this requirement. At that time, Mr. Room explained that this regulation applied to compounding pharmacists in the amount of medication that they could prepare in advance, but did not apply to veterinarians in the amount that they could furnish on a patient-by-patient basis. While the concept is for the veterinarian to furnish an average of a 120-hour supply to each patient, Section 1735.2(c)(3) does not dictate or limit the professional decisions that a veterinarian makes in the course of patient treatment. Therefore, if a veterinarian feels that they must provide more than a 120-hour supply of a medication to a given patient, they are free to do so.

At the time that Section 1735.2(c)(3) was passed, it was anticipated that a compounding pharmacist could provide medication pursuant to receipt of a patient-specific prescription in four days time. The CVMA positively attests that more often than not, this is not the case. To that end, the CVMA would like to request that the Board of Pharmacy increase the average supply of medication that a pharmacy can prepare in advance to a seven day average supply per patient, based on anticipated needs as identified by the veterinarian. The CVMA proposes the following specific wording change to CCR 16 section 1735.2(c)(3):

> *Is sufficient for administration or application to patients solely in the prescriber's office, or for furnishing of not more than a ~~120-hour~~ seven day supply per animal patient for veterinarian prescribers ~~veterinary medical practices~~, solely to the veterinarian prescriber's own ~~veterinary~~ patients ~~seen as part of regular treatment in the prescriber's office~~, as fairly estimated by the veterinarian prescriber in anticipation of their patient needs and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing.*

Thank you for your consideration.

Dan Baxter
Executive Director

Enclosure

1400 River Park Drive, Suite 100
Sacramento, CA 95815-4505
916-649-0599
fax 916-646-9156
staff@cvma.net
www.cvma.net

January 19, 2022

California Board of Pharmacy c/o
Anne Sodergren, Executive Officer
2720 Gateway Oaks Drive, Suite 100
Sacramento, CA 95833

RE: Lack of Crucial Veterinary Medications in California

Dear Ms. Sodergren,

The California Veterinary Medical Association (CVMA), representing over 7,800 veterinarians, registered veterinary technicians, and veterinary students, would like to inform the Board of Pharmacy (BOP) of a critical issue facing veterinarians due to a combination of changes to state compounding regulations and BOP enforcement action (also being termed "pharmacist education.")

Several times in the past, including most recently on October 23, 2020, the CVMA has communicated to the BOP that enforcement activities which discourage and inhibit the work of compounding pharmacists would result in California veterinarians losing access to important medications that may only be obtained from compounding pharmacies that compound from active pharmaceutical ingredients. During public comment at BOP meetings, including those of the Compounding and Enforcement Committees, BOP members encouraged the CVMA to report back any issues that we become aware of relating to drug availability or lack thereof. Those issues are summarized below.

Veterinary Drugs Now Currently Unavailable in California

CVMA members have reported that the following drugs are currently unavailable in California:

- **Tolazoline:** this alpha-2 receptor antagonist is used in veterinary medicine on an emergency basis to reverse sedation by alpha-2 agonists such as xylazine or detomidine. California Code of Regulations, title 16, section 2030(f)(12) requires that all registered veterinary premises have appropriate drugs readily available to treat an animal emergency. Tolazoline can be included as one of those drugs. Veterinarians need this drug and others to be able to provide life-saving medical care to animal patients. While alternatives such as yohimbine and atipamezole are available, they are less preferable than tolazoline primarily because of the more reliable, consistent and effective nature of

tolazoline, and the impracticality of using yohimbine and atipamezole in equine and livestock patients due to the high volumes needed to achieve an effect.

- **Thyrotropin-Releasing Hormone:** Thyrotropin-releasing hormone (TRH; protirelin) is most commonly used in veterinary medicine as a diagnostic agent (TRH stimulation test) for diagnosing pituitary pars intermedia dysfunction (PPID) in horses. While other test methods exist, such as a dexamethasone suppression test or an endogenous adrenocorticotropic hormone test, the TRH stimulation test is supported in current literature as being an important component in accurate testing, especially for detection of early cases.

- **Tissue Plasminogen Activase:** Alteplase (tPA) is an enzyme (serine protease) that binds to fibrin in clots, converting the plasminogen component of the clot to plasmin. In veterinary practice, it is most commonly injected intracamerally to lyse intraocular fibrin and blood clots following cataract surgery. No effective alternatives exist.

Because no equivalent products approved by the United States Food and Drug Administration (FDA) exist, the only available supply of these critical medications must be derived through compounding from active pharmaceutical ingredients (bulk drug substances). Indeed, the FDA itself has demonstrated sensitivity to this need, as reflected in a statement made in its draft Guidance for Industry #256:

> FDA has generally exercised enforcement discretion with regard to animal drug compounding from bulk drug substances under certain circumstances when no other medically appropriate treatment options exist. This guidance, a continuation of this practice, is intended to provide additional information and clarity to veterinarians and pharmacists about FDA's current thinking with respect to animal drug compounding from bulk drug substances.
>
> At this time and based on our current understanding of the risks of animal drugs compounded from bulk drug substances, FDA does not intend to take enforcement action for violations of the FD&C Act's requirements for approval, adequate directions for use, and cGMP requirements, for these products that meet the circumstances described below. The policies described in this document aim to protect human and animal health by limiting the use of animal drugs compounded from bulk drug substances primarily to situations in which a veterinarian is acting within a valid veterinarian-client-patient relationship (VCPR) 3 and there is no medically appropriate drug that is FDA approved, conditionally approved, or on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (indexed) to treat the animal.

The FDA's statement reflects its recognition of the clinical importance of bulk drug compounding.

Status of 503b Outsourcing Facilities Providing Veterinary Drugs in California

Currently, out of the small number of registered 503b facilities in California, only two provide appreciable lines of veterinary products. They are: Wedgewood Connect, LLC, formerly registered as Leiter's Compounding, San Jose, CA; and Stokes Pharmacy dba Epicur Pharma, in Mt. Laurel Township, NJ. The CVMA has researched all of the registered 503b facilities that we know of in California,[1] including the "veterinary" ones mentioned above, and has determined that none of them offer tolazoline, thyrotropin releasing hormone, or tissue plasminogen activase in California. If the BOP is aware of other veterinary outsourcing facilities in California, the CVMA would welcome their identification. The CVMA would also like to request that the BOP post all California-registered 503b facilities on its website here: https://www.pharmacy.ca.gov/applicants/outsrc.shtml

In the meantime, the CVMA has contacted both Wedgewood and Epicur and have been told that, other than Wedgewood researching the prospect of adding tPA to its product line, those entities will not be pursuing approval to add these drugs to their catalogues. Accordingly, we would like the BOP to be aware of the harm that is resulting from the collective changes to California compounding regulations and from BOP enforcement policy which has resulted in 503a pharmacies discontinuing product lines in California.

Please share this letter with the members of the Board of Pharmacy. If you or any of them care to discuss these matters further, the CVMA is available to meet or to appear at a Board or committee meeting in the future.

Thank you for your consideration.

Dan Baxter
Executive Director

cc: Jessica Sieferman, Executive Officer, California Veterinary Medical Board

[1] The CVMA's research was conducted based on this FDA list: https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities.

california **pharmacists** association

February 10, 2023

Maria Serpa, Chair Enforcement and Compounding Committee
California Board of Pharmacy
2720 Gateway Oaks Dr, Ste 100
Sacramento, CA 95833

Re: Proposed Changes to Regulations Related to Pharmaceutical Compounding of Nonsterile Preparations

Dear Chair Serpa,

The California Pharmacists Association (CPhA) appreciates the discussion and work of the Enforcement and Compounding Committee Meeting in relation to the regulations related to pharmaceutical compounding of nonsterile preparations, specifically with the recent USP 795 recommendations on flavoring agents. CPhA writes to encourage the Board of Pharmacy to evaluate the implementation timeline of the USP 795 recommendations and to provide direct communication to pharmacies of the proper documentation requirements and enforcement guidance. We also request that the Board inspectors not begin to review compliance any earlier than November 1, 2023. This will allow pharmacists the necessary time to implement USP 795 guidelines.

As the largest pharmacy association in the state representing all areas of pharmacy practice, we recognize firsthand how important it is for children to take their medicines. The ability to alter the taste of medication increases patient adherence and plays an important role in our patient's health. Flavoring can be the difference between children taking their medicine or not, as is the case of numerous real-life examples of children with long-term conditions like epilepsy or autism, or children struggling to get over serious infections. In short, children, parents, pediatricians, and pharmacists all understand how important flavoring is to ensure that children take their prescribed medication as directed by their pediatricians and clinicians.

We appreciate the opportunity to comment and provide feedback to the Board on ensuring patients in the state continue to receive optimal pharmacists delivered care. Should you have any questions about this recommendation, please feel free to contact me at rvaidya@cpha.com.

Founded in 1869, the California Pharmacists Association (CPhA) is the largest statewide association representing the pharmacy profession in all practice settings. Our mission is to advance the practice of pharmacy for the promotion of health.

Thank you for your consideration.

Sincerely,

Rajan Vaidya, PharmD
Vice President, Practice & Professional Development

4030 Lennane Drive • Sacramento, California 95834
Phone: 916.779.1400 • Fax: 916.779.1401 • www.cpha.com

Damoth, Debbie@DCA

From: John P Teague <JTeague@pmhd.org>
Sent: Friday, February 10, 2023 4:47 PM
To: Damoth, Debbie@DCA
Subject: Enforcement and Compounding Committee USP<795>

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Enforcement and Compounding Committee Members,

I am writing to request that the California Board of Pharmacy continue to keep language on the books that carves flavoring out of compounding. We use flavoring to help children take their medicine all the time. It is one of the most effective tools we have to improve pediatric compliance. Our customers appreciate the service and have come to rely on it. We have been offering flavoring to our customers for years and have not heard one single complaint. We certainly haven't hurt any kids by flavoring their medicine. If the new language up for consideration is adopted as written, we will likely stop offering flavoring to our customers for fear of violating one of the requirements. Flavoring is such a simple thing that has a tremendous impact on children's quality of life. I urge everyone at the Board of Pharmacy: Please don't change your position when it comes to flavoring, I've seen several children benefit from added flavoring to manufactured medications that already contain flavoring.

Thank you,

John Teague, Pharm.D., A.Ph.
Director of Pharmacy
Pioneers Memorial Healthcare District

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From: Cheryl Konig
To: Damoth, Debbie@DCA
Subject: California State Pharmacy Board
Date: Thursday, April 13, 2023 6:37:46 PM

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To Whom It May Concern,

The goal is to have our children take all their medication when sick.

If you take away the ability of our local pharmacies from being able to customize the flavor to a taste our children prefer or make it more difficult for parents to get flavored medicine, this will make a stressful situation worse.

It is tough enough dealing with a sick child. Please don't make it more complicated.

Cheryl

Sacramento

From: Claudia Isabel Ramírez B.
To: Damoth, Debbie@DCA
Subject: California State Pharmacy Board Members
Date: Friday, April 14, 2023 1:44:12 PM

WARNING: This message was sent from outside the CA Gov network. Do not open attachments unless you know the sender: claudisa2@hotmail.com

Dr. Pharmacy Board Members,

Don't eliminate flavored medicine options for children. Flavored medication makes it more palatable for children, and as a parent, I can be confident that they will take all the medicine. Removing this option would be hard on children and families.

Please reconsider this proposal and ensure that flavored medication remains available for those who need it.

Claudia Ramirez

100 Daingerfield Road, Suite 100
Alexandria, VA 22314
www.a4pc.org

Alliance for Pharmacy Compounding

Compounding the Joy of Living

April 12, 2023

Anne Sodergren, Executive Officer
Seung Oh, Board President
California Board of Pharmacy
2720 Gateway Oaks Drive, Suite 100
Sacramento, CA 95833

Dear President Oh and Director Sodergren:

Thank you for the opportunity to comment on the California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposed new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.

The Alliance for Pharmacy Compounding is the voice for pharmacy compounding, representing more than 600 compounding pharmacies and facilities across the U.S., including compounding pharmacists and technicians in both 503A and 503B settings, as well as prescribers, educators, researchers, and suppliers.

APC supports the Board's statutory mission to protect California consumers, and we believe it's in the interest of the pharmacy compounding profession to have robust enforcement of reasonable regulation that safeguards patient safety. Yet it is not clear how many of the current proposed changes protect patients. In fact, in some cases, the effect of these proposals will be to eliminate patient access entirely – an action at odds with the agency's stated mission.

We urge the Board to communicate its rationale for proposing regulations that impose more restrictive rules and procedures than USP standards or FDA guidance. Is there evidence that the Board's proposals advance patient safety? Licensees would benefit from access to the research, testing, or other data the Board has collected that validate the need for many of these proposals. Sharing that evidence will be invaluable in training and compliance for compounding pharmacies licensed in your state.

Without such evidence, many of these proposals appear arbitrary. The Board seems to be taking the stance that some licensees have failed to adhere to current regulations and the entire profession needs new, even more stringent regulations. But a result of some of the proposed regs, if approved, will be a chilling effect on access to sterile compounded preparations for California residents.

Our specific concerns, suggestions, and questions are itemized in the attached document. To summarize here:

- Many of these proposals exceed USP standards and FDA guidance with no clear or verifiable rationale stated for why the more stringent regulation is necessary. The Board should share the research and testing it has conducted that demonstrates that California patients will be safer and better protected as a result of those proposals.

- Some proposals – particularly the prohibition on compounding substances that appear on the FDA's interim bulk substances list – will result in an immediate loss of access to essential medications for many California patients.

We certainly respect your desire to protect Californians. Yet we are concerned that many of these proposed regulations, while advocated for by Board staff, have not yet been thoroughly considered and discussed by the Board itself. We urge that the Board delay action on these proposals so that it can invite and carefully hear and consider further stakeholder input and then better enunciate a rationale for any resulting proposed regulatory changes.

With patient access to essential medications at risk, incorporating these considerations can help improve outcomes for all involved.

Thank you for the opportunity to comment. If I may be helpful to the Board, please contact me at scott@a4pc.org.

Sincerely,

Scott Brunner, CAE
Chief Executive Officer

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.

Page	Section	Statement	Clarification Requested
153	1736(a)	"Certificate of Analysis" (COA) means a document produced by the manufacturer that certifies the quality of the component and demonstrates that the component conforms to the defined specifications, has been manufactured under recognized principles of current good manufacturing practices and is suitable for use in pharmaceuticals and meets the requirements in USP.	As per the new USP chapter <797>, CofA is a report from the SUPPLIER of a component, container, or closure that accompanies the supplier's material and contains the specifications and results of all analyses and a description of the material. The manufacturer COA as a stand-alone doc may not capture the evidence of GMP and pharmaceutical use, but that info may be found on such documents as an FDA registration, inspection report, GMP certificate, product label. In addition, not all chemicals have a USP monograph, meaning a COA cannot meet USP requirements.
153	1736(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.	A commercially available drug product includes 503B products. "FDA-approved" drug products would be more appropriate language. What is the definition of "comparable"' in active ingredients to commercial products, and does this account for routes of administration?
153	1736(e)	"Diluent" means a liquid with no pharmacological activity used in reconstitution, such as sterile water for injection.	Diluents such as lactated ringers, dextrose or sodium chloride in many cases do encompass pharmacological activity. How are these accounted for?
	1736(h)	"Preparation" means a compounded drug or nutrient.	What is the definition of nutrient?

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
154	1736(j)	"Quality" means the degree to which the components and preparation meets the intended use or purpose, complies with relevant law and regulation, and means the absence of harmful levels of contaminants, including but not limited to filth, putrid, or decomposed substances, the absence of active ingredients other than those listed on the label, or the absence of inactive ingredients other than those listed on the master formula record as specified in USP 797.	FDA-approved drugs contain a small allowable limit of impurities. Will this limit for compounded preparations be in place as well?
154	1736.1©	A limited quantity of CNSP may be prepared and stored in advance of receipt of a patient specific prescription document where, and solely in such quantity, as is necessary to ensure continuity of care for individual patients of the pharmacy based on a documented history of prescriptions for those individual patients. This includes authority to prepare and furnish a limited quantity of CSPs to veterinarians for office dispensing of not more than a 120-hour supply, solely to the prescriber's owner veterinary patients seen as part of regular treatment in the prescriber's officer, as fairly estimated by the prescriber and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing	This references a cNsp when this is a section talking about sterile compounding, should be CSP. A VCPR documentation on the purchase order may be difficult when patients may not be known in advance particularly for office use drugs.

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
155	1736.1(d)(3)	In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that is made with a component for which a conventionally manufactured sterile product is available and appropriate for the intended CSP.	Depending on the batch size and compounding set-up, using a conventionally manufactured sterile product as opposed to bulk ingredients could cause more sterility assurance issues and potency variability among units prepared (e.g., exponentially increased manual manipulations by repetitively entering vials or bags to transfer a portion of liquid to the finished preparation increases the potential for contamination and variability as these processes are primarily manual).
155	1736.1(d)(4)	In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that cannot be sterilized within the licensed location.	The revised <797> states: "Injectable compounded preparations that contain nonsterile components or that come into contact with nonsterile devices (e.g., containers, tubing) during any phase of the compounding procedure must be sterilized within 6 h after completing the preparation to minimize the generation of endotoxins in CSPs." If one were to successfully have the CSPs transferred to a local third party for terminal sterilization within the 6-hour window, would this be acceptable?

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
156	1736.2©	Aseptic manipulation ongoing training and competency shall occur each time the quality assurance program yields an unacceptable result as defined in the SOPs referenced in section 1736.17 that may indicate microbial contamination of CSPs. Aseptic manipulation ongoing training and competency procedures shall be defined in the facilities SOPs.	Requiring a media fill each time there is a sterility failure of a CSP implies that all sterility failures are due to poor aseptic technique, which may not be accurate. A more scientific approach would be to require an investigation with each OOS result, and personnel retraining / repeat compentency as appropriate/applicable.
	1736.4 (f)	No CSP shall be compounded if the compounding environment fails to meet criteria specified in the law or the facilities SOPs.	USP 797 states that BUDs revert to the most limited BUDs if pressure differential is different. BUD could go to Category 1 in this situation rather than Category 2. This is an important distinction for patient care to continue. If you can compound in a SCA for sterile with Category 1 BUDs then it would seem that you could revert to those BUDs as well
159	1736.6(a)	SOPs shall specify steps to be taken when the microbiological air and surface monitoring action levels are exceeded including the investigative and corrective actions, allowable activities, and resampling procedures.	Implies the SOP has to predict all possible reasons why a microbiological excursion could happen in a hypothetical future and outline all possible corrective actions to take. A more scientific approach would be to require the SOP to state that a root cause investigation and associated corrective actions appropriate to the root cause(s) identified are carried out.
	1736.7 (b)	Reusable cleaning supplies shall not be stored within 1 meter of the PEC.	Can the Contec Easy Reach tool be stored within a meter of the PEC?

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
	1736.8	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.	Items would go from the unclassified area to the dirty side of the ante-room and then to the clean side of the ante-room, then to buffer room, and then to a PEC. This could be read as a somewhat random list of areas, but staging happens between more areas than this.
160	1736.9(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.	**All** components, including excipients? All components cannot come from an FDA-registered manufacturer. APIs come from FDA registered manufacturers as required by 503A and other components may not all be available from FDA registered manufacturers. Also, what is meant by 'suitable for use in sterile pharmaceuticals'? A limited number of chemicals within USP have additional specifications when the chemical will be used in a parenteral preparation. Does the board have specific criteria or expectations for what makes a chemical suitable for this use?

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.

Page	Section	Statement	Clarification Requested
161	1736.9(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 approve 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.	FDA made it clear the purpose of the interim list is to prevent the lapse in patient access to legacy compounds until FDA can review each substance and make the final determination. This proposed regulation will eliminate patient access to several compounds in California while FDA reviews each bulk substance. Take note other states have not imposed such an unnecessarily restrictive regulation, and this proposal will cause Californians to go to other states to obtain these medications while they wait (most of the time many years) for FDA to review and approve or deny the use of the bulk in compounding.
161	1736.10.(a-d, f)	(a) Dry heat depyrogenation shall be done in compliance with USP Chapter 1228.1, Dry Heat Depyrogenation. (b) Sterilization by filtration shall be done in compliance with USP Chapter 1229.4, Sterilizing Filtration of Liquids. (c) Steam sterilization shall be done in compliance with USP Chapter 1229.1, Steam Sterilization by Direct Contact. (d) Dry heat sterilization shall be done in compliance with USP Chapter 1229.8, Dry Heat Sterilization. (f) Sterilization and depyrogenation of supplies and/or container–closure systems shall be done in compliance with USP Chapter 1229, Sterilization of Compendial Articles.	This is a misapplication of the USP Chapters in a way that USP itself states the chapters above 1000 are not intended to be applied. While pointing a compounder to the USP chapters referenced to carry out best practices and to learn more about a given subject is encouraged, according to USP General Notices, 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.

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
161	1736.10(e)	No compound of a CSP from nonsterile components shall be prepared when the licensed location cannot also sterilize the CSP as described in this section.	Implies that CSPs made from nonsterile starting materials must have the option of being sterilized via filtration (as most compounds currently are) as well as being terminally sterilized via dry heat or steam. Many CSPs are heat sensitive and cannot maintain their physicochemical properties after exposure to extreme heats as seen in dry heat ovens and autoclaves. This seems to remove ebeam/radiation sterilization since its not a described method, limiting compounds utilizing this method.
162	1736.11 ©	A compounding record shall be a single document. The document shall satisfy the requirements of USP Chapter 797, as well as the following:	The expectation that a compounding record be a single document is unweildy and impractical, as proper documentation of the process will produce numerous attachments and become several pages in length (e.g., quality control tests such as visual inspection, photos of in-process and/or finished preparation, release test results from a 3rd party lab, microbiological and environmental monitoring results, etc.).

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
162	1736.11©(3)	The manufacturer, lot number, and expiration date shall be recorded for each component for CSPs.	As most compounders engaged in nonsterile to sterile compounding purchase bulks from FDA-registered repackers, they have been historically limited to the identity of the original manufacturer. As such, these compounders often are limited to stating the wholesaler in place of the manufacturer. Recommend allowing the name of the wholesaler in place of the manufacturer in such situations.
163	1736.12(b)	Validation of an alternative method for sterility testing shall be done in compliance with USP Chapter 1223, Validation of Alternative Microbiological Methods and shall document the method-suitability for each CSP formulation for which the alternate method is used.	While pointing a compounder to the USP chapters referenced to carry out best practices and to learn more about a given subject is encouraged, according to USP General Notices, 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.
	1736.12 ©	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.	It is unreasonable to test all CSPs made from a nonsterile ingredient for endotoxin, and it's not a requirement of USP. Doing so would delay the release of these Cat 1 compounds that are already short-dated. This requirement also does not fit the model of Category 2 where CSPs can be released without sterility testing using a limited BUD.

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.

Page	Section	Statement	Clarification Requested
	1736.15	A single-dose container entered or punctured inside of an ISO class 5 area must be discarded within 12 hours.	Is the container expected to be kept in the ISO 5 area after being punctured?
165	1736.16	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.	What is the definition of a compounded stock solution? Is it one that is prepared well in advance of an intended preparation for compounding that may be used for several different lots? Or is the definition akin to a subformula, where a starting ingredient must be manipulated/mixed into an intermediate ingredient, which is then used to prepare the final parent compound? Also, it is not possible to comply with all 3 Categories of CSP. Suggest changing "and" to "or" in that sentence so that you comply with one of the CSP Categories instead of all of them.
165	1736.17(a)	(1) Comply with USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding. (2) In addition to the SOPs required in USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding, SOPs must also be developed to describe the following:	While pointing a compounder to the USP chapters referenced to carry out best practices and to learn more about a given subject is encouraged, according to USP General Notices, 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.

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
166	1736.18(a)	The quality assurance program shall comply with section 1711 and the standards contained in USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding. In addition, the program shall include the following:	While pointing a compounder to the USP chapters referenced to carry out best practices and to learn more about a given subject is encouraged, according to USP General Notices, 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.
167	1736.21(b)	Compounding of allergenic extracts are limited to patient-specific prescriptions and the conditions limited to Category I and Category 2 CSPs as specified in USP 797.	Are there are no situations in which BUDs can be extended? Both USP and FDA state that a BUD of up to one year can be provided to these preparations.

Comments on Proposed CA Nonsterile Compounding Regulations

Rick Rhoads, Pharm.D.

February 14th, 2023

1735.1. Introduction and Scope-Nonsterile Compounding

In addition to the standards in the USP Chapter 795, the preparation of CNSP shall meet the following requirements of this article.

(a) For the purposes of this article, nonsterile compounding occurs, by or under the supervision of a licensed pharmacist, pursuant to a patient specific prescription.

(b) Repackaging of a conventionally manufactured drug product shall be not considered compounding but must be compliant with USP General Chapter 1178 titled Good Repackaging Practices.

(c) Reconstitution of a conventionally manufactured drug product in accordance with directions that have not been Food and Drug Administration (FDA) approved in accordance with 21 U.S.C.A Section 3S5 is considered compounding and this article applies.

(d) Unless otherwise provided in this article, no CNSP shall be compounded unless the CNSP is compounded for an identified individual patient based on the receipt of a valid prescription order or a notation, approved by the prescriber and the CNSP otherwise meets the requirements of section 503A of the Federal Food. Drug and Cosmetic Act (21 U.S.C. section 353a), as applicable.

If the compounded preparation is essentially a copy of a commercial medication, a notation must be made on the prescription that the compound is necessary for the identified patient.

