USP 795 AND 797 CHAPTER UPDATES

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FINANCIAL DISCLOSURE AND RESOLUTION

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I have no relevant financial relationships with ineligible companies to disclose.

I am employed by the OU College of Pharmacy and on the Expert Panel for Radiopharmaceuticals (August 2017 to present). This presentation represents my own views and I am not speaking on behalf of either organization.

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PROFESSIONAL PRACTICE GAP

- The standard setting United States Pharmacopeia (USP) has published revisions to general chapters <795> and <797>. The revisions have significant changes from the last revisions of 2014 for <795> and 2008 for <797>.
- USP is not an enforcing body, but it is recognized as the standard for pharmaceuticals since 1820. State Board of Pharmacies may adopt or reject any of the USP standards. The FDA has recognized <795> and <797> in Federal Statutes and considers them enforceable once they are official.

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LEARNING OBJECTIVES

At the completion of this activity, pharmacists will be able to:

1. Report the major changes in USP compounding chapters
2. Classify a sterile preparation given the environmental engineering controls
3. Identify the appropriate beyond-use date for acquired data

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Which is a major change in BOTH <795> and <797> chapters?

- Categories of risk
- Cleaning, sanitizing, and garbing
- Clarification of active water content
- Use of other technologies not described in these chapters to extend BUDs

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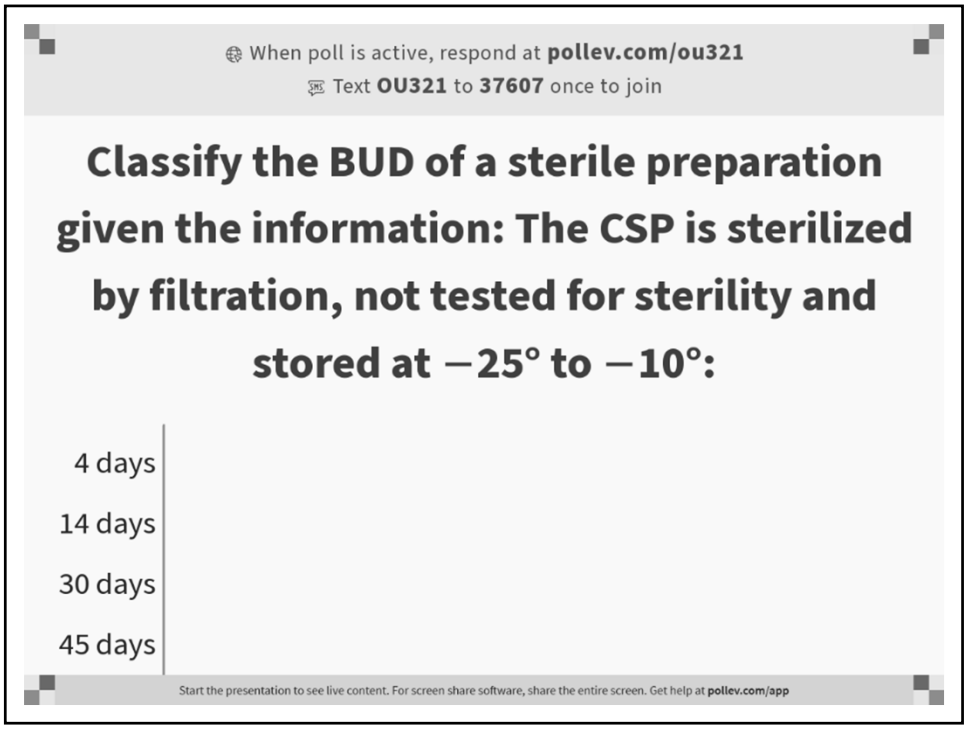

