This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

Summary of USP 797 Proposed Changes July 2018

77 Pursuant to *General Notices, 2.30 Legal Recognition*, assuring compliance with *USP* standards is the responsibility of regulatory bodies. Accreditation or credentialing organizations may adopt and enforce *USP* standards. USP has no role in enforcement.

For guidance on administration of CSPs, see the Centers for Disease Control and Prevention's (CDC) *Safe Injection Practices to Prevent* 17 *Transmission of Infections to Patients.* Administration of medication, including withdrawal of doses, is out of the scope of this chapter.

23Preparation of non-hazardous CSPs for a single patient using only sterile starting ingredients when administration will begin within 1 hour of beginning the preparation (e.g., within 1 hour of initial entry into or
26 puncture of a single-dose container) is not required to meet the standards in this chapter.

134This chapter distinguishes two categories of CSPs, Category 1 and Category 2, primarily based on the conditions under which they are made, the probability for microbial growth, and the time period within which they must be used.

137 Category 1 CSPs are those assigned a BUD of 12 hours or less at controlled room temperature or 24 hours or less when refrigerated if made in accordance with all of the applicable requirements for Category 1 CSPs in this chapter.

140 Category 2 CSPs are those that may be assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours if refrigerated (see *12. Establishing Beyond-Use Dates*) if made in accordance with all of the applicable requirements for Category 2 CSPs in this chapter. See *Table 1* for a summary of the minimum requirements in this chapter for Category 1 and 2 CSPs.

Table 1. Summary of Minimum Requirements for Category 1 and Category 2 CSPs[a]

Category 1 CSPs	**Category 2 CSPs**
Personnel Qualifications	
Visual observation of hand hygiene and garbing	
Every 6 months	Every 6 months
Gloved fingertip and thumb sampling	
Every 6 months	Every 6 months
Media fill testing	
Every 6 months	Every 6 months
Requalification	
Every 12 months	Every 12 months

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

154**Buildings and Facilities**
Placement of the primary engineering control (PEC)

1 CSPs Category	**2 CSPs**
Not required placed in a classified area	Required placed in a classified area
Every 6 months for the PEC	Recertification Every 6 months for the PEC and secondary engineering control (SEC)
Nonviable airborne monitoring	
Every 6 months	Every 6 months

Microbiological Air and Surface Monitoring
Viable air sampling

1 CSPs Category	**2 CSPs**
Every 6 months	Every 6 months
Surface sampling (note change)	
Monthly	Monthly
Release Testing	
Visual inspection	
Required	Required
Sterility testing	
Not required	Based on assigned BUD
Endotoxin testing	
Not required	Based on assigned BUD (e.g., if sterility testing is required) and if prepared from nonsterile ingredient(s)
BUD assignment	
≤12 hours at controlled room temperature or ≤24hours if refrigerated (see *Table 11*)	>12 hours at controlled room temperature or >24 hours if refrigerated (see *Table 12*)

This table summarizes the requirements that apply specifically to Category 1 and Category 2 CSPs.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

2. PERSONNEL QUALIFICATIONS— TRAINING, EVALUATION, AND REQUALIFICATION

157All personnel involved in the compounding of CSPs must be initially trained and qualified by demonstrating proficiency in compounding CSPs. Personnel must complete **requalification every 12 months** in appropriate sterile compounding principles and practices. Training, evaluation, and requalification of personnel must be documented. Each compounding facility must develop a written training program that describes the required training, the frequency of training, and the process for evaluating the performance of individuals involved in preparing CSPs. This program should equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks.

2.1 Demonstrating Proficiency in Core Competencies

168Before beginning to prepare CSPs independently, all compounding personnel must complete training and be able to demonstrate knowledge of theoretical principles and proficiency of skills for performing sterile manipulations and achieving and maintaining appropriate environmental conditions. Competency must be demonstrated in at least the following:

- 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 (e.g., master formulation and compounding records)
- Principles of high-efficiency particulate air (HEPA)-filtered unidirectional airflow within the ISO Class 5 area
- Proper use of primary engineering control (PECs)
- Principles of movement of materials and personnel within the compounding area.

All compounding personnel must demonstrate competency through written testing and proficiency through hands-on demonstration of skills **every 12 months**. Any other personnel handling CSPs and/or accessing the compounding area must complete training and demonstrate competency in maintaining the quality of the environment in which they are performing their assigned task. The designated person must ensure that any person who enters the sterile compounding area maintains the quality of the environment.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

195 2**.2 Demonstrating Competency in Garbing and Hand Hygiene**
All compounding personnel **must be visually observed every 6 months** by a qualified person while performing hand hygiene and garbing procedures
(see 198 *3. Personal Hygiene and Garbing*). The **visual audit must be documented** and the documentation maintained to provide a record of personnel competency.
Gloved fingertip and thumb sampling is important because direct touch contamination is the most likely source of microorganisms. Initial gloved fingertip and thumb sampling evaluates a compounder's competency in correctly performing hand hygiene and garbing (see *Box 2-1*)**. Before being allowed to independently compound, all compounders must successfully complete an initial competency evaluation, including visual observation and gloved fingertip and thumb sampling, no fewer than 3 separate times**. Each fingertip and thumb evaluation must occur after performing a separate and complete hand hygiene and full garbing procedure. **After the initial competency evaluation**, compounding personnel must successfully **complete gloved fingertip and thumb sampling every 6 months after completing the media-fill test.**

Successful completion of initial gloved fingertip and thumb sampling is defined as zero colony-forming units (cfu).
Successful completion of subsequent gloved fingertip and thumb sampling after media-fill testing is defined as ≤3 cfu. Action levels for gloved fingertip and thumb sampling results are shown in *Table 2*.

Table 2. Action Levels for Gloved Fingertip and Thumb Sampling
Gloved Fingertip and Thumb Sampling Action Levels (total number of cfu on both hands)

Initial sampling after garbing ≥1
Subsequent sampling after media-fill testing (every 6 months) >3
Action levels are based on the total cfu count on both hands.

Initial gloved fingertip and thumb sampling must be performed on donned sterile gloves in the ISO Class 7 buffer room or segregated compounding area (SCA). Subsequent gloved fingertip and thumb sampling must be performed on donned sterile gloves inside of an ISO Class 5 PEC.

If conducting gloved fingertip and thumb sampling in a compounding aseptic isolator (CAI), compounding aseptic containment isolator (CACI), or an isolator, samples must be taken from the sterile gloves placed over the gauntlet gloves.

225 **Box 2-1. Gloved Fingertip and Thumb Sampling Procedures**
• Use one sampling device per hand (e.g., plates, paddles, or slides) containing general microbial growth agar [e.g., trypticase soy agar (TSA)] supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) as this agar supports both bacterial and fungal growth.

• Label each contact sampling device with a personnel identifier, whether it was from the right or left hand, and the date and time of sampling.

• Do not disinfect gloves immediately before touching the sampling device because this could cause a false-negative result. (1)Hank note standard procedure may call for this decontamination step this approach leads to false positives
• Using a separate sampling device for each hand, collect a gloved fingertip and thumb sample from both hands by rolling finger pads and thumb pad over the agar surface.
• Incubate the sampling device at a temperature of 30°–35° for no less than 48 hours and then at 20°–25° for no less than 5 additional days. If using plates or slides, invert them during incubation to prevent condensate from dropping onto the agar and affecting the accuracy of the cfu reading.
• Record the number of cfu per hand (left hand, right hand).
• Determine whether the cfu action level is exceeded by counting the total number of cfu on both hands.

2.3 Competency Testing in Aseptic Manipulation

227After successful completion of the initial hand hygiene and garbing competency evaluation, all compounding personnel must have their sterile technique and related practices evaluated during a media-fill test (see *Box 2-2*). When performing a media-fill test, use the most difficult and challenging compounding procedures and processing conditions encountered by the person during a work shift (e.g., the most manipulations, most complex flow of materials, longest time to compound, size of batch), replacing all the components used in the CSPs with soybean–casein digest media. If using a commercial sterile microbial growth medium, either verify that the growth medium is growth promoting (see *Sterility Tests ⟨71⟩, Culture Media and Incubation Temperatures, Growth Promotion Test of Aerobes, Anaerobes, and Fungi*), or obtain a certificate of analysis (COA) from the supplier of the growth medium to ensure that it will support the growth of microorganisms. Store microbial growth media in accordance with manufacturer instructions and use before the expiration date. If preparing a sterile microbial growth medium in-house, the growth promotion capability of the medium must be demonstrated for each batch and documented (see 2⟨71⟩).

Failure is indicated by visible turbidity or other visual manifestations of growth in the medium in one or more container–closure unit(s) on or before the end of the incubation period. Investigate media-fill failures to determine possible causes (e.g., sterilizing filter failure ??). Evaluation results must be documented and the documentation 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 expiration date and lot number, the results, and the signatures of the person evaluated and the observer.

256 **Box 2-2. Media-Fill Testing Procedures**

If all of the starting components are sterile to begin with, manipulate
them in a manner that simulates sterile-to-sterile compounding activities, and transfer the sterile soybean–casein digest media into the same types of container–closure systems commonly used at the facility. Do not further dilute the media unless specified by the manufacturer.
• If some of the starting components are nonsterile to begin with, use a nonsterile soybean–casein digest powder to make a solution. The solution must be prepared according to *Sterility Tests ⟨71⟩, Culture Media and Incubation Temperatures*. Manipulate it in a manner that simulates nonsterile-to-sterile compounding activities.

• Once the compounding simulation is completed and the final containers are filled with the test media, incubate them in an incubator for 7 days at 20°–25° followed by 7 days at 30°–35° to detect a broad spectrum of microorganisms. Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container–closure unit(s) on or before 14 days.

2.4 Reevaluation, Retraining, and Requalification

258 REQUALIFICATION AFTER FAILURE

Personnel who fail the visual observation of hand hygiene, garbing, and/or aseptic technique; gloved fingertip and thumb sampling; and/or media-fill testing must successfully pass reevaluations in the deficient area(s) before they can resume compounding of sterile preparations. The designated person must identify the cause of failure and determine appropriate retraining requirements. All failures, retraining, and reevaluations must be documented.

REQUALIFICATION PROGRAM

267Compounding personnel must successfully complete requalification **every 12 months in the core competencies** listed in *2.1 Demonstrating Proficiency in Core Competencies*. Successful completion must be demonstrated through written testing and hands-on demonstration of skills.

271TIMING OF REEVALUATION AND REQUALIFICATION

Visual observation: Compounding personnel must be visually observed while performing hand hygiene and garbing procedures initially, and then at least every 6 months.
Gloved fingertip and thumb sampling: Compounding personnel must perform fingertip and thumb sampling 3 times initially and then every 6 months (in conjunction with media-fill testing).

278**Media-fill testing:** After initial qualification, conduct a media-fill test of all personnel engaged in compounding CSPs at least every 6 months (in conjunction with gloved fingertip and thumb sampling).
Cleaning and disinfecting: Retrain and requalify personnel in cleaning and disinfecting compounding areas in conjunction with any change(s) in cleaning and disinfecting procedures.
After a pause in compounding: Personnel who have not compounded CSPs in more than 6 months must be requalified in all core competencies before they may resume compounding duties.

288 **3. PERSONAL HYGIENE AND GARBING**

Personal hygiene and garbing are essential to maintaining microbial control of the environment. Most microorganisms detected in cleanrooms are transferred from individuals. Squamous cells are normally shed from the human body at a rate of 10_6 or more per hour, and those skin particles are covered with microorganisms.[1,2] To minimize contamination of the environment and CSPs, individuals entering a compounding area must be properly garbed and must maintain proper personal hygiene.

Individuals that may have a higher risk of contaminating the CSP and the environment (e.g., personnel with rashes, sunburn, recent tattoos, oozing sores, conjunctivitis, or active respiratory infection) must report these conditions to their supervisor. The designated person is responsible for evaluating whether these individuals should be excluded from working in compounding areas before their conditions have resolved because of the risk of contaminating the CSP and the environment.

3.1 Personnel Preparation

304 Individuals entering a compounding area must take appropriate steps to minimize microbial contamination of the environment and the CSPs, including hand hygiene (*3.2 Hand Hygiene*), garbing (*3.3 Garbing Requirements*), and consideration of needed materials to be brought into the compounding area. Before entering a compounding area, individuals must remove any items that are not easily cleanable or that are not necessary for compounding. At a minimum, individuals must:

- Remove personal outer garments. (new)
- Remove all cosmetics because they shed flakes and particles.
- Remove all hand, wrist, and other exposed jewelry including piercings 314 that could interfere with the effectiveness of garbing (e.g., the fit of gloves, cuffs of sleeves, and eye protection) or otherwise increase the risk of contamination of the CSP. Cover any jewelry that cannot be removed.
- Not wear ear buds or headphones.
- Not bring electronic devices that are not necessary for compounding or other required tasks into the compounding area.
- Keep nails clean and neatly trimmed to minimize particle shedding and avoid glove punctures. Nail polish, artificial nails, and extenders must not be worn.

Additional restrictions on items may be necessary based on the risk of contaminating the environment and the CSP.

3.2 Hand Hygiene

327 Hand hygiene must be performed before entering a compounding area (see *Box 3-1*). Alcohol hand sanitizers alone are not sufficient for washing hands and forearms. All hygiene products must be used sequentially and not concurrently because of potential chemical incompatibilities and adverse dermatologic reactions. Brushes must not be used for hand hygiene because of the potential for skin irritation and increased bacterial shedding. Hand driers must not be used because of the risk of creating air turbulence and circulating contamination in the compounding area. Perform hand hygiene after donning shoe covers, head and facial hair covers, and a face mask. [NOTE—The order of garbing must be determined the facility and documented in the facility's standard operating procedure (SOP).] After hands are washed and dried, don remaining garb except sterile gloves, and then perform hand antisepsis using an alcohol-based hand rub with persistent antimicrobial activity immediately before donning sterile gloves. [NOTE—Soap must not be added to a partially empty soap dispenser. This practice of "topping off" dispensers can lead to bacterial contamination of soap.]

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

Box 3-1. Hand Hygiene Procedures

345• Remove debris from underneath fingernails under warm running water using a disposable nail cleaner. Wash hands and forearms up to the elbows with soap and water for at least 30 seconds.

• Dry hands and forearms to the elbows completely with low-lint disposable towels or wipes.

• Apply an alcohol-based hand rub with persistent antimicrobial activity to dry skin, following the manufacturer's instructions for application times, and use a sufficient amount of product to keep the hands wet for the duration of the application time.

• Allow hands to dry thoroughly before donning sterile gloves.

3.3 Garbing Requirements

346 Personnel intending to enter a buffer room or SCA must be properly garbed. Garb must be put on in an order that reduces the risk of contamination. The order of garbing must be determined by the facility and documented in the facility's SOP. Donning and doffing garb must not occur in the ante-room or the SCA at the same time.