> ***Reason:*** *Unless the prescribed medication is an essential copy, prescribers rarely notate that the compound is necessary for the patient. This is implied by the submission of the prescription. Calling the prescriber for every prescription would significantly delay care.*

In addition to prohibitions and requirements for compounding established in federal law pursuant to 21 U.S.C. section 353a, no CNSP shall be prepared that:

[l} Is essentially a copy of one or more commercially available drug products. unless:

(A) the drug product appears on an ASHP (American Society of Health-System Pharmacists} or FDA Drug Shortages Database that are in short supply at the time of compounding and at the time of dispense, or

(B) the compounding of that CNSP is justified by a specific, documented medical need made known to the pharmacist prior to compounding. A copy of the documentation of the shortage or the specific medical need shall be maintained

in accordance with Business and Profession Code section 4081 for three years from the date of receipt of the documentation.

(2) Is made with any component not suitable for use in a CNSP for the intended patient population.

Reason: *The word "intended" could potentially become problematic for several ingredients used appropriately in nonsterile compounding. Manufacturers of components may not intend for their products to be used specifically in nonsterile compounding, but they still may be appropriate for use in compounding. For example, Cetaphil cream is often used as a topical cream base, but the manufacturer does not intend for it to be used in compounding. This could also apply to components made for pharmaceutical manufacturing, but not compounding. Changing the word from "intended" to "suitable" would clarify this.*

1735.2. Personnel Training and Evaluation

(d) Compounding personnel or personnel with direct oversight over personnel performing compounding. verifying and/or handling a CNSP who fails any aspect of training or demonstrated competency shall not be involved in the compounding process related to the sections failed until after successfully passing reevaluations in the deficient area(s) detailed in the facility's standard operating procedures (SOPs) for nonsterile compounding as described in section 1735.11.

Reason: *If an employee fails a section of training for a new and completely separate competency (eg. they are currently trained on compounding creams and then later begin to learn compounding capsules), they would be barred from compounding creams. I think this could have a negative unintended consequence of pharmacies choosing less stringent training with fewer domains for fear of employees becoming disqualified from doing any compounding at all.*

Comments on Proposed CA Nonsterile Compounding Regulations

Rick Rhoads, Pharm.D.

February 14th, 2023

1735.7. Master Formulation and Compounding Records

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) A CNSP shall not be compounded until the pharmacy has first prepared a written master formulation record in compliance with Section 7.1 of USP Chapter 795 and identified in that document the following additional elements:

(ll) The referenced source material (e.g., peer reviewed article, published scientific book) used to support the assigned beyond-use date (BUD), if it exists: each source referenced shall be readily retrievable at the time of compounding and shall be maintained for three years from the date each CNSP is dispensed.

Reason: *Compounders are required to consider stability data for all BUDs assigned and it is appropriate to cite this data to support the BUD. However, some preparations don't have any stability data. If so, a conservative BUD must be assigned within the limits of Table 4 in USP <795>. The current language may be interpreted to mean that compounders must have stability studies for all preparations (instead of just for the preparations with extended BUDs).*

(b) Where a pharmacy does not routinely compound a particular drug preparation, the master formulation record for that preparation may be recorded on the prescription document itself. This record shall comply with USP Chapter 795 standards and this section.

(c) A compounding record shall be a single document. The document shall satisfy the compounding record requirements in Section 7.2 of USP Chapter 795. as well as the following:

(1) The date or date and time of preparation, if the BUD is listed in hours. The time of preparation is when compounding the CNSP started, which also determines when the assigned BUD starts if the BUD is listed in hours.

(2) The manufacturer, lot number, and expiration date for each component.

(3) The assigned internal identification number shall be unique for each CNSP.

(4) The total quantity compounded shall include the number of units made and the volume or weight of each unit.

Comments on Proposed CA Nonsterile Compounding Regulations

Rick Rhoads, Pharm.D.

February 14th, 2023

(5) The identity of each person performing the compounding, have direct oversight of compounding, and pharmacist verifying the final drug preparation.

> ***Reason:*** *This language is helpful to clarify that the date and/or time of compounding refers to when the compounding process started. However, this language may be confused to mean that the BUD must specify a day and time (eg. Discard after 06/15/2023 at 1PM). However, most BUDs are assigned in days only, which would make the time started irrelevant. The time compounded would only be applicable when the BUD is listed in hours.*

(4) The total quantity compounded shall include the number of units made and the volume or weight of each unit, if immediately packaged into the final dispensing container after compounding.

> ***Reason:*** *Anticipatory compounding often includes storing the preparation in a bulk container and later packaging in the final dispensing device when the prescription is received. It is difficult to anticipate the exact quantity of medication that will be prescribed.*

Maria Serpa, PharmD
Chair Enforcement and Compounding Committee
California Board of Pharmacy
2720 Gateway Oaks Dr, Ste 100
Sacramento, CA 95833

March 23, 2023

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

Dear Chair Serpa,

I am writing this letter in support of my verbal comments during the Enforcement and Compounding Committee meeting on March 23, 2023. I appreciate the opportunity to provide comment and suggestion for the Board to consider during its evaluation of the *Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations*.

CPS Solutions manages multiple hospital pharmacies throughout California, many of which are smaller hospitals with less resources than large health systems. I encourage the Board to keep in mind these local community hospitals that provide basic healthcare to the people of California, while still keeping them safe.

I respectfully submit the following for consideration:

1736.1 STERILE COMPOUNDING SCOPE
(b) CSPs for direct and immediate administration as provided in the Chapter shall only be done in those limited situations where the failure to administer could result in loss of life or intense suffering. Any such compounding shall be only in such quantity as is necessary to meet the immediate need. Documentation for each such CSP shall include identification of the CSP, compounded date and time, number of units, the patient's name and patient's unique identifier and the circumstance causing the immediate need.

<u>Comment:</u>
Smaller hospitals that compound in a Segregated Compounding Area (SCA) with a single PEC occasionally experience failures of that PEC but must still meet the patient's sterile compounded medication needs. In the acute hospital setting, all medications are important and potentially lifesaving. Without a PEC, these hospitals must resort to immediate use compounding of medications that, if not given, could lead to greater complications. These immediate use compounds may not always be considered to "prevent loss of life or intense suffering", but still provide critical medication treatment.

Of important note, the USP Committee specifically removed the language in the current USP 797 v2008 discussing immediate use compounding, "*where there is a need for emergency or immediate patient administration of a CSP*", from the USP 797 revision v2022.

I agree that pharmacies should not compound immediate use as a matter of routine. However, we do need to find a way to allow pharmacies with only one PEC to provide critical sterile compounded medications during periods when their PEC needs service or so that outsourcing can be set up.

Recommendation:

1) Remove subsection (b) completely, or;
2) Consider language that allows immediate use for non-emergent medications in limited situations in which the PEC is not operational for a short period of time.

1736.4 FACILITIES AND ENGINEERING CONTROLS

(c)(1) Designated compounding area(s) shall typically be maintained at a temperature of 20° Celsius or cooler and shall provide comfortable conditions for compounding personnel attired in the required garb.

Comment:

For reference, USP 797 v2022 section states, "*The cleanroom suite should be maintained at a temperature of 20° or cooler and a relative humidity of 60% or below to minimize the risk of microbial proliferation and to provide comfortable conditions for compounding personnel attired in the required garb*." It appears the proposed regulation has changed "cleanroom suite" to "designated compounding area(s)". Presumably, a designated compounding area would include a Segregated Compounding Area (SCA), in addition to a cleanroom suite.

Many smaller hospitals without the resources of large hospital systems do not have full cleanroom suites. They must compound in SCAs that are often located within the pharmacy or in rooms adjacent without their own HVAC system. Requiring a temperature of 20°C (68°F) or less in the SCA would often mean that pharmacy medications are stored at 20°C/68°F or less. As we know, "room temperature" drug storage typically means a temperature of 20-25°C/68-77°F as defined by USP. By requiring a temperature of 20°C/68°F or less in SCAs, the pharmacy has a 1-degree window (20°C/68°F exactly) to comply with both CCR 1736.4(c)(1) and BPC 4119.7(b)[1].

Lastly, note also that the USP 797 v2022 designates SCAs as Category 1, which would limit Beyond Use Dates (BUDs) to 12 hours room temperature and 24 hours refrigerated. These reduced BUDs further limit any potential contamination that may be increased by higher temperatures while compounding.

Recommendation:

1) Remove subsection (c)(1) completely, or;
2) Change "Designated compounding area(s)" to "Cleanroom suites" in order to exclude SCAs from the restrictive temperature requirements.

[1] Reference (BPC 4119.7(b)):

A health care facility shall store and maintain drugs in accordance with national standards regarding the storage area and refrigerator or freezer temperature, and otherwise pursuant to the manufacturer's guidelines. The health care facility's policies and procedures shall specify these storage parameters.

1736.4 FACILITIES AND ENGINEERING CONTROLS

(e) Except as provided in (e) dynamic interactions between areas and rooms with classified air shall be controlled through a heating, ventilation, and air condition (HVAC) system. No passive ceiling or wall penetrations are allowed.

Comment:
Many hospitals without brand new HVAC systems struggle to maintain required pressure differentials within their cleanroom suite. Remedies have included using passive airflow vents from one controlled space to another (e.g., anteroom to buffer room). I do agree that no passive ceiling or wall penetrations should be allowed between controlled ISO space and uncontrolled air space (e.g., general pharmacy area to anteroom or buffer room). However, passive penetrations from controlled space to controlled space does not pose an increased safety risk as long as air changes, pressure differentials, cleaning procedures, and proper airflow are maintained.

Recommendation:
Change regulation to state, "No passive ceiling or wall penetrations *from controlled space to uncontrolled space* are allowed."

1736.13 LABELING
(b) Any CSP dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required by Business and Professions Code section 4076 and section 1707.5.

Comment:
Health facilities, as defined in H&SC 1250, should be exempt from the requirements of outpatient labeling when administered by a health care professional to an inpatient of that facility. Sterile compounds administered in a licensed health care facility to an inpatient do not need to have all of the information on the label (e.g., pharmacy address, physician name, etc.) that is easily accessible via the readily available medical record. Only sterile compounds dispensed outpatient and not administered by a health care professional should be required to have this information.

Recommendation:
Add language which exempts H&SC 1250 facilities from BPC 4076 and CCR 1707.5 labeling requirements.

Thank you again for the opportunity to comment the sterile compounding proposed regulations. I appreciate the Board for considering mine and the public's suggestions for keeping the public safe through essential pharmacy services like sterile compounding. I would also like to recognize the hard work of important persons behind the scenes that help develop and enforce these regulations such Supervising Inspector Christine Acosta.

Please don't hesitate to contact me should you have any questions or require additional information.

Sincerely,

Robert Jackson, PharmD
Director, Compliance and Regulatory Services
CPS Solutions
robert.jackson@cps.com

Much Shelist, P.C.
Attorneys at Law

191 N. Wacker Drive
Suite 1800
Chicago, IL 60606

312.521.2000
muchlaw.com

March 23, 2023

DIRECT DIAL:312.521.2482
nmilenkovich@muchlaw.com

Via FedEx
Eileen Smiley, DCA Staff Counsel
Enforcement and Compounding Committee
California State Board of Pharmacy
2720 N. Gateway Oaks Drive, Suite 100
Sacramento, CA 95833

Re: Proposed Changes to Regulations Concerning the Addition of Flavorings to Nonsterile Preparations

Dear Ms. Smiley:

Our firm represents FLAVORx, Inc. We are writing to provide additional information to the Enforcement and Compounding Committee (the "Committee") for its consideration at the next available meeting when the below described topic will be discussed whether it be at a Committee meeting or a meeting of the Full Board.

As you know, FLAVORx and other stakeholders have previously communicated their opposition to the Committee's proposal to amend the Board of Pharmacy's regulations so that the definition of compounding would no longer exclude "the addition of flavoring agent(s) to enhance palatability" of commercially-manufactured drugs, a practice that enhances patient compliance, particularly among children.

Please be assured that this letter does not repeat anything that our client has already told the Committee previously and instead addresses the Committee's ***only*** stated reason for the proposed revision: that Business & Professions Code §4126.8 requires the Board to make such a change. **In fact, the Board is not required to do so**. As we make clear below, the Board may continue to exclude flavorings from the definition of compounding and respect the public policy decisions it made when it adopted the current definition in 16 CCR § 1735(b). Notably, it does not appear that the legislature has raised any concerns about the Board's current policy of treating flavorings as a practice that is not subject to its compounding rules, which reinforces this point.

Section 4126.8 requires that "***compounding*** of drug preparations" follow standards that are "consistent with the ***standards*** established in the pharmacy compounding chapters of the current version of the United States Pharmacopeia…." (emphasis added). This means that when a pharmacy compounds drugs, it must comply with the procedures and requirements set forth in USP Chapter <795>. Further, when the Board adopts standards of its own in rules, the procedures and requirements in those rules must be consistent with the ones in USP Chapter <795>. Significantly, § 4126.8 does not define "compounding." In fact, no provision of the Pharmacy Law or, for that matter, any other California statute, defines that term. Further,

section 4126.8 does not adopt or incorporate USP Chapter <795> in its entirety, but rather, only the requirement that compounding follow its procedures. As a result, the definition of compounding in that Chapter is not part of the Pharmacy Law. The legislature has left intact the Board's authority to define "compounding" in its regulations, just as the legislature has vested the Board with the power to adopt regulations that define any other term not expressly defined in the Pharmacy Law. The Board can therefore exclude flavorings from the definition of "compounding" by regulation, as it has done for years, and no action taken by the legislature impedes the Board from continuing to do so.

Since the legislature does not restrict the Board's authority to exclude flavorings from compounding, the proposed amendment to 16 CCR § 1735(b), which would eliminate the phrase "the addition of flavoring agent(s) to enhance palatability," remains a solution in search of a problem. Accordingly, FLAVORx respectfully requests that the Committee retain the current definition of compounding in any revisions to its compounding regulations and continue to exclude flavorings from that definition.

While it is clear that amending the present regulation to include flavoring within the definition of compounding will not make flavoring illegal in California, the practical effect of this change will make it nearly impossible to access this valuable pharmacy service at local neighborhood pharmacies due to the overly burdensome requirements that USP 795 would impose on a pharmacy attempting to engage in adding a flavoring to a medication. That would undoubtedly bring harm to millions of California children who rely on flavoring to help them comply with their medication regimen.

I also request that this letter be made available to each California Board of Pharmacy Enforcement Compounding Committee Member and all California Board of Pharmacy Members for their review and consideration at least 7 days prior to the next meeting scheduled to discuss the issue of excluding flavorings from compounding in California.

Sincerely,

Ned Milenkovich, PharmD, JD

cc: Seung Oh, Licensee Member, President
Maria Serpa, Licensee Member, Vice President
Anne Sodergren, Executive Officer
Christine Acosta, Supervising Inspector
Stuart Amos, CEO, FLAVORx
Chad Baker, Senior Vice President, FLAVORx

Attachment 2c

Article 4.6 draft regulation text

related to sterile compounding

Title 16. Board of Pharmacy

Proposed Regulation

Repeal Article 7 and sections 1751-1751.12 of Article 7 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 to read as follows:

1736 Sterile Compounding Definitions

The definitions in in this section shall be applicable to this Article and supplement the definitions provided in USP Chapter 797.

(a) "Compounding personnel" means any person involved with any procedure, activity or oversight of the compounding process.

(b) "Designated person(s)" means one or more individuals assigned by the pharmacist-in-charge to be responsible and accountable for the performance and operation of the facility and personnel as related to the preparation of the compounded sterile preparations ("CSP" for the purposes of this article). Nothing in this definition allows for the designated person to exceed the scope of their issued license. When the designated person is not a pharmacist, the Pharmacist-in-Charge (PIC) must review all practices related to the operations of the facility that require professional judgement.

(c) "Diluent" means a liquid with no pharmacological activity used in reconstitution, such as sterile water for injection.

(d) "Designated compounding area or compounding area" means a restricted location with limited access designated for the preparation of CSP, where only activities and items related to compounding are present.

(e) "Essentially a copy" of a commercially available drug product means all preparations that include the same API(s) , as the 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.

(f) "Integrity" means retention of potency until the beyond use date provided on the label, when the preparation is stored and handled according to the label directions.

(g) "Quality" means the degree to which the components and preparation meets the intended specifications, complies with relevant law and regulation, and means the absence of harmful levels of contaminants, including but not limited to filth, putrid, or decomposed substances, the absence of active ingredients other than those listed on the label, or the absence of inactive ingredients other than those listed on the master formula record as specified in USP 797.

(h) "Strength" means amount of active ingredient per unit of a compounded drug preparation.

Note: Authority cited: Sections 4001.1, 4005, 4126.8, 4127 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4127, 4301 and 4332 of the Business and Profession Code.

1736.1 Introduction and Scope.

This article applies to compounded sterile preparations (CSP)s as defined in United States Pharmacopeia (USP) General Chapter 797 (Chapter 797), titled *Pharmaceutical Compounding – Sterile Preparations*. In addition to the standards in the USP Chapter 797, the preparation of a CSP shall meet the following requirements of this article.

(a) For the purposes of this article, sterile compounding occurs, by or under the supervision of a licensed pharmacist, pursuant to a patient specific prescription, unless otherwise specified in this article.

(b) CSPs for direct and immediate administration as provided in the Chapter shall only be done in those limited situations where the failure to administer could result in loss of life or intense suffering. Any such compounding shall be only in such quantity as is necessary to meet the immediate need. Documentation for each such CSP shall include identification of the CSP, compounded date and time, number of units, the patient's name and patient's unique identifier and the circumstance causing the immediate need. Such documentation may be available in the patient's medical record and need not be redocumented by the compounding staff if already available

(c) Notwithstanding subdivision (a) a limited quantity of CSP may be prepared and stored in advance of receipt of a patient specific prescription document where, and solely in such quantity, as is necessary to ensure continuity of care for individual patients based on a documented history of prescriptions for those patient populations.

(d) A reasonable quantity of a compounded drug preparation may be furnished to a veterinary office for use by the veterinarian that is sufficient:

(1) for administration or application to veterinary patients solely in the veterinarian's office
(2) for furnishing of not more than a 120-hour supply, as fairly estimated by the prescriber and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing;
(a)With the exception of a topical ophthalmics where up to a 28 days supply may be furnished to veterinarian's office for individual patient. Such topical ophthalmics shall be complaint with USP 797 section 14.5, Multiple-Dose CSPs .

(e) In addition to prohibitions and requirements for compounding established in federal law, no CSP shall be prepared that:
(1) Is essentially a copy of one or more commercially available drug products, unless:
(A) that drug product appears on an ASHP (American Society of Health-System Pharmacists) or FDA Drug Shortages Database that are in short supply at the time of compounding and at the time of dispense, or
(B) the compounding produces a clinically significant difference of the medical need of an identified individual patient, as determined:
(1) by the prescribing practitioner,
(2) the compounding pharmacist, and
(3) the dispensing pharmacist(s).
(C)) Documentation describing the conditions in (1)(A) & (1) (B) is maintained in a readily retrievable format
(2) Is made with any component not suitable for use in a CSP for the intended patient population, unless allowable under Animal Medicinal Drug Use Clarification Action of 1994 (AMDUCA).
(3) Is made with a non-sterile component for which a conventionally manufactured sterile product is available and appropriate for the intended CSP.
(4) Where sterilization is required, it cannot be sterilized within the licensed location.

(f) Prior to allowing any CSP to be compounded within a pharmacy, the pharmacist-in-charge shall complete a self-assessment consistent with the requirements established in section 1715.

(g) In addition to the provisions provided in Section 1707.2, consultation shall be provided to the patient and/or patient's agent concerning proper use, storage, handling and disposal of the CSP and related supplies furnished.

(h) CSPs with human whole blood or human whole blood derivatives shall be done in compliance with Health and Safety Code section 1602.5.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and

4127, Business and Professions Code.

1736.2 PERSONNEL TRAINING AND EVALUATION

The requirements of this section apply to sterile compounding in addition to the standards in USP Chapter 797.

(a) In addition to the training required by USP 797, training and competencies procedures for all personnel who compound or have direct oversight of compounding personnel training shall also address the following topics:

(1) Quality assurance and quality control procedures,
(2) Container closure and equipment selection,
(3) Component selection and handling, and
(4) Sterilization techniques, when applicable.

(b) Aseptic manipulation competency initial training and competency and ongoing training and competency documentation shall include the Primary Engineering Control (PEC's) type and PEC unique identifier used during the evaluation. Aseptic manipulation competency evaluation and requalification shall be performed using the same procedures, type of equipment, and materials used in aseptic compounding. Aseptic qualifications from one premises may be used for another premises if all of the following conditions are met:

1. The SOPs related to compounding are identical
2. The SEC facility designs are sufficiently similar to accommodate the use of the same SOPs.
3. The PECs are of the same type and sufficiently similar to accommodate the use of the same SOPs describing use and cleaning.

(c) Aseptic manipulation ongoing training and competency shall occur each time and for each staff member involved in an event where the quality assurance program yields an unacceptable result as defined in the SOPs referenced in section 1736.17 that may indicate microbial contamination of CSPs due to poor practices. Aseptic manipulation ongoing training and competency procedures shall be defined in the facilities SOPs.

(d) Compounding personnel or persons with direct oversight over personnel performing compounding, who fail any aspect of the aseptic manipulation ongoing training and competency evaluation shall not be involved in compounding or oversight of the preparation of a CSP until after successfully passing training and competency in the deficient area(s) as detailed in the facility's SOPs. A person with only direct oversight over personnel who fails any aspect of the aseptic manipulation ongoing training and competency evaluation, may continue to provide only direct oversight for no more than 14 days while applicable aseptic manipulation ongoing training and competency evaluation results are pending.

(e) Any person assigned to provide the training specified in this section shall have demonstrated competency in the skills in which the person will provide training or observe and measure competency described in the facilities SOPs as referenced in section 1736.17. Documentation must be maintained demonstrating compliance.

Note: Authority cited: Sections 4001.1, 4005, 4126.8, 4127 of Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4057, 4114, 4115, 4127, 4301 and 4332 of the Business and Profession Code.

1736.3 PERSONNEL HYGIENE AND GARBING

The requirements of this section apply sterile compounding in addition to the requirements in USP Chapter 797.

(a) The pharmacist overseeing compounding shall not allow personnel with potentially contaminating conditions to enter the compounding area.

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

(c) Garb shall be donned in an anteroom or immediately outside the segregated compounding area (SCA). Donning and doffing garb shall not occur in the anteroom at the same time unless the facility's SOP define specific processes that must be followed to prevent contamination.

(d) Restricted access barrier system (RABS) and pharmaceutical isolator sleeves and gloves shall be changed according to both the manufacturer's recommendations and the facility's SOP.

(e) Any garbing accommodations provided by the designated person shall be documented and the record shall include the name of the individual granted the accommodation, date granted and description of the reasons for granting the accommodation. The record shall be retained in accordance with Business and Professions Code section 4081.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.4 FACILITIES AND ENGINEERING CONTROLS

The requirements of this section apply to sterile compounding in addition to the requirements in USP Chapter 797.

(a) A sink used for compounding or hand hygiene shall not be part of a restroom or water closet.

(b) If an SCA is used:

(1) Except for walls, the SCA's visible perimeter shall be at least 1 meter from all sides of the PEC or in a separate room.

(2) Surfaces within the SCA shall be smooth, impervious, free from cracks and crevices, and non-shedding so they can be easily cleaned and disinfected and to minimize spaces in which microorganisms and other contaminants can accumulate.

(c) (1) Designated compounding area(s) shall typically be maintained at a temperature of 20° Celsius or cooler and also provide comfortable conditions for compounding personnel attired in the required garb.

(2) The temperature shall be monitored in each room of the designated compounding area each day that compounding is performed, either manually or by a continuous recording device.

(d) Where a pass-through is installed in a secondary engineering control after [OAL insert effective date], the doors must be interlocking. An existing secondary engineering control that has a pass-through that is not an interlocking device, may continue to be used if the SOPs document that two doors may not be opened at the same time.

(e) Except as provided in (d) dynamic interactions between areas and rooms with classified air shall be controlled through a heating, ventilation, and air condition (HVAC) system. No passive ceiling or wall penetrations are allowed.

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

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.5 CERTIFICATION AND RECERTIFICATION

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) Testing and certification of all classified areas shall be completed by a

qualified technician knowledgeable with certification methods and procedures outlined within the Controlled Environment Testing Association (CETA)'s Certification Guide for Sterile Compounding Facilities as specified in this section. Testing shall be performed in accordance with CETA Certification Guide for Sterile Compounding Facilities (CAG-003, Revised 2022), which is hereby incorporated by reference.

(b) CETA standard(s) used to perform certification testing in all classified areas shall be recorded on report issued by the certifying technician.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.6 MICROBIOLOGICAL AIR AND SURFACE MONITORING

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) SOPs shall specify steps to be taken when the microbiological air and surface monitoring action levels are exceeded including the investigative and corrective actions, allowable activities, and resampling procedures.

(b) At a minimum every 6 months, air and surface sampling results shall be identified to at least the genus level, regardless of the CFU count to trend for growth of microorganisms. Professional judgement and SOPs shall be used to determine the appropriate action necessary to remedy identified trends. Investigation must be consistent with the deviation and must include evaluation of trends.

