California State Board of Pharmacy
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Business, Consumer Services and Housing Agency
Department of Consumer Affairs
Gavin Newsom, Governor

Enforcement and Compounding Committee Report
March 23, 2023

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

I. Call to Order, Establishment of Quorum, and General Announcements

II. Public Comments on Items Not on the Agenda/Agenda Items for Future Meetings
Note: The Committee may not discuss or take action on any matter raised during this public comment section that is not included on this agenda, except to decide whether to place the matter on the agenda of a future meeting. [Government Code sections 11125, 11125.7(a)]

III. Discussion, Consideration and Approval of Draft Minutes from the February 15, 2023, Enforcement and Compounding Committee Meeting

Attachment 1 includes a copy of the draft minutes.

IV. Presentation on US Pharmacopeia (USP) General Chapter 797, Pharmaceutical Compounding – Sterile Preparations

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 FAQs are being revised. The Board recommends licensees check with the USP website for updates.

During the meeting members will receive a brief overview of the provisions established in

the Chapter. A copy of the USP 797 FAQ (Nov. 1, 2022) and presentation slides are provided in **Attachment 2**.

V. 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)

Relevant California Law

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 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.

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 official date of Chapter 797, it is appropriate to review the Board's regulations to determine, in the interest of patient safety, where changes are appropriate.

As a reminder, as part of the Committee's January 2023 meeting an overview of federal requirements for compounding was provided.

For Committee Consideration and Discussion

During the meeting members will have the opportunity to consider draft regulation language developed by staff to replace existing regulations. A copy of the regulation language is provided in **Attachment 3**.

VI. Future Committee Meeting Dates

- April 13, 2023, via WebEx
- July 18, 2023, in person and via WebEx
- October 19, 2023, in person and via WebEx

VII. Adjournment

Attachment 1

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Business, Consumer Services and Housing Agency
Department of Consumer Affairs
Gavin Newsom, Governor

DRAFT ENFORCEMENT AND COMPOUNDING COMMITTEE MEETING MINUTES

DATE: February 15, 2023

LOCATION: Department of Consumer Affairs
1625 N Market Blvd, 1st Floor Hearing Room
Sacramento, CA 95834

Participation was also through WebEx.

COMMITTEE MEMBERS PRESENT: Maria Serpa, Licensee Member, Chair
Jig Patel, Licensee Member, Vice Chair
Renee Barker, Licensee Member
Indira Cameron-Banks, Public Member
Seung Oh, Licensee Member
Ricardo Sanchez, Public Member (remote participation via WebEx)

STAFF MEMBERS PRESENT: Anne Sodergren, Executive Officer
Eileen Smiley, DCA Staff Counsel
Debbie Damoth, Executive Manager Specialist

I. Call to Order, Establishment of Quorum, and General Announcements

Chairperson Maria Serpa called the meeting to order at 9:02 a.m. Dr. Serpa reminded all present that the Board is a consumer protection agency. Dr. Serpa advised the meeting was being conducted with participation through WebEx and being webcast. The meeting moderator provided updated WebEx instructions.

Chairperson Serpa took roll call. Members present included: Renee Barker, Licensee Member; Indira Cameron-Banks, Public Member; Seung Oh, Licensee Member; and Maria Serpa; Licensing Member. A quorum was established.

II. Public Comments on Items Not on the Agenda/Agenda Items for Future Meetings

Members of the public were provided the opportunity to provide comments for

items not on the agenda; however, there were no comments made.

Member Patel arrived at 9:09 a.m.

III. Approval of January 23,2023, Enforcement and Compounding Committee Meeting Minutes

Chairperson Serpa referenced the draft minutes for the January 23, 2023, Enforcement and Compounding Committee Meeting.

Members were provided an opportunity to provide comments on the draft minutes; however, no comments were made.

Motion: Approve the January 23, 2022, Committee Meeting Minutes as presented in the meeting materials

M/S: Oh/Patel

Members of the public were provided with an opportunity to provide public comment; however, no comment was provided in Sacramento or via WebEx.

Support: 5 Oppose: 0 Abstain: 0 Not Present: 1

Committee Member	Vote
Barker	Support
Cameron-Banks	Support
Oh	Support
Patel	Support
Sanchez	Not Present
Serpa	Support

IV. Presentation on US Pharmacopeia (USP) General Chapter 795, Pharmaceutical Compounding – Nonsterile Preparations

Chairperson Serpa introduced Supervising Inspector (SI) Peg Panella-Spangler who provided a presentation on US Pharmacopeia (USP) General Chapter 795, Pharmaceutical Compounding – Nonsterile Preparations.

Member Sanchez joined the meeting via WebEx at approximately 9:19 a.m.

SI Panella-Spangler provided a review on USP 795 including the following sections: Introduction and Scope; Personnel Training and Evaluation; Personal Hygiene and Garbing; Building and Facilities; Cleaning and Sanitizing; Equipment, Supplies and Components; Master Formulation and Compounding Records; Release Inspection and Testing; Labeling; Establishing Beyond-Use Dates; Standard Operating Procedures; Quality Assurance and Quality Control; CNSP Packaging and Transporting; and Documentation.

Members were provided the opportunity to comment.

President Oh thanked SI Panella-Spangler for the presentation.

Member Patel inquired if there was a document that highlights changes. Dr. Panella-Spangler indicated there wasn't one but could check. Dr. Serpa commented Member Patel may be interested in a California regulation before and after versus USP.

Members of the public were provided the opportunity to comment. Members of the public at the physical location did not have any comments.

The Committee heard a comment via WebEx about the availability of meeting materials. The commenter was advised the slides, materials and presentation would be available on the Board's website.

The Committee took a break from 10:00 a.m. to 10:10 a.m. Roll call was taken. Members present included Jignesh Patel, Licensee Member; Renee Barker, Licensee Member; Seung Oh, Licensee Member; Ricardo Sanchez, Public Member; and Maria Serpa, Licensee Member. A quorum was established.

V. Discussion, Consideration and Possible Action on Proposed Changes to Regulations Related to Pharmaceutical Compounding of Nonsterile Preparations (Amend Title of Article 4.5 and Repeal Sections 1735, 1735.1, 1735.2, 1735.3, 1735.4, 1735.5, 1735.6, 1735.7, and 1735.8 of Article 4.5, and Adopt New Titles and Sections 1735, 1735.1, 1735.2, 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)

Chairperson Serpa advised as the Committee continued the work on reviewing the various USP chapters and reviewing current and proposed regulations that may be necessary to implement, clarify, or make more specific requirements related to those respective chapters, it was appropriate that any such regulations mirror the structure of the respective USP chapters. Dr. Serpa noted this meant the numbering format and section title for proposed regulations would mirror the USP chapter. Dr. Serpa advised the goal was to clarify or make more specific the requirements. Dr. Serpa added if no clarification was needed or additional requirements was necessary for public safety, there was no additional language being proposed. Dr. Serpa advised significant parts of existing regulation were proposed to be repealed and replaced with new shorter regulations because the Board was no longer repeating USP language or the new USP chapter now incorporated the higher standards the Board previously required.