The **minimum garbing requirements for preparing CSPs include:**

• Non-cotton, low-lint garment with sleeves that fit snugly around the wrists and that is enclosed at the neck

• Low-lint, disposable covers for shoes

• Low-lint, disposable covers for head that cover the ears and forehead

• Face mask (vision problem)

• Low-lint, disposable covers for all facial hair

• Sterile gloves

• If using a restricted-access barrier system (RABS), such as a CAI or CACI, disposable gloves (e.g., cotton, either nonsterile or sterile) must be worn inside gauntlet gloves and sterile gloves must worn over gauntlet gloves (new)

Gowns and other garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing). Garb must be replaced immediately if it becomes visibly soiled or if its integrity is compromised. When personnel exit the compounding area, **garb cannot be reused and must be discarded. (new)**

If compounding an HD, appropriate personal protective equipment (PPE) must be worn in accordance with ⟨800⟩.

GLOVES Hank note this is not consistent with fingertip testing see box 2.1

371 Gloves must be sterile and powder free. Application of sterile 70% isopropyl alcohol (IPA) to gloves must occur throughout the compounding process and whenever nonsterile surfaces (e.g., vials, counter tops, chairs, or carts) are touched.

Contaminated gloved hands can be disinfected by rubbing sterile 70% IPA onto all contact surface areas of the gloves and letting the gloves dry thoroughly.

Gloves on hands and gauntlet sleeves on RABS and isolators must be inspected routinely for holes, punctures, or tears and must be replaced immediately if such defects are detected.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

4. FACILITIES AND ENGINEERING CONTROLS

382 Sterile compounding facilities must be designed, outfitted, and maintained properly to minimize the risk of contamination of CSPs. The required air quality must be achieved and maintained through PECs and secondary engineering controls (SECs). The ante-room, buffer room, and SCA must be separated from areas not directly related to compounding and must be appropriately controlled to achieve and maintain the required air quality classifications. The design of the facility should take into account the number of personnel and their movements, and the equipment, supplies, and components to maintain and facilitate the maintenance of air quality. The number of operations being performed, the equipment (e.g., PECs, carts, computers etc.), the personnel in the compounding area (and in adjacent areas), and the complexity of the compounding procedures are critical considerations for maintaining control of environmental conditions in the facility.

4.1 Protection from Airborne Contaminants

397 Sterile compounding facilities must be designed to minimize the risk of airborne contamination of the area in which sterile compounding occurs. Proper design and controls are required to minimize the risk that CSPs will be exposed to airborne contaminants that may cause microbial contamination.

AIR QUALITY STANDARDS

403 The ISO standards for air quality in controlled environments are provided in *Table 3* and referenced throughout this chapter.

Table 3. ISO Classification of Particulate Matter in Room Air ISO Class Particle Count

[a] Adapted from ISO 14644-1, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration. [b] Limits for number of particles ≥0.5 µm measured under dynamic operating conditions.

DESIGN REQUIREMENTS TO MAINTAIN AIR QUALITY

407 Facilities used for compounding CSPs must be designed so that air quality improves with movement through separate operational areas to the PEC. Classified areas in which the air quality is controlled (see *Table 3*) include ante-rooms, buffer rooms, and PECs.

- Ante-rooms providing access to positive pressure buffer rooms must meet at least ISO Class 8 classification. Ante-rooms providing access to negative pressure buffer rooms must meet at least ISO Class 7 classification (see ⟨800⟩). Typically, personnel hand hygiene and garbing procedures, staging of components, and other activities that potentially generate higher levels of particulates are performed in the ante-room. Ante-rooms are also transition areas to ensure that proper air classification and pressure relationships are maintained between designated areas.
- A buffer room must meet at least ISO Class 7 air quality. Activities in the buffer room must be controlled to minimize any effects on air quality in the area where CSPs are prepared.
- CSPs must be prepared in an ISO Class 5 or better PEC.

If compounding only Category 1 CSPs, the PEC may be placed in an unclassified SCA.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

4.2 Facility Design and Environmental Controls

427In addition to minimizing airborne contamination, sterile compounding facilities must be designed and controlled to provide a well-lighted and comfortable working environment (see *Physical Environments That Promote Safe Medication Use* ⟨1066⟩). The cleanroom suite should be continuously maintained at a temperature of 20° or cooler and a relative humidity below 60% to minimize the risk for microbial proliferation and provide comfortable conditions for compounding personnel attired in the required garb**. The temperature and humidity must be monitored in the cleanroom suite each day that compounding is performed, either manually or by a continuous recording device, and the results must be readily retrievable, reviewed by the designated person, and documented.** Temperature and humidity in the cleanroom suite must be controlled through an efficient heating, ventilation, and air conditioning (HVAC) system. **Free-standing humidifiers/dehumidifiers and air conditioners must not be used within the classified area.**

Temperature monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer. (2) hank note -no requirement for verification of humidity monitoring devices)

A person or persons must be designated as the person responsible for ensuring that each area related to CSP preparation meets the classified air quality standard appropriate for the activities to be conducted in that area. They must also ensure that the ISO Class 5 areas are located, operated, maintained, monitored, and certified to have appropriate air quality.

448TYPES OF SECS AND DESIGN

The PEC must be located in an SEC, which may be either a cleanroom suite (buffer room with ante-room) or an SCA (see *Appendix 2: Example Designs for Sterile Non-Hazardous Compounding Areas* for examples of facility designs).

453**Cleanroom suite:** The ISO-classified ante-room must be separated from the surrounding unclassified areas of the facility by fixed walls and doors, and controls must be in place to minimize the flow of lower-quality air into the more controlled areas. Air supply to the cleanroom suite must be introduced through HEPA filters that are located in the ceiling of the buffer and ante-rooms. Returns must be low on the wall unless **a visual smoke study demonstrates dilution of particles and sweeping out of particles from the entire room.** This smoke study must be repeated whenever a change to the placement of the PEC within the room is made. The **classified rooms must be equipped with a pressure-differential monitoring system**. The ante-room must have a line of demarcation to separate the clean side from the dirty side. The ante-room is entered through the dirty side, and the clean side is the area closest to the buffer room. Required garb must be worn on the clean side of the line of demarcation (see *3. Personal Hygiene and* 467 *Garbing*).

468 **Segregated compounding area (SCA):** A PEC may be located within an unclassified area, without an ante-room or buffer room. This type of design is called an SCA. **Only Category 1 CSPs can be compounded in an SCA.** The SCA must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, all of which may adversely affect the air quality in the PEC. An SCA must not be located adjacent to environmental control challenges

(e.g., restrooms, warehouses, or food preparation areas). The impact of activities that will be conducted around or adjacent to the SCA must be considered carefully when designing such an area. A visible perimeter must establish the boundaries of the SCA.

The PEC must be located in the buffer room of the cleanroom suite or the SCA in a manner that minimizes conditions that could increase the risk of microbial contamination. For example, strong air currents from opened doors, personnel traffic, or air streams from the HVAC system(s) can disrupt the unidirectional airflow of an open-faced PEC such as a laminar airflow workbench (LAFW). Access to the SEC must be restricted to authorized personnel and required materials. It is also critical to control materials (e.g., supplies and equipment) as they move from classified areas of lower quality to those of higher quality (e.g., ISO Class 8 ante-room to ISO Class 7 buffer room to ISO Class 5 PEC) to minimize the influx of contaminants. Airlocks and interlocking doors can be used to facilitate better control of air balance between areas of differing ISO classification (e.g., between the buffer room and ante-room), or between a classified area and an unclassified area (e.g., between the ante-room and an unclassified area such as a hallway). If a pass-through is used, both doors must never be opened at the same time, and doors should be interlocking.

Due to the interdependence of the various rooms or areas that make up a sterile compounding facility, it is essential to carefully define and control the dynamic interactions permitted between areas and rooms. When designing doors, consider the placement of door closures, door surfaces, and the movement of the doors, all of which can affect airflow. Seals and sweeps should not be installed at doors between buffer and ante-rooms. Access doors should be hands-free. Tacky surfaces must not be used in ISO- classified areas.

THE CSP COMPOUNDING ENVIRONMENT

503The PEC must be certified to meet ISO Class 5 or better conditions (see *Table 3*) during dynamic operating conditions and must be designed to prevent contamination during compounding of CSPs. Unidirectional airflow must be maintained in the PEC. HEPA-filtered air must be supplied to the PEC at a velocity sufficient to sweep particles away from critical sites and maintain unidirectional airflow during operations. Proper design, control, and use minimize turbulence and creation of eddies or stagnant air in the PEC.

TYPES OF PECS AND PLACEMENT

512 Proper placement of the PEC is critical to ensuring an ISO Class 5 environment for preparing CSPs. Placement of the PEC must allow for cleaning around the PEC. See *Table 4* for a summary of minimum requirements for the placement of PECs for preparing non-HD CSPs.

Types of PEC and their placement include:

517 **Laminar airflow system (LAFS):** An LAFS provides an ISO Class 5 or better environment for sterile compounding. The LAFS provides unidirectional HEPA-filtered airflow that is designed to prevent contamination of a sterile compounding environment. The unidirectional airflow within the LAFS helps protect the direct compounding area (DCA) from process-

generated contamination (e.g., opening wrappings of sterile containers, compounder movement, etc.) as well as from outside sources. *Types of LAFS:* Examples of LAFS include LAWFs, integrated vertical laminar flow zones (IVLFZs), and biological safety cabinets (BSCs).

LAMINAR AIRFLOW WORKBENCH (LAFW): An LAFW is a device that provides an ISO Class 5 or better environment for sterile compounding. The LAFW provides either horizontal or vertical unidirectional HEPA-filtered airflow. [NOTE—An LAFW must not be used for preparation of antineoplastic and/or active pharmaceutical ingredient (API) HDs (see ⟨800⟩).]

INTEGRATED VERTICAL LAMINAR FLOW ZONE (IVLFZ): An IVLFZ is a designated ISO Class 5 area serving as the PEC within an ISO Class 7 or cleaner buffer room. In the IVLFZ, unidirectional airflow is created by placing HEPA filters in the ceiling over stainless steel work tables. The unidirectional HEPA-filtered zone must be separated from the ISO Class 7 area with a physical barrier located at the ceiling to direct the airflow downward over the work area to separate the DCA from potential sources of contamination. [NOTE— Smoke studies have shown that it is difficult to achieve this type of design and also achieve and maintain unidirectional airflow under dynamic operating conditions.] [NOTE—A IVLFZ must not be used for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

542 CLASS II BIOLOGICAL SAFETY CABINET (BSC): A Class II BSC is a ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered (3)Hank note studies have shown that airflow in a BSC is not unidirectional airflow and HEPA-filtered exhaust. The BSC is designed to provide worker protection from exposure to airborne drugs and to provide an ISO Class 5 or better environment for preparing CSPs. [NOTE—The exhaust air from the BSC must be externally vented for preparation of antineoplastic and/or API HDs (see ⟨800⟩).]

549 *Placement of LAFS:* The LAFS must be located out of traffic patterns and away from room air currents that could disrupt the intended airflow patterns inside the PEC. **If used to prepare only Category 1 CSPs, the ISO Class 5 PEC may be located in an unclassified SCA(new)**. If used to prepare Category 2 CSPs, the LAFS must be located within a cleanroom suite with an ISO Class 7 or better buffer room and ISO Class 8 or better ante-room. A dynamic airflow smoke pattern test must be performed initially and at least every 6 months to ensure that 1) the LAFS is properly placed into the facility, and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA.

559 **Restricted-access barrier system (RABS):** A RABS is an enclosure that provides HEPA-filtered ISO Class 5 unidirectional air. It 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 compounding operations.

564*Types of RABS:* Examples of RABS include CAIs and CACIs. In a CAI or CACI, glove ports are used to provide physical separation between the surrounding area and the aseptic manipulations.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

567 COMPOUNDING ASEPTIC ISOLATOR (CAI): A CAI is designed for compounding non-HD CSPs. It is designed to maintain an ISO Class 5 environment throughout the compounding and material transfer processes. Air exchange into the CAI from the surrounding environment must not occur unless the air has first passed through a HEPA filter.

572 COMPOUNDING ASEPTIC CONTAINMENT ISOLATOR (CACI): A CACI is designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes, and to maintain an ISO Class 5 environment for compounding sterile HD preparations (see ⟨800⟩). Air exchange with the surrounding environment must not occur unless it is first passed through a HEPA filter capable of containing airborne concentrations of the physical size and state of the drug being compounded.

580 *Placement of RABS:* If used to prepare only Category 1 CSPs, the ISO Class 5 environment may be achieved by placing the RABS in an unclassified SCA. If used to prepare Category 2 CSPs, the RABS must be located within a cleanroom suite with an ISO Class 7 or better buffer room and an ISO Class 8 or better ante-room. All transport ports on the RABS must be closed during compounding. **When a RABS is used, the recovery time after opening to achieve ISO Class 5 air quality must be documented**, and internal procedures must be developed to ensure that adequate recovery time is allowed after opening and closing the RABS, both before and during compounding operations. An airflow smoke pattern test must be performed under dynamic operating conditions initially and at least every 6 months to ensure that the RABS is properly integrated into the facility and that the compounder understands how to utilize the unidirectional airflow to maintain first air in the DCA. For placement of a CACI used for the preparation of antineoplastic and/or API HDs, see ⟨800⟩

595 **Isolator:** An isolator provides isolation from the surrounding area and 596 maintains ISO Class 5 air quality during dynamic operating conditions. **A CAI or CACI is not an isolator.** An isolator comprises four elements (see ISO 14644-7):
1.Controlled workspace: This is the defined volume that is created by using a combination of aerodynamic and physical means of separation, in order to achieve the necessary means of assurance of maintaining separation.
2. Transfer device(s): This is the means whereby materials are transferred in and out of the work zone. There is a range of transfer devices including simple doors, air-purged transfer chambers, and double door transport ports. It should be possible to demonstrate that unfiltered air from the environment cannot enter the isolator during decontamination or compounding procedures.
3. Access device(s): This is the means whereby the activity or process in the work zone is carried out. Access devices include gloves and gauntlets for the operator and/or remote controlled robotic devices.
4. Decontamination system: This is the means of decontaminating the isolator itself and materials entering and leaving it using a generator that distributes a sporicidal agent throughout the chamber.

Placement of Isolators: An isolator used to prepare only Category 1 CSPs can be placed in an unclassified SCA. If the isolator is used to prepare Category 2 CSPs, the area surrounding the isolator must at minimum be placed in an ISO Class 8 or better air quality buffer room. [NOTE—

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

An ante- room is not required when using an isolator.] A dynamic airflow smoke pattern test must be performed initially and at least every 6 months to ensure that the isolator is properly placed into the facility and that the designated person and compounder understand how to utilize the unidirectional airflow to maintain first air in the DCA. For placement of an isolator used for the preparation of HDs, see ⟨800⟩. (4)Hank note no mention isolator placement in USP 800.

625**Table 4. Summary of Minimum Requirements for Placement of PEC for Compounding Non-HD CSPs**[a] **PEC Type Device Type Placement for Compounding**

		Category 1CSPs	Category 2 CSPs
LAFS			
LAFW	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room	
IVLFZ	N/A	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room	
BSC	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room	
RABS			
CAI/ CACI	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room	
Isolator			
Isolator	Unclassified SCA	ISO Class 8 positive pressure room	

[a] For compounding HDs, refer to ⟨800⟩.
[b] An IVLFZ must not be used in an unclassified area.