(c) Environmental sampling shall be done in compliance with the most recent edition of the Controlled Environment Testing Association (CETA)'s Certification Application Guide USP <797> Viable Environmental Sampling & Gowning Evaluation (CAG-009, Revised October 2022), which is hereby incorporated by reference.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.7 CLEANING, DISINFECTING, AND APPLYING SPORICIDAL DISINFECTANTS AND STERILE 70% IPA

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) Any cleaning, disinfecting, and sporicidal disinfectants used by the facility to meet the requirements in this article shall be used in accordance with manufacturers' specifications

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

(c) In addition to the documentation requirements in USP Chapter 797, the facility's documentation of each occurrence of the cleaning, disinfecting, and applying of sporicidal disinfectants in the compounding area shall include a record of the identity of the person completing the cleaning and sanitizing as well as the product name of the cleaning and sanitizing agents used.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.8 INTRODUCING ITEMS INTO THE SEC AND PEC

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

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 anteroom, 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.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.9 EQUIPMENT, SUPPLIES, AND COMPONENTS

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) All equipment and supplies used to compound CSP shall be used, in accordance with manufacturers' specifications and shall be surface

compatible.

(b) Incubators used by the facility shall be cleaned, maintained, calibrated, and operated in accordance with manufacturers' specifications. For incubators without specific manufacturers' specifications, cleaning shall take place at least every 30 days and calibration shall take place at least every 12 months. SOPs shall specify the frequency and process of cleaning, maintenance, and calibration, including when incubation of samples is taking place such that samples are not compromised. All cleaning, maintenance, and calibration shall be documented and dated as defined in the SOPs.

(c) Any component used to compound a CSP shall be used and stored in accordance with all federal laws and regulations and industry standards including the manufacturers' specifications and requirements.

(d) All API and excipient components used to compound a CSP shall be manufactured by an FDA-registered facility, be accompanied by a Certificate of Analysis (COA) and suitable for use in sterile pharmaceuticals. A 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, unless components are commercially available drug products. API and excipient components provided without this data shall not be used in a CSP

(1) When the COA is received from a supplier, it must provide the name and address of the manufacturer .

(e) When 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 21 CFR 216, unless authorized by a public health official in an emergency use situation for a patient specific compounded sterile preparation.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.10 STERILIZATION AND DEPYROGENATION

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

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

(b) Sterilization by filtration shall be done in compliance with USP Chapter 1229.4, Sterilizing Filtration of Liquids.

(1) Filter dimensions and the CSP to be sterilized by filtration shall permit the sterilization process to be completed without the need for replacement of the filter during the process.

(c) Steam sterilization shall be done in compliance with USP Chapter 1229.1, Steam Sterilization by Direct Contact.

(d) Dry heat sterilization shall be done in compliance with USP Chapter 1229.8, Dry Heat Sterilization.

(e) No compound of a CSP from nonsterile components shall be prepared when the licensed location cannot also sterilize the CSP as described in this section.

(f) Sterilization of supplies and/or container–closure systems shall be done in compliance with USP Chapter 1229, Sterilization of Compendial Articles.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.11 MASTER FORMULATION AND COMPOUNDING RECORDS

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) A CSP shall not be compounded until the facility has first prepared a written master formulation record in compliance with USP Chapter 797 and identified in that document the following additional elements:

(1) When a source is referenced to support the assigned beyond-use date (BUD); each source referenced shall be readily retrievable at the time of compounding and shall be maintained for three years from the date each CSP is dispensed.

(2) Instructions for storage and handling the compounded drug preparation.

(b) Where a facility does not routinely compound a particular drug preparation, the master formulation record for that preparation may be recorded on the prescription document itself. This record shall comply with USP Chapter 797 and this section.

(c) A compounding record (CR) shall be a single document. The document shall satisfy the requirements of USP Chapter 797, as well as the following:

(1) The date and time of preparation. The time of preparation is the time when compounding the CSP started, which also determines when the assigned BUD starts.

(2) The assigned internal identification number shall be unique for each CR.

(3) The manufacturer, lot number, and expiration date shall be recorded for each component for CSPs.

(4) The total quantity compounded shall include the number of units made and either the volume or the weight of each unit.

(5) The identity of each person performing the compounding, that has direct oversight of compounding, and pharmacist verifying the final drug preparation

(6) When applicable, endotoxin level calculations and results.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4081, 4114, 4115, 4126.8, 4169 and 4127, Business and Professions Code.

1736.12 RELEASE INSPECTIONS AND TESTING

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) A pharmacist performing, or supervising sterile compounding is responsible for the integrity, quality, and labeled strength of a CSP until the beyond use date indicated on the label provided the patient or the patient's agent follows the label instructions provided on the CSP for storage and handling after receiving the CSP.

(b) Validation of an alternative method for sterility testing shall be done in compliance with USP Chapter 1223, Validation of Alternative Microbiological Methods and shall document the method-suitability for each CSP formulation for which the alternate method is used.

(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 USP Chapter 85, Bacterial Endotoxins. Results must

be reviewed and documented in the compounding record prior to release.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.13 LABELING

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) A CSP label shall also include the following:
(1) Route of intended administration, and
(2) the solution utilized, if applicable and
(3) Instructions for administration.
(A)For admixed CSPs, the rate of infusion, or range of rates of infusion as prescribed, or the duration, when the entire CSP shall be administered
(4) Name of compounding facility and dispensing facility (if different).

(b) Any CSP dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required by Business and Professions Code section 4076 and section 1707.5.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4076, 4114, 4115, 4123, 4126.8, and 4127, Business and Professions Code.

1736.14 ESTABLISHING BEYOND-USE DATES

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) A CSP's beyond-use date (BUD) shall not exceed:
(1) The chemical and physical stability data of the active pharmaceutical ingredient and any added substances in the preparation,

(2) The compatibility of the container–closure system with the finished preparation (e.g., possible leaching, interactions, and storage conditions),

(3) The shortest remaining expiration date or BUD of any of the starting components.

(b) A CSP labeled with a BUD with only a date shall expire at 11:59 p.m. on that date.

(c) Prior to dispensing a CSP that requires sterility and endotoxin testing for BUD determination, test results shall be received. Results must be within acceptable limits. Test results must be retained as part of the compounding record.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.15. USE OF CONVENTIONALLY MANUFACTURED PRODUCTS AS COMPONENTS

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) A single-dose container entered or punctured outside of an ISO Class 5 area, must be discarded immediately.

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

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.16. USE OF CSPS AS COMPONENTS

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) A compounded stock solution intended for use in a CSP must comply with all provisions of this article including Category 1, Category 2, or Category 3.
(b) Nothing in this section shall prohibit the use of a CSP obtained from a California licensed outsourcing facility.

1736.17 Standard Operating Procedures (SOPS)

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) The facility's standard operating procedures (SOPs) for sterile compounding shall be followed and shall:

(1) Comply with USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding.

(2) In addition to the SOPs required in USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding, SOPs must also be developed to describe the following:

(A) Methods by which the supervising pharmacist will ensure the quality of compounded drug preparations.

(B) Procedures for handling, compounding, and disposal of infectious materials. The written SOPsS shall describe the facility protocols for cleanups and spills in conformity with local health jurisdictional standards.

(C) The methods a pharmacist will use to determine and approve the ingredients and the compounding process for each preparation before compounding begins.

(D) The method for complying with any other requirements specifically required to be addressed in the facility's SOPS as described in this article.

(b) The SOPs shall specify the steps to be taken if a classified area(s) fails to meet the specified ISO classification including the investigative and corrective actions, allowable activities, and retesting procedures.

(c) The SOPs shall be reviewed on an annual basis by the pharmacist-in-charge. Such review shall be documented by the pharmacist-in-charge consistent with the SOPs. The SOPs shall be updated to reflect changes to compounding processes, facility changes or other changes that impact the CSP. Such SOP changes shall be disseminated to the affected staff prior to implementation.

(d) Failure to follow written SOPs shall constitute a basis for enforcement action.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.18 QUALITY ASSURANCE AND QUALITY CONTROL

The requirements of this section apply to sterile compounding in addition to the standards established in USP Chapter 797.

(a) The quality assurance program shall comply with section 1711 and the standards contained in USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding. In addition, the program shall include the following:

(1) A written procedure for scheduled action, such as a recall, in the event any compounded drug preparation is discovered to be outside the expected standards for integrity, quality, or labeled strength.

(2) A written procedure for responding to out-of-range temperature variations within the medication storage areas where a furnished drug may be returned for furnishing to another patient.

(b) Recalls and adverse reporting must be completed in compliance with relevant provisions of law.

(c) In addition to subsection (b), all complaints related to a potential quality problem with a CSP and all adverse events shall be reviewed by the pharmacist-in-charge within 72 hours of receipt of the complaint or occurrence. Such review shall be documented and dated as defined in the SOPs.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8, 4127, 4127.2, and 4127.11, Business and Professions Code.

1736.19 CSP HANDLING, STORAGE, PACKAGING, SHIPPING, AND TRANSPORT

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) There shall be written procedures for qualification of storage, shipping containers and transportation of temperature sensitive CSPs to preserve quality standards for integrity, quality and labeled strength.

(b) Packaging materials shall protect CSPs from damage, leakage, contamination, degradation, and adsorption while preventing inadvertent exposure to transportation personnel.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.20 DOCUMENTATION

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) Records shall be maintained as required by USP Chapter 797 or this article, in a readily retrievable form, for at least three years from the date the record was created or relied upon. If only recorded and stored electronically, on magnetic media, or in any other computerized form, the records shall be maintained as specified by Business and Professions Code section 4070.

(b) Records created shall be created and maintained in a manner to provide an audit trail for revisions and updates of each record document. Prior versions of each record must be maintained in a readily retrievable format and include the

changes to the document, identification of individual who made the change, and the date of each change.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4081, 4105, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

1736.21 COMPOUNDING ALLERGENIC EXTRACTS

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) Any allergenic extract compounding shall take place in a dedicated PEC. No other CSP may be made in this PEC.

(b) Compounding of allergenic extracts are limited to patient-specific prescriptions and the conditions limited to Category I and Category 2 CSPs as specified in USP 797.

(c) Any stock solution made shall comply with the requirements established in USP 51, Antimicrobial effectiveness testing and container closure integrity tests consistent with USP Chapter 1207, Sterile Product Packaging – Integrity Evaluation. Compounding records are required for stock solutions.

Authority cited: Sections 4001.1, 4005, 4126.8, and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4114, 4115, 4126.8 and 4127, Business and Professions Code.

Attachment 2d

Comments received related to sterile compounding, including any comments received after the Committee's discussion

Title 16 Board of Pharmacy Proposed Regulations – Sterile Compounding

Institution/Contact	**Cedars-Sinai Medical Center** Department of Pharmacy Services 310-423-5611 Rita Shane, PharmD, Vice President & Chief Pharmacy Officer; rita.shane@cshs.org Vipul Patel, PharmD, Executive Director, Pharmacy & Oncology Services; Vipul.patel@cshs.org

Proposed Language	**Recommendations/Comments**
CCR 1736.2 Personnel Training and Evaluation. subsection (b): Aseptic manipulation competency initial training and competency and ongoing training and competency documentation shall include the Primary Engineering Control (PEC's) type and unique identifier used during the evaluation. Aseptic manipulation competency evaluation and requalification shall be performed using the same procedures, type of equipment, and materials used in compounding drug preparations. Aseptic qualifications from one premises may be used for another premises if all of the following conditions are met: 1. The SOPs are identical 2. The facility designs are identical 3. The PECs are of the same type and sufficiently similar to accommodate the use of the same SOPs describing use and cleaning	**Rationale:** • The new USP 797-chapter requires a significant increase in the frequency of observation, garbing, glove finger testing, media fill and surface sampling. This coupled with the growth in census volumes, complexity of patient diseases requiring IV therapy[1] and the workforce challenges[2,3,] creates significant constraints for hospital pharmacies to complete competency training for each compounding site for all compounding personal. The inability to have staff perform compounding in another licensed site with identical SOPs and PECs would delay patient care and result in potential patient harm • Statement #2 indicating "Facility designs are identical" would further increase the requirements above and associated costs. It is rare and not common that the physical layout of clean rooms or segregated compounding areas are identical. If the intent of the Board is to differentiate the type of room (i.e classified vs non-classified) recommend removing #2 and update #3 to include Secondary Engineering Controls (SEC) are the same type to meet the intent of #2. **Recommendation:** 1. *The SOPs are identical.* ~~2. *The facility designs are identical*~~ 3. *The PECs and SECs are of the same type and sufficiently similar to accommodate the use of the same SOPs describing use and cleaning* References: 1. Drug Shortages List. American Society of Health-System Pharmacy. https://www.ashp.org/drug-shortages/current-shortages/drug-shortages-list?page=CurrentShortages. Accessed March 20, 2023. 2. Pharmacy technician shortage survey findings executive summary. American Society of Health-System Pharmacy. March 2020. Accessed March 20, 2023. 3. Hospitals Scramble as Pharmacy Technician Shortage Persists (ashp.org) https://www.ashp.org/News/2022/05/02/hospitals-scramble-as-pharmacy-technician-shortage-persists. Accessed March 20, 2023.

Title 16 Board of Pharmacy Proposed Regulations – Sterile Compounding

Proposed Language	Recommendations/Comments
CCR 1736.11 Master Formulation and Compounding Records. subsection (c)(3): The manufacturer, lot number, and expiration date shall be recorded for each component for CSPs.	**Rationale:** Current language in CCR 1735.3 states: (F) The manufacturer, expiration date and lot number of each component. If the manufacturer name is demonstrably unavailable, the name of the supplier may be substituted. If the manufacturer does not supply an expiration date for any component, the records shall include the date of receipt of the component in the pharmacy, and the limitations of section 1735.2, subdivision (l) shall apply. (i) Exempt from the requirements in this paragraph (1735.3(a)(2)(F)) are sterile preparations compounded in a single lot for administration within seventy-two (72) hours to a patient in a health care facility licensed under section 1250 of the Health and Safety Code and stored in accordance with standards for "Redispensed CSPs" found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP37-NF32) Through 2nd Supplement (37th Revision, Effective December 1, 2014), hereby incorporated by reference. **Recommendation:** Add back the language above: 1736.11 Master Formulation and Compounding Records, subsection (c)(3): ***The manufacturer, lot number, and expiration date shall be recorded for each component for CSPs.*** *(i) Exempt from the requirements in this paragraph are sterile preparations compounded in a single lot for administration within seventy-two (72) hours to a patient in a health care facility licensed under section 1250 of the Health and Safety Code.*
CCR 1736.1 Sterile Compounding Scope. Subsection (b): CSPs for direct and immediate administration as provided in the Chapter shall only be done in those limited situations where the failure to administer could result in loss of life or intense suffering. Any such compounding shall be only in such quantity as is necessary to meet the immediate need. Documentation for each such CSP shall include identification of the CSP, compounded date and time, number of units, the patient's name and patient's unique identifier and the circumstance causing the immediate need.	**Rationale:** In the instance of a code blue in a hospital, the requirement for additional documentation goes against the very purpose of making a drip to prevent a loss of life. The burden of completing additional documentation while attempting to save a life, could work to the detriment of a patient in an emergent situation. We recommend the board to remove language requiring documentation due to patient safety concerns. **Recommendation:** ***1736.1 Sterile Compounding Scope. Subsection (b)*** *CSPs for direct and immediate administration as provided in the Chapter shall only be done in those limited situations where the failure to administer could result in loss of life or intense suffering. Any such compounding shall be only in such quantity as is necessary to meet the immediate need.* ~~*Documentation for each such CSP shall include identification of the CSP, compounded date and time, number of units, the patient's name and patient's unique identifier and the circumstance causing the immediate need.*~~

Title 16 Board of Pharmacy Proposed Regulations – Sterile Compounding

Proposed Language	Recommendations/Comments
CCR 1736.1 Sterile Compounding Scope. Subsection (d) (1) (A): (d) In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that: (1) Is essentially a copy of one or more commercially available drug products, unless: (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, or	**Rationale:** • The ASHP and FDA drug shortage lists do not always reflect real-time real time drug shortages. Health systems have monitoring strategies in place to track these drug shortages real-time from drug manufacturers or wholesalers before these shortage drugs get added to the ASHP and FDA drug shortage lists. **Recommendation:** Recommend the board to add language regarding recent drug shortages that may not be reflected on the ASHP and FDA lists to ensure that health systems are compliant with requirements. ***1736.1 Sterile Compounding Scope. Subsection (d) (1) (A):*** *(d) In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that:* *(1) Is essentially a copy of one or more commercially available drug products, unless:* *(A) that drug product appears on an ASHP (American Society of Health- System Pharmacists), ~~or~~ FDA list of drugs, or recent drug shortage that has not been added to the aforementioned lists that are in short supply at the time of compounding and at the time of dispense, or*
CCR 1736.11 Master Formulation and Compounding Records subsection (c): A compounding record shall be a single document. The document shall satisfy the requirements of USP Chapter 797, as well as the following: (1) The date and time of preparation. The time of preparation is the time when compounding the CSP started, which also determines when the assigned BUD starts. (2) The assigned internal identification number shall be unique for each compounded drug preparation. (3) The manufacturer, lot number, and expiration date shall be recorded for each component for CSPs. (4) The total quantity compounded shall include the number of units made and either the volume or the weight of each unit. (5) The identity of each person performing the compounding and pharmacist verifying the final drug preparation (6) When applicable, endotoxin level calculations and results.	**Rationale:** • Current documentation practices in Health-System pharmacies include utilizing electronic record keeping systems/software. However, it is not always feasible for the required elements of the electronic records to be pulled from computer software on a single document. **Recommendation:** Recommend the Board of Pharmacy to consider removing the requirement of "single document" to readily retrievable document to satisfy the requirements of USP Chapter 797 ***CCR 1736.11 Master Formulation and Compounding Records subsection (c):*** *A compounding record shall be a readily-available ~~single~~ document. The document shall satisfy the requirements of USP Chapter 797, as well as the following:*

Title 16 Board of Pharmacy Proposed Regulations – Sterile Compounding

Proposed Language	Recommendations/Comments
CCR 1736.13 Labeling subsection (b): (b) Any CSP dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required by Business and Professions Code section 4076 and section 1707.5.	**Rationale:** Currently, a health facility, as defined in Section 1250 of the Health and Safety Codes, are exempt from patient centered label requirements. **Recommendations:** To be consistent with current regulations, recommend adding exemption language to the current proposed language for HSC 1250 (a) licensed facilities as the administration of compounded medications to patients are done by health care personnel authorized to administer medications and not dispensed for outpatient use. ***CCR 1736.13 Labeling subsection (b):*** *(b) Any CSP dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required by Business and Professions Code section 4076 and section 1707.5.* *(i) Exempt from this requirement are health facilities, as defined in Section 1250 of the Health and Safety Code, if the prescriptions are administered by a licensed health care professional. Prescriptions dispensed to a patient in a health facility that will not be administered by a licensed health care professional or that are provided to the patient upon discharge from the facility shall be subject to the requirements of this section and the regulations promulgated pursuant to subdivision (b).*

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RECEIVED
APR 11 2023
California State
Board of Pharmacy

Ms. Maria Serpa
Enforcement and Compounding Committee
California Board of Pharmacy
2720 Gateway Oaks Dr Suite 100
Sacramento, CA 95833

April 10, 2023

Dear Ms. Serpa:

I would like to expand on my testimony at the March 23, 2023 meeting of the Enforcement and Compounding Committee. Three minutes is insufficient to present important comments as they relate to future regulations.

I offer the following:

The proposed new CCR (California Code of Regulations) Section 1736.4(e)was the subject of discussion at the Enforcement and Compounding Committee hearing.

The new regulation states that no passive ceiling or wall penetration is allowed between areas and rooms with classified air. Chief Inspector Acosta opined that "passive penetration" I.e., one-way vents which allow low air flow from one ISO area to another ISO area is not acceptable. Despite testimony that this is the conventional and currently acceptable design to assure that ISO areas have an outlet for air pressure, the Inspector indicated the design was not acceptable.

In multi-cleanroom suites, the greatest pressure differential occurs when the cleanest ISO-classified rooms share a wall with the surrounding classified environment. When ISO-classified environments share a wall, pressure levels in each room must be moderated employing passive air vents to reduce air pressure. Again, this is the standard design for clean rooms. This section should be deleted.

The proposed new CCR (California Code of Regulations) § 1736.12 (c) as written will adversely affect patient care in California.

The language of the statute, as proposed, will add confusion to the very clear requirements of USP <797> (effective 11/1/2023).

Section 12.3 of USP does not require endotoxin testing for Category 1 CSPs but does require it for Category 2 and 3, **when sterility testing is required**. The language, as written, deviates from USP by requiring all injectable CSPs **regardless of category** and whether or not they require sterility testing to undergo endotoxin testing. This would adversely affect patient care because each CSP compounded from non-sterile component would have to be tested. Per USP<1163>: "Testing every compounded preparation is neither practical nor officially required."

In compounding an injectable medication for an individual patient as the result of a patient specific prescription, testing each CSP for endotoxin is not necessary and is impractical with large prescription volume compounding facilities. To provide an example: if endotoxin testing is performed by a third party or in-house, this will require one to four days for completion. Per USP, the Beyond Use Date of a

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Category 2 preparation will be four days, and thus will make obtaining medications impossible. That will severely impact the patient care for an additional step that is unnecessary.

The USP Expert Committee spent many years drafting the changes to USP <797>. Having compounded and dispensed hundreds of thousands of prescriptions over the past 30 years and having performed extensive research on endotoxin testing, I am convinced that it is not necessary to add a new regulation requiring every CSP compounded from non-sterile ingredients for specific patient in California be tested for endotoxins.

Chief Inspector Acosta presented a case of a compounded preparation made from non-sterile ingredients, which was administered to multiple patients resulting in adverse events associated with each patient. In this example, the preparation was non-patient specific, which is a deviation from Section 503 (A) of the FD&CA. This vial should have been considered a batch which was given to multiple patients. The minutes of the March 23, 2023, Enforcement and Compounding meeting (page 41): "Dr. Acosta noted the concern was products made in category one that may be inadvertently used on multiple patients without any sterility or endotoxin testing." But that is not what the language of Section 1736.12 (c) states: it will require all CSPs to undergo endotoxin testing.

In conclusion, I respectfully request CCR Section 1736. 12 (c) be deleted from the regulations or for the committee to consider incorporating language that requires endotoxin testing for any non-sterile to sterile preparations that will be administered to more than one patient.

Sincerely,

William A. Stuart RPh
President

HM
hartleymedical

RECEIVED
APR 11 2023
California State
Board of Pharmacy

Dr. Renee Barker
Enforcement and Compounding Committee
California Board of Pharmacy
2720 Gateway Oaks Dr Suite 100
Sacramento, CA 95833

April 10, 2023

Dear Dr. Barker:

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I offer the following:

The proposed new CCR (California Code of Regulations) Section 1736.4(e) was the subject of discussion at the Enforcement and Compounding Committee hearing.

The new regulation states that no passive ceiling or wall penetration is allowed between areas and rooms with classified air. Chief Inspector Acosta opined that "passive penetration" I.e., one-way vents which allow low air flow from one ISO area to another ISO area is not acceptable. Despite testimony that this is the conventional and currently acceptable design to assure that ISO areas have an outlet for air pressure, the Inspector indicated the design was not acceptable.

In multi-cleanroom suites, the greatest pressure differential occurs when the cleanest ISO-classified rooms share a wall with the surrounding classified environment. When ISO-classified environments share a wall, pressure levels in each room must be moderated employing passive air vents to reduce air pressure. Again, this is the standard design for clean rooms. This section should be deleted.

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In conclusion, I respectfully request CCR Section 1736. 12 (c) be deleted from the regulations or for the committee to consider incorporating language that requires endotoxin testing for any non-sterile to sterile preparations that will be administered to more than one patient.

Sincerely,

William A Stuart RPh
President

Cc: California Board of Pharmacy

california **pharmacists** association

March 21, 2023

Maria Serpa, Chair Enforcement and Compounding Committee
California Board of Pharmacy
2720 Gateway Oaks Dr, Ste 100
Sacramento, CA 95833

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

Dear Chair Serpa,

The California Pharmacists Association (CPhA) appreciates the discussion and work of the Enforcement and Compounding Committee Meeting in relation to the regulations related to pharmaceutical compounding of sterile preparations.

CPhA writes to encourage the Board of Pharmacy to provide direct communication to pharmacies of their interpretations of proposed regulation and enforcement expectations as it relates to compounded sterile preparations (CSP). Furthermore, CPhA highlights that the Boards purpose of protecting California consumers also includes ensuring timely and appropriate access to safely compounded sterile preparations and the development of regulations based on USP Chapters 1000 and above which would establish them as a regulatory requirement. These USP Chapters are not the actual standards for enforcement, but are intended to be informational.

We also request that the Board inspectors allow pharmacies the appropriate time to ensure compliance of the USP official date of November 1, 2023. This will allow pharmacists the necessary time to implement the updated USP 797 guidelines in a safe and effective manner to ensure the continued care and safety of our communities.

In regards to the proposed changes to the regulations related to pharmaceutical compounding of sterile products, CPhA would like to provide some feedback for consideration for the following sections:

1) Section 1736 (a) "Certificate of Analysis" as defined requires the COA to be produced by the manufacturer, however there are instances that products may be obtained from wholesale suppliers and the original COA may not be available.

Recommendation: "Certificate of Analysis" (COA) means a document produced by the manufacturer ***or wholesaler*** *that certifies…*

2) Section 1736 (d) "Essentially a copy" as proposed includes an addition of the word "comparable" may be ambiguous and cause unintended interpretations and is not consistent with the current FDA definition. For example, different dosage types may be considered comparable or same class of drugs may be considered comparable.

Recommendation: Remove the term "comparable" from Section 1736 (d)

3) Section 1736.2 Personnel Training and Evaluation (d) may potentially reduce access to CSP as a pharmacist providing direct oversight may be ineligible to supervise if they were to fail an aseptic manipulation evaluation even if they do not regularly compound themselves.