Chairperson Serpa reminded all the Board is a consumer protection agency and as development of regulations were considered, it would be through the lens of the Board's consumer protection mandate as the law makes clear whenever the protection of the public is inconsistent with other interests sought to be promoted, the protection of the public shall be paramount. Dr. Serpa noted this was a dynamic process and there would be opportunities to participate throughout the development and rulemaking process.

Chairperson Serpa advised licensees of the Board generally must comply with a myriad of state and federal laws and at times, a licensee may be so focused on a specific section of the law, that they may forget the larger picture and other provisions of law that may be relevant. Dr. Serpa noted this was seen in several areas of pharmacy practice, but it was quite pronounced in compounding.

Chairperson Serpa reminded participants of the excellent overview Counsel Smiley provided during the last meeting covering the requirements for authorized individuals to qualify for some exemptions to federal law under provisions of section 503A. Dr. Serpa added the livestream of the meeting and the slide presentation were available on the Board's website and encouraged those interested in this area to watch the livestream. Dr. Serpa noted it was important to emphasize again:

- The Committee would not be looking to add to regulations requirements already laid out in the USP chapters or federal law. The Committee would be concerned solely with detailing additional California state requirements related to the changes to the USP chapters.
- The discussions would be dealing with the standard for compounding pharmacies and compounding pharmacists operating in compliance with the exemption in Section 503A of the federal Food Drug and Cosmetic Act and not with 503B or outsourcing facilities.

Chairperson Serpa advised Section 503A was quite extensive, but it was appropriate to highlight that one of the specific conditions a licensee must meet to be eligible for the exemptions provided under 503A was that the drug product was compounded in compliance with USP chapters on pharmacy compounding. Dr. Serpa reminded participants it was important that members and stakeholders understand for the discussion. Dr. Serpa advised while the Board has the opportunity and authority to add additional regulations to go beyond USP requirements, it cannot promulgate a lesser standard in its regulation. Dr. Serpa noted this was further emphasized in BPC section 4126.8. Dr. Serpa added based on the written comments received in advance of the meeting, there may be some misunderstanding and thought it was appropriate to do some level setting at the front end of the discussion.

Chairperson Serpa noted the first proposed change was the repeal of current Section 1735 and replacement with the proposed Section 1735 that included definitions beyond those established in the USP Chapter including the Board's definition of "essentially a copy of a commercially available drug product" incorporating a requirement for the deviation to produce a clinically significant difference in the patient. Dr. Serpa highlighted the proposed definition of designated person didn't limit the types of individuals that may serve in such a capacity; however, it did make specific that where clinical judgement was necessary and the designated person was not a pharmacist, the PIC would review the practices that require professional judgement.

Chairperson Serpa highlighted compounding was not defined in this section and was an example where, it was recommended that additional regulation was not necessary, rather, the Board would rely solely on the definitions in federal law and USP. Dr. Serpa reminded participants federal law states that the definition of "compounding does not include mixing, reconstituting, or other such actions that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer's directions consistent with that labeling." Referencing the meeting materials, Dr. Serpa added USP defined nonsterile compounding as combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug product or bulk drug substance to create a nonsterile preparation.

Chairperson Serpa addressed some of the comments received noting appreciation for comments. Dr. Serpa provided the regulation of compounding had changed dramatically over time and there were additional regulations implemented to ensure patient safety. Dr. Serpa advised comments were received late in the day prior to the meeting. Those comments were posted on the website and were in the back of the room at the physical DCA location. Dr. Serpa provided apparent with

both federal requirements as well as changes in several of the USP Chapters, the focus must remain on patient safety.

Chairperson Serpa recalled the Board is a consumer protection agency and its licensees must comply with state and federal law. In preparation for the meeting today, Dr. Serpa reviewed some of the supplemental information and FAQs provided by USP that addressed many of the comments received requesting the Board consider lower the USP requirements. Dr. Serpa specifically noted the issue of adding flavoring to medications where it was clear that the USP expert committee thoroughly considered the issue. Dr. Serpa didn't believe the Board had the authority to carve out an exemption for flavoring agents nor would Dr. Serpa support such an approach. Dr. Serpa recommended commentors provide information to help the Board strike a balance of public safety and with patient access and assurance that the Board does have the authority to consider such changes. Dr. Serpa added during public comment it would be helpful to the Board for stakeholders to highlight such information as opposed to asking the Board to take action that it lacks the authority.

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 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.

(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 the 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 purified water or sterile water for injection.

(d) "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.

(e) "Product" means a commercially or conventionally manufactured product evaluated for safety and efficacy by the FDA in accordance with the Federal Food Drug and Cosmetic Act.

(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.

Chairperson Serpa believed the proposed language in section 1735 provided was appropriate both legally and for consumer protection. Members were provided the opportunity to comment.

President Oh asked if each section would have definitions. Supervising Inspector Christine Acosta provided each USP Chapter was a standalone Chapter. Dr. Oh recommended this be clarified.

Member Barker inquired about (c) requesting clarification be added in front of "water." Dr. Acosta provided the intent was to leave it broad. Dr. Barker was concerned with someone reading it and thinking tap water could be used.

Members of the public were provided the opportunity to comment.

At the Sacramento location a representative of Flavor Rx and through WebEx a pharmacy owner commented in support of allowing flavoring agents to be added to medicine to help children take liquid medicine without being considered non-sterile compounding. The Flavor Rx representative was not aware of any negative impacts on patients as a result of flavoring being added. The pharmacy owner commented that she would now have to complete the compounding self-assessment now for the flavoring she adds to children's medicine.

Dr. Serpa clarified the Board wasn't proposing that flavoring was not appropriate and was clinically relevant but now falls under the auspices of compounding per USP.

Dr. Acosta recommended adding the word "purified" before water to address Dr. Barker's concern.

Chairperson Serpa referenced Section 1735.1 Introduction and Scope where the current section would be repealed and a new section proposed would be added.

~~**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 - 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 355 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, on the prescription that a compounded preparation is necessary for the identified patient and the CSNP otherwise meets the

requirements of section 503A of the Federal Food, Drug and Cosmetic Act (21 U.S.C. section 353a), as applicable.