If a robotic enclosure is used as the PEC, a dynamic smoke visualization test must be performed initially and every 6 months thereafter to ensure that it is properly integrated into the facility, that there is no turbulence or refluxing at any critical site, that room air does not enter the PEC where sterile products and/or preparations may be exposed, and that all processes can be performed without introducing contamination to the DCA(s).

633 AIR EXCHANGE REQUIREMENTS
For cleanroom suites, adequate HEPA-filtered airflow to the buffer room(s) and ante-room(s) is required to maintain the appropriate ISO classification during compounding activities. Airflow is measured in terms of the number of air changes per hour (ACPH). The ACPH may need to be higher to maintain the required ISO classification and microbial state of control depending on these factors: number of personnel permitted to work in the area, number of particulates that may be generated from activities and processes in the area, the equipment located in the room, the room pressure, and the effects of temperature.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

See *Table 5* for a summary of ACPH requirements for non-HD sterile compounding areas. **A minimum of 30 total HEPA-filtered ACPH must be supplied to ISO Class 7 rooms**:
• The total HEPA-filtered air change rate must be adequate to maintain ISO Class 7 during dynamic operating conditions considering the factors listed above
• At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling
• The HEPA-filtered air from the PEC, when added to the HVAC-supplied HEPA-filtered air, increases the total HEPA-filtered ACPH to at least30 ACPH
• If the PEC is used to meet the minimum total ACPH requirements, the PEC must not be turned off except for maintenance
• The ACPH from HVAC, ACPH contributed from the PEC, and **the total ACPH must be documented on the certification report**
A minimum of 20 ACPH of HEPA-filtered air must be supplied to ISO Class 8 rooms from the HVAC through HEPA filters that are located in the ceiling:
• The total HEPA-filtered air change rate must be adequate to maintain ISO Class 8 under dynamic operating conditions considering the factors listed above
• Ante-rooms where activity levels are high may require more HEPA-filtered ACPH to maintain ISO Class 8 under dynamic operating conditions

667**Table 5. Summary of ACPH Requirements for Non-HD Sterile Compounding Areas**
Compounding Area ACPH Requirement
Unclassified SCA No requirement: ISO Class 7 room(s)≥30 ACPH: ISO Class 8 room(s) ≥20

ESTABLISHING AND MAINTAINING PRESSURE DIFFERENTIALS
670Continuous differential positive pressure is required to minimize airflow from an area with lower air-quality classification to an area of higher air- quality classification**. In a cleanroom suite, a minimum differential positive pressure of 0.02-inch water column is required between each ISO classified area (e.g., between the buffer room and ante-room). The pressure differential between the ante-room and the unclassified area must not be less than 0.02-inch water column. No pressure differential is required between the SCA and the surrounding area. See ⟨800⟩ for pressure requirements for compounding HD CSPs.**
(5 Hank note there is no requirement in terms accuracy for the pressure control or measurement instruments)

In a cleanroom suite, a pressure differential monitoring system must be used to **continuously monitor the pressure differential** between the ante-room(s) and buffer room(s) and between the ante-room and the general environment outside the classified room(s) or area(s). The **results from the pressure monitoring system must be reviewed and documented at least daily on the days when compounding is occurring.** All pressure monitoring devices must be **tested for accuracy and performance at least every 6 months.**

686 FACILITIES PREPARING CSPS FROM NONSTERILE STARTING INGREDIENT(S) OR COMPONENT(S)
If preparing a Category 2 CSP from nonsterile ingredient(s) or components(s), **presterilization procedures, such as weighing and mixing, must be completed in no worse than an ISO**

Class 8 environment. **Presterilization procedures must be performed in a containment ventilated enclosure (CVE), BSC, or CACI to minimize the risk of airborne contamination.** **Hank 795** Presterilization procedures must not adversely affect the required air quality of the SEC as demonstrated during certification under dynamic operating conditions. Personnel must follow the hygiene and garbing requirements as described in *3. Personal Hygiene and Garbing* during presterilization procedures.

698 **4.3 Creating Areas to Achieve Easily Cleanable Conditions**

CLEANROOM SUITE - The surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified area must be smooth, impervious, free from cracks and crevices, and non-shedding so they can be easily cleaned and disinfected and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces should be resistant to damage by cleaning agents, disinfectants, and tools used to clean. Junctures between the ceiling and the walls and between the walls and the floor must be sealed to eliminate cracks and crevices where dirt(change word to contamination) can accumulate. If ceilings consist of inlaid panels, the panels must be caulked or otherwise sealed and secured around each panel to seal them to the support frame. Ceiling panels must be washable, scrubbable(??) and soil resistant, and designed for use in a cleanroom environment. Walls must be constructed of, or may be covered with, durable material (e.g., epoxy painted walls or heavy-gauge polymer) and the integrity of the surface must be maintained. Panels must be joined together and sealed to each other and the support structure. Floors must be smooth, sealed (e.g., with continuous, welded seams), and impervious. Floors must include coving to the sidewall. Classified areas should minimize dust-collecting overhangs such as utility pipes and ledges such as window sills. If overhangs or ledges are present, they must be easily cleanable. The exterior lens surface of ceiling light fixtures must be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls must be sealed.

723 SCA - The SCA and all surfaces (e.g., walls, floors, counters, and equipment) in the SCA must be clean, uncluttered, and dedicated to compounding. Surfaces in the SCA should 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. Surfaces should be resistant to damage by cleaning agents, disinfectants, and tools used to clean. Dust-collecting overhangs such as utility pipes and ledges such as windowsills should be minimized. If overhangs or ledges are present, they must be easily cleanable.

734 4.4 Water Sources - The facility where CSPs are prepared must be designed so that activities such as hand hygiene and garbing will not adversely affect the ability of the PEC to function as designed. Sinks should enable hands-free use with a closed system of soap (i.e., non-refillable container) to minimize the risk of extrinsic contamination. **In facilities with a cleanroom suite, the sink used for hand hygiene may be placed either inside or outside of the ante-room**. The buffer room must not contain sink(s), eyewash(es), shower(s), or floor drain(s). The ante-room must not contain floor drain(s). If installed, sprinkler systems should be recessed and covered, and must be easily cleanable. In a facility with an **SCA design, the sink**

must be accessible but located at least 1 meter away from the PEC. The sink must not be located inside the perimeter of the SCA.

746 **4.5 Placement and Movement of Materials**

Only furniture, equipment, and other materials necessary for performing compounding activities are permitted in the classified area or SCA, and they should be low-shedding and easily cleaned and disinfected. Their number, design, location, and manner of installation must not impact environmental air quality and must promote effective cleaning and disinfecting. Certain items are not permitted on the clean side of ante-room(s) and in buffer room(s), including, but not limited to, corrugated cardboard, external shipping containers, and nonessential paper (e.g., paper towels and tissues).

Carts used to transport components or equipment into classified areas must be constructed from nonporous materials with cleanable casters and wheels to promote mobility and ensure ease of cleaning and disinfection. All items must be wiped with low-lint wipers and an appropriate disinfectant by personnel wearing gloves before they are brought into the clean side of ante-room(s), placed into pass-through(s), or brought inside the perimeter of the SCA.

In a cleanroom suite, carts must not be moved from the dirty side to the clean side of the ante-room unless the entire cart, including casters, is cleaned and disinfected.

Only equipment necessary for performing compounding activities is permitted in the PEC. Proper placement of equipment in a PEC must be verified by a smoke visualization study under dynamic operating conditions to verify that there is minimal disruption in airflow.

Equipment and other items used in a classified area or an SCA should not be removed except for calibration, servicing, cleaning, or other activities associated with maintenance. If removed, these items must be cleaned and disinfected before they are returned to the classified area or inside the perimeter of the SCA.

7734**.6 Certification and Recertification**

Before a compounding area is used to compound either Category 1 or Category 2 CSPs, it must be certified using procedures in the current Controlled Environment Testing Association (CETA) certification guide for *Sterile Compounding Facilities* or an equivalent guideline. (Hank note certification procedures contained in CETA CAG-002 2006 contain a health risk that has been reported to USP and OSHA) Certification indicates that the compounding area is meeting its design and air quality specifications (see *Table 3*). It is important to place special emphasis on certifying the ISO Class 5 areas. Certification of the classified areas including the PEC must be performed initially, and recertification must be performed at least every 6 months and must include:

• Airflow testing: Airflow testing is performed to determine acceptability of the air velocity and volume, the air exchange rate, and the room pressure cascade to ensure that air consistently flows from clean to dirty areas, and that the appropriate quality of air is maintained under dynamic operating conditions. The ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH must be documented on the certification report.

• HEPA filter integrity testing: HEPA filters must be leak tested at the factory and then leak tested again after installation and as part of recertification.
• Total particle count testing (see *Monitoring Air Quality for Nonviable Airborne Particles*): Total particle count testing must be performed under dynamic operating conditions using current, state-of-the-art electronic equipment.
• Smoke visualization studies: Smoke visualization studies must be performed for each PEC during dynamic operating conditions to demonstrate unidirectional airflow and sweeping action over and away from the preparation(s).

Classified areas must additionally be recertified if there are changes to the area such as redesign, construction, or replacement or relocation of any PEC, or alteration in the configuration of the room that could affect airflow or air quality.

All certification and recertification records must be reviewed by the designated person to ensure that the classified environments comply with the minimum requirements in this chapter. Records must be maintained in accordance with the requirements in *17. Documentation*. A corrective action plan must be implemented and documented in response to any out-of-range results.

812 MONITORING AIR QUALITY FOR NONVIABLE AIRBORNE PARTICLES
It is imperative that all engineering control equipment function as designed and that the levels of nonviable airborne particles remain within acceptable limits during compounding (see *Table 3*). A monitoring program for nonviable airborne particles must be developed and implemented to measure the performance of the engineering controls that are being used to provide the specified levels of air cleanliness (e.g., in the ISO Class 5 PEC and ISO Class 7 and 8 rooms).

820 NONVIABLE AIR SAMPLING—TIMING AND LOCATIONS
Total nonviable airborne particle count testing must be conducted in all classified areas during dynamic operating conditions at least every 6 months. Nonviable air sampling sites must be selected in all classified areas. Measurements of nonviable airborne particles must be taken in each PEC at locations where there is greatest risk to the exposed CSPs, containers, and closures. When conducting sampling of the PEC, care should be taken to avoid disturbing the unidirectional airflow within the PEC. All sampling sites and procedures must be described in the facility's SOP. Measurements of nonviable airborne particles in other classified areas, including the buffer room(s) and ante-room(s), should be taken at representative locations that reflect the quality of air in the room(s).

833DATA EVALUATION AND ACTION LEVELS
If levels measured during the nonviable air sampling program exceed the criteria in *Table 3* for the ISO classification of the area sampled, the cause must be investigated and corrective action taken. Some examples of corrective action include process or facility improvements or HEPA filter replacement or repair. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

841 5. MICROBIOLOGICAL AIR AND SURFACE MONITORING

An effective air and surface monitoring program provides information on the environmental quality of the compounding area. In addition, an effective air and surface monitoring program identifies environmental quality trends over time, identifies potential routes of contamination, and allows for implementation of corrective actions to minimize the risk of CSP contamination. Sterile compounding facilities must develop and implement written procedures for air and surface monitoring (see *9. SOPs and Master Formulation and Compounding Records*). All air and surface monitoring 850 procedures, the test results, and the corrective actions must be documented, and the records must be maintained in accordance with the requirements in *17. Documentation*.

853 5.1 General Monitoring Requirements

The microbiological air and surface monitoring program must include 1) viable impact volumetric airborne particulate sampling, and 2) surface sampling. The goals of an air and surface monitoring program are to determine whether contamination is present at unacceptable levels and to assess whether proper personnel practices are being followed, cleaning and disinfecting agents are effective, and environmental quality is maintained.

The air and surface monitoring program involves the collection and evaluation of samples from various air and surface locations to detect airborne and surface contaminants. The data from airborne and surface sampling are then used to assess risks for contamination, potential routes of contamination, and the adequacy of cleaning and disinfection agents and procedures. Regular review of the sampling data must be performed to detect trends such as elevated levels of microbial bioburden, elevated levels of nonviable particulates, or other adverse changes within the environment.

In addition, results from air and surface sampling must be reviewed in conjunction with personnel data (i.e., training records, visual observations, competency assessments) to assess the state of control and to identify potential risks of contamination. Prompt corrective action in response to any adverse findings is essential to maintain the necessary environmental quality for preparation of CSPs. Data must also be reviewed following corrective actions to confirm that the actions taken have been effective in achieving the required air and surface quality levels (see *Table 3*, *Table 6*, and *Table 7*).

Air and surface monitoring must be performed initially for sterile compounding facilities to establish a baseline level of environmental quality. After initial sampling, the environment in which sterile compounding activities are performed must be monitored according to the minimum frequencies described in this section to ensure that the environment remains suitable for sterile compounding. Evaluating results collected over a period of time can be useful in identifying trends or determining that a significant change has occurred, even when the results fall within the specified limits. Air and surface monitoring must be conducted during dynamic operating conditions to confirm that the required environmental quality in classified areas is maintained. In addition to the specific sampling frequencies described in this section, sampling must be performed in any of the following circumstances:

- In conjunction with the certification of new facilities and equipment
- After any servicing of facilities or equipment (see *4. Facilities and Engineering Controls*)
- In response to identified problems (e.g., positive growth in sterility tests of CSPs)

• In response to identified trends (e.g., repeated positive gloved fingertip and thumb sampling results, failed media fill testing, or repeated observations of air or surface contamination)
• In response to changes that could impact the sterile compounding environment (e.g., change to cleaning agents) The air and surface monitoring program must be clearly described in the facility's SOPs, which must include a diagram of the sampling locations, procedures for collecting samples, frequency of sampling, size of samples (e.g., surface area, volume of air), time of day of sampling in relation to activities in the compounding area, and action levels that will trigger corrective action. The times and locations of sampling should be carefully selected based on their relationship to the activities performed in the area. It is important to obtain samples from locations that pose the highest possible risk of contamination to the CSP and that are likely to be representative of the conditions throughout the area. To obtain air and surface samples that are representative of the typical compounding conditions at the facility, air and surface sampling must be conducted during dynamic operating conditions in all PECs and classified rooms. However, the monitoring program must be designed and conducted in a manner that minimizes the chance that the sampling itself will contribute to contamination of the CSP or the environment.

It is important that personnel be trained in the proper operation of the air and surface sampling equipment to ensure accurate and reproducible sampling. All air sampling devices must be serviced and calibrated as recommended by the manufacturer.

920 **5.2 Monitoring Air Quality for Viable Airborne Particles**
A monitoring program for viable airborne particles must be developed and implemented to assess microbiological air quality in all classified areas.