*Recommendation: "…*who fail any aspect of aseptic manipulation evaluation shall not be involved in compounding ~~**or oversight of the preparation**~~ of a CSP

4) Section 1736.3 Personnel Hygiene and Garbing (b) "..shall not allow personnel to enter the compounding area with non-removable piercings…" in 797 FAQ #65 allows for an adhesive bandage or head cover to be used to cover non-removable jewelry.

*Recommendation: Either modifying language to "**visible** non-removable piercings" or allowance of adhesive bandages to cover non-removable piercings*

5) Section 1736.6 (b) "…Professional judgement shall be used to determine the appropriate action.." the professional judgment should be interpreted as that of the pharmacist involved with the CSP

*Recommendation: "…the professional judgment **of the pharmacist supervising** shall be used to determine appropriate action…"*

6) Section 1736.16 USE OF CSPS AS COMPONENTS – "…provisions of this article including Category 1, Category 2, and Category 3" to clarify that components cannot meet all three categories

Recommendation: …provisions of this article including Category 1, Category 2, ~~**and**~~ **or** Category 3."

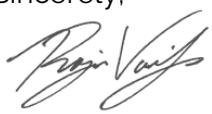
7) Typo of "CNSP" in Sections 1736.1 (c) and 1736.9 (c) should read **CSP**

We appreciate the opportunity to comment and provide feedback to the Board on ensuring patients in the state continue to receive optimal pharmacists delivered care. Should you have any questions about this recommendation, please feel free to contact me at rvaidya@cpha.com.

Founded in 1869, the California Pharmacists Association (CPhA) is the largest statewide association representing the pharmacy profession in all practice settings. Our mission is to advance the practice of pharmacy for the promotion of health.

Thank you for your consideration.

Sincerely,



Rajan Vaidya, PharmD
Vice President, Practice & Professional Development

March 20, 2023

Debbie Damoth
debbie.damoth@dca.ca.gov
California Board of Pharmacy
2720 Gateway Oaks Drive, Suite 100
Sacramento CA 95833

Re: Comments Relative to the Discussion, Consideration and Possible Action on 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)

Dear Ms. Damoth and Members of the Board of Pharmacy,

I thank you for the opportunity to submit my comments regarding proposed regulation changes relative to sterile compounding. I have owned and operated Pacific Compounding Pharmacy in Stockton for 17 years. I have a passion for caring for my patients and a profound desire to comply with the regulations promulgated by this Board. I appreciate the reorganization of the compounding regulations to synchronize with the new USP <795> and <797> chapters and I hope that you find my input useful, clear, and balanced.

Though you may not agree with all of my comments below, I hope that you will recognize the critical need for clarity in the word choices for this evolution of compounding regulations in California. If we (the Board, licensees, and community) do this process right, we will avoid repeating the drawn out process we endured with the last revision of the sterile compounding regulations.

Specifically, I request that each of you assure that the regulations you approve are clear, concise, and necessary for patient safety. It is hugely problematic for both compounding licensees and inspectors when regulations are written with poorly defined words, may have multiple interpretations, or conflict with other regulations. I believe that the compounding community and your inspectors would agree that an easy to understand set of regulations will make all our lives better (and potentially improve the relations between licensees and inspectors, as well).

Further, poorly defined words used in regulations actually have a negative impact on patient care and safety. First, the compounder struggles to understand what the regulation requires and has difficulty, frustration, or unnecessary expenses with the attempt to comply. Then enforcement may be inconsistent amongst inspectors who have (reasonably) different interpretations of the poorly defined words used in the regulations. These are both followed by compounders and business owners deciding that the guessing game of compliance is not worth the stress nor expense and they stop offering compounding altogether!

But the patients of California still need safe, high-quality compounding.

The result of poorly defined regulatory wording will ultimately be patient suffering because compounding will not be readily available in the state of California. Limited access to compounds will make safe, high-quality compounds harder for patients to locate and more expensive to acquire.

Patient safety should not be compromised, but due attention to the importance of establishing a body of regulations that create an environment owners are willing operate within, is simultaneously critical to the longevity of pharmacy compounding in California.

Thank you for your time and consideration of my comments above and below,

Marie Cottman, Pharm.D.

312 Lincoln Center Stockton CA 95207
ph 209-474-7271 fax 209-474-7168

BOP Proposed Item 1736 (c):

"Designated person(s)" means one or more individuals assigned by the pharmacist-in-charge to be responsible and accountable for the performance and operation of the facility and personnel as related to the preparation of the compounded sterile preparations ("CSP" for the purposes of this article). Nothing in this definition allows for the designated person to exceed the scope of their issued license. When the designated person is not the pharmacist, the Pharmacist-in-Charge (PIC) must review all practices related to the operations of the facility that require professional judgement."

Comment: This language is directly out of USP and is a good first example of how USP is written as a guideline, not regulation. What does it mean for the PIC to be "responsible and accountable"? If the PIC supervises the DP who follows 100% all the guidelines for training, validation, quality assurance, etc. and an employee makes a mistake that is undetectable on final review, is the PIC now accountable for that human error?
If a pharmacist who has been through and passed all the appropriate training neglects to follow an SOP, is that the responsibility of the PIC?
Further, in what situations will PIC be held "accountable" for the performance of the facility? If the power goes out, is it now my fault? This may seem ridiculous, but the language is so broad and encompassing that it discourages pharmacists from being willing to be PIC or DP.

When language in a regulation causes licensees to ask so many questions, it probably should be clarified as to the intent of the regulation and how it will improve patient safety.

Recommendation 1736 (c):
"Designated person(s)" means one or more individuals assigned by the pharmacist-in-charge as described in USP <797>. Nothing in this definition allows for the designated person to exceed the scope of their issued license. When the designated person is not the pharmacist, the Pharmacist-in-Charge (PIC) must review all practices related to the operations of the facility that require professional judgement."

BOP Proposed Item 1736 (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.

Comment: The FDA has already defined "essentially a copy" in its January 2018 Guidance for Compounding and adding ANOTHER different definition of the same term is confusing. Further, the term "comparable" is open to interpretation as it does not have a succinct definition. Adopting the language from FDA's guidance document would be more appropriate.

Recommendation 1736 (d): ***Change to read like FDA guidance:***
"Essentially a copy"
A compounded drug preparation will be considered essentially a copy of a commercially available drug product if it has all of the following characteristics:
a) has the same API(s) as a commercially available drug product and
b) has the same, similar, or easily substitutable dosage strength as a commercially available drug product and
c) can be used by the same route of administration as the commercially available drug product
unless a prescriber determines that there is a change, made for an identified individual patient, which produces, for that patient, a significant difference from the commercially available drug product.

Reference:
The FDA has already defined "essentially a copy" on page 5 of **Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act Guidance for Industry.**

BOP Proposed Item 1736 (h):

"Preparation "means a compounded drug or nutrient."

Comment:
Why define preparation differently from USP <797>? USP applies to "…preparing compounded sterile preparations (CSPs) for human and animal drugs".
What is the definition of "nutrient"? What is the difference between a nutrient and a dietary supplement?
Since all compounding must be done pursuant to a prescription, if a nutrient is prescribed, does it not become a drug by CCR 4022(c)? Even though the nutrient itself is not a "dangerous drug," since it cannot be made by a 503A compounder without the order of a prescription, by default it becomes one.
Further, proposed regulation 1736.9 (e) prevents compounding without a USP monograph or an API listed on the 21 CFR 216, making this definition irrelevant.

Recommendation 1736 (h):
Remove this definition

BOP Proposed Item 1736 (j):

"Quality" means the degree to which the components and preparation meets the intended use or purpose, complies with relevant law and regulation, and means the absence of harmful levels of contaminants, including but not limited to filth, putrid, or decomposed substances, the absence of active ingredients other than those listed on the label, or the absence of inactive ingredients other than those listed on the master formula record as specified in USP 797.

Comment: Currently "quality" is defined in section 1735.1 (ae) which is virtually the same as in the proposed revisions of section 1735(f) for NSCPs: "Quality" means the absence of harmful levels of contaminants, including filth, putrid, or decomposed substances, or the absence of active ingredients other than those listed on the label, or the absence of inactive ingredients other than those listed on the master formulation record."
The addition of "the degree to which to components and preparation meets the intended use or purpose" puts an unreasonable expectation that when a compounder makes a preparation on the order of a prescriber, it will ALWAYS meet the intended purpose. (i.e. if the preparation is intended to treat cancer, but the cancer doesn't disappear, has the compounder not made a "quality" preparation?) Compounders cannot be responsible for the ***therapeutic outcome*** of the preparation.

Recommendation 1736 (d): ***Continue to have the SAME definition of quality for all compounded preparations.***
"Quality" means the absence of harmful levels of contaminants, including filth, putrid, or decomposed substances, or the absence of active ingredients other than those listed on the label, or the absence of inactive ingredients other than those listed on the master formulation record as specified in USP Chapter 797.

References: CCR 1735.1 (ae) and Minutes from 2/27/2023 Compounding and Enforcement Committee Meeting.

BOP Proposed Item 1736.1 (c):

"A limited quantity of CNSP may be prepared and stored in advance of receipt of a patient specific prescription document where, and solely in such quantity, as is necessary to ensure continuity of care for individual patients of the pharmacy based on a documented history of prescriptions for those individual patients."

Comment:
1- Minor typo of "CNSP" should be "CSP"
2- Section 503A of the FDC Act **allows** limited quantity compounding in anticipation of prescriptions for individual patients. The subtle change of the wording in this proposed 1736.1(c) only allows for anticipatory compounding for existing/known patients. Some prescribers are ordering a limited number of doses for NEW patients each week which would eliminate preparing CSPs prior to receipt of that individual patient's prescription. This will delay care as the pharmacist will have to wait for the prescription before preparing the CSP which may also require USP <71> and or <85> testing prior to release. This will have a particularly detrimental effect on patient's access to custom eye drops for severe and complex eye infections at 4:30pm on a Friday afternoon.

Recommendation 1736.1 (c): ***Keep and renumber the existing language from CCR 1735.2 (b).***
"A pharmacy may prepare and store a limited quantity of a compounded drug preparation in advance of receipt of a patient specific prescription where and solely in such quantity as is necessary to ensure continuity of care for an identified population of patients of the pharmacy based on a documented history of prescriptions for that patient population."

References: CCR 1735.2 (b)

BOP Proposed Item 1736.1 (d)(2):

"(d) In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that:
(2) Is made with any component not intended for use in a CSP for the intended patient population."

Comment: Compounding is often a solution for patients with unique and unusual needs. The language of "intended patient population" is too broad. I believe this language was meant to prevent compounding with a component that is **known to be contraindicated in a specific patient**. But that is not what it says. If this becomes letter of the law, it will be too restrictive. Estrogen will not be able to be used in a man (who might be undergoing transition therapy), nor methotrexate for a pregnant patient (with an ectopic pregnancy).

Recommendation 1736.1 (d)(2): Remove this clause from 1736.1 (d) and allow our Scope of Practice to suffice: *"4050(b) Pharmacy practice is a dynamic,* ***patient-oriented health service that applies a scientific body of knowledge to improve and promote patient health by means of appropriate drug use, drug-related therapy****, and communication for clinical and consultative purposes. Pharmacy practice is continually evolving to include more sophisticated and comprehensive patient care activities." (bold emphasis added)*

References: BPC 4050(b)

BOP Proposed Item 1736.1 (d)(3):

"(d) In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that:
(3) Is made with a component for which a conventionally manufactured sterile product is available and appropriate for the intended CSP."

Comment:
What is the intent of this section? I can't figure out what I am prohibited from preparing. Does it mean, "Don't use conventionally manufactured sterile products"?
Paragraph d is clear: Do not compound a CSP that…
Paragraph 3 is **unclear**: … is made with a component that is manufactured sterile. And
… is appropriate for the intended CSP.

Further, USP <797> Section 9.3.1 State "Conventionally manufactured sterile products should be used when available and appropriate for the intended CSP."

Recommendation 1736.1 (d)(3):
Remove section (3) and allow Section 9.3.1 of USP <797> to say enough.

References: <797> Section 9.3.1

BOP Proposed Item 1736.2 (b):

"Aseptic manipulation competency initial training and competency and ongoing training and competency documentation shall include the Primary Engineering Control (PEC's) type and unique identifier used during the evaluation. Aseptic manipulation competency evaluation and requalification shall be performed using the same procedures, type of equipment, and materials used in compounding drug preparations. Aseptic qualifications from one premises may be used for another premises if all of the following conditions are met:
1. The SOPs are identical
2. The facility designs are identical
3. The PECs are of the same type and sufficiently similar to accommodate the use of the same SOPs describing use and cleaning."

Comment: This is a great concept! The idea of allowing compounding personnel to learn aseptic manipulations and transfer that skill to another facility is fantastic (especially with the shortage of technicians and absenteeism)!

Based on the text of USP <797> (Section 2.3), "aseptic manipulation competency evaluation consists of a visual observation, media-fill testing, followed by a gloved fingertip and thumb sampling of both hands, and surface sampling of the direct compounding area…"

However, the specifics in this proposed CCR are too specific.
Sentence two is the key *Aseptic manipulation competency evaluation and requalification shall be performed using the same procedures, type of equipment, and materials used in compounding drug preparations.* How an employee moves in the cleanroom, how they puncture a vial with a needle, where they place their items in a Laminar Air Flow Work Bench are skills that can be used in multiple similar settings. (An independent pharmacy's LAFW to a hospital's LAFW, for instance.) Further, the fingertip touch test and the media fill tests validate that a compounder can "manipulate" in a specific type of PEC (LAFW vs BSC vs CACI, etc) and these tests take 7 days and 14 days respectively. In contrast, gowning and cleaning P&P can be taught quickly! I believe it will negate the usefulness of this CCR to require that the SOPs and facility designs are IDENTICAL. I do agree that the PEC's need to be of the same type.

Recommendation 1736.2 (b): Change the conditions 1, 2, and 3. To be:
Aseptic manipulation competency initial training and competency and ongoing training and competency documentation shall include the Primary Engineering Control (PEC's) type and unique identifier used during the evaluation. Aseptic manipulation competency evaluation and requalification shall be performed using the same procedures, type of equipment, and materials used in compounding drug preparations. Aseptic qualifications from one premises may be used for another premises if all of the following conditions are met:

1. *The PECs are of the same type (LAF, BSC, CACI, etc)at both premises*
2. *The compounder has read all the sterile policies and procedures and*
3. *The compounder has at minimum, completed training on policies and procedures for gowning, cleaning, and compounding records at the additional premises.*

BOP Proposed Item 1736.2 (c):

"Aseptic manipulation ongoing training and competency shall occur each time the quality assurance program yields an unacceptable result as defined in the SOPs referenced in section 1736.17 that may indicate microbial contamination of CSPs. Aseptic manipulation ongoing training and competency procedures shall be defined in the facilities SOPs."

Comment:
Based on the text of USP <797> (Section 2.3), "aseptic manipulation competency evaluation consists of a visual observation, media-fill testing, followed by a gloved fingertip and thumb sampling of both hands, and surface sampling of the direct compounding area…" and (<797> Section 18) "quality assurance is a **system** of procedures, activities, and oversight…"
Thus the phrases "quality assurance program yields an unacceptable result" and "may indicate microbial contamination" are problematic.

a. Both a QA and QC program will have detailed SOPs (as required by <797> Section 18) these SOPs should define "unacceptable results" and provide actions when they occur. Forcing manipulation competency on an unspecified number of compounders may shut down an operation for

up to 2 weeks with the way that 1736.2(c) is currently written.

b. What does "may indicate microbial contamination" mean? Is it when a compounder fails a fingertip touch plate (which would be part of a QC program)? Is it when quarterly testing yields colonies above the action limit? Is it when a sterility test fails?

Further, who will receive the training? Everyone involved and/or overseeing the process, or just the compounder?

Recommendation 1736.2 (c): Change language to be clear and followable by DPs and PICs.
Aseptic manipulation ongoing training and competency shall be defined in the facilities SOPs. Aseptic manipulation ongoing training and competency shall additionally occur for personnel directly involved with the compounding of a CSP found to have microbial contamination.

References: USP <797>

BOP Proposed Item 1736.2 (d):

"Compounding personnel or persons with direct oversight over personnel performing compounding, verifying and/or handling CSPs who fail any aspect of aseptic manipulation evaluation shall not be involved in compounding or oversight of the preparation of a CSP until after successfully passing training and competency in the deficient area(s) as detailed in the facility's SOPs."

Comment:
I believe that this is too punitive. Note that USP <797> (Section 2.3) **defines** "aseptic manipulation competency evaluation" and it includes all of the following: a) a visual observation, b) media-fill testing, c) gloved fingertip and thumb sampling of both hands, and d)surface sampling of the direct compounding area…"

1) Those who can't do, teach. A pharmacist who has oversight of other compounders and only performs gloved fingertip touch testing every 3 to 6 months, may have a failure (1 cfu = failure), but this does not mean that they are suddenly incapable of overseeing technicians compounding CSPs for the next 7 days that it takes to pass competency (what about the oversight they had during the 7 days that you assumed they would pass?) As A PIC, should I let the pharmacist have a week off because they cannot oversee compounding?
2) Further, a technician who fails a surface testing after successfully completing media fill testing may continue to be very capable of cleaning and disinfecting the cleanroom. Please consider deferring to the facilities SOPs for actions on failures during the aseptic manipulation evaluation.
3) Additionally, USP <797> FAQ #52 specifically says that compounders who fail part of the aseptic competency do NOT have to stop compounding, but facility must evaluate cause of failure and determine appropriate corrective actions. If Ca BOP wants to be more restrictive, there should be a patient safety rational for the increased restriction.

Recommendation 1736.2 (d): Remove and defer to SOPs for corrective actions. (but if you don't like that, consider the following)
Compounding personnel who fail an aspect of initial aseptic manipulation evaluation shall not be involved in compounding a CSP until they have passed. When compounding personnel fail an aspect of an ongoing aseptic manipulation, the DP shall initiate and document an evaluation of the cause of failure and follow the facilities SOPs for appropriate corrective actions.

References: USP <797>, BOP Meeting Materials for 3/23/23 Compounding and Enforcement Committee.

BOP Proposed Item 1736.2 (e):

"Any person assigned to provide the training specified in this section shall obtain training and demonstrated competency in any subject in which the person will provide training or observe and measure competency described in the facilities SOPs as referenced in section 1736.17. Documentation must be maintained demonstrating compliance."

Comment:
Is it the board's intent that a compounder cannot train themselves? How do I know when I have satisfied this? Do you have a specific meaning for "obtain."

"Subject" can be a very broad, encompassing word.
Both of our trainers have been sterile compounding for 20+ years and consistently pass aseptic manipulation competency, sterility, and endotoxin testing. I last attended aseptic training in 2012, how will the board inforce this requirement when initial documentation is lacking?
How long is the documentation maintained for? All other pharmacy related documentation is 3 years--- is this forever? (three years seems reasonable and should be re-demonstrated anyway!)

Recommendation 1736.2 (e):
Clarify language to prevent unnecessary barriers to continuing sterile compounding and to make this clear and followable.
Any person assigned to provide the training specified in this section shall have demonstrated competency in the skills in which the person will provide training or observe and measure competency described in the facilities SOPs as referenced in section 1736.17. Documentation of the trainer's competency must be maintained for three years.

BOP Proposed Item 1736.3 (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."

Comment:
USP <797> FAQ #65 addresses dermal (non-removable) piercings to be covered with an adhesive bandage or head cover.
How does a non-removable piercing differ from a permanent hearing aid? What is the increased risk to a CSP from the skin of a healthy, healed, non-removable piercing?
Further, this is covered in proposed section 1736.3 (a) which states "The pharmacist overseeing compounding shall not allow personnel with potentially contaminating conditions to enter the compounding area." So if the piercing were at risk to contaminate a CSP, the personnel would already be restricted from entering the compounding area.

Recommendation 1736.3 (b):
Remove this and allow USP <797> FAQ #65 to guide.

References:
USP <797> FAQ #65 and Proposed CCR 1736.3 (a)

BOP Proposed Item 1736.4 (e):

"Except as provided in (e) dynamic interactions between areas and rooms with classified air shall be controlled through a heating, ventilation, and air condition (HVAC) system. No passive ceiling or wall penetrations are allowed."

Comment:
Minor typo… Section e should not reference its own section. Should be referencing item (d)?

Recommendation 1736.4 (e):
Except as provided in (d) dynamic interactions between areas and rooms with classified air shall be controlled through a heating, ventilation, and air condition (HVAC) system. No passive ceiling or wall penetrations are allowed.

BOP Proposed Item 1736.6 (b):

"At a minimum, to trend for growth of microorganisms, during biannual (every 6 months) recertification, any microorganism recovered (growth) shall be identified at least to the genus species, regardless of the CFU count. Professional judgement shall be used to determine the appropriate action necessary to remedy identified trends regardless on the action level. Investigation must be consistent with the deviation and must include evaluation of trends."

Comment:
This paragraph is very hard to follow and to determine what is expected of the DP. 1) "At a minimum" is presumed with all of USP <797> and BOP CCRs. It does not need to be stated. 2) Everything else in USP <797> is P&P based. Who will apply their Professional judgement? Why not an SOP like everything else? 3) the last sentence has no reference and is just tacked on.
Minor typo: "*identified trends regardless on the action…" "on" would make more sense as "of"*

Recommendation 1736.6 (b): Clarify what needs to happen and who determines the course of action.
During biannual (every 6 months) re-certifications, to trend for growth of microorganisms, any microorganism recovered shall be identified at least to the genus and species levels, regardless of the CFU count. The DP should use professional judgement to evaluate the microbial growth trends. If a deviation is identified, the DP should conduct and investigation and carry out actions to remedy the identified trends.

BOP Proposed Item 1736.9 (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."

Comment:
"Component" is a term that causes this proposed regulation to conflict with other USP uses of "component." For instance, blood components, commercially available sterile products used as components, sub preparations used as components, etc. Further, container closures may not have COAs if terminal sterilization is conducted.
Based on the requirement to receive and evaluate a COA and the specificity of "compendial name" one might assume that this regulation is meant to refer to all chemical ingredients as "components".
If this is referencing all chemical ingredients, then it excludes using commercially available ingredients because they do not have a COP. We already have in current law (1735.3 (c)) an allowance for use of an FDA approved product ***without*** a COA.

Recommendation 1736.9 (d):
Change the term "components" to "ingredients" and add the phrase from current 1735.3(c) to the end of this paragraph.
All ingredients 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. Certificates of purity or analysis are not required for drug products that are approved by the FDA.

References:USP <797> Section 1, 9.2 (description of supplies), 9.3 (components include ingredients and container closures)

BOP Proposed Item 1736.9 (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 approve 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."

Comment:

"If" should be replaced by "When"
Minor typo: "FDA approve**d** drug"
If California does not allow the sterile compounding of Category 1 Bulk Drug Substances, patients who want those preparations will find other states to compound for them. If you allow your licensees to compound with Cat 1 with the strict guidelines that are being set forth in USP<797>, you will at least have control over the quality of preparation that the people of California can access. Otherwise, patients will find substandard preparations from out of state.

Further, compounders are in need of clarification as to the use of 503B preparations in our 503A preparations. This may come into play with drug shortages or sterile items that can only be procured from an Outsourcing Facility.

A "public health official" is far too undefined. Internet definition: *Any person from the department of Health and Human Services.* A "public health official" may not even be a doctor, nor have the basic knowledge of compounding. Further, without any guidance, this allows public health official to authorize use of ANY drug substance, including those on the "do not compound list or Category 3 of the Bulk Drug Substances List? How will a DP know that the "public health official" actually has authorization to violate item 1736.9 (e)?

Recommendation 1736.9 (e):
When 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, be made by a 503B facility registered in California, be listed in CFR List of Bulk Drug Substances That Can Be Used To Compound Drug Products, 21 CFR 216, or be on the Category 1 of the 503A Bulk Drug Substances List.

In an emergency use situation for a patient specific CSP that is not compliant with the above references, a DP may request an immediate waiver of 1736.9 (e) with the Board of Pharmacy.

BOP Proposed Item 1736.14 (a)(1):

"A CSP's beyond-use date (BUD) shall not exceed:
(1) The chemical and physical stability data of the active pharmaceutical ingredient and any added substances in the preparation,"

Comment:
Data is an undefined term subject to a wide variety of interpretations, which creates difficulty with compliance. "Data" could mean information from referenced journals, extrapolated information from text references, summary data from private sources, or raw data from specific commissioned analysis. Without understanding how this term will be applied to CSPs, a business cannot determine the cost, appropriateness, or applicability of their pharmacist judgement in establishing a BUD. USP's intent is clear that they require that a pharmacist "consider" relevant parameters that could affect quality of the CSP (Section 14.2) which easily could include literature review and compounding knowledge to result in a professional judgement regarding a BUD.
1736.14(a)(1) has the potential as written to compel every pharmacy in every setting to have to independently collect "data" to justify their BUDs rather than using pharmacist judgement.
This comment is in no way alluding to extension of a BUD. What data will the inspectors look for to adequately demonstrate that a formula is stable, both chemically and physically, for 1 day, for 7 days, or frozen for 45 days?

Recommendation 1736.14 (a)(1):
A CSP's beyond-use date (BUD) shall not exceed:
(1) The anticipated chemical and physical stability of the active pharmaceutical ingredient and any added substances in the preparation. The process of evaluating of the chemical and physical stability of the ingredients in each formulation must be documented on the MFR and include at a minimum considerations from USP chapter <1191> Stability Considerations.