(e) Notwithstanding subdivision (e), 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.

(f) 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:

(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 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 intended for use in a CNSP for the intended patient population.

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

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

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

(j) CNSPs considered to be hazardous drugs as defined in USP Chapter 800 *titled Hazardous Drugs – Handling in Healthcare Settings* shall be handled in compliance with that Chapter and relevant provisions of Pharmacy Law.

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.

Chairperson Serpa was comfortable with the language and appreciated the clarity being provided specifically to the requirements for the repackaging of conventionally manufactured drug products and provisions for reconstitution. Dr. Serpa believed the cross references provided for hazardous compounding to be a helpful reminder. Members were provided the opportunity to comment.

President Oh asked regarding (e) if USP was silent on that section; for clarification on (f)(2); and if new (i) was necessary. Dr. Acosta advised the (e) subdivision was wrong and it would need to be edited. Dr. Acosta provided (f)(2) was for patient populations where a type of CSNP should never be done (e.g., pediatric patient

should never be made a CSNP with tetracycline, etc.). Dr. Acosta noted new subsection (i) was reminding the reader.

Members of the public were provided an opportunity to comment.

A Sutter Health representative in Sacramento commented (b) referenced USP 1178 and if it should reference something that doesn't apply as USP 1178 doesn't apply to pharmacists engaged in dispensing prescription drugs in accordance with state practice of pharmacy. Dr. Serpa advised it was considered in a different way. Dr. Acosta provided it was not relevant to immediate dispensing practice but was related to taking a 1,000-count bottle and making a number of different bottles with different numbers of capsules in it. Dr. Acosta stated it was still relevant because it was not a dispensing feature.

A representative of CSHP commented from WebEx with concern about the prior comment on how this affected the process of packaging unit dose dosage forms where the doses aren't immediately dispenses and inquired if that would be considered compounding.

Chairperson Serpa referenced Section 1735.2 Compounding Limitations and Requirements; Self-Assessment where the current section was being proposed to be amended.

~~**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.~~

(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 ordered by the prescriber or the prescriber's agent using a purchase order or other documentation received by the pharmacy prior to furnishing that lists the number of patients seen or to be seen in the prescriber's office for whom the drug is needed or anticipated, and the quantity for each patient that is sufficient for office administration; and~~

~~(2) Is delivered to the prescriber's office and signed for by the prescriber or the prescriber's agent; and~~

(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 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; ~~and~~

~~(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 USP Chapter 795's requirements, training, evaluation, and requalification procedures for personnel who compound or who 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 to the pharmacy prior to furnishing.

(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 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.

(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 1735.11.

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.

Dr. Serpa believed language was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa added sharing appropriate training was vital to patient safety and the cross reference to the facility's SOPs assures that the issue was fully considered in the compounding operations. Dr. Serpa noted

provisions specific to compounding for veterinary office use were not being proposed to change. Dr. Serpa ensured all members received public comment on the issue and noted there were no suggested changes to current language. Dr. Serpa advised the comment received was specifically related to the provisions of anticipatory compounding for veterinary office dispensing. Dr. Serpa believed the current language was appropriate and was not in favor of changing it. Dr. Serpa appreciated the comments and stated as a pet owner who has needed compounding veterinary medications did not believe changes were necessary. Dr. Serpa noted pharmacy compounding was generally intended for patient specific use and not volume compounding; however, the Board recognized the need to start treatment in a timely fashion and currently allows for limited office supply to strike a balance to allow a patient to receive sufficient medications to start treatment while the patient specific medication was being compounded. Dr. Serpa noted should the veterinary practice choose to do so, they can purchase sufficient supplies from an outsourcing facility or for non-patient specific use if the practice wishes to dispense the full treatment regimen beyond the five days that was allowed. Dr. Serpa reminded outsourcing facilities have extensive FDA requirements and regulations as a 503B facility and were regulated under the requirements by both the Board and the FDA. Dr. Serpa continued the patient specific was typically done by a 503A facility.

Members were provided the opportunity to comment.

President Oh inquired if the remaining section was being left where it was. Ms. Sodergren advised the language was being left where it currently resided. Ms. Sodergren noted it was not contemplated in USP and the current structure was retained for the provision in the existing law.

Members of the public were provided the opportunity to comment.

A veterinarian representative from the California Veterinary Medical Association commented in Sacramento regarding submitted comments and respectfully disagreed with Dr. Serpa. The representative added a list of drugs were provided that they are not able to get because of excessive compounding regulations. The representative said four days was not enough time to obtain patient specific prescriptions as most pharmacies are located in the east coast and were asking to extend for a seven-day period. The representative added there were only two 503B facilities in California that provide any kind of appreciative product for animals and then have to rely on 503A facilities. The representative pointed out 120-hour average wasn't telling him what he could or couldn't do with his patients and was within his ability to provide more medication to a patient. He noted this was what a pharmacist could do in anticipation of his needs. The representative didn't want to see pharmacists controlling veterinarians.

A pharmacist representative of CPhA commented in Sacramento regarding (d) re-emphasizing the potential concern regarding the interpretation and opportunity for clarification noting USP states there must be immediate corrective action in the deficient area and not all of the compounding.

A pharmacist representative of Sutter Health commented on (a) regarding the additional competency requirements in addition to USP 795 identifies additional individuals who will be required to have compounding training with only these additional components. The representative noted it was unclear who the personnel was and frequency wasn't included. The representative requested if the intent was those would be annual competencies that should be related.

The Moderator read a comment left through WebEx, "Following up on the question being discussed what the policy for compounding the office supply where we do not have patient specific data (e.g., veterinary, etc.) also what about non-veterinary offices (e.g., topical compounds, etc.) for during and post laser treatments."

Members were provided an opportunity to comment.

President Oh asked regarding training confirming it was every 12 months. Dr. Serpa provided it was referenced in another section.

Chairperson Serpa referenced Section 1735.3 Personnel Hygiene and Garbing where proposed the current section would be repealed and a new section added.

~~**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 detergent 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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa noted personnel hygiene and garbing were core components to avoid contamination of a compounded preparation. Dr. Serpa believed the flexibilities provided in the language struck a balance and were appropriate for nonsterile preparations where the risk to patients was not as great.

Members were provided the opportunity to comment.

Member Barker inquired about (d) if the Board needed to clarify "wiped" in the verbiage. Dr. Acosta provided the only change was "should" to "shall" and any change would be outside what the Chapter provided. Dr. Serpa clarified it was current USP language and the Board changed it to make it a requirement. Dr. Acosta referenced USP FAQ 23 that might help to clarify.