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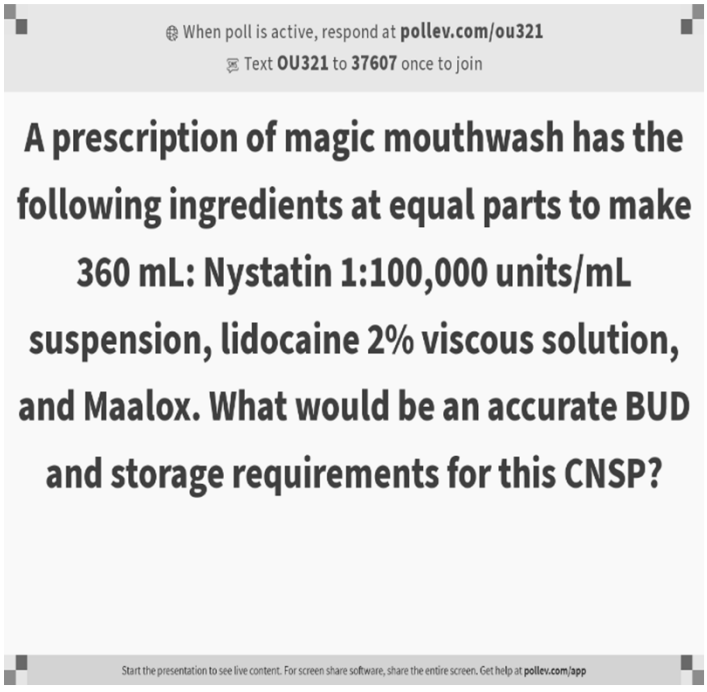
Identify the appropriate beyond-use date for acquired data:



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ENFORCEABILITY

- USP is not an enforcement agency - 2022 revisions become official Nov. 1 2023.
- Ensuring compliance, USP says to refer to your State regulations and your State statutes – States may have different official dates or regulations based on the particular jurisdiction
- FDA – modernization act 1997 (updated DQSA 2013) call out 795 & 797
  - 503a-(b)(1)(A)(i)(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding
  - Federally enforceable
- CMS accreditation and credentialing agencies have different conditions of participation - They get to choose how they are going to inspect, whether they incorporate USP chapters or not, or all, or in parts

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USP CALLS OFFICIAL CHAPTERS, ETC. TO BE COMPENDIAL APPLICABLE

- A general chapter numbered below 1000 becomes compendially applicable and thus is considered a required standard when:
  - Recognized by Federal Statue
  - A monograph references the chapter
  - A general chapter less than 1000 references another general chapter less than 1000
  - General Notices directly reference a general chapter below 1000
- A general chapter numbered above 1000 are considered recommendations

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LAYOUT OF BOTH CHAPTERS

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⟨795⟩ PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS

Change to read:

▲1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed for the preparation of compounded nonsterile preparations (CNSPs) for humans and animals. For purposes of this chapter, nonsterile compounding is defined as combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug product or bulk drug substance to create a nonsterile preparation.

The requirements in this chapter must be followed to minimize harm, including death, to human and animal patients that could result from 1) excessive microbial contamination, 2) variability from the intended strength of correct ingredients (e.g., ±10% of the labeled strength), 3) physical and chemical incompatibilities, 4) chemical and physical contaminants, and/or 5) use of ingredients of inappropriate quality.

Handling of nonsterile hazardous drugs (HDs) must additionally comply with *Hazardous Drugs—Handling in Healthcare Settings* ⟨800⟩.

1.1 Scope

1.1.1 CNSPs subject to the requirements in this chapter: CNSPs that must comply with this chapter include but are not limited to the following dosage forms:

- Solid oral preparations
- Liquid oral preparations
- Rectal preparations
- Vaginal preparations
- Topical preparations (i.e., creams, gels, and ointments)
- Nasal and sinus preparations intended for local application (i.e., nasal sprays and nasal irrigation)
- Otic preparations (excluding use in perforated eardrums)

1.1.2 Practices not subject to the requirements in this chapter: The following practices are not considered compounding and are not required to meet the requirements of this chapter. Handling of nonsterile HDs should additionally comply with ⟨800⟩. Refer to facility SOPs for additional safe practices (e.g., labeling).

- *Nonsterile radiopharmaceuticals:* Compounding of nonsterile radiopharmaceuticals is subject to the requirements in *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩.
- *Reconstitution:* Reconstitution of a conventionally manufactured nonsterile product in accordance with the directions contained in the manufacturer approved labeling
- *Repackaging:* Repackaging of conventionally manufactured drug products (see *Good Repackaging Practices* ⟨1178⟩ for recommendations)
- *Splitting tablets:* Breaking or cutting a tablet into smaller portions
- *Administration:* Preparation of a single dose for a single patient when administration will begin within 4 h. This

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problems within their operations. Personnel engaged in the compounding and dispensing of CNSPs must also comply with laws and regulations of the applicable regulatory jurisdiction.