References:<USP 797> and <1191>

BOP Proposed Item 1736.15:

USE OF CONVENTIONALLY MANUFACTURED PRODUCTS AS COMPONENT

Comment:
Does this include manufactured 503B products?

Recommendation 1736.15:
In section 1736 STERILE COMPOUNDING DEFINITIONS, Add a definition of “Conventionally Manufactured Products” Ingredient components from any FDA registered entity.

Comments on Proposed CA Sterile Compounding Regs

Rick Rhoads, Pharm.D.

March 21, 2023

1736 Sterile Compounding Definitions

"Certificate of Analysis" (COA) means a document produced by the manufacturer or supplier that certifies the quality of the component and demonstrates that the component conforms to the defined specifications, and, if applicable, meets the requirements in USP.

> **Reason:** The content in this definition is important for pharmacists to analyze, however, it may go beyond what a COA typically offers. Therefore, most COAs would likely be deficient. The supplier usually does not give the original COA from the manufacturer, instead it transcribes the data supplied by the manufacturer into a new COA. Also, I rarely see COAs that include the manufacturing conditions (ie. cGMP) and the suitability of use in pharmaceuticals. This could be accomplished by ensuring the manufacturer is registered with FDA and analyzing the grade of the material. There are other minor changes that I think would be more appropriate for compounders.
>
> The following is the definition in USP <797>:
>
> ***Certificate of analysis (COA):*** *A report from the supplier of a component, container, or closure that accompanies the supplier's material and contains the specifications and results of all analyses and a description of the material.*

(d) "Essentially a copy" of a commercially available drug product means all preparations that are comparable in active ingredients, strength, and dosage form 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.

> **Reason:** The current definition may be interpreted quite broadly so that any compounded preparation with similar ingredients, but a different strength or route of administration might be considered an essential copy.

(j) "Quality" means the degree to which the components and preparation meets the intended characteristics , complies with relevant law and regulation, and means the

absence of harmful levels of contaminants, including but not limited to filth, putrid, or decomposed substances, the absence of active ingredients other than those listed on the label, or the absence of inactive ingredients other than those listed on the master formula record as specified in USP 797.

> **Reason:** The current definition may be confused with the effectiveness of the preparation (eg. the ability to cure an infection) instead of meeting the intended characteristics of the medication prescribed.

1736.1 Sterile Compounding Scope.

(d) In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that:
(1) Is essentially a copy of one or more commercially available drug products, unless:
(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, or
(B) the compounding of that CSP is justified by a specific, documented medical need made known to the pharmacist prior to compounding. Documentation of the shortage or the specific medical need shall be maintained in a readily retrievable format.
(2) Is made with any component not suitable for use in a CSP for the intended patient population.

(4) Cannot be sterilized within the licensed location.

> **Reason:** For subsection 2, I believe “suitable” may be better verbiage because it is difficult to know if the manufacturer intended the component for compounding. For subsection 3, it is unclear what this is referring to. Conventionally manufactured products are often used as components of CSPs.

(f) In addition to the provisions provided in Section 1707.2, consultation shall be provided orally or in writing to the patient and/or patient’s agent concerning proper use, storage, handling and disposal of the CSP and related supplies furnished.

> **Reason:** Many compounded medications are shipped to the patient with written instructions and an offer for a verbal consultation. The current language may be interpreted that oral consultations are always required for shipped prescriptions.

Comments on Proposed CA Sterile Compounding Regs

Rick Rhoads, Pharm.D.

March 21, 2023

1736.2 PERSONNEL TRAINING AND EVALUATION

(b) Aseptic manipulation competency initial training and competency and ongoing training and competency documentation shall include the Primary Engineering Control (PEC's) type and unique identifier used during the evaluation. Aseptic manipulation competency evaluation and requalification shall be performed using the same procedures, type of equipment, and materials used in aseptic compounding . Aseptic qualifications from one premises may be used for another premises if all of the following conditions are met:
1. The SOPs are identical
2. The facility designs are identical
3. The PECs are of the same type and sufficiently similar to accommodate the use of the same SOPs describing use and cleaning.

Reason: The current language may be interpreted to require the presterilization equipment and materials (eg. beakers, graduated cylinders, spin plates, etc) to be exactly the same during the media fill. These are irrelevant to the aseptic manipulation competency.

(c) Aseptic manipulation ongoing training and competency shall occur each time and for each staff member involved in an event where the quality assurance program yields an unacceptable result as defined in the SOPs referenced in section 1736.17 that may indicate microbial contamination of CSPs due to poor practices. Aseptic manipulation ongoing training and competency procedures shall be defined in the facilities SOPs

> **Reason:** It is not clear how to implement this requirement. For example, if a new staff member has poor aseptic technique, would all sterile compounders and supervising pharmacists need to redo training? Also, would this apply to environmental monitoring issues or component selection issues? I think it would be helpful to narrow this to the staff members involved in poor practices.

(d) Compounding personnel or persons with direct oversight over personnel performing compounding, verifying and/or handling CSPs who fail any aspect of aseptic manipulation evaluation shall not be involved in compounding or oversight of the preparation of a CSP until after successfully passing training and competency in the deficient area(s) as detailed in the facility's SOPs, except that this does not apply to:

(1) Persons performing direct oversight, verifying and/or handling CSPs who retake and successfully pass the competency within 30 days of the original failed attempt.

> **Reason:** If a pharmacist overseeing compounding fails any aspect of the aseptic competency, the earliest they would be able to successfully complete a new competency is 2 weeks. This could be very problematic for pharmacies with fewer pharmacists. It is reasonable to require pharmacists to pass this competency for educational purposes, but I think giving more leeway would be helpful for compliance and would not adversely affect quality.

1736.6 MICROBIOLOGICAL AIR AND SURFACE MONITORING

(b) At a minimum, to trend for growth of microorganisms, viable air sampling must occur every 6 months, and any microorganism recovered (growth) shall be identified at least to the genus species, regardless of the CFU count. Professional judgement shall be used to determine the appropriate action necessary to remedy identified trends regardless on the action level. Investigation must be consistent with the deviation and must include evaluation of trends.

> **Reason:** I agree with this requirement, however it should be separated from certifications because viable air sampling is not required to be in conjunction to re-certification.

1736.9 EQUIPMENT, SUPPLIES, AND COMPONENTS

(d) All active pharmaceutical ingredients 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, unless components are commercially manufactured drug products.

Reason: Some components such as container closures or sterile tubing are not manufactured in FDA registered facilities, however the details of the sterilization methods are on the COA.

1736.10 STERILIZATION AND DEPYROGENATION

(f) Sterilization of supplies and/or container–closure
systems shall be done in compliance with USP Chapter 1229, Sterilization of Compendial Articles.

> **Reason:** This may be a typo, but USP <1229> doesn't address depyrogenation.

1736.11 MASTER FORMULATION AND COMPOUNDING RECORDS

(1) The source referenced to support the assigned beyond-use date (BUD), if it exists; each source referenced shall be readily retrievable at the time of compounding and shall be maintained for three years from the date each CSP is dispensed.

> **Reason:** Compounders are required to consider stability data for all BUDs assigned and it is appropriate to cite this data to support the BUD. However, some preparations don't have any stability data. If so, a conservative BUD must be assigned within the limits in USP <797>. The current language may be interpreted to mean that compounders must have stability studies for all preparations (instead of just for the Category 3 CSPs).

(1) The date, or date and time of preparation, if the BUD is listed in hours. The time of preparation is the time when compounding the CSP started, which also determines when the assigned BUD starts, if the BUD is listed in hours.

> **Reason:** This language is helpful to clarify that the date and/or time of compounding refers to when the compounding process started. However, this language may be confused to mean that the BUD must specify a day and time (eg. Discard after 06/15/2023 at 1PM). However, most BUDs are assigned in days only, which would make the time started irrelevant. The time compounded would only be applicable when the BUD is listed in hours.

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, or Category 3.

Reason: The language may be interpreted that CSPs as components must comply with all CSP categories, instead of only the one that is applicable.

brava

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 Sterile Compounding Regulations

Dear Ms. Serpa:

My name is Erik Clausen and I serve as the Pharmacist-in-Charge for Brava CA, LLC, a compounding pharmacy located in Novato, CA specializing in veterinary medicine. I would like to take the opportunity to thank the committee for the opportunity to provide comments to the proposed updates to California's compounding regulations. Brava is committed to provide high quality compounded medications to veterinary patients both in California and throughout the United States.

As a compounding pharmacy specializing in the veterinary space, Brava adheres to the many of the same standards as a pharmacy compounding human medications, however, our patients do have unique needs which require additional consideration to ensure that the unique differences between veterinary patient and human patient needs are being met appropriately.

General Comments:

While we support the efforts to update the regulations to harmonize California's regulations with recent change to both federal guidance and industry standards (USP), we believe the approach presented create regulatory burdens on compounding pharmacies which will result in the disruption of patient care thereby negatively impacting the quality of care enjoyed by California residents and their pets.

a. Many sections of the proposed rules include new language with subjective terms thereby overriding the plain language of the standard that the Board is attempting to adopt. Terms such as "comparable" or "suitable" are subject to professional judgment and open to interpretation which makes maintaining a compliance plan for the pharmacy difficult at best.

b. The proposed rules fail to take into full consideration a number of provisions allowed under federal law such as interim bulk lists which will put California patients at a disadvantage to continue to receive compounded medications that they rely upon which are otherwise allowed under federal law.

For these reasons, we strongly encourage the committee to reconsider the approach to formally adopt the USP standards by simply referencing the actual standards into the regulations as written by USP which almost all other states have done (or are in the process of doing). This preserves the original plain language of the standard thereby providing clearer guidance for a pharmacy's compliance program.

Please note our comments to the following specific provisions.

1. <u>General USP References</u>:

There are numerous references to USP Chapters 1000 and above which would establish them as a regulatory requirement. These USP Chapters are not the actual standards, but are intended to be informational. We are concerned that the manner in which they are referenced exceeds the intent of the USP Board as it would in effect establish those chapters as requirements for pharmacies to adhere to. Our recommendation is that the regulations should clearly reflect the informational nature of these chapters which correspond to the intent of their use by USP.

2. 1736 (a) "Certificate of Analysis" definition as proposed would require a COA to be produced by a manufacturer...demonstrates that the component confirms to the specifications....manufactured under cGMP, is suitable for use in pharmaceuticals and meets the requirements of USP.

   We are very concerned about the term "suitable for use in pharmaceuticals". Who makes that determination? Is it the pharmacist in exercising their professional judgment or is it at the determination of an inspector? How are they reconciled without formal disciplinary action if there is a disagreement as to what is suitable or not?

   Our pharmacies collect Certificates of Analysis for our APIs and other pharmaceutical components used in compounding, they are often provided by our wholesale supplier and as such may not be an original COA from the manufacturer. We trust that this practice still meets the requirements under this definition. It should be noted that the FDA regards the original COA as confidential commercial information which is one of the reasons that it is not always provided in its original format from the manufacturer.

Further, specifically for veterinary compounding, not all components (which we interpret to mean an actual ingredient, whether active or inert), that we use have a USP monograph for APIs specific to veterinary preparations. Because of this any COA we receive may not fully conform to the proposed definition.

3. 1736 (d) Essentially a copy definition...means all preparations that are ***comparable*** in active ingredients to commercially available drug products.

   We are concerned that the inclusion of the word "comparable" will create ambiguity and conflict with established definitions provided by the FDA in their regulations and guidance documents. The determination of what is considered comparable is open to any number of determinations and places pharmacies at risk should an inspector disagree with the professional judgment of the pharmacist.

   As the FDA retains enforcement rights under the FDCA and manufacturers themselves have private rights of action, we question whether this is an area that the State would want to focus its enforcement resources which are likely to occur due to interpretations of the definition being proposed.

4. 1736.1 Sterile Compounding Scope (d)(1)(A)

   (d)(1)(A) ....drug product appears on an ASHP or FDA list of drugs that are in short supply...

   We recognize that this is the current regulation, however these lists do not cover veterinary drug shortages. The FDA animal drug shortage page is not updated in a timely enough manner to reflect animal drugs that are in short supply. Manufacturers of animal drugs are not required to report shortages as manufacturers of human drugs are required to do. Therefore, these lists would not be accurate for a pharmacy engaged in veterinary medicine.

   We recommend also allowing wholesaler BO reports to satisfy documentation requirements that the drug is in short supply. Compounding pharmacies, particularly in the veterinary space, are a viable solution to ensuring continuity of care when these shortages occur.

5. 1736.1 Sterile Compounding Scope (d)(2)

   (d)(2) Is made with any component not intended for use in a CSP for the intended patient population.

Many medications prescribed by veterinarians are prescribed as "off-label". We are not sure how we would meet this requirement for our veterinary patients since the prescription is for a drug approved for human use, but recognized by veterinarians for treatment of animals. Assuming component means ingredient, who determines what component is "intended" for use in compounded sterile preparation for the patient population? Will documented human standards apply to veterinary patients? Is the prescription and medical opinion of the prescribing veterinarian the standard?

6. 1736.3 Personnel Hygiene and Garbing (b)

   (b)...shall not allow personnel to enter the compounding area with non-removable piercings...

   We ask that this be modified to include "visible" non-removable piercings. Without this clarification we are concerned about meeting the requirement while balancing privacy protections and rights of our employees.

7. 1736.9(d) Equipment, Supplies, and Components

   (d) All *components* .... Shall be manufactured by an FDA-registered facility and *suitable for use* in sterile pharmaceuticals.

   Compounding pharmacies use a number of inactive ingredients that are not manufactured in an FDA registered facility, but have been approved by FDA for pharmaceutical purposes.

   In addition, use of the phrase "suitable for use in sterile pharmaceuticals" is vague and open to interpretation. Who would determine suitability? Is this left to a pharmacist's professional judgement? We are very concerned that there would be differences in opinions even between inspectors which will make compliance difficult at best.

8. 1736.12(b): Establishes that an alternative method for sterility testing can be used so long as it is validated according to USP Chapter 1223.

   We support the inclusion of the alternative method for sterility testing, however are unsure if the validation must be completed by the pharmacy or if the lab performing the testing may provide it.

9. 1736.17(d): Failure to follow written SOPs shall constitute a basis for enforcement action.

The current rule contains a similar provision but it provides for disciplinary action for a "material" failure. As proposed, "any" failure, whether material, single occurrence or multiple occurrences could all trigger enforcement action. We strongly recommend maintaining the current language which provides that a material failure to serve as the impetus for disciplinary action, not the mere occurrence of an event, no matter how insignificant or minor.

Compliance to SOPs within a pharmacy is important but there are any number of examples where it would be excessive to bring an enforcement action against a pharmacy for an identified gap in following an SOP. There could be periods where the pharmacy is changing a procedure and the actual update to the SOP could occur a few days later (as well as training on the new procedure). Another example is there may be a miss of a minor detail in an SOP that has no impact on the quality or efficacy of the compounded product and this may be remedied immediately. Would identification of this miss during an inspection give rise to full enforcement action? SOPs are internal working policies and procedures. If there is a pattern of non-adherence to the pharmacy's SOPs, then it could be indicative of a problem. We recommend modifying this language to reflect a pattern of inconsistency or material events and not single event occurrences.

Again, thank you for the time to present these comments to the committee for consideration.

Sincerely,

Erik Clausen, PharmD
General Manager and Pharmacist-in-Charge

Maria Serpa, PharmD
Chair Enforcement and Compounding Committee
California Board of Pharmacy
2720 Gateway Oaks Dr, Ste 100
Sacramento, CA 95833

March 23, 2023

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

Dear Chair Serpa,

I am writing this letter in support of my verbal comments during the Enforcement and Compounding Committee meeting on March 23, 2023. I appreciate the opportunity to provide comment and suggestion for the Board to consider during its evaluation of the *Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations*.

CPS Solutions manages multiple hospital pharmacies throughout California, many of which are smaller hospitals with less resources than large health systems. I encourage the Board to keep in mind these local community hospitals that provide basic healthcare to the people of California, while still keeping them safe.

I respectfully submit the following for consideration:

1736.1 STERILE COMPOUNDING SCOPE
(b) CSPs for direct and immediate administration as provided in the Chapter shall only be done in those limited situations where the failure to administer could result in loss of life or intense suffering. Any such compounding shall be only in such quantity as is necessary to meet the immediate need. Documentation for each such CSP shall include identification of the CSP, compounded date and time, number of units, the patient's name and patient's unique identifier and the circumstance causing the immediate need.

<u>Comment:</u>
Smaller hospitals that compound in a Segregated Compounding Area (SCA) with a single PEC occasionally experience failures of that PEC but must still meet the patient's sterile compounded medication needs. In the acute hospital setting, all medications are important and potentially lifesaving. Without a PEC, these hospitals must resort to immediate use compounding of medications that, if not given, could lead to greater complications. These immediate use compounds may not always be considered to "prevent loss of life or intense suffering", but still provide critical medication treatment.

Of important note, the USP Committee specifically removed the language in the current USP 797 v2008 discussing immediate use compounding, "*where there is a need for emergency or immediate patient administration of a CSP*", from the USP 797 revision v2022.

I agree that pharmacies should not compound immediate use as a matter of routine. However, we do need to find a way to allow pharmacies with only one PEC to provide critical sterile compounded medications during periods when their PEC needs service or so that outsourcing can be set up.

Recommendation:

1) Remove subsection (b) completely, or;
2) Consider language that allows immediate use for non-emergent medications in limited situations in which the PEC is not operational for a short period of time.

1736.4 FACILITIES AND ENGINEERING CONTROLS

(c)(1) Designated compounding area(s) shall typically be maintained at a temperature of 20° Celsius or cooler and shall provide comfortable conditions for compounding personnel attired in the required garb.

Comment:

For reference, USP 797 v2022 section states, "*The cleanroom suite should be maintained at a temperature of 20° or cooler and a relative humidity of 60% or below to minimize the risk of microbial proliferation and to provide comfortable conditions for compounding personnel attired in the required garb*." It appears the proposed regulation has changed "cleanroom suite" to "designated compounding area(s)". Presumably, a designated compounding area would include a Segregated Compounding Area (SCA), in addition to a cleanroom suite.

Many smaller hospitals without the resources of large hospital systems do not have full cleanroom suites. They must compound in SCAs that are often located within the pharmacy or in rooms adjacent without their own HVAC system. Requiring a temperature of 20°C (68°F) or less in the SCA would often mean that pharmacy medications are stored at 20°C/68°F or less. As we know, "room temperature" drug storage typically means a temperature of 20-25°C/68-77°F as defined by USP. By requiring a temperature of 20°C/68°F or less in SCAs, the pharmacy has a 1-degree window (20°C/68°F exactly) to comply with both CCR 1736.4(c)(1) and BPC 4119.7(b)[1].

Lastly, note also that the USP 797 v2022 designates SCAs as Category 1, which would limit Beyond Use Dates (BUDs) to 12 hours room temperature and 24 hours refrigerated. These reduced BUDs further limit any potential contamination that may be increased by higher temperatures while compounding.

Recommendation:

1) Remove subsection (c)(1) completely, or;
2) Change "Designated compounding area(s)" to "Cleanroom suites" in order to exclude SCAs from the restrictive temperature requirements.

[1] Reference (BPC 4119.7(b)):

A health care facility shall store and maintain drugs in accordance with national standards regarding the storage area and refrigerator or freezer temperature, and otherwise pursuant to the manufacturer's guidelines. The health care facility's policies and procedures shall specify these storage parameters.

1736.4 FACILITIES AND ENGINEERING CONTROLS

(e) Except as provided in (e) dynamic interactions between areas and rooms with classified air shall be controlled through a heating, ventilation, and air condition (HVAC) system. No passive ceiling or wall penetrations are allowed.

Comment:
Many hospitals without brand new HVAC systems struggle to maintain required pressure differentials within their cleanroom suite. Remedies have included using passive airflow vents from one controlled space to another (e.g., anteroom to buffer room). I do agree that no passive ceiling or wall penetrations should be allowed between controlled ISO space and uncontrolled air space (e.g., general pharmacy area to anteroom or buffer room). However, passive penetrations from controlled space to controlled space does not pose an increased safety risk as long as air changes, pressure differentials, cleaning procedures, and proper airflow are maintained.

Recommendation:
Change regulation to state, "No passive ceiling or wall penetrations *from controlled space to uncontrolled space* are allowed."

1736.13 LABELING
(b) Any CSP dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required by Business and Professions Code section 4076 and section 1707.5.

Comment:
Health facilities, as defined in H&SC 1250, should be exempt from the requirements of outpatient labeling when administered by a health care professional to an inpatient of that facility. Sterile compounds administered in a licensed health care facility to an inpatient do not need to have all of the information on the label (e.g., pharmacy address, physician name, etc.) that is easily accessible via the readily available medical record. Only sterile compounds dispensed outpatient and not administered by a health care professional should be required to have this information.

Recommendation:
Add language which exempts H&SC 1250 facilities from BPC 4076 and CCR 1707.5 labeling requirements.

Thank you again for the opportunity to comment the sterile compounding proposed regulations. I appreciate the Board for considering mine and the public's suggestions for keeping the public safe through essential pharmacy services like sterile compounding. I would also like to recognize the hard work of important persons behind the scenes that help develop and enforce these regulations such Supervising Inspector Christine Acosta.

Please don't hesitate to contact me should you have any questions or require additional information.

Sincerely,

Robert Jackson, PharmD
Director, Compliance and Regulatory Services
CPS Solutions
robert.jackson@cps.com

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.

APhA
American Pharmacists Association

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

Attachment 2e

Article 4.7 draft regulation text

related to hazardous drugs

Title 16. Board of Pharmacy
Proposed Regulation

Proposal to Add Article 4.7 and add new titles and section 1737 – 1737.18 to Division 17 or Title 16 of the California Code of Regulations to read as follows:
Article 4.7 Hazardous Drugs

1737 Handling of Hazardous Drugs
In addition to the standards established by United States Pharmacopeia (USP) General Chapter 800 (USP Chapter 800), titled *Hazardous Drugs – Handling in Healthcare Setting* shall meet the requirements of this Article.

A licensee performing non-sterile and sterile HD compounding shall comply with this article in addition to Article 4.5 and Article 4.6.

1737.1 Introduction and Scope
The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

In addition to providing consultation in compliance with section 1707.2, consultation shall be provided to the patient and/or patient's agent concerning on handling and disposal of an HD or related supplies furnished.

1737.2 List of Hazardous Drugs
The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) Designated person" is a single individual approved by the pharmacist-in-charge to be responsible and accountable for the performance and operation of the facility and personnel as related to the handling of hazardous drugs. Nothing in this definition allows for the designated person to exceed the scope of their issued license. When the designated person is not a pharmacist, the Pharmacist-in-Charge (PIC) must review all practices related to the operations of the facility that require professional judgement.
(b) If an assessment of risk is performed as allowed in USP Chapter 800, it shall be performed or approved and documented at least every 12 months by the designated person and the pharmacist-in-charge, professional director of a clinic, or designated representative-in-charge, as applicable.

(c) The facility's list of HDs must be reviewed and approved by the designated person and the pharmacist-in-charge, professional director of a clinic, or

designated representative-in-charge, as applicable. Approval shall be documented at least every 12 months.

1737.3 Types of Exposure

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

Each entity shall ensure that all employees are aware of the types of risks of HD exposures that may occur as documented in the Chapter. This shall be documented in SOPs and training documents.

1737.4 Responsibilities of Personnel Handling Hazardous Drugs

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

The Pharmacist-in-charge, designated representative-in-charge, or professional director, as applicable shall be responsible for all activities and decisions made or approved by the designated person.

1737.5 Facilities and Engineering Controls

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) When a containment primary engineering control (C-PECs), used for nonsterile and sterile HDs is placed in the same room, biannual certification must document that the room can continuously maintain ISO 7 classification throughout the nonsterile compounding activity. Specific standard operating procedures (SOPs) shall be written to address the maintenance of the ISO 7 classification.

(c) Compounding volatile HDs:
(1) HEPA filters shall not be the only means of containment used.
(2) for sterile compounding, a biological-safety cabinet (BSC) as defined in USP Chapter 800 Class II Type A1 shall not be used
(b) Where a pass-through is installed in a C-SEC the doors must be gasketed and interlocking. A pass-through is not allowed between the C-SEC into an unclassified space.

(c) Effective January 1, 2026, all pass-through doors shall be a HEPA purge type.

(d) Facility room pressure monitoring equipment shall be placed consistent with CETA Guidelines CAG-003:2022. SOPs shall address corrective and remedial actions in the event of pressure differentials and air changes per hour excursions.

(e) Containment Supplemental Engineering Controls (CSTDs) shall not be used to extend the in-use time, BUD, or expiration of any manufactured product or HD CSP.

1737.6 Environmental Quality and Control

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) An entity's SOPs shall address environmental wipe sampling for HD surface residue, its frequency, areas of testing, levels of measurable contamination, and actions when those levels are exceeded.

(b)When actionable levels of contamination is found, at minimum the following shall occur:

(1) Reevaluate work practices
(2) Reevaluate the appropriateness of deactivation, decontamination and cleaning agents
(3) Re-train personnel on deactivation, decontamination and cleaning
(4) Re-train personnel on donning and doffing appropriate PPEs

1737.7 Personal Protective Equipment (PPE)

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) Two pairs of gloves that meet the ASTM D-6978 standard shall be worn for handling HD waste, cleaning HD spills, and performing routine cleaning in HD areas.

(b) The outer pair of gloves that meets the ASTM D-6978 standard chemotherapy gloves shall be changed every 30 minutes during compounding unless otherwise recommended by the manufacturer's documentation. Documentation from the manufacturer shall be readily retrievable. For sterile compounding both pairs of gloves labeled to meet the ASTM D-6978 standard chemotherapy gloves shall be sterile.