923VIABLE AIR SAMPLING—TIMING AND LOCATIONS
Volumetric active air sampling of all classified areas using an impaction device must be conducted in each classified area [e.g., ISO Class 5 PEC and ISO Class 7 and 8 room(s)] during dynamic operating conditions at least every 6 months. Air sampling sites must be selected in all classified areas.
When conducting sampling of the PEC, care should be taken to avoid disturbing unidirectional airflow. See *Box 5-1* for active air sampling procedures. A general microbiological growth medium that supports the growth of bacteria and fungi must be used (e.g., TSA medium). COAs from the manufacturer must verify that the medium meets the expected growth promotion, pH, and sterilization requirements. Samples must be incubated in a calibrated incubator at temperatures that will promote growth of bacteria and fungi. The incubator temperature must be monitored during incubation, either manually or by a continuous recording device, and the results must be reviewed and documented. The microbiological incubator must be placed in a location outside of the sterile compounding area. All air sampling activities must be performed by trained individuals.

Box 5-1. Active Air Sampling Procedures for Viable Airborne Monitoring
942• Follow the manufacturer's instructions for operation of the active air sampling device, including placement of media.

• **Using the sampling device, test at least 1 cubic meter or 1000 liters of air from each location sampled. (new)**
• At the end of the sampling, retrieve the media plates/devices and cover them.
• Invert the media and incubate at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.
• Then incubate the inverted media at 20°–25° for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.
• Alternatively, two pieces of media may be collected for each sample location and incubated concurrently in separate incubators at 30°–35° for no less than 5 days and at 20°–25° for no less than 5 days. Record the total number of discrete colonies of microorganisms on each plate as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.

DATA EVALUATION AND ACTION LEVELS

943 Evaluate cfu counts against the action levels in *Table 6*, and examine counts in relation to previous data to identify adverse results or trends. If two pieces of media are collected at a single location, all recovered growth on each is documented and action levels are applied to each device. If levels measured during the viable air monitoring program exceed the levels in *Table 6* for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. The corrective action plan must be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented. If levels measured during viable air sampling exceed the levels in *Table 6*, the genus of any microorganism recovered must be identified (see *Microbial Characterization, Identification, and Strain Typing* ⟨1113⟩) with the assistance of a microbiologist.

960**Table 6. Action Levels for Viable Airborne Particle Air Sampling[a] ISO Class Air Sampling Action Levels [cfu per cubic meter (1000 liters) of air per plate]**
ISO 5 >1, ISO 7 >10, ISO 8 >100
[a] Adapted from *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. U.S. Department of Health and Human Services, FDA, September 2004.

5.3 Monitoring Surfaces for Viable Particles
961 Surface sampling is an important tool used to assist in maintenance of a suitably controlled environment for compounding CSPs, especially because transfer of microbial contamination from improperly disinfected work surfaces via inadvertent touch contact by compounding

personnel is a potential source of contamination of CSPs. Surface sampling is useful for evaluating facility cleaning and material handling procedures, work surface cleaning and disinfecting procedures, and personnel competency in work practices such as cleaning and disinfecting of component and/or vial surfaces. All sampling sites and procedures must be described in the facility's SOP.

SURFACE SAMPLING: TIMING AND LOCATIONS
972 **Surface sampling of all classified areas must be conducted at least monthly**. (new)
Surface sampling for microbial contamination must be performed in all classified areas (see *Microbiological Control and Monitoring of Aseptic* 975 *Processing Environments* ⟨1116⟩).
Each classified area must be sampled, including the following:
• The interior of the PEC and the equipment contained in it
• Staging or work area(s) near the PEC
• Frequently touched surfaces
• Pass-through chamber(s) (new)

When conducted, surface sampling must be performed at the end of the compounding activities or shift, but before the area has been cleaned and disinfected.

SAMPLING PROCEDURES
985 Surface sampling devices (e.g., plates, paddles, or slides) containing microbial growth media must be used for sampling flat surfaces. COAs from the manufacturer must verify that the devices meet the expected growth promotion, pH, and sterilization requirements. Surface sampling devices must contain general microbial growth media (e.g., TSA) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) to neutralize the effects of any residual disinfecting agents. If used, contact plates must have a raised convex surface.
Sterile swabs wetted with sterile water or a sterile neutralizing buffer may be used when sampling irregular surfaces and difficult-to-reach locations, such as crevices, corners, and spaces between surfaces. After sampling, the sampled area must be thoroughly cleaned and disinfected (see *6. Cleaning and Disinfecting Compounding Areas*). See *Box 5-2* for the procedures for surface sampling on flat surfaces and *Box 5-3* for the procedures for surface sampling on irregular surfaces.

Box 5-2. Using Devices for Flat Surface Sampling
1000 • Remove the cover from the contact sampling device. Using a rolling motion, firmly press the media surface onto the surface to be sampled. The contact sampling device will leave a residue of growth medium on the sample site. After sampling, use a low-lint sterile wiper to thoroughly clean the sampled area with sterile 70% IPA.
• Cover each contact sampling device. If using plates, invert the plates.
• Incubate the contact sampling devices at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu per sample on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
• Incubate the contact sampling device at 20°–25° for no less than 5 additional days. Examine the device for growth. Record the total number of discrete colonies of microorganisms (cfu per

sample) on the environmental sampling record based on sample type (i.e., surface), sample location, and sample date. sampling record based on sample type (i.e., surface), sample location, and sample
• Alternatively, two devices may be collected for each sample location and incubated concurrently in separate incubators at 30°–35° for no less than 5 days and at 20°–25° for no less than 5 days. Record the total number of discrete colonies of microorganisms (cfu/sample) on the environmental date.

Box 5-3. Using Devices for Irregular Surface Sampling
1001 • Sterile swabs wetted with sterile water or a sterile neutralizing buffer should be used.
• If using the neutralizing buffer, the residue must be removed from the surface after sampling using sterile 70% IPA. Swabs sampled with sterile water must be processed with a neutralizing buffer or plated in a neutralizing medium.
• After swabbing the area, place the swab in appropriate diluent or sterile packaging until it can be processed. The swab must be processed using a diluent and an extraction step to aid in the removal of any microorganisms from the swab.
• Plate all or a portion of the diluent in TSA (or TSA with neutralizers). If the diluent is diluted, the dilution factor must be applied to the raw count to determine the actual total microbial count.
• Incubate the plates at 30°–35° for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu per sample on an environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
• Incubate the plates at 20°–25° for no less than 5 additional days. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu per sample on the environmental sampling form based on sample type (i.e., surface), sample location, and sample date.
• Alternatively, two devices may be collected for each area and incubated concurrently in separate incubators at 30°–35° for no less than 5 days and at 20°–25° for no less than 5 days.

Record the total number of discrete colonies of microorganisms on each plate as cfu per sample on the environmental sampling form based on sample type (i.e., surface), sample location, and sample date.

DATA EVALUATION AND ACTION LEVELS
1002 Evaluate cfu counts against the action levels in *Table 7*, and examine counts in relation to previous data to identify adverse results or trends. If two devices were collected at a single location, all recovered growth on each is documented and action levels are applied to each device. If levels measured during surface sampling exceed the levels in *Table 7* for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. The corrective action plan must be dependent on the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation should be consistent with the deviation and should include an evaluation of trends. The corrective action plan must be documented. If levels measured

during surface sampling exceed the levels in *Table 7*, the genus of any microorganism recovered must be identified (see ⟨1113⟩) with the assistance of a microbiologist.

Table 7. Action Levels for Surface Sampling
1018 **ISO Class Surface Sampling Action Levels (cfu/device or swab)**
ISO 5 >3,
ISO 7>5,
ISO 8 >50

6. CLEANING AND DISINFECTING COMPOUNDING AREAS

1020 Cleaning and disinfecting are important because surfaces in classified areas and SCA are a potential source of microbial contamination of CSPs. The process of cleaning involves removing organic and inorganic materials from surfaces, usually with a manual or mechanical process and a cleaning agent. The process of disinfecting involves destruction of microorganisms, usually with a chemical agent. Surfaces must be cleaned prior to being disinfected unless an Environmental Protection Agency (EPA) registered one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step. Some EPA registered one-step disinfectant cleaners may have sporicidal properties. Cleaning and disinfecting surfaces must occur at the minimum frequencies specified in *Table 8* or, if compounding is not performed daily, cleaning and disinfecting must be completed before initiating compounding. Cleaning and disinfecting must be repeated when spills occur; when surfaces, floors, and walls are visibly soiled; and when contamination is known or suspected in the compounding areas.

All cleaning and disinfecting activities must be performed by trained and appropriately garbed personnel using facility-approved agents and procedures, which must be described in written SOPs. Cleaning must be performed in the direction of clean to dirty areas. The frequency, method(s), and location(s) of cleaning and disinfection agent use must be established in written SOPs, in accordance with the manufacturer's instructions, and must be followed by all cleaning personnel. The manufacturer's directions or published data for the minimum contact time must be followed for the cleaning, disinfecting, and sporicidal agents used. All cleaning and disinfecting activities must be documented.

1051 **Table 8. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidals in Classified Areas and within the Perimeter of the SCA**
Site
PEC(s) and Equipment inside the PEC(s).

Cleaning -The horizontal work surface at the beginning and end of each shift, after spills, and when surface contamination is known or suspected. The ceiling, walls, bars and any equipment inside the PEC on each day that compounding is performed and when contamination is known or suspected.

Disinfect all interior surfaces of the PEC at the beginning and end of each shift, after spills, and when surface contamination is known or suspected. Disinfect the horizontal work surface at least every 30 minutes while compounding if the compounding process takes 30 minutes while compounding process of a single batch or preparation takes more than 30 minutes, compounding

must not be disrupted and the work surface of the PEC must be disinfected immediately after compounding.

Applying Sporicidal – Monthly

	Cleaning	Disinfecting	Apply Sporicidal
Surfaces of sink(s)	Daily	Daily	Monthly
Pass-through(s)	Daily	Daily	Monthly
Work surface(s) outside the PEC	Daily	Daily	Monthly
Floor(s)	Daily	Daily	Monthly
Wall(s), door(s), and door frame(s)	Monthly	Monthly	Monthly
Ceiling(s)	Monthly	Monthly	Monthly
Storage shelving and storage bins	Monthly	Monthly	Monthly

[a] Many disinfectants registered by the EPA are one-step cleaning and disinfecting agents, which means that the disinfectant has been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step.

6.1 Cleaning, Disinfecting, and Sporicidal Agents

1052 Cleaning and disinfecting agents must be selected and used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues or fumes. Considerations when selecting and using disinfectants include their antimicrobial activity, inactivation by organic matter, residue, shelf life, preparation requirements of the agent, and suitability for surfaces being disinfected (see and *Disinfectants and Antiseptics* ⟨1072⟩). After the disinfectant is applied and wiped on the surface to be disinfected, the disinfectant must be allowed to dwell for the minimum contact time specified by the manufacturer, during which time the surface cannot be disturbed. Sporicidal agents, shown to be effective against *Bacillus* species, must be used at least monthly to disinfect all surfaces in classified and SCAs. The disinfecting agents (e.g., 70% IPA) used in the ISO 5 PEC must be sterile.

See *Table 9* for a summary of the purposes of the cleaning, disinfectant, and sporicidal agents.

Table 9. Purpose of Cleaning, Disinfecting, and Sporicidal Agents

1067 **Type of Agent Purpose**

Cleaning agent An agent for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Disinfectant A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria. Sporicidal disinfectant agents are considered a special class of disinfectants that also are effective against bacterial endospores.

Sporicidal agent A chemical or physical agent that destroys bacterial and fungal spores when used at a sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

6.2 Cleaning Supplies

1068 All cleaning supplies (e.g., wipers, sponges, and mop heads) with the exception of tool handles and holders must be low-linting. Wipers, sponges, and mop heads should be disposable.

If disposable cleaning supplies are used, they must be discarded after each cleaning activity. Reusable cleaning tools must be made of cleanable materials (e.g., no wooden handles) and must be cleaned before and after each use. Reusable cleaning tools must be dedicated for use in the classified areas or SCA and must not be removed from these areas except for disposal. They must be discarded after an appropriate amount of time, to be determined based on the condition of the tools. Dispose of cleaning supplies used in the classified areas and SCAs in a manner that minimizes the potential for dispersing contaminants into the air (e.g., with minimal agitation, away from work surfaces).

6.3 Cleaning and Disinfecting the PEC

1081 Clean and disinfect the PEC at the minimum frequencies specified in *Table 8*. See *Box 6-1* for procedures for cleaning and disinfecting the PEC. If the PEC contains a removable work tray, all sides of the work tray and the area underneath the work tray must be cleaned and disinfected at least monthly. Hank Note – the work tray is in the direct compounding area and should be cleaning and disinfected daily

Box 6-1. Procedures for Cleaning and Disinfecting the PEC

1086• Remove any particles, debris, or residue with an appropriate solution (e.g., *Sterile Water for Injection* or *Sterile Water for Irrigation*) using sterile, low-lint wipers.
• Apply a cleaning agent (e.g., EPA-registered one-step disinfectant cleaner).
• Disinfect with a sterile disinfectant (e.g., sterile 70% IPA).
• Allow the surface to dry completely before beginning compounding.
• The PEC must be wiped Hank wipe vs spray with a sporicidal agent at least monthly.

6.4 Cleaning and Disinfecting Compounding Supplies for the
1087 **Classified Areas and SCAs**

No shipping carton(s) or other corrugated or uncoated cardboard are allowed in the classified area or SCA. Before compounding supplies are introduced into a classified area or SCA, they must be wiped with a sporicidal agent or sterile disinfectant (e.g., sterile 70% IPA) using low-lint wipers. After the sporicidal or sterile disinfectant is applied and wiped on the surface, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer, during which time the item cannot be disturbed. The agent used for wiping the packaging must not alter the product label.
Any item to be transferred into the PEC must be wiped with a sporicidal agent or sterile disinfectant (e.g., sterile 70% IPA) using low-lint wipers. The agent must be allowed to dwell for the minimum contact time specified by the manufacturer, during which time the item cannot be disturbed. The agent used for wiping the packaging must not alter the product label.

6.5 Disinfecting Critical Sites within the PEC

Critical sites (e.g., vial stoppers, ampule necks, and intravenous bag 1104 septums) must be disinfected by wiping them with sterile 70% IPA in the PEC. The critical site must be wiped in

one direction ensuring that both chemical and mechanical actions are used to remove, contaminants. The sterile 70% IPA must be allowed to dry before entering or puncturing stoppers/septums with sterile needles or breaking the necks of ampules.

7. EQUIPMENT, SUPPLIES, AND COMPONENTS

7.1 Equipment

PECs are described in *Types of PECs and Placement.* Other equipment used in compounding CSPs [e.g., automated compounding devices (ACDs), repeater pumps, and balances] should be of suitable composition such that the surfaces that contact components are not reactive or sorptive.

Equipment that must be brought into classified areas must be wiped with disinfectant using low-lint wipers. Equipment must be placed in a manner that facilitates sterile compounding operations. The equipment must be capable of operating properly and within required performance parameters. Compounding personnel must establish and follow SOPs for the calibration, maintenance, cleaning, and use of the equipment based on the manufacturer's recommendations. Personnel must maintain records from equipment calibration, verification, and maintenance in accordance with the requirements in *17. Documentation*. ACDs, repeater pumps, and other similar equipment are designed to assist in the compounding of preparations by delivering specific volumes of 1127 solution(s) automatically under computerized control. Before using ACDs, repeater pumps, 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. The precision of the equipment can be monitored based on an assessment of day-to-day variations in its accuracy measures. Compounding personnel must keep a daily record of the accuracy measurements on the days the equipment is in use. Corrective actions must be implemented if accuracy measurements are outside the manufacturer's specification.