Member Barker commented on (e) on the term germicidal detergent where most products say cleaner and detergent is a component of a cleaner. Dr. Acosta added the verbiage was from current law. The proposed subsection (e) was updated to read: (e) Non-disposable garb shall be cleaned with a germicidal detergent cleaner and sanitized with 70% isopropyl alcohol before re-use.

Members of the public were provided an opportunity to comment.

A representative from Sutter Health commented in Sacramento regarding (b) referencing a closed system processing device seemed to intersect with USP 800 and was curious if that could be interpreted not specific to hazardous drugs. The representative inquired of a requirement being added specifically around closed system processing device noting there was no definition in the current regulations

regarding closed system processing device and could be added. Dr. Acosta provided closed system processing devise was provided in USP. Dr. Serpa added while the Board was attempting to not have duplication, there were examples where it has repeated to ensure clarity.

There were no commenters via WebEx.

Members were provided the opportunity to comment.

President Oh agreed with Member Barker that clarification would be helpful and it was noted.

Chairperson Serpa referenced Section 1735.4 Building and Facilities where proposed the current section would be repealed and a new section added.

~~**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 USP Chapter 795 or the pharmacy's written SOPs referenced in section 1735.11.

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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate.

Members were provided the opportunity to comment.

President Oh inquired about (b) being a huge undertaking for facilities. Dr. Acosta provided some facilities use this water already and noted large amount of contaminates in tap water.

Members of the public were provided an opportunity for comment; however, there were no comments in Sacramento or via WebEx.

Chairperson Serpa referenced Section 1735.5 Cleaning and Sanitizing where proposed the current section would be repealed and a new section added.

~~**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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa agreed with the documentation requirements.

Members were provided the opportunity to comment; however, no comments were made.

Members of the public were provided the opportunity to comment; however, there were no comments in Sacramento or via WebEx.

Chairperson Serpa referenced Section 1735.6 Equipment and Components where proposed the current section would be repealed and a new section added.

~~**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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa believed that

such requirements would go without saying but regrettably have been advised by staff, that this was not always the case.

Members were provided the opportunity to comment; however, no comments were made.

Members of the public were provided the opportunity to comment; however, there were no comments in Sacramento or via WebEx.

Chairperson Serpa referenced Section 1735.7 Master Formulation and Compounding Records where proposed the current section would be repealed and a new section added.

~~**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 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:

(1) The referenced source material (e.g., peer reviewed article, published scientific book) used 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 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 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 CNSP.

(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, have 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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa noted there was a change in terms from the prior version of USP from master formula to master formulation. Dr. Serpa agreed that documentation on the referenced sourced material must be maintained and appreciated the flexibility to allow the prescription document to serve as the master formulation record. Dr. Serpa recalled seeing several enforcement-related matters that involved violations with compounding records. Dr. Serpa appreciated the specificity in the draft language and believed it provided clarity to the regulated public.

Members were provided the opportunity to comment; however, no comments were made.

Members of the public were provided the opportunity to comment.

A representative of Sutter Health commented in Sacramento regarding (c) (4) agreeing with the statement noting the number in USP mentions "if other than one or default to one" and recommended adding as Sutter Health's records default to one. The representative commented about the statement "that every single volume would require its own unique master formulation" versus being referenced within the master formulation for different amounts and appreciated clarification. SI Panella-Spangler advised it was addressed in USP FAQ #44.

A commenter from WebEx appreciated working with the Board and staff on new regulations noting a step forward to harmonize with USP. The commenter made the following comments: (a)(2) noting it was important to include that but there were times where there was no stability data adding it could be interpreted to mean that stability data is required even if assigning a BUD within the limits in Table 4 of USP 795 and recommended saying "if it exists"; (c)(1) clarifying the date and time of the preparation adding if BUD was listed in hours, the date and time of preparation was needed because most of the time the BUD was listed in days; and (c)(4) including the number of units made and the volume or weight of each unit and recommended "if immediately packaged into final dispensing containers after compounding."

Dr. Acosta expressed concern about "if it exists" for (a)(1) and could work on the verbiage. Dr. Acosta advised date and time of preparation was to harmonize with USP 797 but doesn't normally get down to the hours on non-sterile preparation so verbiage could be developed there. Dr. Acosta noted (c)(4) was more of a dispensing feature.

Chairperson Serpa recommended discussing changes to (a)(1) and (c)(1) but agreed (c)(4) was dispensing or possibly repackaging. Members were provided the opportunity to comment. Board staff would work offline to address verbiage for (a)(1) and (c)(1).

Chairperson Serpa referenced Section 1735.8 Release Inspections and Testing where proposed the current section would be repealed and a new section added.

~~**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 by other authorized personnel 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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa noted it should be well understood that a pharmacist was responsible and appreciated clearly stating as such.

Members were provided the opportunity to comment; however, no comments were made.

Members of the public were provided the opportunity to comment; however, there were no comments in Sacramento or via WebEx.

Chairperson Serpa referenced Section 1735.9 Labeling which was a proposed new section.

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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa highlighted there was a difference between a label and labeling.

Members were provided the opportunity to comment; however, no comments were made.

Members of the public were provided the opportunity to comment; however, there were no comments in Sacramento or via WebEx.

Chairperson Serpa referenced Section 1735.10 Establishing Beyond-Use Dates which was a proposed new section.

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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa appreciated the very clear language in section (a) and noted regrettably, there had been many enforcement-related matters that include violations where the BUD of the preparation exceeds the expiration date of one of the ingredients used.

Members were provided the opportunity to comment; however, no comments were made.

Members of the public were provided the opportunity to comment; however, there were no comments in Sacramento or via WebEx.

Chairperson Serpa referenced Section 1735.11 Standard Operating Procedures (SOPs) which was a proposed new section.

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 policies and procedures shall describe the pharmacy 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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa appreciated the cross-reference to USP Chapter 1163 providing clarity to the licensees about the requirement and believed the specified elements as well as frequency of review were appropriate for SOPs. Dr. Serpa noted failure to follow SOPs was a basis for enforcement action, which Dr. Serpa believed should go without saying; however, to ensure everyone has a clear understanding, Dr. Serpa was agreeable to explicitly stating it in the proposed language.

Members were provided the opportunity to comment; however, no comments were made.

Members of the public were provided the opportunity to comment; however, there were no comments in Sacramento or via WebEx.

Chairperson Serpa referenced Section 1735.12 Quality Assurance and Quality Control which was a proposed new section.

1735.12. Quality Assurance And Quality Control

The requirements of this section apply to nonsterile compounding in addition to the standards established by 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 to compliance with those standards, 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 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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa appreciated the cross references to other sections again providing more clarity to licensees. Dr. Serpa noted many of the requirements included in this section go the Board's core consumer protection function including mandating review of adverse events.