1.1.4 Oversight by designated person(s): The compounding facility must designate one or more individuals to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of CNSPs. The responsibilities of the designated person(s) include but are not limited to:

- Overseeing a training program to ensure competency of personnel involved in compounding, handling, and preparing CNSPs
- Selecting components
- Monitoring and observing compounding activities and taking immediate corrective action if deficient practices are observed
- Ensuring that standard operating procedures (SOPs) are fully implemented. The designated person(s) must ensure that follow-up is carried out if problems, deviations, or errors are identified
- Establishing, monitoring, and documenting procedures for the handling and storage of CNSPs and/or components of CNSPs

The designated person(s) must be identified in the facility's SOPs. If the compounding facility has only one person responsible for all compounding in the facility, then that person is the designated person.

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2. PERSONNEL TRAINING AND EVALUATION

All personnel who compound or have direct oversight of compounding CNSPs must be initially trained and qualified by demonstrating knowledge and competency according to the requirements in this section (*2. Personnel Training and Evaluation*) before being allowed to perform their job functions independently.

Designated person(s) are responsible for creating and implementing a training program that describes the required training, the frequency of training, and the process for evaluating the competency of personnel. This program must equip personnel with knowledge and training in the required skills necessary to perform their assigned tasks. Personnel who compound or have direct oversight of compounding personnel must complete training initially and at least every 12 months in appropriate compounding principles and practices as described in this section. Other personnel, who do not compound and only perform functions such as in-process checks, final verification, or dispensing of CNSPs, must undergo training as required by the facility's SOPs.

Training and competency of personnel must be documented as described in *14. Documentation*.

Before beginning to compound CNSPs independently or have direct oversight of compounding personnel, personnel must complete training and be able to demonstrate knowledge of principles and competency of skills for performing nonsterile manipulations as applicable to their assigned tasks. Knowledge and competency must be demonstrated initially and at least every 12 months in at least the following core competencies:

- Hand hygiene
- Garbing
- Cleaning and sanitizing
- Handling and transporting components and CNSPs
- Measuring and mixing
- Proper use of equipment and devices selected to compound CNSPs
- Documentation of the compounding process (e.g., *7. Master Formulation and Compounding Records*)

Steps in the training procedure must include the following:

- Understand the requirements in this chapter
- Understand and interpret safety data sheets (SDSs) and, if applicable, certificates of analysis (COA)
- Read and understand procedures related to their compounding duties

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and demonstrated competency, and they must comply with the other requirements of this chapter.

3. PERSONAL HYGIENE AND GARBING

Individuals entering the compounding area must maintain appropriate personal hygiene. Individuals must evaluate whether they have a personal risk of potentially contaminating the compounding environment and CNSP (e.g., personnel with rashes, recent tattoos, oozing sores, conjunctivitis, or active respiratory infection). Individuals must report these conditions to the designated person(s). Because of the risk of contaminating the CNSP and the environment, the designated person(s) is responsible for evaluating whether these individuals should be excluded from working in compounding areas until their conditions have resolved.

3.1 Personnel Preparation

Personnel engaged in compounding must maintain appropriate hand hygiene and maintain appropriate cleanliness required for the type of compounding performed.

Before entering the compounding area, compounding personnel must remove any items that are not easily cleanable and that might interfere with garbing. At a minimum, personnel must:

- Remove personal outer garments (e.g., bandanas, coats, hats, and jackets)
- Remove all hand, wrist, and other exposed jewelry, including piercings that could interfere with the effectiveness of garbing or hand hygiene (e.g., watches or rings that may tear gloves)
- Remove earbuds or headphones

The designated person(s) may permit accommodations provided that the quality of the environment and CNSP will not be affected. All accommodations should be documented.

3.2 Hand Hygiene

Personnel must perform procedures necessary for appropriate hand hygiene when entering the compounding area to compound as described in *Box 1*.