(c) Outer gloves used for compounding must be changed between each different HD drug and the standards established in Chapter 800 if continuously compounding a single HD preparation. The facilities SOPs shall define the

circumstances under which the gowning and gloves must be changed between HD handling/preparations.

(d) PPE shall be removed to avoid transferring contamination to skin, the environment, and other surfaces. PPE worn during compounding shall be disposed of in the proper waste container before leaving the C-SEC. SOPS must be in place which describe in detail the donning and doffing of PPE and where it takes place in the C-SEC.

(e) An appropriate full-facepiece, chemical cartridge-type respirator, or powered air-purifying respirator (PAPR) shall be worn when there is a risk of respiratory exposure to HDs, including when:

(1) Attending to HD spills larger than what can be contained with a spill kit
(2) Deactivating, decontaminating, and cleaning underneath the work surface of a C-PEC
(3) There is a known or suspected airborne exposure to powders or vapors.

1737.8 Hazard Communication Program

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

The designated person is responsible for participating in the development of the entity's hazardous communication program. The program shall be documented in SOPs and training documents.

1737.9 Personnel Training

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) Any person assigned to provide the training specified in this section shall have demonstrated competency in the skills in which the person will provide training or observe and measure competency described in the facilities SOPs as referenced in section 1737.17. Documentation must be maintained demonstrating compliance.

(b) Personnel of any facility responsible for handling HD who fail any aspect of training in handling HDs, shall not be involved in handling HDs until after successfully passing reevaluations in the deficient area(s), as detailed in the facility's SOPs. A person with only direct oversight over personnel who fails any aspect of handling HD and ongoing training and competency evaluation, may

continue to provide only direct oversight for no more than 14 days while applicable handling HD ongoing training and competency evaluation results are pending.

1737.10 Receiving

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

All HD API and antineoplastic HDs shall be shipped and received from the supplier in segregated impervious plastic and labeled as HD on the outside of the delivery container.

1737.11 Labeling, Packaging, Transport and Disposal

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) Any compounded HD preparation dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required by Business and Professions Code section 4076 and section 1707.5.

(b) All HD API and antineoplastic HDs shall be transported in an impervious plastic container and labeled as HD on the outside of the container.

1737.12 Dispensing Final Dosage Form

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

Equipment used in nonsterile compounding shall be dedicated for use with HDs and shall be decontaminated after each use.

1737.13 Compounding

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) A disposable preparation mat shall be placed on the work surface of the C-PEC when compounding HD preparations. Where the compounding is a sterile preparation, the preparation mat shall be sterile. The preparation mat shall be changed immediately if a spill occurs, after each HD drug, and at the end of daily compounding activity.

(b) Only one HD drug may be handled in a C-PEC at one time if making multiple preparations.

1737.14 Administering

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) When dispensing an HD to a patient or caregiver for administration, the pharmacy shall

1. Place the HD in a decontaminated impervious plastic container with an HD label on the outside of the container and
2. For an antineoplastic HDs, attach and prime all tubing and attach a CSTD when appropriate.

(b) There shall be a sufficient supply of gloves that meet the ASTM D-6978 standard, to allow for appropriate administration, handling, and disposal of HD drugs by the patient or the patient's agent when dispensing an antineoplastic HD.

1737.15 Deactivation, Decontamination, Cleaning, and Disinfecting

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) Deactivating, decontaminating, cleaning, disinfecting and sporicidal agents shall be used in accordance with manufacturers' specifications and shall be surface compatible.

(b) Agents used for deactivation, decontamination, cleaning and disinfecting all areas and equipment involved in HD handling shall be applied through the use of wipes wetted with appropriate solution and shall not delivered by a spray bottle to avoid spreading HD residue.

(c) SOPs for decontamination and deactivation procedures for the final HD preparation shall be created by the entity in accordance with the entity's SOPs and approved by the pharmacist-in-charge, professional director of a clinic, designated representative-in-charge, as applicable.

1737.16 Spill Control

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) The entity shall have an SOP addressing the use of appropriate full-facepiece, chemical cartridge-type respirator, or powered air-purifying respirator (PAPR) if the capacity of the spill kit is exceeded or if there is known or suspected airborne exposure to vapors or gases.

(b) The entity shall maintain a list of properly trained and qualified personnel able to clean up an HD spill. An SOP shall outline how a qualified personal will be available at all times while HDs are handled.

1737.17 Documentation and Standard Operating Procedures
The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

(a) Any entity engaged in the compounding or handling of HDs shall maintain and follow written SOPs.

(b) The SOPs for compounding or handling HDs shall include at least the following:

(1) Hazard communication program
(2) Occupational safety program
(3) Designation of HD areas
(4) Receipt
(5) Storage
(6) Compounding, if applicable
(7) Use and maintenance of proper engineering controls (e.g., C-PECs, C-SECs, and CSTDs), if applicable
(8) Hand hygiene and use of PPE based on activity (e.g., receipt, transport, compounding, administration, spill, and disposal), if applicable
(9) Deactivation, decontamination, cleaning, and disinfection
(10) Dispensing, if applicable
(11) Transport
(12) Administering, if applicable
(13) Environmental monitoring (e.g., wipe sampling)
(14) Disposal
(15) Spill control
(16) Medical surveillance

(c) The pharmacist-in-charge, professional director of a clinic, designated representative-in-charge, as applicable, shall work with the entity's designated person to ensure HD handling SOPs are reviewed at least every 12 months and this review is documented.

(d) SOPs shall be updated whenever changes are implemented. Such changes shall be disseminated in a written format to the staff responsible for handling HDs prior to implementation. All notifications of such changes and the changes shall be documented in SOPs and training documents.

(e) Failure to follow written SOPs shall constitute a basis for enforcement action.

1737.18 Medical Surveillance

The requirements of this section apply to the handling of HDs in addition to the standards in USP Chapter 800.

Elements of a medical surveillance program shall be consistent with the entity's Human Resource policies and employees handling HDs must be aware of the program.

Attachment 2f

Comments received related to the handling of hazardous drugs, include any comments received after the Committee's discussion

April 12, 2023

Debbie Damoth
debbie.damoth@dca.ca.gov
California Board of Pharmacy
2720 Gateway Oaks Drive, Suite 100
Sacramento CA 95833

Re: Comments Relative to the Discussion, Consideration and Possible Action on Proposal to Add Article 4.7 and add new titles and section 1737 – 1737.18 to Division 17 or Title 16 of the California Code of Regulations to read as follows: Article 4.7 Hazardous Drugs

Dear Ms. Damoth and Members of the Board of Pharmacy,

I thank you for the opportunity to submit my comments regarding proposed regulation changes relative to compounding. I have owned and operated Pacific Compounding Pharmacy in Stockton for 17 years. I have a passion for caring for my patients and a profound desire to comply with the regulations promulgated by this Board. I continue to appreciate the reorganization of the compounding regulations to synchronize with the new USP <795>, <797>, and <800> chapters and I hope that you find my input useful, clear, and balanced.
I apologize for getting these comments to you only hours prior to the meeting, but I hope you still find them useful.

Thank you for your time and consideration of my comments,

Marie Cottman, Pharm.D.

Pacific Compounding Pharmacy and Consultations

Contact	Marie Cottman, Pharm.D. Pacific Compounding Pharmacy and Consultations 312 Lincoln Center, Stockton, CA 95207 209-474-7271

Proposed Language	Recommendations/Comments
CCR 1737.2 List of Hazardous Drug	**Recommendation:** • Change name to List of Hazardous Drugs **Rationale:** sounds better and is consistent with title of 1737
CCR 1737.2 (c) "Designated person" is a single individual approved by the pharmacist-in charge to be responsible and accountable for the performance and operation of the facility and personnel as related to the handling of hazardous drugs. Nothing in this definition allows for the designated person to exceed the scope of their issued license. When the designated person is not a pharmacist, the Pharmacist-in-Charge (PIC) must review all practices related to the operations of the facility that require professional judgement.	**Recommendation #1:** • Move this to letter (a) and let other proposed language follow as the DP is referenced in proposed part (a) and part (b). **Rationale:** The definition should come prior to the use of the term. **References:** none **Recommendation #2:** • "Designated person" is a single individual. This individual is either the pharmacist-in-charge or approved by the pharmacist-in charge to be responsible and accountable for the performance and operation of the facility and personnel as related to the handling of hazardous drugs. Nothing in this definition allows for the designated person to exceed the scope of their issued license. When the designated person is not a pharmacist, the Pharmacist-in-Charge (PIC) must review all practices related to the operations of the facility that require professional judgement. **Rationale:** Reword to clarify that the DP can be the PIC. The proposed language sounds like the PIC and the DP cannot be the same individual.
CCR 1737.4 The Pharmacist-in-charge, designated representative-in-charge, professional director, as applicable shall be responsible for all activities and decisions made or approved by the designated person.	**Recommendation:** • The Pharmacist-in-charge, designated representative-in-charge, or professional director, as applicable shall be responsible for all activities and decisions made or approved by the designated person. **Rationale:** Add the word "or" to clarify that it does not have to be all three individuals.
CCR 1737.5 (c) Handling volatile HDs: (1) HEPA filters shall not be the only means of containment used. (2) for sterile compounding, a biological-safety cabinet (BSC) as defined in USP Chapter 800 Class II Type A1 shall not be used.	**Recommendation:** • Please define "volatile" for this context. **Rationale:** Volatile is not defined in USP 800 and the term can have different interpretations. For instance, google definition of volatile is "(of a substance) easily evaporated at normal temperatures." whereas the EPA states "A [volatile organic compound] is any organic compound having an initial boiling point less than or equal to 250° C measured at a standard atmospheric pressure of 101.3

	kPa.[5, 6, 7] VOCs are sometimes categorized by the ease they will be emitted. For example, the World Health Organization (WHO) categorizes indoor organic pollutants as: • Very volatile organic compounds (VVOCs) • Volatile organic compounds (VOCs) • Semi-volatile organic compounds (SVOCs)" **References:** EPA website: https://www.epa.gov/indoor-air-quality-iaq/technical-overview-volatile-organic-compounds
CCR 1735.5 (d) Where a pass-through is installed in a containment SEC the doors must be gasketed and interlocking. Effective January 1, 2026, all pass-through doors shall be a HEPA purge type pass-through vented to an unclassified space. A pass-through is not allowed between the containment SEC into an unclassified space.	**Recommendation:** • Remove "Effective January 1, 2026, all pass-through doors shall be a HEPA purge type pass-through vented to an unclassified space. A pass-through is not allowed between the containment SEC into an unclassified space." **Rationale:** 1. This is in direct conflict with USP 800 Section 5.3.2 that states "A method to transport HDs, HD CSPs, and HD waste into and out of the negative pressure buffer room to minimize the spread of HD contamination. This may be accomplished by use of a pass-through chamber between the negative-pressure buffer area and adjacent space." 2. USP 800 Definition: **Pass-through**: An enclosure with interlocking doors that is positioned between two spaces for the purpose of reducing particulate transfer while moving materials from one space to another. A pass-through serving negative-pressure rooms needs to be equipped with sealed doors. 3. If a pass through *without* a HEPA purge is good enough for USP and for California in 2023, why does that change in January of 2026?
CCR 1735.5 (e) Facility room pressure monitoring equipment shall be placed consistent with CETA Guidelines CAG-003:2022. SOPs shall address corrective and remedial actions in the event of pressure differentials and air changes per hour excursions.	**Recommendation:** • Remove this regulation. **Rationale:** 1. CAG-003:2022 is already outdated; it was approved in October 2022 prior to the release of the most current USP 797 on November 1, 2023. 2. CAG-003:2022 does not have an obvious reference to the placement of room pressure monitoring equipment. 3. If specific placement is desired for room pressure monitoring equipment, then specify, please do not leave it to an unspecific document that is 52 pages about how to certify a cleanroom. **Reference:** https://coeta.memberclicks.net/assets/application-guides/CAG-003%20Final_Signed.pdf
CCR 1735.5 (g) CSTDs shall be used when compounding antineoplastic HDs when the dosage form allows.	**Recommendation:** • Remove this regulation. It is adequately addressed with the SHOULD in USP 800 **Rationale:** 1. We use CSTDs in our practice almost daily as adjunct controls to minimize pressure issues while working with HDs. However, sometimes they fail; sometimes they don't allow for retrieval of all of the HD from the vial; sometimes they are on backorder; sometimes they don't fit the top of the vial. If the proposed 1735.5 (g) is approved with the term SHALL, when any of these situations arise, it

	will be illegal to provide the HD (often chemotherapy) to the patient without utilizing CSTDs. Further, compounders are well served by understanding negative pressure techniques which have been used for many decades to prevent exposure to HD while compounding. 2. "When the dosage form allows" is poor wording. The dosage form does not give permission. **Reference:** **Section 5.3 of USP 800 refers to CSTDs as "adjunct controls."**
CCR 1737.6 (a) An entity's SOPs shall address environmental wipe sampling for HD surface residue, its frequency, areas of testing, levels of measurable contamination, and actions when those levels are exceeded. (b)When actionable contamination is found, at minimum the following shall occur: (1) Reevaluate work practices (2) Reevaluate the appropriateness of deactivation, decontamination and cleaning agents (3) Re-train personnel on deactivation, decontamination and cleaning (4) Re-train personnel on donning and doffing appropriate PPEs	**Recommendation:** • Remove this regulation. **Rationale:** 1. USP 800 states "There are currently no studies demonstrating the effectiveness of a specific number or size of wipe samples in determining levels of HD contamination." And states "There are currently no certifying agencies for vendors of wipe sample kits." When USP doesn't know how to define an effective environmental HD sampling program, how can you expect pharmacists to do so? There is no clarity of what testing frequency would be appropriate, what action level is reasonable, and furthermore, what action to take to resolve the HD contamination. This regulation is like throwing darts in the dark at an unknown target. **2.** Experts say there are limitations for surface sampling (from Surface Wipe Sampling for Antineoplastic (Chemotherapy) and Other Hazardous Drug Residue in Healthcare Settings: Methodology and Recommendations)**:** "Surface sampling data are best used as a screening tool... and additional difficulties with reproducibility of sampling techniques… There are a number of other limitations to performing wipe sampling for antineoplastic drugs, as summarized below: Some drugs may not be stable in the environment or on the sampling materials and will be under-reported or may not be detected during analysis. Other drugs such as cyclophosphamide are very stable in the environment and may represent spills or other sources of contamination that have taken place at an earlier date (e.g., days or weeks). In some instances, interferences may be caused by agents used to clean surfaces and other contaminates. Collecting too few samples may lead to problems with characterizing potential sources of surface contamination. *No accepted standards are available for these drugs for surface contamination in healthcare settings…*" **Reference:** USP 800. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5138855/
CCR 1737.7 Personal Protective Equipment (PPD) **(a)** Two pairs of gloves labeled to meet the ASTM D-6978 standard shall be worn for handling HD waste, cleaning HD spills, and performing routine cleaning in	**Recommendation:** • remove the word "labeled" and change the language to : Two pairs of gloves <u>that</u> meet the ASTM D-6978 standard shall be worn for handling HD waste, cleaning HD spills, and performing routine cleaning in HD areas.

HD areas.	**Rationale:** The ASTM labeling is a “pay to play” logo. The logo itself does not improve the quality of the glove. Some gloves meet the standard but don’t pay to have the logo. 1. Direct communication with Kathe Hooper, ASTM Manager of Rights and Permissions states that the logo does not indicate that ASTM has conducted any additional testing, but merely that the glove manufacturer has completed and passed certified testing and then paid to have the “ASTM” logo applied to their packaging. 2. Glove manufacturers that have completed and passed certified testing meet the same standard without paying for the logo so if a compounder has adequate documentation of appropriate ASTM level testing for a particular glove, that should be sufficient. **Reference:** https://www.astm.org/logo-policy
CCR 1737.7 (b) The outer pair of gloves labeled to meet the ASTM D-6978 standard chemotherapy gloves shall be changed every 30 minutes during compounding unless otherwise recommended by the manufacturer’s documentation. Documentation from the manufacturer shall be readily retrievable. For sterile compounding both pairs of gloves labeled to meet the ASTM D-6978 standard chemotherapy gloves shall be sterile.	**Recommendation:** • remove this section as it is overly restrictive (shall and labeled) **Rationale:** Why the requirement for "Shall?” Is there a scientific basis for this? Is there evidence that harm has been encountered because gloves have been worn too long (35 rather than 30 minutes)? If CA is going to establish more restrictive, and costly, regulations beyond the expert guidance of USP, it should be done with evidence of necessity. This was the position taken by The Supreme Court’s in Industrial Union Department AFLCIO v American Petroleum Institute, in 1980 where the court ruled regarding creating stricter regulations for benzene handling that were costly to the business, the judge ruled that “before he can promulgate any permanent health or safety standard, the Secretary [of Labor] is required to make a threshold finding that a place of employment is unsafe—in the sense that significant risks are present and can be eliminated or lessened by a change in practices”. Government can't just make costly regulations because of the perception that it is needed to be safer. It has some obligation to justify its actions. **Reference:**
1735.7 (c) Outer gloves used for compounding must be changed between each different type of HD preparation and the standards established in Chapter 800 if continuously compounding a single HD preparation. The facilities SOPs shall define the circumstances under which the gowning and gloves must be changed between HD handling/preparations. Outer gloves used for compounding must be changed between each different type of HD preparation and the standards established in Chapter 800 if continuously compounding a single HD preparation. The facilities SOPs shall define the circumstances under which the gowning and gloves must be changed between HD handling/preparations.	**Recommendation:** • remove this language **Rationale:** 1. The term “type of HD” is too vague. 2. Gloves should already be changed every 30 minutes and when contamination is known or suspected. 3. If there is no suspected contamination during handling, why presume contamination? Does CA have evidence that this is a relevant risk that needs to be managed better than that described by USP expert committees? 4. A chemo compounder might change gloves 20 times per day; once for each different type of chemo.

1735.7 (d) PPE shall be removed cautiously to avoid transferring contamination to skin, the environment, and other surfaces. PPE worn during compounding shall be disposed of in the proper waste container before leaving the C-SEC. SOPS must be in place which describe in detail the donning and doffing of PPE and where it takes place in the C-SEC.	**Recommendation:** • remove the middle sentence, and the last 3 words: PPE shall be removed cautiously to avoid transferring contamination to skin, the environment, and other surfaces. SOPS must be in place which describe in detail the donning and doffing of PPE and where it takes place. **Rationale:** 1. This is only relevant if the facility does not have a dedicated ante room for the HD C-SEC. Removing PPE in the SEC will expose my buffer area to unnecessary additional hair and skin that could contaminate my cleanest work areas. Doffing should occur in my HD ante room. 2. Further, this is redundant as USP already states "MUST" in section 5.3.2 "Although not a recommended facility design, if the negative-pressure HD buffer room is entered though the positive-pressure non-HD buffer room, the following is also required: • A line of demarcation **must** be defined within the negative-pressure buffer room for donning and doffing PPE"
1737.10 Receiving "All HD API and antineoplastic HD shall be received from the supplier in segregated impervious plastic and labeled as HD on the outside of the delivery container."	**Recommendation:** • remove this!! **Rationale:** 1. I have no control over how the supplier packages my order! If it did not come packaged correctly, a) would I be able to identify it from looking at the outer packaging? b) assuming I could tell, would this require me to return it because it uses the term "SHALL"? 2. This places an undue burden of supplier regulatory compliance onto pharmacies/pharmacists. 3. The Board has regulations regarding wholesalers, repackagers, and manufacturers. Put this regulation somewhere in Article 11 Wholesalers and Manufacturers where they have control over how to package and label HD products.

Attachment 2g

Article 4.8 draft regulation text

related to radiopharmaceuticals

Repeal:

~~**1708.3. Radioactive Drugs.**~~

~~A radioactive drug is any substance defined as a drug in Section 201(g)(1) of the Federal Food, Drug and Cosmetic Act or a radioactive biological product as defined in 21 CFR 600.3(ee) which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any such drug or biological product which is intended to be made radioactive. This definition includes non-radioactive reagent kits and nuclide generators which are intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds, potassium-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides.~~

~~Authority cited: Section 4005, Business and Professions Code. Reference: Section 4025, Business and Professions Code.~~

~~**1708.4. Pharmacist Handling Radioactive Drugs.**~~

~~A pharmacist handling radioactive drugs must be competent in the preparation, handling, storage, receiving, dispensing, disposition and pharmacology of radioactive drugs. He must have completed a nuclear pharmacy course and/or acquired experience in programs approved by the Board. Education and experience in non-approved programs may be granted partial or equivalent credit, if, in the opinion of the Board, such programs provide the level of competence as approved programs or the Nuclear Pharmacy Competency Statement adopted by the Board.~~

~~Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4021, 4022, 4025, 4036 and 4037, Business and Professions Code.~~

~~**1708.5. Pharmacy Furnishing Radioactive Drugs.**~~

~~A pharmacy furnishing radioactive drugs is any area, place or premises described in a permit issued by the board where radioactive drugs are stored, processed, compounded, repackaged, or dispensed. A pharmacy exclusively furnishing radioactive drugs shall be exempt from the patient consultation area requirements of Title 16 Cal. Code of Regulations Section 1714(a) unless the Board finds that the public health and safety require their application.~~

~~A pharmacist qualified under Section 1708.4 to furnish radioactive drugs shall be in the pharmacy whenever the furnishing of radioactive drugs occurs. All personnel involved in the furnishing of radioactive drugs shall be under the immediate and direct supervision of such a qualified pharmacist.~~

~~Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4008 and 4008.2, Business and Professions Code.~~

Proposal to Add Article 4.8 as proposed with the following:

Article 4.8 Radiopharmaceutical- Preparation, Compounding, Dispensing, and Repackaging

1738. Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging

This article applies to radiopharmaceuticals as defined in USP Chapter 825. In addition to the requirements provided in this Article, the processing of radiopharmaceuticals shall comply with the standards established by United States Pharmacopeia General Chapter 825, titled *Radiopharmaceuticals –*

Preparation, Compounding, Dispensing, and Repackaging ("USP Chapter 825" for the purposes of this Article).

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.1 INTRODUCTION

In addition to the definitions contained in USP Chapter 825, the following definitions apply to this Article and supplement the standards established in USP Chapter 825 when not otherwise provided in USP Chapter 825.

(a) "Added substances" means ingredients that are necessary to compound a preparation but are not intended or expected to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation. The term is used synonymously with the terms inactive ingredients, excipients, and pharmaceutical ingredients.

(b) "Designated person" means a pharmacist identified as assigned, responsible, and accountable for the performance and operation of the radiopharmaceutical processing facility and for personnel who prepare, compound, dispense, and repackage radiopharmaceuticals.

(c) "Component" means any ingredient used in the compounding of a preparation, including any active ingredient, added substance, or conventionally manufactured product.

(d) "Diluent" means a liquid with no pharmacological activity used in reconstitution, such as sterile water for injection.

(e) "Processing," "processed" or "processing activity" means the preparation, compounding, repackaging, or dispensing of a radiopharmaceutical.

(f) The use of technologies, techniques, material, and procedures not described in USP 825 shall be based upon published peer-reviewed literature or documents meeting FDA approved labeling requirements in accordance with sections 201.56 and 201.57 of title 21, Code of Federal Regulations, showing the technologies, techniques, material, and procedures to be equivalent or superior to those described in USP Chapter 825.

(g) Processing with human whole blood or human whole blood derivatives shall be done in compliance with Health and Safety Code section 1602.5.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.2 RADIATION SAFETY CONSIDERATIONS

In addition to the standards in the USP Chapter 825, the processing of radiopharmaceuticals shall meet the following radiation safety requirements of this section.

(a) Radiation detectors and measuring devices, and other necessary equipment may be placed inside an ISO Class 5 PEC but must be placed in a manner that minimizes disruptions of airflow.

(b) Disposable absorbent pads shall be changed after each type of radiopharmaceutical processing.

(c) Any deviation made to lower radiation exposure to workers shall be evaluated and documented in an SOP by the designated person prior to the deviation occurring. Exceptions to the environmental controls requirements must be documented in the specific radioactive materials license conditions issued by the California Department of Public Health pursuant to section 30190 of Title 17 of the California Code of Regulations, or a specific radioactive materials license issued by another state or the United States Nuclear Regulatory Commission pursuant to pursuant to section 32.72 of title 10 of the Code of Federal Regulations.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.3. IMMEDIATE USE OF STERILE RADIOPHARMACEUTICALS

The processing of radiopharmaceuticals for immediate use may only be done in a patient care setting meeting the applicable requirements in this Article. The patient care facility shall maintain all records required in Section 9 of USP Chapter 825 in accordance with Business and Professions Code section 4081.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4081, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.4 PERSONNEL QUALIFICATIONS, TRAINING, AND HYGIENE

In addition to the requirements in the USP Chapter 825, the processing of radiopharmaceuticals shall comply with all of the requirements of this section.

(a) Processing personnel experiencing any of the following: rashes, recent tattoos or oozing sores, conjunctivitis, active respiratory infection or and other conditions which could contaminate a sterile radiopharmaceutical, or the environment shall not be allowed to enter the compounding area unless approved by the designated person. Any approvals provided by the designated person shall be documented and the record shall include the name of the individual granted approval, the approval date and time, the reason for granting approval, and the identification of the designated person making the decision.

(b) The pharmacist with direct oversight over personnel performing radiopharmaceutical processing shall demonstrate proficiency in skills necessary to ensure the integrity, potency, quality, and labeled strength of radiopharmaceuticals as defined in the facilities SOPs.