Members were provided the opportunity to comment.

President Oh inquired about (a)(2) and requested the intent to be explained. Dr. Acosta advised current law related to mostly to acute care so when something patient-specific was dispensed and it would go to a nursing unit to be held to the actual administration time, the refrigerators in the nursing units or medication rooms would need to have the temperatures within range so it was stored appropriately. Dr. Serpa added it also includes the pharmacy itself (e.g., when it is 110 degrees in California).

Members of the public were provided the opportunity to comment; however, there were no comments in Sacramento or via WebEx.

Chairperson Serpa referenced Section 1735.13 Package and Transport which was a proposed new section.

1735.13. 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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa believed the incorporation of procedures for storage, shipping containers, and transportation of temperature sensitive preparations was essential especially where medications were mailed or delivered.

Members were provided the opportunity to comment; however, no comments were made.

Members of the public were provided the opportunity to comment; however, there were no comments in Sacramento or via WebEx.

Chairperson Serpa referenced Section 1735.14 Documentation which was a proposed new section.

1735.14. Documentation

The requirements of this section apply to nonsterile compounding in addition to the standards established by USP Chapter 795.

(a) Facilities shall maintain each record 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.
(b) Records created shall be created and maintained in a manner to provide an "audit trail" to the Board that includes a detailed, chronological record of all revisions and updates made by the facility's personnel of each record document in accordance with this section. To meet the "audit trail" requirement of this section, each record must include the original document created, each subsequent version of that document showing change to the original document, an 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.

Chairperson Serpa believed the language as presented was appropriate and consistent with the Board's consumer protection mandate. Dr. Serpa added this section emphasized that documentation required must be maintained in a readily retrievable form for three years, similar to other pharmacy records, and established audit trail provisions necessary to understand document history.

Members were provided the opportunity to comment.

President Oh expressed concern about a pharmacy open for 10 years may have a large and hard to maintain audit trail. Dr. Acosta advised the law requires three years. Ms. Sodergren provided this might be an area where the FAQ may be helpful.

Members of the public were provided the opportunity to comment; however, there were no comments in Sacramento or via WebEx.

Chairperson Serpa thanked all for participation in the meeting and provided an overview of the summary of the identified changes:

- 1735 (d) – diluent
- 1735.1 (e) – subdivision needed a correction
- 1735.3 (e) – germicidal detergent
- 1735.7 (a)(1) – regarding reference source materials
- 1735.7 (c)(1) – date and time of preparation
- 1735.10 (a) – BUD dates
- 1735.14 – FAQ record requirement be explained

Chairperson Serpa advised the agenda item for Enforcement Statistics was added in error and would not be discussed.

VII. Future Committee Meeting Dates

Chairperson Serpa reminded the next meeting was scheduled for March 23, 2023, noting the meeting would also be conducted in person, in Sacramento and members of the public were welcome to attend either in person or via WebEx. Dr. Serpa advised the Board respectfully requested that individuals attending in person follow COVID protocols.

VIII. Adjournment

The meeting adjourned at 11:39 a.m.

Attachment 2

Attachment 2

USP 797 FAQ

(Nov. 1, 2022)

NOTE: USP's website indicates that to help ensure clarity and consistency, the FAQs are being revised. The Board recommends licensees check with the USP website for updates.

<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 2

USP General Chapter 797
PHARMACEUTICALCOMPOUNDING –
STERILE PREPARATIONS
COMPENDIAL ON 11/1/23
Presentation

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.

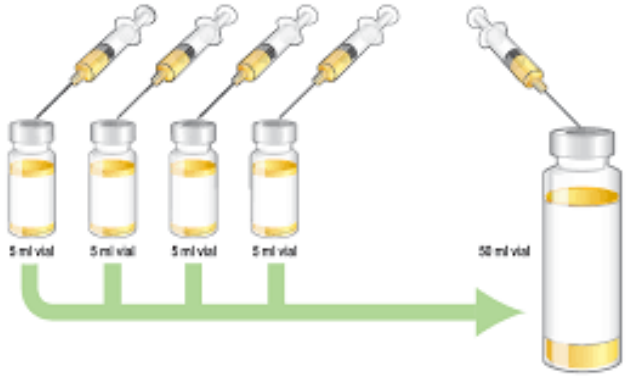
USP <797>
Section 2. Personnel Training and Evaluation

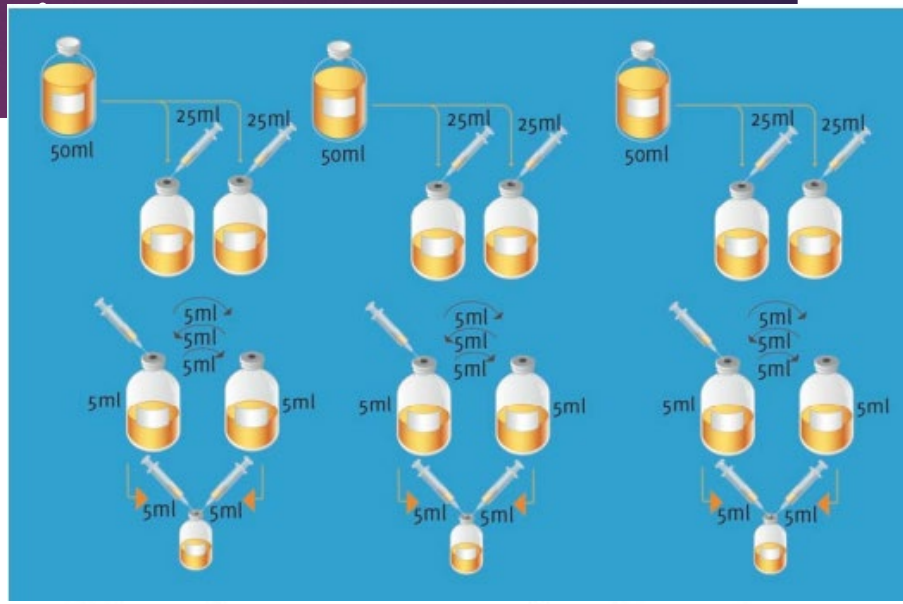
USP <797> Section 2. Personnel Training and Evaluation

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:

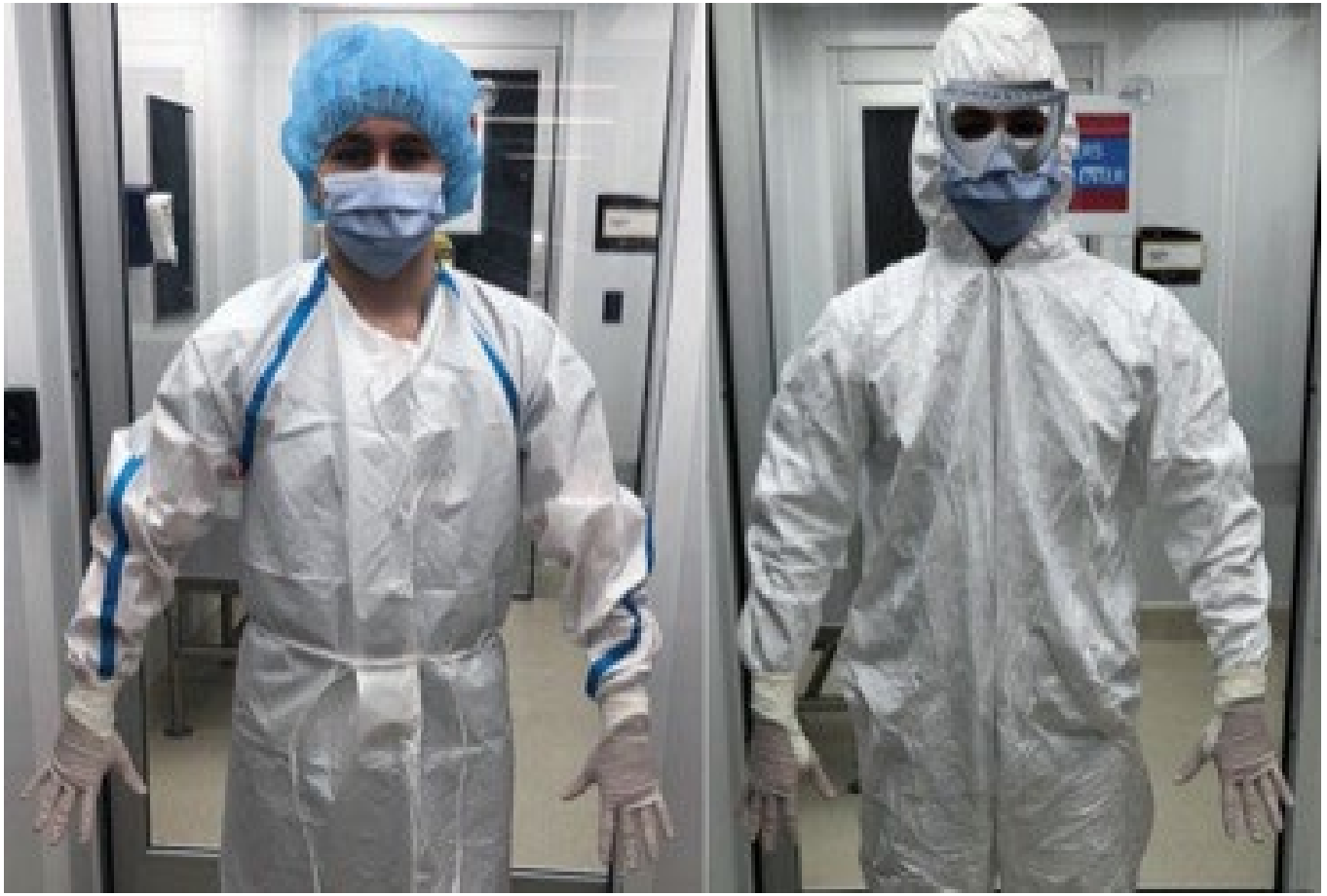
- Low-lint garment with sleeves that fit snugly around the wrists and an enclosed neck
  - May be reused for a shift
- Low-lint covers for shoes
- Low-lint cover for head that covers the hair and ears, and if applicable, cover for facial hair
- Low-lint face mask
- Sterile powder-free gloves
  - must 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

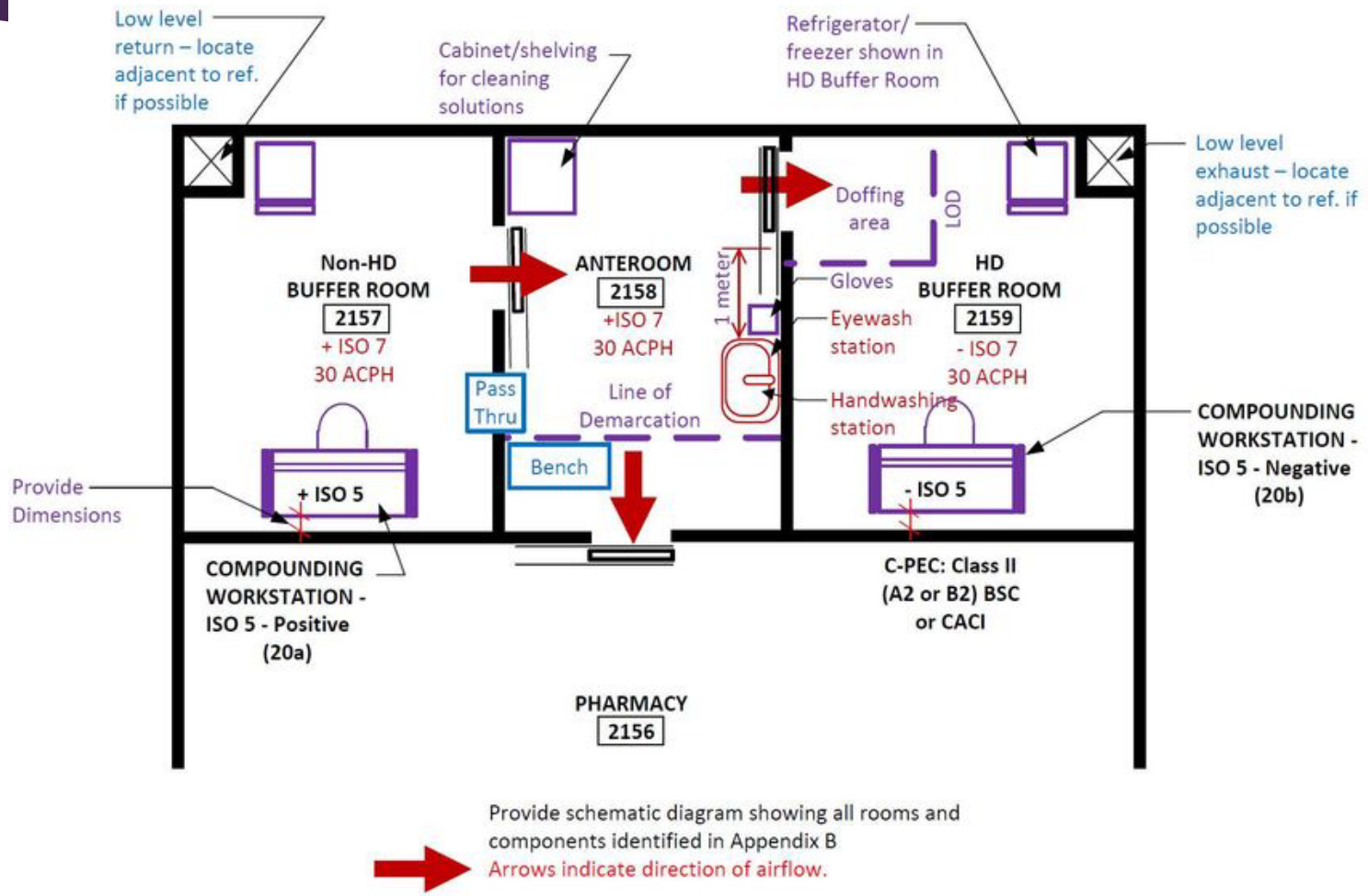
- Temperature and Humidity monitored each day when compounding takes place.