The use of alcohol-based hand rub alone is not sufficient.

Box 1. Hand Hygiene Procedures

- Wash hands with soap and water for at least 30 s
- Dry hands completely with disposable towels or wipers
- Don gloves

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with ⟨800⟩.

4. BUILDINGS AND FACILITIES

4.1 Compounding Area

An area must be designated for nonsterile compounding. The method of designation must be described in the facility's SOPs. Other activities must not be occurring in the compounding area at the same time as compounding. The compounding area must be well lit and must be maintained in a clean, orderly, sanitary condition and in a good state of repair. There should not be carpet in the compounding area.

The compounding area must provide for the orderly placement of equipment and materials to prevent mix-ups among components, containers, labels, in-process materials, and finished CNSPs. The area should be designed, arranged, and used in a way that minimizes cross contamination from noncompounding areas.

4.2 Storage Area

Compounding personnel must monitor temperatures in the storage area(s) either manually at least once daily on days that the facility is open, or continuously with a temperature recording device to ensure the temperature remains within the appropriate range for the CNSPs and components. The results of the temperature readings must be documented on a temperature log or stored in the continuous temperature recording device and must be retrievable. All temperature monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.

The compounding facility must adhere to SOPs to detect and reduce the risk of temperature excursions within the storage area(s).

When it is known that a CNSP or component has been exposed to temperatures either below or above the storage temperature limits for the CNSP or component, personnel must determine whether the CNSP or component integrity or quality has been compromised, and, if so, the CNSP or component must be discarded.

All CNSPs, components, equipment, and containers must be stored off the floor in a manner that prevents contamination and permits inspection and cleaning of the storage area(s).

4.3 Water Sources

A source of hot and cold water and an easily accessible sink must be available. The sink must be emptied of all items unrelated to compounding and must be cleaned if visibly soiled before being used to clean any equipment used in nonsterile compounding. The plumbing system must be free of defects that may contribute to the contamination of any CNSP. *Purified Water* (see *Water for Pharmaceutical Purposes* ⟨1231⟩, *3.1.1 Purified Water*), distilled water, or reverse osmosis water should be used for rinsing equipment and utensils.

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osmosis water should be used for rinsing equipment and utensils.

5. CLEANING AND SANITIZING

Cleaning and sanitizing the surfaces in the nonsterile compounding area(s) must occur on a regular basis at the minimum frequencies specified in *Table 1* or, if compounding is not performed daily, cleaning and sanitizing must be completed before initiating compounding. Cleaning and sanitizing must be repeated when spills occur and when surfaces are visibly soiled. Applicable cleaning and sanitizing must be documented daily on days when compounding occurs.

Surfaces should be resistant to damage by cleaning and sanitizing agents. Floors in the compounding area should be easily cleanable and should not be porous or particle generating.

Cleaning and sanitizing agents must be selected and used with consideration of compatibilities, effectiveness, and minimal potential to leave residues.

If cleaning and sanitizing are performed as separate steps, cleaning must be performed first.

Table 1. Minimum Frequency for Cleaning and Sanitizing in Nonsterile Compounding Area(s)—Surfaces

Site	Minimum Frequency
Work surfaces	• At the beginning and end of each shift on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Between compounding CNSPs with different components
Floors	• Daily on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected
Walls	• When visibly soiled, after spills, and when surface contamination (e.g., from splashes) is known or suspected
Ceilings	• When visibly soiled and when surface contamination (e.g., from splashes) is known or suspected
Storage shelving	• Every 3 months, after spills, and when surface contamination (e.g., from splashes) is known or suspected

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6. EQUIPMENT AND COMPONENTS

6.1 Equipment

The equipment and components used for compounding a CNSP must be suitable for the specific compounding process.

Equipment surfaces that contact components must not be reactive, additive, or sorptive, and must not alter the quality of the CNSP. Disposable or dedicated equipment may be used to reduce the chance of bioburden and cross contamination.