7.2 Supplies

1137 Supplies (e.g., beakers, utensils, needles, syringes, filters, and tubing sets) should be of suitable composition such that the surfaces that contact components are not reactive or sorptive. Supplies in direct contact with the CSP must be sterile and depyrogenated. When sterile supplies are receive in sealed pouches designed to keep them sterile until opening, the sterile supplies may be removed from the covering pouches as the supplies are introduced into the ISO Class 5 PEC without the need to disinfect the individual sterile supply items.

7.3 Components

1146 Compounding personnel must follow facility SOPs, which must address the selection, receipt, evaluation, handling, storage, and documentation of all CSP components, including all ingredients, containers, and closures. Packages of components that must be brought into classified areas must be wiped with a sporicidal agent or sterile disinfectant using low-lint wipers.

COMPONENT SELECTION

Conventionally manufactured sterile products should be used when available and appropriate for the intended CSP. All APIs must be accompanied by a COA that includes the specifications and test results and shows that the API meets the specifications of the *USP–NF* monograph, if one

exists. All other ingredients must be accompanied by documentation (e.g., COA, labeling) that includes the specifications and shows that the ingredient meets the specifications. In the US, APIs used in compounding must be obtained from an FDA- registered facility and must comply with the criteria in the *USP–NF* 1161 monograph, if one exists. All ingredients other than API(s) should preferably be obtained from an FDA-registered facility and must comply with the criteria in the *USP–NF* monograph, if one exists. If ingredients other than APIs (e.g., excipients and preservatives) cannot be obtained from an FDA-registered facility, the designated person must select an acceptable and reliable source (see *Good Distribution Practices for Bulk Pharmaceutical Excipients* ⟨1197⟩). The compounding facility must establish the identity, strength, purity, and quality of the ingredients obtained from that supplier by reasonable means. Reasonable means may include visual inspections, evaluation of a COA supplied by the manufacturer, and/or verification by analytically testing a sample to determine conformance with the COA or other specifications. 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). If sterilization and depyrogenation of supplies or container–closure systems are performed on site, the efficacy of each process must be established and documented (see *Sterilization of Compendial Articles* ⟨1229⟩).

COMPONENT RECEIPT

1181Upon receipt of each lot of a component, the external packaging must be examined for evidence of deterioration and other aspects of unacceptable quality. Facility personnel must verify the labeling and condition of the component, [e.g., whether the outer packaging is damaged and whether temperature-sensing indicators show that the component has been exposed to excessive temperature(s)].

Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated to prevent use before appropriate disposal. Any other lots of that component from that vendor must be examined to determine whether other lots have the same defect. The date of receipt by the compounding facility must be clearly marked on each API or inactive ingredient package that lacks a vendor expiration date. Packages of ingredients (i.e., API and inactive ingredients) that lack a vendor's expiration date must be assigned a conservative expiration date, not to exceed 1 year after receipt by the compounding facility.

COMPONENT EVALUATION BEFORE USE

1198Compounding personnel must ascertain before use that ingredients for CSPs are of the correct identity, appropriate quality, within expiry date, and have been stored under appropriate conditions. The following information should be used to make this determination: prescription or medication order, compounding record, master formulation record (if used), vendor labels, COAs of API(s) and inactive ingredient(s), product labeling of conventionally manufactured sterile products, labeling of CSPs, and documentation of the compounding facility storage conditions and practices.

All components must be re-inspected before use. All packages must be re- inspected to detect container breaks, looseness of the cap or closure, and deviation from the expected appearance,

aroma, and texture of the contents that might have occurred during storage. Sterile container–closures must be visually re-inspected to ensure that they are free from defects that could compromise sterility and are otherwise suitable for their intended use. If components intended for use in preparing CSPs do not meet expected quality attributes, they must be promptly rejected, clearly labeled as rejected, and segregated to prevent use before disposal.

COMPONENT HANDLING AND STORAGE
1216All components must be handled and stored in a manner that prevents contamination, mix-ups, and deterioration. Ingredients must be stored in closed containers under temperature, humidity, and lighting conditions consistent with those indicated in official monographs or specified by the suppliers and/or manufacturer.

8. STERILIZATION AND DEPYROGENATION

1223When selecting the sterilization method for CSPs prepared from one or more nonsterile starting components, personnel must take into consideration the nature of the component(s), their physical and chemical properties, and the intended container–closure system. The sterilization method used must sterilize the CSP without degrading its physical and chemical stability (e.g., affecting its strength, purity, and quality) or the packaging integrity. See also the ⟨1229⟩ family of chapters.

The following must be considered when selecting an appropriate sterilization method:
• Terminal sterilization (e.g., dry heat, steam, or irradiation) is the preferred method unless the specific CSP or container–closure system cannot tolerate terminal sterilization
• Steam sterilization is not an option if moisture, pressure, or the temperatures used would degrade the CSP or if there is insufficient moisture to sterilize the CSP within the final, sealed container–closure system (e.g., anhydrous oils and solid CSPs)
• Filtration is not an option when compounding a suspension if the suspended drug particles are removed by the filter being used CSPs that are terminally sterilized (e.g., dry heat, steam, or irradiation) must use a process intended to achieve a sterility assurance level (SAL) of 10^{-6}. An SAL of 10^{-6} is equivalent to a probability that 1 unit in a million is nonsterile. An SAL value cannot be applied to CSPs that are aseptically filled into a sterile container following sterilization by filtration because sterilization by filtration is not terminal sterilization.
A description of the terminal sterilization and depyrogenation process, including the temperature, pressure (if applicable), duration, permissible load conditions for each cycle, and results of biological indicators must be included in the facility's SOPs. SOPs must include training of personnel on all sterilization methods and equipment used by the facility. In addition, the SOPs must include a schedule and method for establishing and verifying the effectiveness of the terminal sterilization and depyrogenation methods selected, as well as the methods for maintaining and cleaning the sterilizing and depyrogenation equipment.

8.1 Depyrogenation

1258 See *Dry Heat Depyrogenation* ⟨1228.1⟩. Dry heat depyrogenation must be used to render glassware, metal, and other thermostable containers and components pyrogen-free. Depyrogenation processes typically operate at a range of temperatures, from approximately 170° up to about 400°,depending on the exposure time (e.g., a cycle might hold the items at 250° for

30 minutes to achieve sterility and depyrogenation). The duration of the exposure period must include sufficient time for the items to reach the depyrogenation temperature. The items must remain at the depyrogenation temperature for the duration of the depyrogenation period. The effectiveness of the 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 (see *Bacterial Endotoxins Test* ⟨85⟩). This verification must be documented. Items that are not thermostable must be depyrogenated by rinsing with sterile, pyrogen-free water and then thoroughly drained or dried immediately before use in compounding.

8.2 Sterilization by Filtration

1276 See *Sterilizing Filtration of Liquids* ⟨1229.4⟩. Sterilizing filters must be sterile, depyrogenated, and have a nominal pore size of 0.22 µm or smaller. They must be certified by the manufacturer to retain at least 10_7 microorganisms of a strain of *Brevundimonas diminuta* per square centimeter of upstream filter surface area under conditions similar to those in which the CSPs will be filtered (i.e., pressure, flow rate, and volume filtered). The designated person must ensure—from available published information, from supplier documentation, or through direct challenge (e.g., filtering the CSP)—that the filters 1) are chemically and physically compatible with all ingredients in the CSP (e.g., water-miscible alcohols may damage filter integrity); 2) are chemically stable at the pressure and temperature conditions that will be used; and 3) have enough capacity to filter the required volumes. The filter dimensions and the CSP to be sterilized by filtration should permit the sterilization process to be completed without the need for replacement of the filter during the process. Filter units used to sterilize CSPs must be subjected to the manufacturers' recommended integrity testing, such as a post-use bubble point test. If multiple filters are required for the compounding process, each of the filters must pass a filter-integrity test.

When CSPs are known to contain excessive particulate matter, a prefiltration step must be performed using a filter of larger nominal pore size (e.g., 1.2 µm) or a separate filter of larger nominal pore size should be placed upstream of (i.e., prior to) the sterilizing filter to remove gross particulate contaminants before the CSP is passed through the sterilizing- grade filter. Excessive particulate matter requiring a prefiltration step could potentially be a signal of an inappropriate formulation, and therefore the formulation and the process should be assessed and, if necessary, modified.

CSPs that were prepared using a filter that failed integrity tests must be discarded or resterilized by filtration.

8.3 Sterilization by Steam Heat

1307 Temperatures used to achieve sterilization by steam heat are lower than those used to achieve depyrogenation. The process of thermal sterilization using saturated steam under pressure (i.e., autoclaving) is the preferred method for terminal sterilization of aqueous CSPs in their final, sealed container–closure system(see *Steam Sterilization by Direct Contact* ⟨1229.1). Steam sterilization is not an option if moisture, pressure, or the temperatures used would degrade the CSP.

To achieve sterility when steam sterilization is used, all materials must be directly exposed to steam under adequate pressure for the length of time necessary, as determined by use of appropriate biological indicators, to render the items sterile (e.g., between 20 and 60 minutes at 121° saturated steam under a pressure of 15 psi, depending on the volume or size of the CSP being sterilized). The duration of the exposure period must include sufficient time for the entire contents of the CSP and other items to reach the sterilizing temperature. The CSP and other items must remain at the sterilizing temperature for the duration of the sterilization period. CSPs must be placed in the autoclave to allow steam to reach the CSPs without entrapment of air. Flat, stainless steel trays with low sides or ventilated bottoms will permit steam contact. When preparing items for steam sterilization, the items must be wrapped in low-lint protective fabric or paper or sealed in envelopes that will permit steam penetration and that are designed to prevent post-sterilization microbial contamination. For CSPs, immediately before filling ampules and vials 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.

Sealed containers must be able to generate steam internally. Stoppered and crimped empty vials must contain a small amount of sterile water to generate steam. Deep containers, such as beakers and graduated cylinders, must be inverted or placed on their sides at a downward-sloping angle to minimize air entrapment and to facilitate condensate drainage, or must have a small amount of sterile water placed in them before steam sterilization.

Porous materials and those items with occluded pathways (e.g., tubing) must only be sterilized by steam if the autoclave chamber has suitable cycles for dry goods, such as a pre-vacuum process to remove air before steam is sent into the chamber. Elastomeric closures and many other dry goods will need a drying cycle after steam exposure to remove condensed or absorbed moisture.

The effectiveness of steam sterilization must be verified and documented with each sterilization run or load by using appropriate biological indicators, such as spores of *Geobacillus stearothermophilus*, ATCC 12980, ATCC 7953, or equivalent (see *Biological Indicators for Sterilization* ⟨1229.5⟩), and other confirmation methods such as physicochemical indicators and integrators (see *Physicochemical Integrators and Indicators for Sterilization* ⟨1229.9⟩

The steam supplied must be free of contaminants and generated using water per the manufacturer's recommendation. A calibrated data recorder or chart must be used to monitor each cycle and to examine for cycle irregularities (e.g., deviations in temperature or pressure). The date, run, and load numbers of the steam sterilizer used to sterilize a CSP must be documented in the compounding record.

8.4 Sterilization by Dry Heat

1357Dry heat may be used for those items that cannot be sterilized by steam or other means, when either the moisture would damage the material or the wrapping material is impermeable (see *Dry Heat Sterilization* ⟨1229.8⟩). Sterilization by dry heat requires higher temperatures and longer exposure times than sterilization by steam. The duration of the exposure period must include sufficient time for the entire contents of CSPs and other items to

reach the sterilizing temperature. The CSP and other items must remain at the sterilizing temperature for the duration of the sterilization period. Dry heat sterilization is usually done in an oven designed for sterilization at a temperature of 160° or higher. If lower temperatures are used, they must be shown to achieve effective sterilization (see *Dry Heat Sterilization* ⟨1229.8⟩, *Validation of Dry Heat Sterilization, Biological Indicators*). Heated air must be evenly distributed throughout the chamber, which is typically accomplished by an air blower. The calibrated oven must be equipped with temperature controls and a timer. During sterilization, sufficient space must be left between materials to allow for circulation of the hot air. A calibrated 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 effectiveness of the dry heat sterilization method must be validated, verified, and documented with each sterilization run or load using appropriate biological indicators such as spores of *Bacillus atrophaeus*, ATCC 9372 (see ⟨1229.5⟩), and other confirmation methods (e.g., temperature-sensing devices). The date, run, and load numbers of the dry heat oven used to sterilize a CSP must be documented in the compounding record.

9. SOPS AND MASTER FORMULATION AND COMPOUNDING RECORDS

13849.1 Creating and Following SOPs

Facilities that prepare CSPs must develop SOPs for the compounding process and other support activities. A designated person must ensure that SOPs are appropriate and are implemented, which includes ensuring that personnel demonstrate competency in performing every procedure that relates to their job function. A designated person must follow up to ensure that corrective actions are taken if problems, deviations, failures, or errors are identified. The corrective action must be documented. All personnel who perform or oversee compounding or support activities must be trained in the SOPs.

All compounding personnel must:

• Be able to recognize potential problems, deviations, failures, or errors associated with preparing a CSP (e.g., those related to equipment, facilities, materials, personnel, the compounding process, or testing) that could potentially result in contamination or other adverse impact on CSP quality. Report any problems, deviations, or errors to the designated person SOPs must be reviewed at least every 12 months by the designated person to ensure that they reflect current practices, and the review must be documented. Any changes or alterations to an SOP must be made only by a designated person and must be documented. Revisions to SOPs must be communicated to all personnel involved in these processes and procedures, and personnel should document acknowledgement of the communication.

9.2 Creating Master Formulation Records

1407 A Master Formulation Record must be created for CSPs prepared in a batch for more than 1 patient, or for CSPs prepared from nonsterile ingredient(s). Any changes or alterations to the Master Formulation Record must be made only by a designated person. Any change(s) must be documented with the date and time the change was made and the identity of the person who made the change. *Box 9-1* lists the information that must be included in a Master Formulation Record.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

Box 9-1. Master Formulation Records

A Master Formulation Record must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Identities and amounts of all ingredients
- 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

If applicable, the Master Formulation Record must also include:

- Quality control (QC) procedures (e.g., pH testing, filter integrity testing)
- Sterilization method (e.g., steam, dry heat, irradiation, or filter)
- Other information needed to describe the compounding process and ensure repeatability (e.g., adjusting pH and tonicity)

9.3 Creating Compounding Records

1416 A Compounding Record must be created for all CSPs. The Compounding Record must be created by the compounder preparing the CSP to document the compounding process or repackaging process. A Compounding Record may be in the form of a prescription or medication order, compounding log, or label. If an ACD, repeater pump, workflow management system, or other similar equipment is used, the required information in the compounding record may be stored electronically as long as it is retrievable and contains the required information (see *Box 9-2*). A Master Formulation Record can serve as the basis for preparing the Compounding Record. For example, a copy of the Master Formulation Record can be made that contains spaces for recording the information needed to complete the Compounding Record. *Box 9-2* lists the information that must be included in a Compounding Record.