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



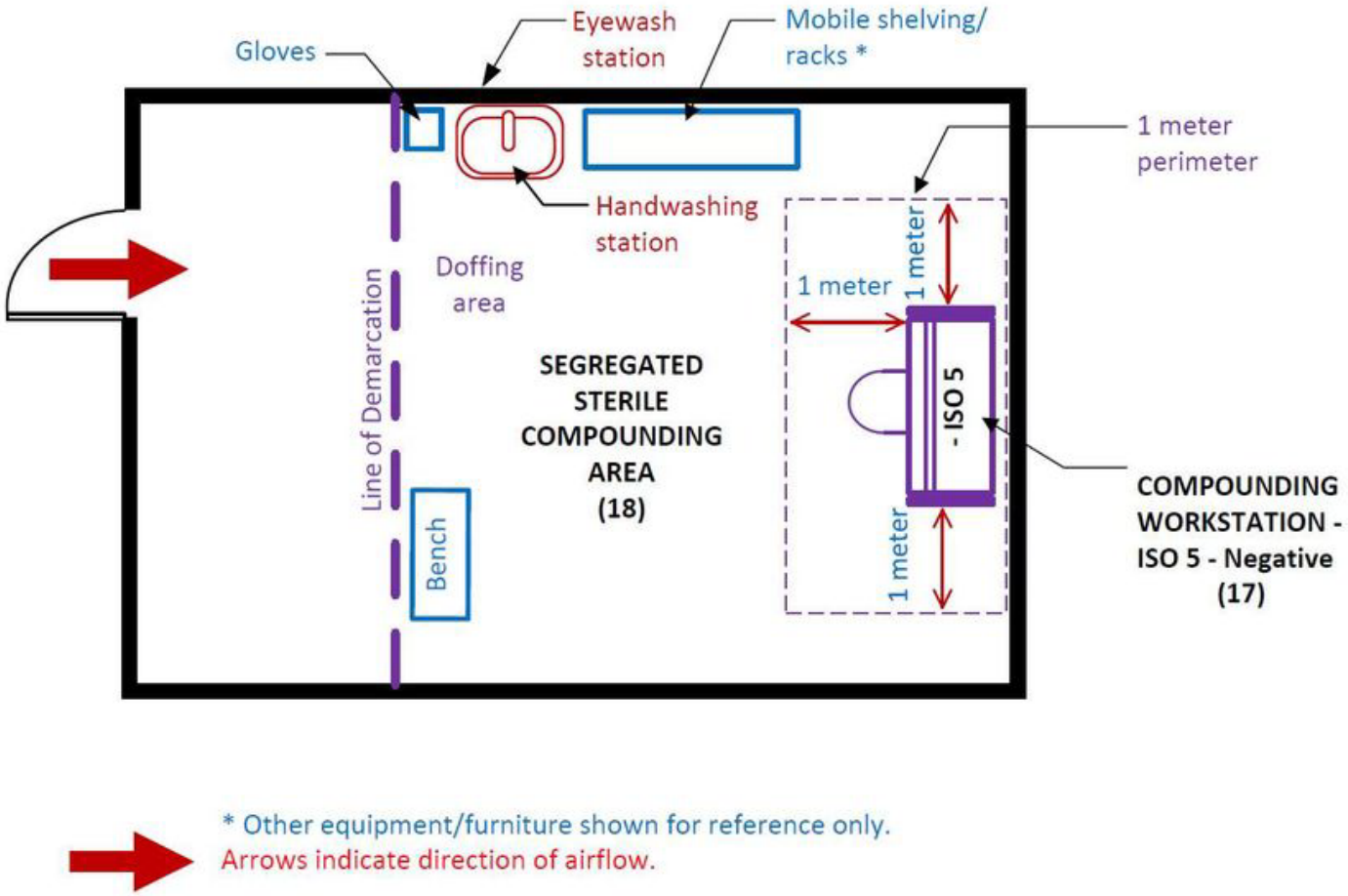
USP <797>

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

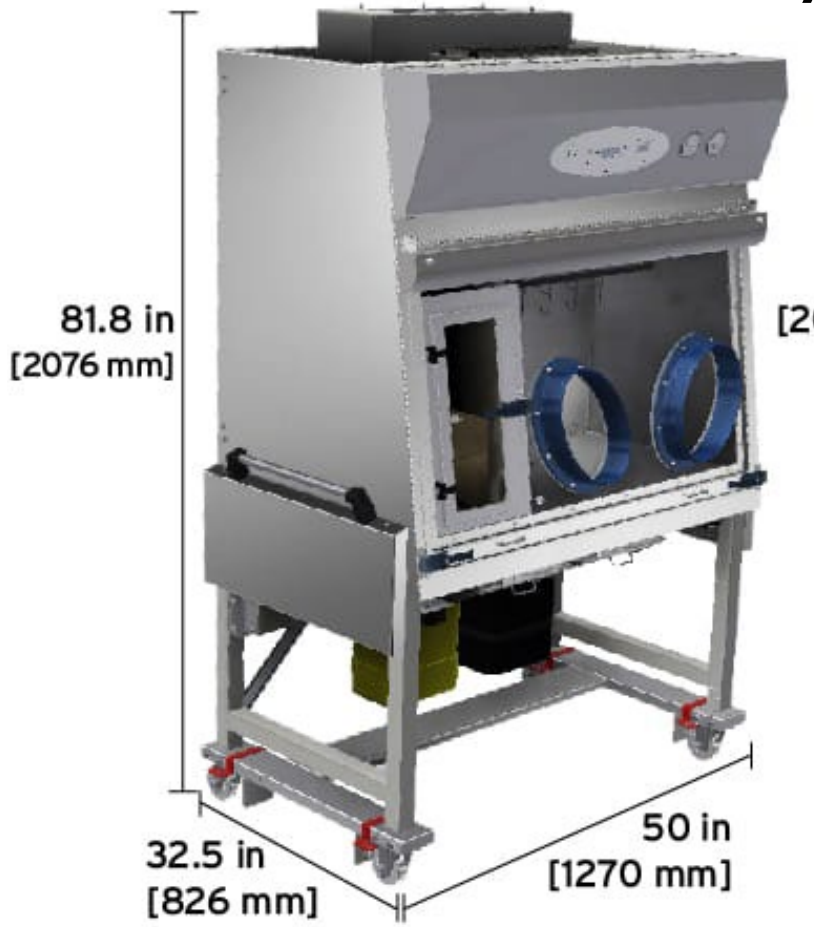


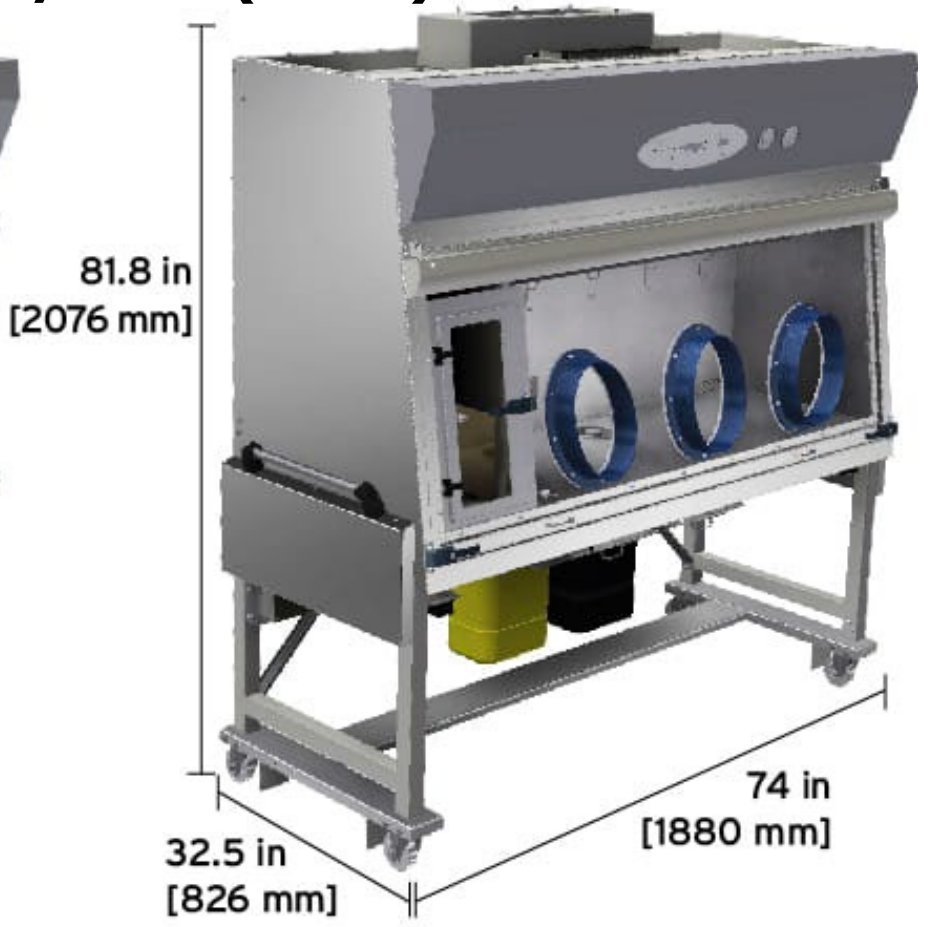
USP <797> Section 4. Facilities and Engineering Controls

- **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)

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?

Attachment 3

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) "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.

(b) "Compounding personnel" means any person involved with any procedure, activity or oversight of the compounding process.

(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.

(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.

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

(f) "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.

(g) "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.

(h) "Preparation" means a compounded drug or nutrient.

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

(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.

(k) "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 Sterile Compounding 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*.

(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.

(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.

(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. 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

(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 intended for use in a CSP for the intended patient population.

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

(4) Cannot be sterilized within the licensed location.

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

(f) 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.

(g) 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 competences 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 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.

(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.

(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.

(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.

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 non-removable piercings that increase the risk of contamination of CSP.

(c) Personal protective equipment shall be donned and removed in an ante-area or immediately outside the segregated compounding area (SCA). Donning and doffing garb shall not occur in the ante-room or the SCA 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 shall 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 (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.

(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-003-2006-13, 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, 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.

(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, current version-20XX-XX, 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 AGENTS IN COMPOUNDING AREAS and Sterile 70% IPA

The requirements of this section apply to performing sterile compounding in addition to the requirements in USP Chapter 797.