Equipment must be stored in a manner that minimizes the risk of contamination and must be located to facilitate equipment use, maintenance, and cleaning. Equipment and devices used in the compounding or testing of compounded preparations must be inspected prior to use and, if appropriate, verified for accuracy as recommended by the manufacturer at the frequency recommended by the manufacturer or at least every 12 months, whichever is more frequent. After compounding, the equipment must be cleaned to prevent cross contamination of the next preparation.

Weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles (e.g., active pharmaceutical ingredients [APIs], added substances, and conventionally manufactured products) must be evaluated to determine if these activities must be performed in a closed-system processing device to reduce the potential exposure to personnel or contamination of the facility or CNSPs. Examples of closed-system processing devices include containment ventilated enclosures (CVEs), biological safety cabinets (BSCs), and single-use containment glove bags. The process evaluation must be carried out in accordance with the facility's SOPs, and the assessment must be documented.

If a CVE or BSC is used, it must be certified at least every 12 months according to manufacturer specifications or other laws and regulations of the applicable regulatory jurisdiction.

If a BSC, CVE, or other nondisposable device is used, it must be cleaned as described in *Table 2*.

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6.2 Components

The compounding facility must have written SOPs for the selection and inventory control of all components from receipt to use in a CNSP.

SDSs must be readily accessible to all personnel working with components located in the compounding facility. Personnel must be instructed on how to retrieve and interpret needed information.

6.2.1 Component selection: Designated person(s) must be responsible for selecting components to be used in compounding.

APIs:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must have a COA that includes specifications (e.g., compendial requirements for quality) and test results for the component that show the API meets expected quality
- In the United States, must be manufactured by an FDA-registered facility
- Outside of the United States, must comply with the laws and regulations of the applicable regulatory jurisdiction

All components other than APIs:

- Should be accompanied by a COA that verifies that the component meets the criteria in the *USP–NF* monograph, if one exists, and any additional specifications for the component
- In the United States, should be manufactured by an FDA-registered facility (If a component cannot be obtained from an FDA-registered facility, the designated person(s) must select a component that is suitable for the intended use.)
- Outside of the United States, must comply with the laws and regulations of the applicable regulatory jurisdiction

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SELECTION OF BULK DRUG (API)

- FDA registered facility- annually
- **§360. Registration of producers of drugs or devices**
- **(a) Definitions**
- (1) the term "manufacture, preparation, propagation, compounding, or processing" shall include repackaging or otherwise changing the container, wrapper, or labeling of any drug package or device package in furtherance of the distribution of the drug or device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user; and
- (2) the term "name" shall include in the case of a partnership the name of each partner and, in the case of a corporation, the name of each corporate officer and director, and the State of incorporation.

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jurisdiction. For information on the handling of HDs, see ⟨800⟩.

7. MASTER FORMULATION AND COMPOUNDING RECORDS

7.1 Creating Master Formulation Records

A master formulation record (MFR) is a detailed record of procedures that describes how the CNSP is to be prepared. An MFR must be created for each unique formulation of a CNSP. CNSPs are prepared according to the MFR, and the details of each preparation are documented on a compounding record (see *7.2 Creating Compounding Records*). Any changes or alterations to the MFR must be approved and documented according to the facility's SOP. See *Box 2* for information that must be included in an MFR.

Box 2. Master Formulation Record

An MFR must include at least the following information:

- Name, strength or activity, and dosage form of the CNSP
- Identities and amounts of all components; if applicable, relevant characteristics of components (e.g., particle size, salt form, purity grade, solubility)
- Container closure system(s)
- Complete instructions for preparing the CNSP including equipment, supplies, and description of compounding steps
- Physical description of the final CNSP
- Beyond-use date (BUD) and storage requirements
- Reference source to support the assigned BUD
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of the API(s)
- Labeling requirements (e.g., shake well)
- Quality control (QC) procedures (e.g., pH testing, visual inspection) and expected results
- Other information needed to describe the compounding process and ensure repeatability (e.g., adjusting pH, temperature)

7.2 Creating Compounding Records

A compounding record (CR) documents the compounding of each CNSP. A CR must be created for all CNSPs. Each CR must be reviewed for completeness before the CNSP is released. The name or other unique identifier of the person completing the review and the date of the review must be documented on the CR. The CR must permit traceability of all components in the case of a recall or known quality issue. The MFR can be used as the basis for preparing the CR. For example, a duplicate can be made of the MFR with blank fields for recording the information necessary to complete the CR. See *Box 3* for information that must be included in a CR.