(c) Aseptic manipulation competency initial training and competency and ongoing training and competency documentation shall include the Primary Engineering Control (PEC's) type and PEC unique identifier used during the evaluation. Aseptic manipulation competency evaluation and requalification shall be performed using the same procedures, type of equipment, and materials used in aseptic compounding. Aseptic qualifications from one premises may be used for another premises if all of the following conditions are met:

1. TheSOPs related to compounding are identical.
2. The SEC facility designs are sufficiently similar to accommodate the use of the same SOPs.
3. The PECs are of the same type and sufficiently similar to accommodate the use of the same SOPs describing use and cleaning.

(d) SOPs must clearly define the acceptable use and cleaning for reusable gowns that prevent possible contamination of the CSP and designated compounding area. However, laundered garb must not be reused beyond one day unless garb is laundered with a validated cycle. The facility's SOPs must describe the process that must be followed should the facility allow for the reuse of garb.

(e) Eyeglasses shall be cleaned as part of hand hygiene and garbing, consistent with the standards specified in the SOPs.

(f) Garb shall be donned and removed in an ante-area or immediately outside the SPRA. Donning and doffing garb shall not occur in the anteroom at the

same time unless the SOPs define specific processes which must be followed to prevent contamination.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.5. FACILITIES AND ENGINEERING CONTROLS

In addition to the requirements in the USP Chapter 825, the processing of radiopharmaceuticals shall comply with all of the requirements of this section.

(a) A sink used for compounding or hand hygiene shall not be part of a restroom or water closet.

(b) The temperature shall be monitored in SRPAs segregated radiopharmaceutical processing area and classified areas each day that processing is performed, either manually or by a continuous recording device.

(c) Storage and elution of non-direct infusion radionuclide generators shall take place in an ISO Class 8 or better area.

(d) If an SRPA is used:

(1) Except for walls, the SRPA's visible perimeter shall be at least 1 meter from all sides of the PEC or in a separate room.

(2) Surfaces within the SRPA shall be smooth, impervious, free from cracks and crevices, and non-shedding so they can be easily cleaned and disinfected and to minimize spaces in which microorganisms and other contaminants can accumulate.

(3) Compounding shall not take place in the SRPA.

(e)(1) Testing and certification of all classified areas shall be completed by a competent individual. A competent individual is a technician who possesses a current accreditation issued by The Controlled Environment Testing Association (CETA), or under the direct supervision of an individual who possesses a current accreditation issued by CETA Certification shall be completed consistent with the provisions established in the USP Chapter 797, titled "Pharmaceutical Compounding—Sterile Preparations" (USP Chapter 797). The facility shall review and maintain a copy of the accreditation documentation in accordance with requirements in section 1738.9.

(2) CETA standard(s) used to perform certification testing in all classified areas shall be recorded on the certification report as required and specified in USP Chapter 797.

(f) SOPs shall specify steps to be taken if a classified area(s) fails to meet the specified ISO classification including the investigative and corrective actions, allowable activities, and retesting procedures.

(g) All classified spaces and equipment must be recertified when there is any change in the Primary Engineering Control (PEC), or the compounding environment. For purposes of this subsection, a change includes when the PEC is moved, repaired or replaced, when the facility is modified in a manner that affects airflow or traffic patterns, or when improper aseptic techniques are observed. Further, SOPs must address the conditions under which recertification must also be completed when relocating a PEC.

(h) Activities and tasks carried out within the SRPA and classified areas shall be limited to only those necessary for processing a radiopharmaceutical.

(i) Food, drinks, and materials exposed in patient care and treatment areas must not enter SRPA or classified areas.

(j) A dynamic airflow smoke pattern test must be performed initially and at least every 6 months for all classified spaces and equipment. All dynamic airflow smoke pattern tests shall be immediately retrievable during inspection. A copy of the test shall be provided to the Board's inspector if requested in accordance with the timeframes set forth in Section 4105 of the Business and Professions Code.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4081, 4105 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.6. MICROBIOLOGICAL AIR AND SURFACE MONITORING

In addition to the requirements in the USP Chapter 825, the processing of radiopharmaceuticals shall comply with all of the requirements of this section.

(a) SOPs shall specify steps to be taken for processing radiopharmaceuticals when the microbiological air and surface monitoring action levels are exceeded, including the investigative and corrective actions, allowable activities, and resampling procedures.

(b) At a minimum every 6 months, air and surface sampling results shall be identified to at least the genus level, regardless of the CFU count to trend for growth of microorganisms. Professional judgement and SOPs shall be used to determine the appropriate action necessary to remedy identified trends. Investigation must be consistent with the deviation and must include evaluation of trends.

(c) Environmental sampling shall be done in compliance with the most recent edition of the Controlled Environment Testing Association (CETA)'s Certification Application Guide USP <797> Viable Environmental Sampling & Gowning Evaluation (CAG-009, Revised October 2022), which is hereby incorporated by reference.

(d) The designated person shall review the sampling results and identify data trends at least every time sample results are received. The designated person shall evaluate trends to determine if corrective action is needed. The results of the review shall be documented in the facility's SOPs and readily retrievable during inspection in accordance with the requirements in section 1738.9.

(e) Incubators must be calibrated and operated in accordance with the manufacturer's specifications and temperatures must be monitored during incubation, either manually or by a continuous recording device, and the results must be reviewed and documented as described in the facility's SOPs.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4081, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.7. CLEANING AND DISINFECTING

In addition to the requirements in the USP Chapter 825, the processing of radiopharmaceuticals shall comply with all of the requirements of this section.

(a) Cleaning, disinfection, and sporicidal agents shall be used in accordance with manufacturers' specifications and shall occur at the minimum frequencies listed in Table 5 of USP Chapter 825. Incubators must be cleaned at least monthly.

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

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.8. ASSIGNING BUD

In addition to the requirements in the USP Chapter 825, the processing of radiopharmaceuticals shall comply with all of the requirements of this section.

(a) A radiopharmaceutical CSP's beyond-use date (BUD) shall not exceed the shortest BUD of any of its components.

(b) No radiopharmaceutical CSP shall be administered after the labeled BUD. A dose shall not be sent for a scheduled administration that would occur after the labeled BUD.

(c) Extension of a conventionally manufactured kit with a suggested use-by time shall not exceed the BUDs in Table 7 of USP Chapter 825, for the sterility of the preparation or product.
Prior to the extension of a suggested use-by time for a conventionally manufactured kit, the SOPs must document at a minimum the following:

(1) Factors which necessitate its extension, which shall include a full assessment of patient needs for the extension.
(2) Evidence which supports that the extension maintains the appropriate quality and purity (radiochemical purity and radionuclidic purity) as specified in individual monographs, and other applicable parameters as clinically appropriate.

For the purposes of this section, the facility shall have SOPs that cover and are specific to each facility's location and kit.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.9. DOCUMENTATION

In addition to the requirements in the USP Chapter 825, the processing of radiopharmaceuticals shall comply with all of the requirements of this section.

(a) A record of a preparation must include a compounding record compliant with section 9.2 of USP Chapter 825.

(b) Records of preparation with minor deviations or compounding shall be a single document. The document shall satisfy the requirements of USP Chapter 825, as well as the following:

(1) The assigned internal identification number shall be unique for each preparation.
(2) The manufacturer, lot number, and expiration date shall be recorded for each component for CSPs. Documenting solely the National Drug Code (NDC) does not meet this requirement.
(3) The total quantity compounded shall include the number of units made and either the volume or the weight of each unit.
(4) The identity of each person performing the compounding and pharmacist verifying the final drug preparation
(5) When applicable, endotoxin level calculations and readings.

(c) Records required by USP Chapter 825 or this Article, shall be maintained in a readily retrievable form, for at least three years from the date the record was created or relied upon. If only recorded and stored electronically, on magnetic media, or in any other computerized form, the records shall be maintained as specified by Business and Professions Code section 4070.

(d) Records created shall be created and maintained in a manner to provide an audit trail for revisions and updates of each record document. Prior versions of each record must be maintained in a readily retrievable format and include the changes to the document, identification of individual who made the change, and the date of each change.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4081, 4105, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.10. PREPARATION

In addition to the requirements in the USP Chapter 825, the processing of radiopharmaceuticals shall comply with all of the requirements of this section.

(a) Processing nonsterile radiopharmaceutical shall:

(1) Follow manufacturer preparation instructions, unless minor deviations are made pursuant to subsection (c).
(2) Only use an area which is suitably cleaned and is uncluttered.
(3) Have documented processes in its SOPs for activities (e.g., cleaning) between the preparation cycles of different nonsterile products.

(b) Processing sterile radiopharmaceutical (including intravascular devices) shall:

(1) Follow manufacturer preparation instructions, unless minor deviations are made pursuant to subsection (c).
(2) Use at least the minimum environmental standards from section 7 of USP Chapter 825.

(c) When preparing radiopharmaceuticals with minor deviations ("preparation with minor deviations" as defined in the USP Chapter 825) an SOP shall at least define the circumstances which necessitated the deviation and all quality control testing requirements and limits. Such circumstances shall, at a minimum, include patient need or facts that support the deviation that maintains the appropriate quality and purity (radiochemical purity and radionuclidic purity) as specified in individual monographs, and other applicable parameters as clinically appropriate in the professional judgment of the pharmacist.

For the purposes of this section, the facility shall have SOPs that cover and are specific to each location and manufacturer. Preparations with minor deviations shall maintain the same ingredients but may differ in their proportions. A deviation from the ingredients or proportions thereof exceeds the provisions allowed under a minor deviation and is not allowed under this Article.

(d) Equipment and supplies initially used for processing of blood components (included Red Blood Cells) shall be solely dedicated for processing of blood components. Equipment and supplies shall be thoroughly cleaned and disinfected, in accordance with section 1738.7, prior to initiation of the next patient's prescription.

(e) When processing blood components all garb must be removed and replaced for each patient.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.11. COMPOUNDING

In addition to the requirements in the USP Chapter 825, the processing of radiopharmaceuticals shall comply with all of the requirements of this section.

(a) All compounding of radiopharmaceuticals shall comply with all radioactive materials licensing requirements for appropriate radiation safety considerations issued by the California Department of Public Health pursuant to section 30190 of Title 17 of the California Code of Regulations, another state licensing agency that issues specific radioactive materials licenses, or the United States Nuclear

Regulatory Commission pursuant to pursuant to section 32.72 of title 10 of the Code of Federal Regulations, and utilize applicable environmental controls.

b) All API and excipient components used to compound a CSP shall be manufactured by an FDA-registered facility, be accompanied by a Certificate of Analysis (COA) and suitable for use in sterile pharmaceuticals. A 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, unless components are commercially available drug products. API and excipient components provided without this data shall not be used in a CSP

(1) When the COA is received from a supplier, it must provide the name and address of the manufacturer .

(c) Except for sterile radiopharmaceuticals made for inhalation or ophthalmic administration, prior to releasing a sterile radiopharmaceutical made from one or more nonsterile component(s) results of bacterial endotoxin testing shall be reviewed and recorded. Results shall be documented in the compounding record specified in Section 9.2 of the USP Chapter 825.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.12. DISPENSING

In addition to the requirements in the USP Chapter 825, the processing of radiopharmaceuticals shall comply with all of the requirements of this section.

(a) All dispensed radiopharmaceutical doses shall be labeled with the information required by Business and Professions Code section 4076 and section 1707.5. Outer shielding labels shall contain the name and contact information of the dispensing pharmacy.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.13. REPACKAGING

In addition to the requirements in the USP Chapter 825, the processing of radiopharmaceuticals shall comply with all of the requirements of this section.

(a) The inner container of a repackaged radiopharmaceutical shall be labeled with the following:

(1) Standard radiation symbol
(2) The words "Caution—Radioactive Material"
(3) The radionuclide and chemical form (generic name)
(4) Radioactivity with units at time of calibration and the calibration time

(b)The outer shielding of a repackaged radiopharmaceutical shall be labeled with the following:

(1) Standard radiation symbol
(2) The words "Caution—Radioactive Material"
(3) The radionuclide and chemical form (generic name)
(4) Radioactivity with units at time of calibration and the calibration time
(5) Volume, or number of units (e.g., capsules), as applicable
(6) Product expiration or BUD (consistent with Table 7 of USP Chapter 825), as applicable
(7) Special storage and handling instructions

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

1738.14. QUALITY ASSURANCE AND QUALITY CONTROL

The requirements of this section apply to the processing of radiopharmaceuticals in addition to the standards established in USP Chapter 825.

(a) The quality assurance program shall comply with section 1711 and the standards contained in USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding. In addition, the program shall include the following:

(1) A written procedure for scheduled action, such as a recall, in the event any radiopharmaceutical processing is discovered to be outside the expected standards for integrity, quality, and purity.

(2) A written procedure for responding to out-of-range temperature variations within the medication storage areas where a furnished drug may be returned for furnishing to another patient.

(b) The Board shall be notified in writing within 72 hours of a complaint. Recalls and adverse reporting must be completed in compliance with relevant provisions of law.

(c) In addition to subsection (b), all complaints related to a potential quality problem with a radiopharmaceutical and all adverse events shall be reviewed by the pharmacist-in-charge within 72 hours of receipt of the complaint or occurrence. Such review shall be documented and dated as defined in the SOPs.

(d) The SOPs shall specify the steps to be taken if a classified area(s) fails to meet the specified ISO classification including the investigative and corrective actions, allowable activities, and retesting procedures.

(e) The SOPs shall be reviewed on an annual basis by the pharmacist-in-charge. Such review shall be documented by the pharmacist-in-charge consistent with the SOPs. The SOPs shall be updated to reflect changes to compounding processes, facility changes or other changes that impact the CSP. Such SOP changes shall be disseminated to the affected staff prior to implementation.

(f) Failure to follow written SOPs shall constitute a basis for enforcement action.

Authority cited: Sections 4005, 4008 and 4008.2, Business and Professions Code. Reference: Sections 125.9, 4005, 4126.8, 4301, 4306.5, and 4342, Business and Professions Code.

Attachment 3

Proposal to Amend Business and Professions Code section 4081

(a) All records of manufacture and of sale, acquisition, receipt, shipment, or disposition of dangerous drugs or dangerous devices shall be at all times during business hours open to inspection by authorized officers of the law, and shall be preserved for at least three years from the date of making. A current inventory shall be kept by every manufacturer, wholesaler, third-party logistics provider, pharmacy, veterinary food-animal drug retailer, outsourcing facility, physician, dentist, podiatrist, veterinarian, laboratory, licensed correctional clinic, as defined in Section 4187, clinic, hospital, institution, or establishment holding a currently valid and unrevoked certificate, license, permit, registration, or exemption under Division 2 (commencing with Section 1200) of the Health and Safety Code or under Part 4 (commencing with Section 16000) of Division 9 of the Welfare and Institutions Code who maintains a stock of dangerous drugs or dangerous devices.

(b) The owner, officer, and partner of a pharmacy, wholesaler, third-party logistics provider, or veterinary food-animal drug retailer shall be jointly responsible, with the pharmacist-in-charge, responsible manager, or designated representative-in-charge, for maintaining the records and inventory described in this section.

(c) The pharmacist-in-charge, responsible manager, or designated representative-in-charge shall not be criminally responsible for acts of the owner, officer, partner, or employee that violate this section and of which the pharmacist-in-charge, responsible manager, or designated representative-in-charge had no knowledge, or in which he or she did not knowingly participate.

(d) Pharmacies that dispense nonprescription diabetes test devices pursuant to prescriptions shall retain records of acquisition and sale of those nonprescription diabetes test devices for at least three years from the date of making. The records shall be at all times during business hours open to inspection by authorized officers of the law.

(e) In addition to the records described in subdivision (a) records that must be maintained include staffing schedules, pharmacy personnel job duty statements, consultant reports, and policies and procedures related to pharmacy personnel and pharmacy operations.

Proposal to amend BPC 4105

(a) All records or other documentation required by this Chapter ~~of the acquisition and disposition of dangerous drugs and dangerous devices~~ to-be maintained by any entity licensed by the board shall be retained on the licensed premises in a readily retrievable form.

(b) The licensee may remove the original records or documentation from the licensed premises on a temporary basis for license-related purposes. However, a duplicate set of those records or other documentation shall be retained on the licensed premises.

(c) The records required by this section shall be retained on the licensed premises for a period of three years from the date of making.

(d) (1) Any records that are maintained electronically shall be maintained so that the pharmacist-in-charge, or the pharmacist on duty if the pharmacist-in-charge is not on duty, shall, at all times during which the licensed premises are open for business, be able to produce a hardcopy and electronic copy of all records of acquisition or disposition or other drug or dispensing-related records maintained electronically.

(2) In the case of a veterinary food-animal drug retailer, wholesaler, or third-party logistics provider, any records that are maintained electronically shall be maintained so that the designated representative-in-charge or the responsible manager, or the designated representative on duty or the designated representative-3PL on duty if the designated representative-in-charge or responsible manager is not on duty, shall, at all times during which the licensed place of business is open for business, be able to produce a hardcopy and electronic copy of all records of acquisition or disposition or other drug or dispensing-related records maintained electronically.

(e) (1) Notwithstanding subdivisions (a), (b), and (c), the board may, upon written request, grant to a licensee a waiver of the requirements that the records described in subdivisions (a), (b), and (c) be kept on the licensed premises.

(2) A waiver granted pursuant to this subdivision shall not affect the board's authority under this section or any other provision of this chapter.

(f) When requested by an authorized officer of the law or by an authorized representative of the board, the owner, corporate officer, or manager of an entity licensed by the board shall provide the board with the requested records within three business days of the time the request was made. The entity may request in writing an extension of this timeframe for a period not to exceed 14 calendar days from the date the records were requested. A request for an extension of time is subject to the approval of the board. An extension shall be deemed approved if the board fails to deny the extension request within two business days of the time the extension request was made directly to the board.

Attachment 4

CALIFORNIA® VETERINARY MEDICAL ASSOCIATION

1400 River Park Drive, Suite 100
Sacramento, CA 95815-4505
916-649-0599
fax 916-646-9156
staff@cvma.net
www.cvma.net

March 9, 2023

Maria D. Serpa, PharmD
Chair, Enforcement and Compounding Committee
California Board of Pharmacy
2720 Gateway Oaks Drive, Suite 100
Sacramento, CA 95833

RE: Comments on Board of Pharmacy Discussion, Consideration and Possible Action on Proposed Changes to Regulations Related to Pharmaceutical Compounding of Nonsterile Preparations

Dear Dr. Serpa:

The California Veterinary Medical Association (CVMA), representing over 7,800 veterinarians, registered veterinary technicians, and veterinary students, is requesting for a second time that your Board review California Code of Regulations, Title 16 (16 CCR), section 1735.2(c)(3) and grant our request to increase the amount of stock that 503A compounding pharmacies can prepare in anticipation of veterinarian needs for in-office administration and dispensation.

We submitted the attached letter for your consideration at your February 15, 2023 Compounding and Enforcement Committee meeting. Our request was considered but declined on the stated basis that there are no problems with obtaining compounded medications for veterinary use under the current regulation.

Attached please find a survey of our membership that we recently circulated in our weekly electronic newsletter. In that survey, we asked two questions of our members:

1) *Has your practice experienced difficulties in locating medications (either FDA-approved or compounded) during the past year?*

   89.5% of respondents said Yes. We then asked for examples, which are provided in the survey responses attached.

2) *When ordering a patient-specific compounded medication, have you or your clients had to wait more than five days to receive it?*

   88% of respondents said Yes.

To further clarify our request: at the time that Section 1735.2(c)(3) was passed, it was anticipated that a compounding pharmacist could provide medication upon receipt of a patient-specific prescription in four days, and then permit one day for shipping. Thus, an average of 120-hours per patient of compounded preparation was permitted for pharmacists to prepare in advance for

veterinarians to have on hand in order to meet patient needs. To that end, the CVMA would like to request for a second time that the Board of Pharmacy increase the average supply of medication that a pharmacy can prepare in advance to a seven-day average supply per patient, based on anticipated needs as identified by the veterinarian. Accordingly, the CVMA proposes the following specific wording change to Section 1735.2(c)(3):

> *Is sufficient for administration or application to patients solely in the prescriber's office, or for furnishing of not more than a ~~120-hour~~ seven day supply per animal patient for veterinarian prescribers ~~veterinary medical practices~~, solely to the veterinarian prescriber's own ~~veterinary~~ patients ~~seen as part of regular treatment in the prescriber's office~~, as fairly estimated by the veterinarian prescriber in anticipation of their patient needs and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing.*

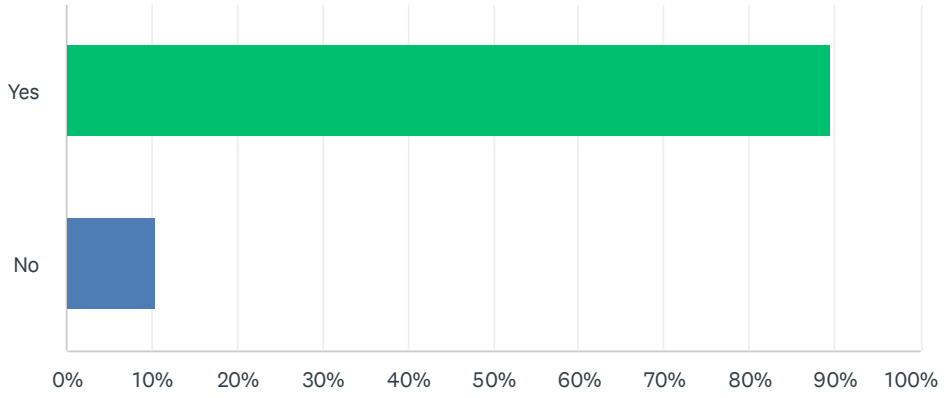
Thank you for your consideration.

Dan Baxter
Executive Director

Enclosure

Q1 Has your practice experienced difficulties in locating medications (either FDA-approved or compounded) during the past year?

Answered: 570 Skipped: 0



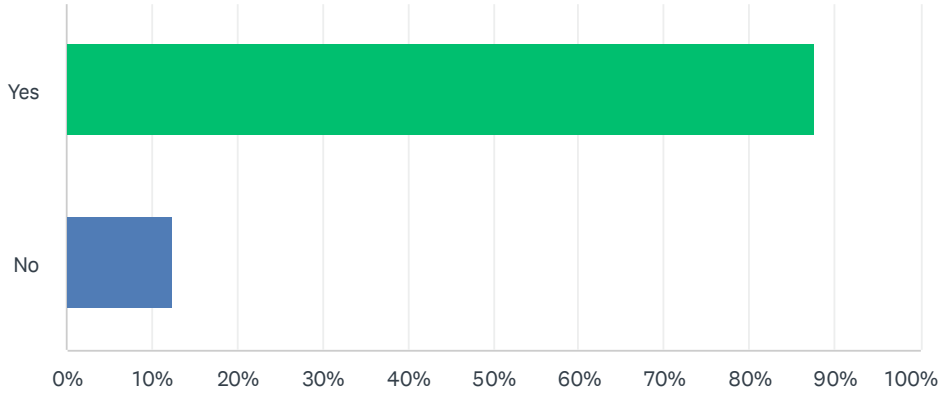
ANSWER CHOICES	RESPONSES	
Yes	89.47%	510
No	10.53%	60
TOTAL		570

#	IF SO, WHICH MEDICATIONS?	DATE
1	L-asparaginase, Cortrysyn and Chlorambucil.	2/25/2023 8:38 PM
2	Prednisolone Cyclosporine	2/25/2023 10:36 AM
3	Lidocaine, atropine, Revolution Plus, ear medications,	2/25/2023 10:06 AM
4	buprenorphine	2/24/2023 4:49 PM
5	Bute, clavamox	2/24/2023 4:42 PM
6	EDTA ophthalmic, tacrolimus ophthalmic, cyclosporine ophthalmic, 5-FU, polydocanol,	2/23/2023 9:46 PM
7	Tacrolimus, nevanac, diazepam	2/23/2023 6:23 PM
8	tacrolimus and cyclosporine ophthalmic, vetmedin	2/23/2023 4:23 PM
9	compounded ophthalmic meds: cyclosporine, cidofovir	2/23/2023 1:21 PM
10	Otic topicals, oral and injectable steroids, cardiac inotropes, oral dewormers	2/23/2023 1:01 PM
11	Leukeran, DES, budesonide	2/23/2023 9:45 AM
12	idoxuridine ophthalmic drops,edetate calcium disodium injection (we treat a lot of exotics with zinc and lead toxicity) and others but these two came to mind quickly.	2/23/2023 8:00 AM
13	A number of medications have gone on backorder. I can't think of all of them right now.	2/23/2023 7:23 AM
14	pilocarpine for oral use	2/23/2023 6:33 AM
15	Too many to list! Top that come to mind: Baytril Otic, Penicillin, anything containing hydrocortisone	2/22/2023 11:31 PM
16	TMS oil suspension	2/22/2023 10:06 PM

17	potassium, many others over the year but can't remember	2/22/2023 9:11 PM
18	tylan, cylosporine ophthalmic	2/22/2023 7:01 PM
19	Metronidazole, Sucralfate, Doxycycline, Ponazuril, Tinidazole	2/22/2023 6:47 PM
20	methimazole, lidocaine, marcaine, sucralfate, ursodiol, SAM-e, ciprofloxacin	2/22/2023 6:43 PM
21	Cyclosporine ophthalmic, theophylline, fluconazole solution	2/22/2023 5:43 PM
22	Calcium EDTA	2/22/2023 5:43 PM
23	ursodiol, mycophenolate, idoxuridine	2/22/2023 5:26 PM
24	Calcium Glubionate, and any medication that requires smaller concentrations for exotic pets (rabbits, guinea pigs, parrots, reptiles, etc.)	2/22/2023 5:20 PM
25	Phenobarbital, gabapentin	2/22/2023 4:48 PM
26	TRH, sucralfate	2/22/2023 4:19 PM
27	Elspar, budesonide, metronidazole, cisapeide, prednisolone	2/22/2023 4:11 PM
28	the last one was the polyflex ear medication	2/22/2023 4:05 PM
29	Interferon	2/22/2023 4:01 PM
30	Sucralfate.	2/22/2023 4:00 PM
31	Cyclosporine ophthalmic, tacrolimus ophthalmic	2/22/2023 3:02 PM
32	antibiotics, pimobendan, trilostane	2/22/2023 2:53 PM
33	Compounded gabapentin	2/22/2023 2:50 PM
34	Thyrotropin-releasing hormone	2/22/2023 2:02 PM
35	phenybutazone, metronidazole	2/22/2023 1:54 PM
36	Pimonendan	2/22/2023 1:39 PM
37	Cisapride, Methimazole, L-Asparaginase, Enrofloxacin	2/22/2023 1:31 PM
38	diazepam inj, butorphanol, vetmedin, vetsulin, amoxicillin, and cyclosporine	2/22/2023 1:27 PM
39	eye medications, transdermal medications, inj Buprenorphine, hydromorphone, morphine	2/22/2023 1:00 PM
40	acetazolamide;	2/22/2023 12:26 PM
41	Too many to list!	2/22/2023 12:02 PM
42	Injectable meds in general (sulfatrim, CaEDTA), non-oil based oral meds that last longer than 14 days, there have been many that I just don't even try to find anymore...	2/22/2023 11:56 AM
43	Penicillin G	2/22/2023 11:55 AM
44	dexamethasone	2/22/2023 11:50 AM
45	Doxycycline, metronidazole, theophylline	2/22/2023 11:32 AM
46	tacrolimus, TpA, acyclovir cream, altrenogest, medroxprogesterone	2/21/2023 11:22 AM

Q2 When ordering a patient-specific compounded medication, have you or your clients had to wait more than five days to receive it?