(a) Cleaning, disinfection, and sporicidal agents shall be used in accordance with manufacturers' specifications.

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

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 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.

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 be of suitable composition such that the surfaces which contact components are not reactive or sorptive.

(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 monthly and calibration shall take place at least every 12 months. SOPs shall specify the frequency and process 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 CNSP shall be used and stored in accordance with all federal laws and regulations and industry standards including the manufacturers' specifications and requirements.

(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.

(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.

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 and depyrogenation 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) The source 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 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 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.

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 compounding is responsible for the integrity, quality, and labeled strength of a compounded drug preparation until the beyond use date indicated on the label, so long as the label instructions for storage and handling are followed after the preparation is received by the patient or patient's agent.

(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 Chapter 85. 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) For admixed CSP, the solution utilized, and
- (3) Instructions for administration. For admixed CSP solutions, the rate of infusion, or range of rates of infusion, 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 except for pH-altering solutions.

(b) A CSP labeled with a BUD with only a date shall expire at midnight at 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 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.

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) Standard operating procedures (SOPs) 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 policies and procedures 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.

(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 policies and procedures 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 performing sterile compounding in addition to the requirements 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 pharmacy 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. 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.

(c) A pharmacist performing or supervising the sterile compounding by other authorized personnel is responsible for the integrity, quality, and labeled strength of a CSP until the beyond-use date indicated on the label so long as label instructions for storage and handling are followed after the preparation is

received by the patient or patient's agent.

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 and container closure integrity closure tests consistent with Chapter 1207. 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.