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8. RELEASE INSPECTIONS AND TESTING

All release inspections must be included in the facility's documentation (see *7. Master Formulation and Compounding Records* and *11. SOPs*). All checks, inspections, and any other required tests to ensure the quality of the CNSP must be detailed in the facility's MFR.

8.1 Visual Inspection

At the completion of compounding, before releasing and dispensing, the CNSP must be visually inspected to determine whether the physical appearance of the CNSP is as expected (e.g., color, texture, physical uniformity). Some CNSPs, as noted in their MFR, also must be visually checked for certain characteristics (e.g., emulsions must be checked for phase separation). The CNSP must be visually inspected to confirm that the CNSP and its labeling match the CR and 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).

When a CNSP will not be released or dispensed on the day of preparation, a visual inspection must be conducted immediately before it is released or dispensed to make sure that the CNSP does not exhibit any defects (e.g., leakage) that could develop during storage. Any CNSP found to be of unacceptable quality (e.g., observed defects) must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal.

9. LABELING

Every CNSP must be labeled with appropriate, legible identifying information to prevent errors during storage, dispensing, and use. The term *labeling* designates all labels and other written, printed, or graphic matter on the immediate container or on or inside any packaging system or wrapper in which the article is enclosed, except any outer shipping container. The term *label* designates the part of the labeling on the immediate container. (See *Labeling* ⟨7⟩.)

All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction.

The label on each container of the prepared CNSP must, at a minimum, display prominently and legibly the following information:

- Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
- Active ingredient(s), and their amount(s), activity(ies), or concentration(s)
- Storage conditions if other than controlled room temperature
- BUD
- Dosage form
- Total amount or volume if it is not obvious from the container

The labeling on the dispensed CNSP should display the following information:

- Route of administration
- Indication that the preparation is compounded
- Any applicable special handling instructions
- Any applicable warning statements
- Compounding facility name, and contact information if the CNSP is to be sent outside of the facility or healthcare system in which it was compounded

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may have an impact on the stability of the formulation

10.3 Establishing a BUD for a CNSP

The BUDs in *Table 4* are based on the ability of the CNSP to maintain chemical and physical stability and to suppress microbial growth. These BUDs represent the limit for CNSPs that are packaged in tight, light-resistant containers unless conditions in *10.4 CNSPs Requiring Shorter BUDs* or *10.5 Extending BUDs for CNSPs* apply.

The aqueous and nonaqueous dosage forms in *Table 4* are defined based on the water activity (a_w) of the most similar drug preparations described in *Table 3* or *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* ⟨1112⟩. In general, the use of a_w aids in assessing the susceptibility of CNSPs to microbial contamination and the potential for API degradation due to hydrolysis. The a_w is different from the water content and may be considered as the available water to support microbial growth and hydrolytic reactions. Nonaqueous dosage forms will not support spore germination or microbial growth due to their low a_w. Reduced a_w greatly assists in the prevention of microbial proliferation in conventionally manufactured products and is expected to convey the same benefit to CNSPs.

Compounders are not required to measure a_w for CNSPs. While the manufactured products in ⟨1112⟩, *Table 2* and compounded preparations in *Table 3* below are not exhaustive, they provide examples of dosage forms that have an $a_w < 0.6$ and those that have an $a_w \geq 0.6$ and can assist personnel in determining the BUD by dosage form using *Table 4*.

When preparing CNSPs, raw materials and equipment contribute a bioburden to the final preparation. CNSPs with an $a_w \geq 0.6$, and a BUD within the limits of *Table 4*, should contain suitable antimicrobial agents to protect against the proliferation of bacteria, yeast, and mold contamination that may be inadvertently introduced anytime during the compounding process or throughout the BUD under appropriate handling and storage conditions. All CNSPs with an extended BUD must follow *10.5 Extending BUDs for CNSPs*. Careful consideration should be taken when selecting a preservative to ensure microbiological effectiveness and stability. When antimicrobial preservatives are contraindicated in a CNSP, storage of the preparation in a refrigerator is required if such storage does not change the physical or chemical properties of the CNSP (i.e., precipitation).