Box 9-2. Compounding Records

1429 Compounding Records 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)
- Identity of all individuals involved in each step (e.g., technician or pharmacist)
- Name, vendor or manufacturer, lot number, and expiration date for each ingredient
- Weight or volume of each ingredient
- Total quantity compounded
- Assigned BUD and storage requirements

If applicable, the Compounding Record must also include:

- Master Formulation Record reference for the CSP
- Calculations made to determine and verify quantities and/or concentrations of components
- Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing)

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

10. RELEASE TESTING

1431All release testing procedures (e.g., visual inspections and testing) must be included in the facility's documentation (see *9. SOPs and Master Formulation and Compounding Records*). Any out-of-specification results must be investigated, and the corrective action plan must be implemented and documented as part of the quality assurance (QA) and QC program (see *15. Quality Assurance and Quality Control*).

10.1 Visual Inspection

1438 At the completion of compounding, before release and dispensing, the CSP must be visually inspected to determine whether the physical appearance of the CSP is as expected (e.g., it is inspected for evidence of inappropriate visible particulates or other foreign matter, discoloration, or other defects). The CSP must be visually inspected to confirm that the CSP and its labeling match the prescription or medication order. The inspection also must include a visual inspection of container–closure integrity (e.g., checking for leakage, cracks in the container, or improper seals). CSPs with observed defects must be discarded, or marked and segregated from acceptable units in a manner that prevents them from being released or dispensed. When a CSP will not be released or dispensed promptly after 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. A CSP with such defects must be immediately discarded, or marked and segregated from acceptable units in a manner that prevents it from being released or dispensed. Any defect may indicate sterility or stability problems that should be investigated to determine the cause (see *15. Quality Assurance and Quality Control*).

10.2 Sterility Testing

1458 Sterility testing is not required for Category 1 CSPs (see *Table 11*). If a Category 2 CSP is assigned a BUD that requires sterility testing (see *Table 12*), the testing must be performed according to ⟨71⟩ or a validated alternative method (see *Validation of Alternative Microbiological Methods* ⟨1223⟩) that is non-inferior to ⟨71⟩ testing. If sterility testing is performed, the minimum quantity of each container to be tested for each medium is specified in *Sterility Tests* ⟨71⟩*, Table 2*, and the number of containers required to be tested in relation to the batch size is specified in *Sterility Tests* ⟨71⟩*, Table 3*. Deviations from the batch sizes specified in *Sterility Tests* ⟨71⟩*, Table 3* are allowable as described below:

- If the number of CSPs to be compounded in a single batch is less than the number of CSPs needed for testing as specified in *Sterility Tests*⟨71⟩*, Table 3*, additional units must be compounded to be able to perform sterility testing.
- If between 1 and 39 CSPs are compounded in a single batch, the sterility testing must be performed on a number of units equal to 10% of the number of CSPs prepared, rounded up to the next whole number. For example:
  - If 1 CSP is compounded, 10% of 1 rounded up to the next whole number would indicate that 1 additional CSP must be prepared for sterility testing.
  - If 39 CSPs are compounded, 10% of 39 rounded up to the next whole number would indicate that 4 additional CSPs must be prepared for sterility testing.

If more than 40 CSPs are prepared in a single batch, the sample sizes specified in *Sterility Tests* ⟨71⟩, *Table 3* must be used.
If sterility testing is performed according to *Sterility Tests* ⟨71⟩, a ⟨71⟩, *Method Suitability Test* must be performed to ensure that contamination can be recovered. If performing sterility testing according to ⟨71⟩, the ⟨71⟩, *Test for Sterility of the Product to be Examined, Membrane Filtration* method is the method of choice when the CSP formulation permits. The preferred alternative is the ⟨71⟩, *Test for Sterility of the Product to be Examined, Direct Inoculation of the Culture Medium* method. If an alternative method is used for sterility testing, the method must be validated (see ⟨1223⟩) and demonstrated to be suitable for that CSP formulation. Sterility tests resulting in failures must prompt an investigation into the possible causes and must include identification of the microorganism, as well as an evaluation of the sterility testing procedure, compounding facility, process, and/or personnel that may have contributed to the failure. The source(s) of the contamination, if identified, must be corrected, and the facility must determine whether the conditions causing the sterility failure affect other CSPs. The investigation and resulting corrective actions must be documented.

10.3 Bacterial Endotoxins Testing
1502Except for inhalation and topical ophthalmic preparations, Category 2 CSPs made from one or more nonsterile ingredient(s) or component(s) and assigned a BUD that requires sterility testing (see *Table 12*) must be tested to ensure that they do not contain excessive bacterial endotoxins (see ⟨85⟩). [NOTE—CSPs that are assigned a BUD that does not require sterility testing are not required to be tested for bacterial endotoxins.] In the absence of a bacterial endotoxins limit in an official monograph or other CSP formula source, the CSP must not exceed the endotoxins limit calculated as described in ⟨85⟩ for the appropriate route of administration. See also *Guidelines on Endotoxins Test* ⟨1085⟩.

11. LABELING
1514 CSPs must be labeled with legible identifying information to prevent errors during storage, dispensing, and use. The term labeling designates all label and other written, printed, or graphic matter on an article's immediate container or on, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term label designates that part of the labeling that is on the immediate container. See *Labeling* ⟨7⟩. The label on the immediate container of the CSP must, at a minimum, display prominently and legibly the following information:
• Assigned internal identification number (e.g., prescription, order, or lot number)
• Active ingredient(s) and their amounts, activities, or concentrations
• Storage conditions if other than controlled room temperature
• Date prepared
• BUD
• Indication that the preparation is compounded
The label on the immediate container of the CSP must additionally display prominently the following information:
• Route of administration if it is not obvious from the container, or when necessary for the safe use of the CSP
• Total amount or volume if it is not obvious from the container
• If it is a multiple-dose container, a statement stating such

• Contact information of the compounding facility if the CSP is to be sent outside of the facility in which it was compounded

Additionally, the labeling of the CSP must provide any applicable special handling instructions or warning statements. Labeling procedures must be followed as described in the facility's SOPs to prevent labeling errors and CSP mix-ups. The label of the CSP must be verified to ensure that it conforms with the:

1. Prescription or medication order;
2. Master Formulation Record, if required (see *9.2 Creating Master Formulation Records*); and
3. Compounding Record (see *9.3 Creating Compounding Records*)

All labels must also comply with applicable jurisdictional laws and regulations.

12. ESTABLISHING BEYOND-USE DATES

12.1 Terminology

Each CSP label must state the date, or the hour and date, beyond which the preparation must not be used or administration must not begin, and after which time the preparation must be discarded. The BUD is determined from the date/time that preparation of the CSP is initiated. The BUD is not intended to limit the time during which the CSP is administered (e.g., infused).

BUDs and expiration dates are not the same. An expiration date identifies the time during which a conventionally manufactured product, active ingredient, or excipient can be expected to meet the requirements of a compendial monograph, if one exists, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the conventionally manufactured product, API, or excipient may be dispensed or used (see *Labeling ⟨7⟩, Labels and Labeling for Products and Other Categories, Expiration Date and Beyond-Use Date*). Expiration dates are assigned by manufacturers based on analytical and performance testing of the sterility, chemical and physical stability, and packaging integrity of the product. Expiration dates are specific for a particular formulation in its container and at stated exposure conditions of illumination and temperature.

See *Table 10* for a summary of terms.

Table 10. Summary of Terms

Term	Definition	Applicability
Beyond-Use Date	Either the date or hour and date after which a CSP must not be used or administration must not begin. The BUD is determined from the date/time that preparation of the CSP is initiated.	Applies to all CSPs
Expiration Date	The time during which a product can be expected to meet the requirements of the compendial monograph, if one exists, provided it is kept under the prescribed storage conditions.	Applies to all conventionally manufactured products, APIs, and excipients

12.2 Parameters to Consider in Establishing a BUD

Multiple factors that affect sterility and chemical and physical stability must be considered when establishing BUDs for CSPs. BUDs should be established conservatively for CSPs to ensure that the drug maintains its required characteristics (i.e., stability and sterility) until its BUD.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

When establishing a BUD for a CSP, compounders must consider factors that may affect stability, including but not limited to:
- The chemical and physical properties of the drug and/or its formulation
- The compatibility of the container–closure system with the finished preparation (e.g., leachables, interactions, and storage conditions)

The BUDs for CSPs in *Table 11* and *Table 12* are based primarily on factors that affect the achievement and maintenance of sterility, which include, but are not limited to, the following:
- Environment in which the CSP is prepared (e.g., PEC in a cleanroom suite or SCA)
- Aseptic preparation and sterilization method
- Components and ingredients (e.g., sterile or nonsterile starting ingredients)
- Whether or not sterility testing is performed
- Storage conditions (e.g., packaging and temperature)

12.3 Establishing a BUD for a CSP
1592BUDs for CSPs must be established in accordance with *Table 11* for Category 1 CSPs and *Table 12* for Category 2 CSPs. One day is equivalent to 24 hours. The BUDs in *Table 11* and *Table 12* for CSPs are based on the risk of 1596 microbial contamination or not achieving sterility despite implementation of the requirements in this chapter. Therefore, it is assumed that the CSP formulation will remain chemically and physically stable, and its packaging will maintain its integrity for the duration of the BUD. A shorter BUD is required when the stability of the CSP or its components is less than the hours or days stated in *Table 11* or *Table 12*. Additionally, the BUD must not exceed the shortest remaining expiration date or BUD of any of the starting components, regardless of the source. *Table 11* establishes the longest permitted BUDs for Category 1 CSPs. Category 1 CSPs may be prepared in an SCA or cleanroom suite (see *4.2 Facility Design and Environmental Controls*).

Table 11. BUDs for Category 1 CSPs
1608**Storage Conditions Controlled Room Temperature (20°–25°)**
Refrigerator (2°–8°)
BUD ≤12 hours room ≤24 hours Refrigerator

Table 12 establishes BUDs for Category 2 CSPs, based on the following factors affecting sterility:
- Aseptic preparation and sterilization method
- Starting components
- Sterility testing
- Storage conditions

Category 2 CSPs must be prepared in a cleanroom suite (see *4.2 Facility Design and Environmental Controls*).

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

ASEPTIC PREPARATION AND STERILIZATION METHOD

1 A CSP may be prepared by the following methods (see *8. Sterilization and Depyrogenation*):

1. **Aseptic preparation**, which includes either 1) compounding with only sterile starting ingredient(s), or 2) compounding with nonsterile ingredient(s) followed by sterilization by filtration. [NOTE—Sterilization by filtration is not a form of terminal sterilization.]

2. **Terminal sterilization**, which includes compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization with a process intended to achieve an SAL of 10^{-6} (e.g., dry heat, steam, or irradiation). Terminal sterilization is the preferred method of sterilization, unless the specific CSP or container–closure system cannot tolerate terminal sterilization. *Table 12* allows for longer BUDs for CSPs that are terminally sterilized than for aseptically prepared CSPs because terminal sterilization using a verified method provides reasonable assurance that a CSP will be sterile.

STARTING COMPONENTS

The use of one or more nonsterile starting component(s) is a risk factor to be considered when preparing a CSP. A longer BUD is permitted in *Table 12* for CSPs that are aseptically prepared from conventionally manufactured sterile starting component(s) than from one or more nonsterile starting component(s).

STERILITY TESTING

Sterility testing (see *10.2 Sterility Testing*) of a CSP can provide additional assurance of the absence of contamination, although passing a sterility test does not guarantee that all units of a batch of CSPs are sterile because contamination may not be uniformly distributed throughout the batch. A longer BUD is permitted in *Table 12* if sterility testing results are within acceptable limits.

STORAGE CONDITIONS

Storage in colder conditions [i.e., in a refrigerator or freezer (see *Packaging and Storage Requirements* ⟨659⟩)] has been shown to slow the growth of most microorganisms. However, the chemical and physical stability of the CSP and its components must be considered when storing in colder conditions (e.g., some formulations may precipitate when stored in a refrigerator or freezer). A longer BUD is permitted in *Table 12* for CSPs stored in colder conditions than for CSPs stored at controlled room temperature. If the CSP will be stored in a frozen state, the container–closure system must be able to withstand the physical stress (i.e., without breaking or cracking) during storage in a freezer. The CSP must be thawed in appropriate conditions to avoid compromising the physical and chemical stability of the preparation and its components (e.g., do not heat in a microwave). Once the CSP is thawed, the CSP must not be re-frozen. CSPs may be stored under different storage conditions before they are used (e.g., CSPs may first be frozen, and then thawed in the refrigerator, and finally kept at controlled room temperature before administration). The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage condition, and BUDs must not be additive. For example, a CSP cannot be stored for 45 days in a freezer, then 3 days refrigerated, and then 1 day at controlled room temperature for a total of 49 days. Once a CSP has been stored under a condition that would require a shorter BUD (i.e., controlled room temperature), the CSP must be used within the timeframe for that storage condition (in this example, 1 day).

Table 12. BUDs for Category 2 CSPs
Preparation Characteristics Storage Conditions Sterilization

Sterility Testing & Passed Controlled Room Refrigerator Freezer
1672 **Preparation Characteristics Storage Conditions**

Sterilization Method	**Sterility Test** Passed	**Room** 20-25	**Refrig** 2—8	**Freeze** -25- -10	
Aseptically prepared CSPs	No	1 day	4 days	45 days	Note A
		4 days	9 days	45 days	Note B
Terminally Sterilized CSP	No	14 days	28 days	45 days	
	Yes	30 days	60 days	90 days	

Note A – Prepared from one or more non sterile starting components
Note B – Prepared from only sterile starting components

12.4 Multiple-Dose CSPs
1673 A compounded multiple-dose container is designed to contain more than one dose, intended to be entered or penetrated multiple times, and usually contains a preservative. The presence of a preservative may inhibit the growth of microorganisms and minimize the risk of contamination. The use of preservatives must be appropriate for the CSP formulation and the route of administration. For example, the preservative must not be inactivated by any ingredients in the CSP and some preservatives are not always appropriate for the patient (e.g., neonates) or route of administration (e.g., intrathecal or ophthalmic injections). The use of preservatives, however, must not be considered a substitute for aseptic technique.
A multiple-dose CSP must be prepared as a Category 2 CSP. A multiple-dose CSP must additionally pass antimicrobial effectiveness testing in accordance with *Antimicrobial Effectiveness Testing* ⟨51⟩. The compounder may rely on 1) antimicrobial effectiveness testing that it conducts (or 1687 contracts for) once for each formulation in the particular container–closure system in which it will be packaged or 2) antimicrobial effectiveness testing results published in peer-reviewed literature sources if the CSP formulation (including any preservative) and container–closure system are exactly the same as those tested.
After a multiple-dose container is initially entered or punctured, the multiple dose container must not be used for longer than the assigned BUD or 28 days if supported by antimicrobial effectiveness testing results (see ⟨51⟩) on the CSP, whichever is shorter.