Answered: 570 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	87.72%	510
No	12.28%	70
TOTAL		570

CALIFORNIA® VETERINARY MEDICAL ASSOCIATION

1400 River Park Drive, Suite 100
Sacramento, CA 95815-4505
916-649-0599
fax 916-646-9156
staff@cvma.net
www.cvma.net

February 6, 2023

Maria D. Serpa, PharmD
Chair, Enforcement and Compounding Committee
California Board of Pharmacy
2720 Gateway Oaks Drive, Suite 100
Sacramento, CA 95833

RE: Comments on Board of Pharmacy Discussion, Consideration and Possible Action on Proposed Changes to Regulations Related to Pharmaceutical Compounding of Nonsterile Preparations

Dear Dr. Serpa:

The California Veterinary Medical Association (CVMA), representing over 7,800 veterinarians, registered veterinary technicians, and veterinary students, would like to ensure that potential changes to California Code of Regulations, Title 16 (16 CCR), section 1735.2(c)(3) do not further harm California's pets, consumers, or the veterinarians who are trying to provide vitally needed medications to their patients.

Now, more than ever, veterinarians are experiencing difficulties in finding and obtaining sources of medications needed to treat patients immediately. The CVMA notified your Board of this growing issue in a letter dated January 19, 2022 (see attached). As stated in that letter, in many instances the pharmaceutical industry falls short of providing FDA-approved medications commonly utilized in veterinary practice. As a result, the veterinary industry relies on compounding pharmacies to provide such medications in order to effectively treat animal patients to alleviate suffering, illness and death. While the recent emergence of 503B outsourcing facilities in California has helped to some degree, only two outsourcers in California currently carry appreciable lines of veterinary products. While some outsourcers advertise sterile compounds for veterinary practice, most of those are chemotherapeutics, which represent a small subset of medications used by veterinarians. Thus, the 503B route is not a complete solution to veterinarians finding medications that they need on hand to help animals in need.

Veterinarians must rely on 503A pharmacies to fill gaps in medication availability, including for medications needed in-house to treat patients. Unlike humans, animals instinctively hide their pain or illness, which results in many of them needing immediate treatment when they come to a veterinary practice. Because so few 503A compounding pharmacies offer veterinary products in California, consumers must often wait several days for a patient-specific prescription to be filled. This is due not only to stringent compounding mandates, but also to delays experienced when trying to locate a pharmacy willing to compound a veterinary medication. It is not uncommon for veterinarians and consumers to wait weeks for an animal patient to receive the medication that it needs pursuant to a patient-specific prescription. And, despite the CVMA's

multiple communications to the Board of Pharmacy over the past decade, this problem has grown worse as a result of regulatory changes that have resulted in an industry shift.

CCR 16 section 1735.2(c)(3) indicates that a 503A compounding pharmacist can prepare in advance, in anticipation of a veterinarian's needs, a supply that is "sufficient for administration or application to patients solely in the prescriber's office, or for furnishing of not more than a 120-hour supply for veterinary medical practices, solely to the prescriber's own veterinary patients seen as part of regular treatment in the prescriber's office, as fairly estimated by the prescriber and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing." At the time that this regulation was instituted, the CVMA met with then BOP Executive Officer Ginny Herold and DAG Joshua Room to discuss the significance of this requirement. At that time, Mr. Room explained that this regulation applied to compounding pharmacists in the amount of medication that they could prepare in advance, but did not apply to veterinarians in the amount that they could furnish on a patient-by-patient basis. While the concept is for the veterinarian to furnish an average of a 120-hour supply to each patient, Section 1735.2(c)(3) does not dictate or limit the professional decisions that a veterinarian makes in the course of patient treatment. Therefore, if a veterinarian feels that they must provide more than a 120-hour supply of a medication to a given patient, they are free to do so.

At the time that Section 1735.2(c)(3) was passed, it was anticipated that a compounding pharmacist could provide medication pursuant to receipt of a patient-specific prescription in four days time. The CVMA positively attests that more often than not, this is not the case. To that end, the CVMA would like to request that the Board of Pharmacy increase the average supply of medication that a pharmacy can prepare in advance to a seven day average supply per patient, based on anticipated needs as identified by the veterinarian. The CVMA proposes the following specific wording change to CCR 16 section 1735.2(c)(3):

> *Is sufficient for administration or application to patients solely in the prescriber's office, or for furnishing of not more than a ~~120-hour~~ seven day supply per animal patient for veterinarian prescribers ~~veterinary medical practices~~, solely to the veterinarian prescriber's own ~~veterinary~~ patients ~~seen as part of regular treatment in the prescriber's office~~, as fairly estimated by the veterinarian prescriber in anticipation of their patient needs and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing.*

Thank you for your consideration.

Dan Baxter
Executive Director

Enclosure

Attachment 5

Board of Pharmacy

Enforcement Workload Statistics FY 2022/23

Complaint Investigations	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Received	912	873	884	0	1,785
Closed	637	822	918	0	1,459
Pending	1,875	1,999	1,955	0	1,955
Average Days for Investigation	173	166	185	0	185

Cases Under Investigation (By Team)	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Quarter Ending
Compliance / Routine	716	732	704	0	704
Drug Diversion / Fraud	251	269	231	0	231
Prescription Drug Abuse	273	319	276	0	276
Compounding	62	48	28	0	28
Outsourcing	20	18	15	0	15
Probation / PRP	87	81	51	0	51
Enforcement	14	10	30	0	30
Criminal Conviction	452	522	529	0	529

Application Investigations	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Received	60	43	41	0	144
Closed					
Approved	30	25	41	0	96
Denied	20	16	23	0	59
Total Closed (includes withdrawn)	***50***	***46***	***67***	***0***	***163***
Pending	100	97	67	0	67

Complaint Closure Outcomes Not Resulting in Further Action	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Insufficient Evidence	135	189	344	0	324
Non-Jurisdictional	135	169	139	0	443
No Violation	67	84	52	0	203
No Further Action	27	112	41	0	180
Other - Non-Substantiated	33	52	47	0	85
Subject Educated	20	36	19	0	75

Letter of Admonishment / Citations	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
LOA Issued	44	48	49	0	141
Citations Issued	281	218	266	0	765
Proof of Abatement Requested	68	55	36	0	159
Appeals Referred to AG's Office	6	20	11	0	37
Dismissed	1	3	5	0	9
Total Fines Collected	***$448,797***	***$643,100***	***$523,984***	***$0***	***$1,615,881***

Administrative Cases	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Referred to the AG's Office	51	53	77	0	181
Pleadings Filed	34	34	38	0	106
Pending					Quarter Ending
Pre-Accusation	94	105	129	0	129
Post-Accusation	140	138	141	0	141
Total Pending	**234**	**215**	**271**	**0**	**271**
Total Closed	46	46	51	0	143

Administrative Case Outcome	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Revocation					
Pharmacist	1	3	5	0	9
Intern Pharmacist	0	0	1	0	1
Pharmacy Technician	7	7	8	0	22
Designated Representative	0	0	0	0	0
Wholesaler	0	0	0	0	0
Pharmacy	2	2	2	0	6
Sterile Compounding	0	1	1	0	2
Outsourcing	0	0	0	0	0
Total	***10***	***13***	***17***	***0***	***40***

Administrative Case Outcomes	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Revocation; stayed suspension/probation					
Pharmacist	1	1	1	0	3
Intern Pharmacist	0	0	0	0	0
Pharmacy Technician	0	0	0	0	0
Designated Representative	0	0	0	0	0
Wholesaler	0	0	0	0	0
Pharmacy	0	0	0	0	0
Sterile Compounding	0	0	0	0	0
Outsourcing	0	0	0	0	0
Total	***1***	***1***	***1***	***0***	***3***

Administrative Case Outcome	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Revocation; stayed; probation					
Pharmacist	11	5	8	0	24
Intern Pharmacist	1	0	1	0	2
Pharmacy Technician	1	2	0	0	3
Designated Representative	0	0	0	0	0
Wholesaler	0	0	0	0	0
Pharmacy	4	5	3	0	12
Sterile Compounding	0	1	1	0	2
Outsourcing	0	0	0	0	0
Total	***17***	***13***	***13***	***0***	***43***

Administrative Case Outcome	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Surrender / Voluntary Surrender					
Pharmacist	5	4	7	0	16
Intern Pharmacist	0	0	0	0	0
Pharmacy Technician	3	1	1	0	5
Designated Representative	0	0	1	0	1
Wholesaler	0	0	0	0	0
Pharmacy	7	6	9	0	22
Sterile Compounding	0	0	1	0	1
Outsourcing	0	0	0	0	0
Total	***15***	***11***	***19***	***0***	***45***

Administrative Case Outcome	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Public Reproval / Reprimand					
Pharmacist	4	2	2	0	8
Intern Pharmacist	0	0	0	0	0
Pharmacy Technician	0	0	1	0	1
Designated Representative	0	0	0	0	0
Wholesaler	0	1	0	0	1
Pharmacy	1	1	2	0	4
Sterile Compounding	0	0	0	0	0
Outsourcing	0	0	0	0	0
Total	***5***	***4***	***5***	***0***	***14***

Administrative Case Outcome	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Licenses Granted					
Pharmacist	0	2	0	0	2
Intern Pharmacist	0	0	0	0	0
Pharmacy Technician	0	1	3	0	4
Designated Representative	0	0	0	0	0
Wholesaler	0	0	0	0	0
Pharmacy	1	0	0	0	1
Sterile Compounding	0	0	0	0	0
Outsourcing	0	0	0	0	0
Total	***1***	***3***	***3***	***0***	***7***

Administrative Case Outcome	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Licenses Denied					
Pharmacist	0	0	0	0	0
Intern Pharmacist	0	0	0	0	0
Pharmacy Technician	0	0	2	0	2
Designated Representative	0	0	0	0	0
Wholesaler	1	0	0	0	1
Pharmacy	2	0	1	0	3
Sterile Compounding	0	0	0	0	0
Outsourcing	0	0	0	0	0
Total	***3***	***0***	***3***	***0***	***6***

Administrative Case Cost Recovery Efforts	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Cost Recovery Requested	***$340,239***	***$476,654***	***$538,651***	***$0***	***$1,355,544***
Cost Recovery Collected	***$154,930***	***$484,154***	***$446,176***	***$0***	***$1,085,260***

Immediate Public Protection Sanctions	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Interim Suspension Orders	2	1	3	0	6
Automatic Suspension Orders	2	0	1	0	3
Penal Code 23 Restrictions	2	2	4	0	8
Cease and Desist - Outsourcing	0	0	0	0	0
Cease and Desist - Unlicensed Activity	0	0	0	0	0
Cease and Desist - Sterile Compounding	0	0	0	0	0

Probation Statistics	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Quarter Ending
Licenses on Probation					
Pharmacist	208	190	178	0	178
Intern Pharmacist	1	1	2	0	2
Pharmacy Technician	17	16	13	0	13
Designated Representative	2	1	1	0	1
Wholesaler / 3PL	3	3	3	0	3
Pharmacy	57	54	53	0	53
Sterile Compounding	8	8	8	0	8
Outsourcing	1	1	1	0	1
Total	***297***	***274***	***259***	***0***	***259***

Probation Statistics	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Probation Office Conferences	16	10	15	0	41
Probation Interviews / Site Inspections	97	56	150	0	303
Probation Terminated / Completed	35	37	32	0	104
Referred to AG for Non-Compliance	2	2	2	0	6

As of 3/31/2023

Board of Pharmacy

Citation and Fine Statistics FY 2022/23

Citation Outcomes	July - Sept	Oct - Dec	Jan - March	Apr - Jun	Total
Pharmacist with Fine	41	24	30	0	95
Pharmacist-in-Charge with Fine*	30	67	13	0	110
Pharmacist no Fine	67	69	61	0	197
Pharmacist-in-Charge no Fine*	44	19	33	0	96
Pharmacy with Fine	110	18	126	0	254
Pharmacy no Fine	30	32	15	0	77
Pharmacy Technician with Fine	5	5	4	0	14
Pharmacy Technician no Fine	1	7	6	0	14
Wholesalers	5	3	1	0	9
Designated Representative	0	1	0	0	1
Clinics	0	0	0	0	0
Drug Room	0	0	0	0	0
Exempt Hospital	1	0	2	0	3
Hospital Pharmacy	6	5	5	0	16
Miscellaneous**	16	19	26	0	61
Unlicensed Premises	1	0	0	0	1
Unlicensed Person	1	1	1	0	3

*These numbers are also represented in the RPH columns, but reflect how many RPHs were cited as PICs

**Intern Pharmacist, Licensed Correctional Facilities, Exempt Pharmacies, Non-Resident Pharmacies, and Vet Retailers

Pharmacists	%	Pharmacies	%	Pharmacists In Charge	%
1716 - Variation from prescription	44%	4113(d) - Every pharmacy shall notify the board in writing within 30 days of the date of a change in pharmacist-in-charge	32%	1716 - Variation from prescription	18%
1707.2(a)(3) - Duty to consult: (a) A pharmacist shall provide oral consultation to his or her patient or the agent of patient in all care settings: (3) Whenever the prescription drug has not previously been dispensed to a patient	18%	1716 - Variation from prescription	24%	1714(C) - Operational Standards and Security; pharmacy, fixtures and equipment shall be maintained in a sanitary and orderly condition	18%
1714(C) - Operational Standards and Security; pharmacy, fixtures and equipment shall be maintained in a sanitary and orderly condition	10%	4113(a) - Pharmacist-in-Charge: Notification to Board; Responsibilities; Every pharmacy shall designate a pharmacist-in-charge within 30 days in writing of the identity and license number of that pharmacist	14%	1707.2(a)(3) - Duty to consult: (a) A pharmacist shall provide oral consultation to his or her patient or the agent of patient in all care settings: (3) Whenever the prescription drug has not previously been dispensed to a patient	11%
4301(g) - Unprofessional Conduct - Knowingly making or signing any certificate or other document that falsely represents the existence or nonexistence of a state of facts	6%	4305(b) - Operation of a pharmacy for more than 30 days without supervision or management by a pharmacist-in-charge shall constitute grounds for disciplinary action	7%	1715(A) - Self-assessment form of a pharmacy by the pharmacist-in-charge; shall complete a self-assessment of pharmacy compliance with federal and state pharmacy law	11%
1707.3 - Duty to review drug therapy	5%	733(a) - Dispensing prescription drugs and devices- No licentiate shall obstruct a patient in obtaining a prescription	6%	4081(a)/1718 - Records of Dangerous Drugs and Devices Kept Open for Inspection; Maintenance of Records, Current Inventory/Current Inventory Defined	11%
1715(A) - Self-assessment form of a pharmacy by the pharmacist-in-charge; shall complete a self-assessment of pharmacy compliance with federal and state pharmacy law	5%	1707.2(a)(3) - Duty to consult: (a) A pharmacist shall provide oral consultation to his or her patient or the agent of patient in all care settings: (3) Whenever the prescription drug has not previously been dispensed to a patient	5%	4059(a) - Furnishing dangerous drugs without a prescription	7%
4081(a)/1718 - Records of Dangerous Drugs and Devices Kept Open for Inspection; Maintenance of Records, Current Inventory/Current Inventory Defined	3%	4301 - Unprofessional Conduct…	3%	733(a) - Dispensing prescription drugs and devices- No licentiate shall obstruct a patient in obtaining a prescription	7%
4301 - Unprofessional Conduct…	3%	1764/56.10(a) - Unauthorized disclosure of prescription and medical information	3%	1715(b)(2) - Self-Assessment of a pharmacy by the pharmacist-in-charge; shall complete a self-assessment within 30 days whenever: there is a change in pharmacist-in-charge	7%
4169(a)(4) - Purchase, trade, sell, or transfer dangerous drugs or dangerous devices after or beyond use date on the label	3%	4113(e) - Pharmacist-in-Charge: Notification to Board; Responsibilities; If a pharmacy is unable, in the exercise of reasonable diligence, to identify within 30 days a permanent replacement pharmacist	3%	4301 - Unprofessional Conduct…	7%
4301(o)/4113.7 - Unprofessional conduct; assist in violation/Chain community pharmacy; Quota for pharmacist or pharmacy technician duties prohibited	3%	1714(c) - Operational Standards and Security; pharmacy, fixtures and equipment shall be maintained in a sanitary and orderly condition	3%	1735.3(a)(2)(I) - For each compounded drug product, the pharmacy records shall include a compounding log consisting of a single document containing all of the following… final quantity or amount of drug	4%

California State Board of Pharmacy
SB 1441 Uniform Standards

The data includes licensees participating in the Pharmacist Recovery Program (PRP) and licensees on probation with substance use disorders. This data includes July 2022 through March 2023.

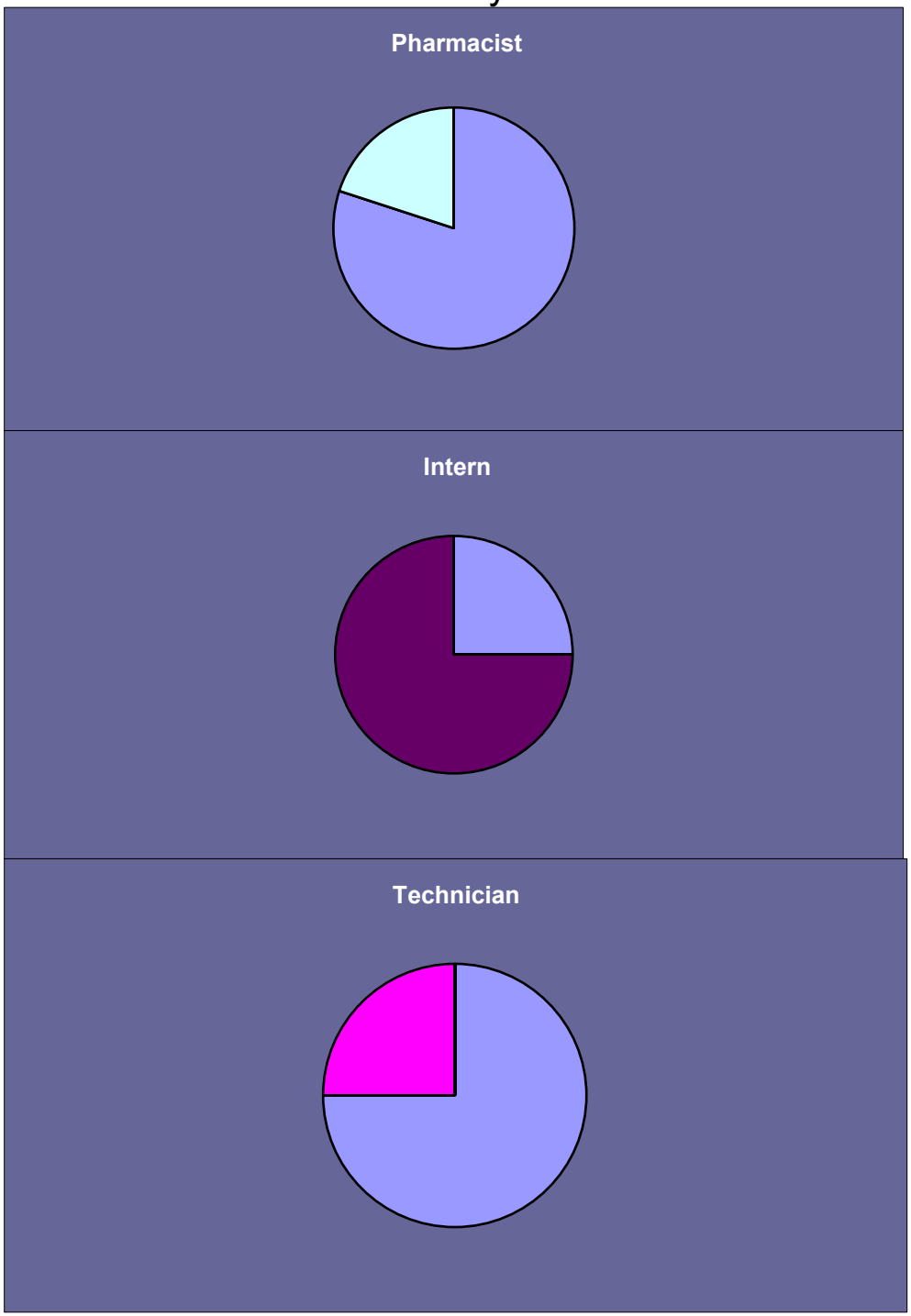
Board of Pharmacy	July -Sep	Oct – Dec	Jan-Mar	Apr-Jun	22/23
PRP Intakes					
PRP Self-Referrals					
PRP Probation Referrals			1		1
PRP Under Investigation	3				3
PRP In Lieu Of (investigation conducted)					
Total Number of PRP Intakes	3		1		4
New Probationers					
Pharmacists	2	1	3		6
Intern Pharmacists			1		1
Pharmacy Technicians		1	2		3
Total New Probationers	2	2	6		10
PRP Participants and Recovery Agreements					
Total PRP Participants	39	34	30		39
Recovery Agreements Reviewed	26	34	26		86
Probationers and Inspections					
Total Probationers	48	5	33		48
Inspections Completed	31	33	24		88
Referrals to Treatment					
Referrals to Treatment (PRP and Probationers)	2		2		4
Drug Tests					
Drug Test Ordered (PRP and Probationers)	435	511	456		1402
Drug Tests Conducted (PRP and Probationers)	431	489	450		1370
Relapses (Break in Sobriety)					
Relapsed (PRP and Probationers)		1	1		2
Major Violation Actions					
Cease Practice/Suspension (PRP and Probationers)	3	3	4		10
Termination from PRP					
Probationers Referred for Discipline			2		2
Closure					
Successful Completion (PRP and Probationers)	12	5	6		23
Termination (Probation)	1		2		3
Voluntary Surrender (Probation)			2		2
Surrender as a result of PTR (Probation)					
Closed Public Risk (PRP)			1		1
Non-compliance (PRP and Probationers)	46	49	13		108
Other (PRP)	1	2	1		4
Patients Harmed					
Number of Patients Harmed (PRP and Probationers)					Zero

SB 1441 Uniform Standards

The data includes licensees participating in the Pharmacist Recovery Program (PRP) and licensees on probation with substance use disorders. This data includes July 2022 through March 2023.

Board of Pharmacy	July -Sep	Oct – Dec	Jan-Mar	Apr-Jun	22/23
Alcohol	2		2		
Ambien					
Opiates					
Hydrocodone	1				
Oxycodone					
Morphine					
Benzodiazepines					
Barbiturates					
Marijuana					
Heroin					
Cocaine					
Methamphetamine					
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Clonazepam					
Tramadol					
Carisprodol					
Phendimetrazine					
Promethazine w/Codeine					
Alcohol			1		
Opiates					
Hydrocodone					
Oxycodone					
Benzodiazepines			3		
Barbiturates					
Marijuana					
Heroin					
Cocaine					
Methamphetamine					
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Clonazepam					
Tramadol					
Carisprodol					
Phendimetrazine					
Promethazine w/Codeine					
Alcohol		1	2		
Opiates					
Hydrocodone					
Oxycodone					
Benzodiazepines					
Barbiturates					
Marijuana					
Heroin					
Cocaine					
Methamphetamine			1		
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Clonazepam					
Tramadol					
Carisprodol					
Phendimetrazine					
Promethazine w/Codeine					

Drug Of Choice - Data entered from July 2022 to March 2023



1 Alcohol
2 Opiates
3 Hydrocodone
4 Oxycodone
5 Benzodiazepines
6 Barbiturates
7 Marijuana
8 Heroin
9 Cocaine
10 Methamphetamine
11 Pharmaceutical Amphetamine

Printed on 4/6/2023