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WATER ACTIVITY (A_W)

- **A sample is placed in the chamber and sealed.**
- Water activity is measured by letting the sample reaches equilibrium relative humidity in a closed temperature-controlled chamber.
- The **free water is allowed to escape into the air in the chamber.** It remains there until all the free water has left the sample.
- **At equilibrium** the relative humidity of the air in the chamber is measured.
- The relation of this reading to pure water is the water activity measurement **expressed as the term Aw.** The range of water activity is from 0.0 to 1.0 **Aw.**

Minimum Aw values for **microorganism** growth in food

• Osmophilic yeasts	0.61
• Xerophilic molds	0.61
• Halophilic bacteria	0.75
• Most molds	0.8
• Most yeasts	0.88
• Most bacteria	0.90

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chemical properties of the CNSP (i.e., precipitation).

Table 3. Water Activity of Common Compounded Nonsterile Dosage Forms[a]

Nonaqueous Dosage Forms: $a_w < 0.6$			Aqueous Dosage Forms: $a_w \geq 0.6$		
Dosage Form	Description	a_w	Dosage Form	Description	a_w
Animal treat	Animal treat (oil flavor)	0.507	Animal treat	Animal treat with 15%–18% aqueous flavor	0.716
Capsule (oil filled)	Olive oil encapsulated	0.468	Cream	Cream vehicle (oil in water emulsion, petrolatum free)	0.968
Capsule (powder filled)	Powder base encapsulated	0.435	Cream	Emollient cream (petrolatum and mineral oil)	0.984
Gel (glycol based)	Propylene glycol, ethoxy diglycol, hydroxypropyl cellulose gel	0.056	Cream	Cream (oil in water emulsion with natural oils)	0.989
Lollipop (sorbitol based)	Sorbitol-based lollipop	0.460	Foam	Foaming surfactant solution	0.983
Ointment	Hydrophilic petrolatum	0.396	Gel (water based)	Alcohol-free aqueous gel	0.990
Ointment	Polyethylene and mineral oil gel base	0.459	Gel (water based)	Hydroxypropyl methylcellulose (HPMC) gel	1.000
Oral solution (glycol based)	20% Polyethylene glycol and 80% propylene glycol	0.009	Lotion	Lotion (oil in water emulsion)	0.986
Oral solution (oil based)	Medium chain triglycerides oil	0.338	Nasal spray	Nasal spray	0.991
Oral suspension (fixed oil)	Fixed oil with thickener	0.403	Oral solution (water based)	Low-sucrose syrup vehicle	0.906

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795 BUD

Table 4. BUD Limit by Type of Preparation in the Absence of a *USP–NF* Compounded Preparation Monograph or CNSP-Specific Stability Information[a]

Type of Preparation	BUD (days)	Storage Temperature[b]
Aqueous Dosage Forms ($a_w \geq 0.60$)		
Nonpreserved aqueous dosage forms[c]	14	Refrigerator
Preserved aqueous dosage forms[c]	35	Controlled room temperature or refrigerator
Nonaqueous Dosage Forms ($a_w < 0.60$)		
Oral liquids (nonaqueous)[d]	90	Controlled room temperature or refrigerator
Other nonaqueous dosage forms[e]	180	Controlled room temperature or refrigerator

[a] A shorter BUD must be assigned when the physical and chemical stability of the CNSP is less than the BUD limit stated in the table (see *10.4 CNSPs Requiring Shorter BUDs*).

[b] See *Packaging and Storage Requirements* ⟨659⟩.

[c] An aqueous preparation is one that has an $a_w \geq 0.6$ (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).

[d] A nonaqueous oral liquid is one that has an $a_w < 0.6$.

[e] Other nonaqueous dosage forms that have an $a_w < 0.6$ (e.g., capsules, tablets, granules, powders, nonaqueous topicals, suppositories, and troches or lozenges).

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795 BUD

cal quality of the final CNSP must not be negatively impacted.