The container–closure system used to package the multiple-dose CSP must be evaluated for and conform to container–closure integrity (see ⟨1207⟩). The container–closure integrity test needs to be conducted only once on each formulation and fill volume in the particular container–closure system in which the multiple-dose CSP will be packaged.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

13. USE OF CONVENTIONALLY MANUFACTURED PRODUCTS

This section addresses the time within which an entered or punctured conventionally manufactured product must be used.

13.1 Use of Conventionally Manufactured Single-Dose Containers

A conventionally manufactured single-dose container is designed for use with a single patient as a single injection/infusion (see *Packaging and* Storage *Requirements* ⟨659⟩*, General Definitions, Injection Packaging Systems*). A conventionally manufactured single-dose container is a container–closure system that holds a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. If a single-dose vial is entered or punctured in worse than an ISO Class 5 air, it must be used within 1 hour or by the end of the case in which it will be used, and any remaining contents must be discarded. If a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 6 hours after initial entry or puncture. Opened single-dose ampuls must not be stored for any time period.

13.2 Use of Conventionally Manufactured Multiple-Dose Containers

1720 A conventionally manufactured multiple-dose container is intended to contain more than one dose of a drug product (see *Packaging and Storage Requirements* ⟨659⟩*, General Definitions, Injection Packaging Systems*). Once initially entering or puncturing the multiple-dose container, the multiple-dose container must not be used for more than 28 days (see ⟨51⟩) unless otherwise specified by the manufacturer on the labeling.

13.3 Use of a Conventionally Manufactured Pharmacy Bulk Package

1727 A conventionally manufactured pharmacy bulk package is a container of a sterile product for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the sterile preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile containers. The pharmacy bulk package must be used according to the manufacturer's labeling (see *Packaging and Storage Requirements* ⟨659⟩*, General Definitions, Injection Packaging System*. The pharmacy bulk package is to be used only in an ISO Class 5 PEC.

14. USE OF CSPS AS COMPONENTS

1738 This section addresses the time within which an entered or punctured CSP must be used.

14.1 Use of Compounded Single-Dose Containers

A compounded single-dose container is intended for one-time administration (e.g., injection, infusion, case) for a single patient. If a compounded single-dose container is entered or punctured only in ISO Class or cleaner air, it may be used for up to 6 hours after initial entry or puncture. The remainder must be discarded. The compounded single-dose container must be stored in conditions applicable to that CSP (e.g.,refrigerator, controlled room temperature).

14.2 Use of Compounded Stock Solutions

1749 A compounded stock solution is a sterile mixture of components that is used to prepare CSP(s). The compounded stock solution must be stored according to storage conditions for the

BUD assigned. The compounded stock solution must only be entered or punctured in an ISO Class 5 or cleaner air. It may be used for up to 6 hours after initial entry or puncture. The remainder must be discarded.

14.3 Use of Compounded Multiple-Dose Containers

1756 After a multiple-dose container is initially entered or punctured, the 1757 multiple-dose container must not be used for longer than the assigned BUD (see *Multiple-Dose CSPs*) or 28 days if supported by antimicrobial effectiveness testing results (see ⟨51⟩) on the CSP, whichever is shorter.

15. QUALITY ASSURANCE AND QUALITY CONTROL

1762 QA is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards. QC is the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CSP. See *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩.

A facility's QA and QC programs must be formally established and documented in SOPs that ensure that all aspects of the preparation of CSPs are conducted in accordance with the requirements in this chapter and applicable jurisdictional laws and regulations. A designated person must ensure that the facility has formal, written QA and QC programs that establish a system of:

1. Adherence to procedures
2. Prevention and detection of errors and other quality problems
3. Evaluation of complaints and adverse events
4. Appropriate investigations and corrective actions

The SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. The overall QA and QC program must be reviewed at least once every 12 months by the designated person. The results of the review must be documented and appropriate action must be taken if needed.

15.1 Notification About and Recall of Out-of-Specification Dispensed CSPs

1784 If a CSP is dispensed or administered before the results of release testing are known, the facility must have procedures in place to:

1. 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), and 2. Determine whether a recall is necessary The 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 disposition and reconciliation of the recalled CSP The sterile compounding facility must document the implementation of the recall procedures. The recall must be reported to appropriate regulatory bodies as required by applicable jurisdictional laws and regulations (e.g., state board of pharmacy, state health department).

15.2 Complaint Handling

1802 Compounding facilities must develop and implement SOPs for handling complaints. Complaints may include, but are not limited to, concerns or reports on the quality, labeling, or possible adverse reactions related to a specific CSP. A designated person must review all complaints to determine whether the complaint indicates a potential quality problem with the CSP. If it does, a thorough investigation into the cause of the problem must be initiated and completed. The investigation must consider whether the quality problem extends to other CSPs. Corrective action, if necessary, must be implemented for all potentially affected CSPs. Consider whether to initiate a recall of potentially affected CSPs and whether to cease sterile compounding processes until all underlying problems have been identified and corrected. A readily retrievable written or electronic record of each complaint must be kept by the facility, regardless of the source of the complaint (e.g., email, telephone, mail). The record must contain the name of the complainant, the date the complaint was received, the nature of the complaint, and the response to the complaint. In addition, to the extent that the information is known, the following should be recorded: the name and strength of the CSP and the assigned internal identification number (e.g., prescription, order, or lot number). The record must also include the findings of any investigation and any follow-up. Records of complaints must be easily retrievable for review and evaluation for possible trends and must be retained in accordance with the record-keeping requirements in *17. Documentation*. A CSP that is returned in connection with a complaint must be quarantined until it is destroyed after completion of the investigation and in accordance with applicable jurisdictional laws and regulations.

15.3 Adverse Event Reporting

1830 Adverse events potentially associated with the quality of CSPs must be reported in accordance with facility SOPs and all applicable jurisdictional laws and regulations. In addition, adverse events potentially associated with the quality of the CSP should be reported to the applicable jurisdictional regulatory body (e.g., state boards of pharmacy, state health departments, FDA's MedWatch program for human drugs, or FDA Form a for animal drugs).

16. CSP STORAGE, HANDLING, PACKAGING, SHIPPING, & TRANSPORT

1840 Processes and techniques for storing, handling, packaging, and transporting CSPs must be outlined in SOPs. Personnel who will be storing, handling, packaging, and transporting CSPs within the facility must be trained in accordance with the relevant SOPs, and the training must be documented.

16.1 Handling and Storing CSPs

1846 CSPs must be handled in a manner that maintains CSP quality and packaging integrity. To help ensure that CSP quality is maintained during storage at the compounding facility, personnel must monitor conditions in the storage areas. A controlled temperature area (see ⟨659⟩) must be established and monitored to ensure that the temperature remains within the appropriate range

for the CSP (see *4.2 Facility Design and Environmental Controls*). The compounding facility must detect and minimize temperature excursions that are outside the temperature limits within the controlled temperature areas. When it is known that a CSP has been exposed to temperatures either below or above the storage temperature limits for the CSP, a designated person must determine (e.g., by consulting literature or analytical testing) whether the CSP is expected to retain its integrity or quality. If this cannot be determined, it must be discarded.

16.2 Packaging of CSPs

1861 Packaging materials should protect CSPs from damage, leakage, contamination, degradation, and adsorption while preventing inadvertent exposure to transport personnel. The facility must select appropriate shipping containers and packaging materials based on the product specifications, information from vendors, and the mode of transport. Compounding personnel must monitor the effectiveness and reliability of the packaging materials.

Alternative modes of transport and/or special packaging (e.g., tamper- evident closures) may be needed to protect the quality of CSPs. If the CSP is sensitive to light, light-resistant packaging materials must be used. In some cases, the CSP must be packaged in a special container (e.g., a cooler) to protect it from temperature fluctuations.

16.3 Shipping and Transporting CSPs

1874 Compounding personnel must select modes of transport that are expected to deliver properly packed CSPs in an undamaged, sterile, and stable condition. Inappropriate transport can adversely affect the quality of CSPs. For example, preparation-specific considerations should be given to physical shaking that might occur during pneumatic tube transport or undue exposure to heat, cold, or light. When shipping or transporting CSPs that require special handling (e.g., CSPs with stability concerns), personnel must include specific handling instructions on the exterior of the container.

17. DOCUMENTATION

1884All facilities where CSPs are prepared must have and maintain written or electronic documentation to demonstrate compliance with the requirements in this chapter. This documentation must include, but is not limited to, the following:

- 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 (e.g., calibration, verification, and maintenance reports)
- Receipt of components
- SOPs, Master Formulation Records (when used), and Compounding Records
- Release testing records
- Information related to complaints and adverse events
- Investigations and corrective actions Documentation must comply with all applicable jurisdictional laws and regulations. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required compounding records for a particular CSP (e.g., Master Formulation Record, Compounding Record, and release testing results) must be readily

retrievable for at least 3 years after preparation or as required by jurisdictional laws and regulations, whichever is longer.

18. COMPOUNDING ALLERGENIC EXTRACTS

1909 Licensed allergenic extracts are defined as single-dose or multiple-dose preparations and dilutions for subcutaneous immunotherapy. Licensed allergenic extracts are routinely mixed and diluted into prescription sets for an individual patient, even though these allergenic extract combinations are not specified in the approved licenses for the licensed biological products [e.g., Biological License Applications (BLA)]. Because patients must be maintained on a maintenance dose of prepared concentrated allergenic extracts for a period of time longer than the BUDs specified for Category 1 and Category 2, longer BUDs are required for prescription sets to achieve effective therapy. Allergenic extracts prescription sets must follow standards at least as stringent as those in this section:

Personnel Qualifications

1. A designated person with training and expertise in allergen immunotherapy is responsible for ensuring that personnel who will be preparing allergen immunotherapy are trained, evaluated, and supervised.
2. Before beginning to independently prepare allergen extracts, all compounding personnel must complete training and be able to demonstrate knowledge of theoretical principles and skills for sterile compounding.
3. Annual personnel training and competency must be documented. Personnel must demonstrate proficiency in these procedures by passing a written exam before they can be allowed to compound allergenic extract prescription sets.
4. Compounding personnel must have their hand hygiene and garbing procedures evaluated using gloved fingertip and thumb sampling(see *Box 2-1*) 3 times before beginning to prepare prescription sets, and then at least annually thereafter.
5. Compounding personnel must have their sterile technique and related practices evaluated annually as demonstrated by successful completion of a media-fill test (see *Box 2-2*).
6. Personnel who fail competency evaluations must successfully pass reevaluations in the deficient area(s) before they can resume compounding of allergenic extract prescription sets. The designated person must identify the cause of failure and determine appropriate retraining requirements.
7. Personnel who have not compounded an allergenic extract prescription set in more than 6 months must be evaluated in all core competencies before resuming compounding duties.

Personnel Hygiene and Garbing

8. Before beginning compounding of allergen immunotherapy prescription sets, personnel must perform hand hygiene procedures (see *Box 3-1*).
9. Compounding personnel must don the:

A. Powder-free sterile gloves
B. Non-cotton, low-lint garment with sleeves that fit snugly around the wrists and that is enclosed at the neck
C. Face mask
D. Low-lint, disposable cover for head and if applicable, disposable cover for facial hair

10. Compounding personnel must disinfect their gloves throughout the process by rubbing sterile 70% IPA onto all surfaces of the gloves and letting the gloves dry thoroughly.

Facilities

11. The compounding process must occur in an ISO Class 5 PEC or in a dedicated allergenic extracts compounding area (AECA). The PEC or AECA used to compound prescription sets must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, all of which may adversely affect the air quality. Neither a PEC nor an AECA may be located adjacent to environmental control challenges (e.g., restrooms, warehouses, or food preparation areas). The PEC or the work surfaces in the AECA must be located at least 1 meter away from a sink. The impact of activities that will be conducted around or adjacent to the PEC or AECA must be considered carefully when designing such an area. A. If used, the PEC must be certified every 6 months (see *4.6* 1980 *Certification and Recertification*).. If used, a visible perimeter must establish the boundaries of the AECA.

I. Access to the AECA during compounding must be restricted to authorized personnel.

II. During compounding activities, no other activity is permitted in the AECA.

III. The surfaces of ceilings, walls, floors, fixtures, shelving, counters, cabinets in the AECA must be cleanable and must be kept clean.

IV. Carpet is not allowed in the AECA.

V. Surfaces should be resistant to damage by cleaning and sanitizing agents.

VI. The surfaces in the AECA upon which the allergenic extract prescription sets are prepared must be smooth, impervious, free from cracks and crevices, and non- shedding to allow for easy cleaning and disinfecting.

VII. Dust-collecting overhangs such as utility pipes, ledges, and windowsills should be minimized. If overhangs or ledges are present, they must be easily cleanable.

VIII. The AECA must be designed and controlled to provide a well-lighted working environment, with temperature and humidity controls for the comfort of compounding personnel wearing the required.

2007 **Cleaning and Disinfecting**

12. In a PEC, all interior surfaces of the PEC must be cleaned and disinfected at the beginning and end of each shift of compounding, when there are spills, and when surface contamination is known or suspected. The horizontal work surface must be disinfected between each prescription set.

13. In an AECA, all work surfaces in the AECA where direct compounding is occurring must be cleaned and disinfected at the beginning and end of each shift of compounding; between each prescription set; when there are spills; and when surface contamination is known or suspected.

14. Vial stoppers on packages of conventionally manufactured sterile ingredients must be disinfected by careful wiping with sterile 70% IPA swabs to ensure that the critical sites are wet and allowed to dry before they are used to compound allergenic extracts prescription sets.

2024 **Establishing BUDs**

15. The BUD for the prescription set must be no later than the earliest expiration date of any allergenic extract or any diluent that is part of the prescription set, and the BUD must not exceed 1 year from the date the prescription set is mixed or diluted.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

Labeling

2030 16. The label of each vial of an allergenic extract prescription set must display the following prominently and understandably:

A. Patient name
B. Type and fractional dilution of each vial, with a corresponding vial number
C. BUD
D. Identity of the compounder and date of preparation
E. Storage conditions

2041 **Shipping and Transport**

17. If shipping or transporting allergenic extract prescription sets, compounding personnel must select modes of transport that are expected to deliver properly packed prescription sets in an undamaged, sterile, and stable condition. Inappropriate transport can adversely affect the quality of allergenic extract prescription sets.

18. When shipping or transporting allergenic extract prescription sets that require special handling, personnel must include specific handling instructions on the exterior of the container.

2051 **Documentation**

19. All facilities where allergen extract prescription sets are prepared must have and maintain written or electronic documentation to include, but not limited to, the following:

A. SOPs describing all aspects of the compounding process
B. Personnel training records, competency assessments, and qualification records including corrective actions for any failures
C. Certification reports of the PEC, if used, including corrective actions for any failures
D. Temperature logs for the refrigerator(s)
E. Cleaning logs
F. Compounding records for individual allergenic extract prescription sets (see *Box 18-1*)
G. Information related to complaints and adverse events
H. Investigations and corrective actions

Box 18-1. Compounding Records for Individual Allergenic Extract Prescription Sets

2069 Compounding Records must include at least the following information:

- Name, concentration, volume, vendor or manufacturer, lot number, and expiration date for each ingredient
- Date and time of preparation of the allergenic extract
- Assigned internal identification number
- Identity of all individuals involved in each step
- Total quantity compounded
- Assigned BUD
- Documentation of results of QC procedures (e.g., visual inspection, second verification of quantities)

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

2070 **GLOSSARY**

Administration: The direct and immediate application of a conventionally manufactured product or a CSP to a patient by injecting, infusing, or otherwise providing a sterile medication in its final form.

Airlock: A space with interlocked doors, constructed to maintain air pressure control when items move between two adjoining areas (generally with different air cleanliness standards). The intent of an airlock is to prevent ingress of particulate matter and microbial contamination from a lesser-controlled area.

Allergenic extract prescription set: 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 BLAs for the licensed biological products.

Allergenic extracts: Biological substances used for the diagnosis and/or treatment of allergic diseases such as allergic rhinitis, allergic sinusitis, allergic conjunctivitis, bee venom allergy, and food allergy.

Ante-room: An ISO Class 8 or cleaner room with fixed walls and doors where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels are performed. The ante-room is the transition room between the unclassified area of the facility and the buffer room.

Aseptic processing or preparation: A process by which separate, sterile components (e.g., drugs, containers, or closures) are brought together under conditions that maintain their sterility. The components can either be purchased as sterile or, when starting with nonsterile components, can be separately sterilized prior to combining (e.g., by membrane filtration, autoclave).

Aseptic technique: A type of technique used to keep objects and areas free of microorganisms and thereby minimize infection risk to the patient. It is accomplished through practices that maintain the microbe count at an irreducible minimum.

Batch: More than 1 unit of CSP prepared in a single process and intended to have uniform characteristics and quality, within specified limits.

Beyond-use date (BUD): Either the date or hour and date after which a CSP must not be used or administration must not begin. The BUD is determined from the date/time that preparation of the CSP is initiated.

Blood components: Any therapeutic constituent of blood that is separated by physical or mechanical means (e.g., red cells, platelets, plasma). It is not intended to capture plasma-derived products.

Buffer room: An ISO Class 7 or cleaner room with fixed walls and doors where PEC(s) that generate and maintain an ISO Class 5 environment are physically located. The buffer room may only be accessed through the ante- room.

Category 1 CSP: A CSP that is assigned a BUD of 12 hours or less at controlled room temperature or 24 hours or less refrigerated that is compounded in accordance with all applicable requirements for Category 1 CSPs in this chapter.

Category 2 CSP: A CSP that is assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours refrigerated that is compounded in accordance with all applicable requirements for Category 2 CSPs in this chapter.

Certificate of analysis (COA): A report from the supplier of a component, container, or closure that accompanies the supplier's material and contains the specifications and results of all analyses and a description of the material.
Class II biological safety cabinet (BSC): A ventilated cabinet with an open front and inward and downward unidirectional Hank note not unidirectional HEPA-filtered airflow and HEPA-filtered exhaust. A BSC used to prepare a CSP must be capable of providing an ISO Class 5 environment for preparation of the CSP.
Classified area: An area that maintains an air quality classification based on the ISO (see also the definition for *ISO class*).
Cleaning agent: An agent for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.
Cleanroom suite: A classified area that consists of both an ante-room and buffer room.
Component: Any ingredient used in the compounding of a preparation, including any active ingredient, added substance, and the container–closure system used to package the preparation.
Compounded sterile preparation (CSP): A preparation intended to be sterile that is created by combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance.
Compounding: The process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile medication. Preparing a conventionally manufactured sterile product in accordance with the directions contained in approved labeling provided by the product's manufacturer is not compounding as long as the product is prepared for an individual patient and follows the provisions for administration.
Compounding area: The area where compounding is occurring (i.e., a cleanroom suite or SCA).
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.
Compounded stock solution: A sterile mixture of components that is used to compound finished CSPs.
Container–closure system: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection.
Conventionally manufactured product: A pharmaceutical dosage form, usually the subject of an FDA-approved application, and manufactured under current good manufacturing practice conditions.
Critical site: A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, and beakers) or openings (e.g., opened ampules and needle hubs) that are exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination.
Designated person: One or more individuals assigned to be responsible and accountable for the performance and operation of the compounding facility and personnel in the preparation of CSPs.

Detergent: A cleaning agent comprised of a hydrophilic component and a lipophilic component. There are four types of detergents: anionic, cationic, amphoteric, and non-ionic.
Direct compounding area (DCA): A critical area within the ISO Class 5 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.
Disinfectant: A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria. Sporicidal disinfectant agents are considered a special class of disinfectants that also are effective against bacterial endospores.
Dynamic operating conditions: Conditions in the SCA or cleanroom suite in which operating personnel are present and performing actual or simulated compounding operations.
Expiration date: The time during which a product can be expected to meet the requirements of the compendial monograph, if one exists, provided that the product is kept under the prescribed storage conditions.
Filter integrity test: A test (e.g., bubble point test) of the integrity of a sterilizing grade filter performed after the filtration process to detect whether the integrity of the filter has been compromised.
First air: The air exiting the HEPA filter in a unidirectional air stream.
Formulation: The specific qualitative and quantitative composition of the final CSP.
Garb: Items such as gloves, gowns, shoe covers, head and facial hair covers, masks, and other items designed to reduce particle-shedding from personnel and minimize the risk of contamination of CSP(s).
Garment: Gowns or coveralls.
Germicidal detergent: See the definition for *One-step disinfection*.
Hazardous drug (HD): Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low dose in humans or animals, genotoxicity, or new drugs that mimic existing HDs in structure or toxicity.
High-efficiency particulate air (HEPA) filtration: Being, using, or containing a filter designed to remove 99.97% of airborne particles measuring 0.3-micron or greater in diameter passing through it.
ISO class: An air-quality classification from the International Organization for Standardization.
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. [NOTE—A CAI or CACI is not an isolator.]
Label: A display of written, printed, or graphic matter on the immediate container of any article.
Labeling: All labels and other written, printed, or graphic matter that are 1) on any article or any of its containers or wrappers, or 2) accompanying such an article.
Laminar airflow system (LAFS): A device or zone within a buffer area that provides an ISO Class 5 or better air quality environment for sterile compounding. The system provides a unidirectional HEPA-filtered airflow.
Laminar airflow workbench (LAFW): A device that is a type of LAFW that provides an ISO Class 5 or better air quality environment for sterile compounding. The device provides a unidirectional HEPA-filtered airflow.
Line of demarcation: A visible line on the floor that separates the clean and dirty sides of the ante-room.

Low-lint wiper: A wiper exhibiting few, if any, fibers or other contamination, visible without magnification, which is separate from, or easily removed from, the wiper material in a dry condition.
Media fill test: A simulation used to qualify processes and personnel engaged in sterile compounding to ensure that the processes and personnel are able to prepare CSPs without contamination.
Multiple-dose container: A container of sterile medication for parenteral administration (e.g., injection or infusion) that is designed to contain more than one dose of the medication. A multiple-dose container is usually required to meet the antimicrobial effectiveness testing criteria. See *Container Content for Injections ⟨697⟩, Determination of Volume of Injection in Containers, Multi-Dose Containers*.
One-step disinfectant: A product with an EPA-registered claim that it can clean and disinfect a non-porous surface in the presence of light to moderate organic soiling without a separate cleaning step.
Outsourced sterile product: A sterile product compounded by an FDA-registered 503B outsourcing facility.
Pass-through: An enclosure with sealed doors on both sides that may be interlocked. The pass-through is positioned between two spaces for the purpose of minimizing particulate transfer while moving materials from one space to another.
Perimeter: A visible line on the floor that defines the boundaries of the SCA or AECA.
Pharmacy bulk package: A conventionally manufactured sterile product for parenteral use that contains many single doses intended for use in a pharmacy admixture program. A pharmacy bulk package may either be used to prepare admixtures for infusion or, through a sterile transfer device, for filling sterile containers.
Positive-pressure room: A room that is maintained at higher pressure than the adjacent spaces, and therefore the net airflow is out of the room.
Preservative: A substance added to inhibit microbial growth.
Primary engineering control (PEC): A device or zone that provides an ISO Class 5 air quality environment for sterile compounding.
Pyrogen: A substance that induces a febrile reaction in a patient.
Quality assurance (QA): A system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards.
Quality control (QC): The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CSP.
Reconstitution: The process of adding a diluent to a solid conventionally manufactured product to prepare a sterile solution or suspension.
Release testing: Testing performed to ensure that a preparation meets appropriate quality characteristics.
Repackaging: The act of removing a sterile product or preparation from its original primary container and placing it into another primary container, usually of smaller size without further manipulation.
Restricted-access barrier system (RABS): An 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. Examples of RABS include CAIs and CACIs.
Secondary engineering control (SEC): The area where the PEC is placed (e.g., a cleanroom suite or an SCA). It incorporates specific design and operational parameters required to minimize the risk of contamination within the compounding area.
Segregated compounding area (SCA): A designated, unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of Category 1 CSPs only.
Single-dose containers: A container of sterile medication for parenteral administration (e.g., injection or infusion) that is designed for use with a single patient as a single injection/infusion. A single-dose container usually does not contain a preservative.
Sporicidal agent: A chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.
Stability: The extent to which a product or preparation retains physical and chemical properties and characteristics within specified limits throughout its expiration or BUD.
Sterility: The absence of viable microorganisms.
Sterility assurance level (SAL): The probability of an item being nonsterile after it has been exposed to a validated sterilization process. An SAL value can only be applied to terminal sterilization.
Sterilization by filtration: Passage of a gas or liquid through a sterilizing-grade membrane to yield filtrates that are sterile.
Sterilizing-grade membranes: Filter membranes that are documented to retain 100% of a culture of 10_7 microorganisms of a strain of *Brevundimonas diminuta* per square centimeters of membrane surface under a pressure of not less than 30 psi. Such filter membranes are nominally 0.22-µm or 0.2-µm pore size.
Terminal sterilization: The application of a lethal process (e.g., dry heat, steam, irradiation) to sealed containers for the purpose of achieving a predetermined SAL of greater than 10_{-6} or a probability of less than one in one million of a nonsterile unit.
Two-step disinfectant: An EPA-registered disinfectant that must be used after a separate cleaning step. The surface must be cleaned to remove soiling prior to application of the disinfectant product.
Unclassified space: A space not required to meet any air cleanliness classification based on the ISO.
Unidirectional airflow: Air within a PEC moving in a single direction in a uniform manner and at sufficient velocity to sweep particles away from the DCA.
Workflow management system: Technology comprised of hardware and software that allows for automation to assist in the verification of components of, and preparation of, CSPs and to document components and processes.
Verify: To confirm that a method, process, system, or equipment will perform as expected under the conditions of actual use.

APPENDICES

2331 **Appendix 1: Acronyms**
ACD - Automated compounding device
ACPH -Air changes per hour

AECA -Allergenic extracts compounding area
API -Active pharmaceutical ingredient
BLA -Biological License Application
BMBL -Biosafety in Microbiological and Biomedical Laboratories
BSC -Biological safety cabinet
BUD -Beyond-use date
CACI -Compounding aseptic containment isolator
CAI -Compounding aseptic isolator
CDC -Centers for Disease Control and Prevention
CETA -Controlled Environment Testing Association
CFU -Colony-forming units
COA -Certificate of analysis
CSP -Compounded sterile preparation
CVE -Containment ventilated enclosure
DCA -Direct compounding area
ECV -Endotoxin challenge vial
EPA -Environmental Protection Agency
FDA -Food and Drug Administration
HDs -Hazardous drugs
HEPA -High-efficiency particulate air
HVAC -Heating, ventilation, and air conditioning
IPA -Isopropyl alcohol
ISO -International Organization for Standardization
IVLFZ -Integrated vertical laminar flow zone
LAFS -Laminar airflow system
LAFW -Laminar airflow workbench
PEC -Primary engineering control
PPE -Personal protective equipment
QA -Quality assurance
QC -Quality control
RABS -Restricted-access barrier system
SAL -Sterility assurance level
SCA -Segregated compounding area
SEC -Secondary engineering control
SOP -Standard operating procedure
TSA -Trypticase soy agar

Appendix 2: Example Designs for Sterile Non-Hazardous Drug
2334 **Compounding Areas**[a] **Type of Facility Design Example Design**
Cleanroom suite[b]
SCA
[a] For examples of designs for hazardous drug compounding areas, see *Hazardous Drugs—Handling in Healthcare Settings* ⟨800⟩*, Appendix 2: Examples of Designs for Hazardous Drug Compounding Areas*. The arrows indicate the direction of airflow.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document

References:

1 U.S. Food and Drug Administration, Guidance for Industry, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice,* September 2004.

2 Guidelines for Environmental Infection Control in Health-Care Facilities, Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC), MMWR, vol. 52, no. RR-10, June 6, 2003, figure 3, pg. 12.

3 NSF/ANSI 49.

4 ISO 14644-4:2001 Cleanrooms and associated controlled environments— Design, construction, and start-up, *Case Postale 56,* CH-1211 Geneve 20, Switzerland, tel. +41 22 749 01 11.

5 By definition (IEST RP CC 001.4), HEPA filters are a minimum of 99.97% efficient when tested using 0.3-µm thermally generated particles and a photometer or rated at their most penetrating particle size using a particle counter.

6 Sample procedures are detailed in CETA Applications Guide CAG-002-2006–section 2.09.

7 Controlled Environment Testing Association, 1500 Sunday Drive, Ste. 102, Raleigh, NC 27607; www.CETAinternational.org.

8 Agalloco J, Akers JE. Aseptic Processing: A Vision of the Future. *Pharmaceutical Technology,* 2005. Aseptic Processing supplement, s16.

9 Eaton T. Microbial Risk Assessment for Aseptically Prepared Products. *Am Pharm Rev.* 2005; 8 (5, Sep/Oct): 46–51.

10 *Guideline for Hand Hygiene in Health care Settings,* MMWR, October 25, 2002, vol. 51, No. RR-16 available on the Internet at *http://www.cdc.gov/handhygiene/*.

11 The use of additional resources, such as the Accreditation Manual for Home Care from the Joint Commission on Accreditation of Healthcare Organizations, may prove helpful in the development of a QA plan.

12 See *American Society of Heating, Refrigerating and Air-Conditioning* 2366 *Engineers, Inc. (ASHRAE), Laboratory Design Guide*.

13 *CETA Applications Guide for the Use of Compounding Isolators in Compounding Sterile Preparations in Healthcare Facilities,* CAG-001-2005, Controlled Environment Testing Association (CETA), November 8, 2005. (Hank creates a health hazard)

14 Agalloco J, Akers JE. Aseptic processing: a vision of the future. *Pharm Technol*. 2005; Aseptic Processing supplement, s16

2 Eaton T. Microbial risk assessment for aseptically prepared products. *Am* 2373 *Pharm Rev*. 2005;8(5):46–51.

This document is a summary of the proposed USP<797> July 2018. Formatted to allow "easier reading" and includes comments from Hank Rahe, Technical and Regulatory Consultant in red. Page number references page numbers in the original USP document