10.5 Extending BUDs for CNSPs

- *CNSPs with a USP–NF monograph:* When compounding from a *USP–NF* compounded preparation monograph for the CNSP, the BUD must not exceed the BUD specified in the monograph.
- *CNSPs with stability information:* If there is a stability study using a stability-indicating analytical method for the API(s), CNSP formulation, and material of composition of the container closure that will be used, then the BUD indicated by the study may be used in lieu of the BUDs specified in *Table 4* for aqueous and nonaqueous dosage forms, up to a maximum of 180 days.

If the BUD of the CNSP is extended beyond the BUDs in *Table 4*, an aqueous CNSP must be tested for antimicrobial effectiveness (see *Antimicrobial Effectiveness Testing* ⟨51⟩). The designated person(s) may rely on antimicrobial effectiveness testing that is conducted (or contracted for) once for each formulation in the particular container closure system—including materials of composition of the container closure system—in which it will be packaged. Alternatively,

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795 COMPARISON OF BUDS

Current Official Chapter	2022 Revised Chapter
Oral water containing 14 days	Any dosage form Nonpreserved aqueous Aw>0.6 = 14 days
Water topical/dermal/mucosal and semi-solid 30 days	Any dosage form Preserved aqueous Aw> 0.6 = 35 days
	Oral liquids nonaqueous Aw<0.6 = 90 days
Nonaqueous 6 months	Nonaqueous Aw<0.6 = 6 months

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795 BUD

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the designated person(s) may rely on antimicrobial effectiveness testing results provided by an FDA-registered facility or published in peer-reviewed literature as long as the CNSP formulation (including any preservative) and container closure materials of composition are the same as those tested (unless a bracketing study is performed). When a bracketing study is performed, antimicrobial effectiveness testing may be performed on a low concentration and on a high concentration of the active ingredient in the formulation to establish preservative effectiveness across various strengths of the same formulation (e.g., bracketing). The concentration of all other ingredients (including preservatives) must fall within the bracketed range.

11. SOPS

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

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

A facility's QA and QC programs must be formally established and documented in the facility's SOPs that ensure that all aspects of the preparation of CNSPs are conducted in accordance with the requirements in this chapter (⟨795⟩) and the laws and regulations of the applicable regulatory jurisdiction. Designated person(s) must ensure that the facility has formal, written QA and QC programs that establish a system of

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jurisdiction)

12.2 Complaint Handling

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 CNSP.

A designated person(s) must review all complaints to determine whether the complaint indicates a potential quality problem with the CNSP. 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 CNSPs. Corrective action, if necessary, must be implemented for all potentially affected CNSPs.

Consider whether to initiate a recall of potentially affected CNSPs and whether to cease nonsterile 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, or mail). The record must contain the name of the complainant or other unique identifier, 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 CNSP 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 *14. Documentation*. A CNSP that is returned in connection with a complaint must be quarantined until it is destroyed after completion of the investigation and in accordance with laws and regulations of the applicable regulatory jurisdiction.

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must be informed.

13. CNSP PACKAGING AND TRANSPORTING

13.1 Packaging of CNSPs

The facility's SOPs must describe packaging of CNSPs. Personnel should select and use packaging materials that will maintain the physical and chemical integrity and stability of the CNSPs. Packaging materials must protect CNSPs from damage, leakage, contamination, and degradation, while simultaneously protecting personnel from exposure.

13.2 Transporting of CNSPs

If transporting CNSPs, the facility must have written SOPs to describe the mode of transportation, any special handling instructions, and whether temperature monitoring devices are needed.

14. DOCUMENTATION

All facilities where CNSPs 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
- Equipment records (e.g., calibration, verification, and maintenance reports)
- COAs and all documentation required for components not conventionally manufactured
- Receipt of components
- SOPs, MFRs, and CRs
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigations and corrective actions
- Records of cleaning and sanitizing the designated compounding area
- Temperature logs
- Accommodations to personnel compounding CNSPs
- Any required routine review (e.g., yearly review of QA and QC programs, yearly review of chemical hazard and disposal information)

Documentation must comply with all laws and regulations of the applicable regulatory jurisdiction. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required CRs for a particular CNSP (e.g., MFR, CR, and release inspection and testing results) must be readily retrievable for at least 2 years after preparation or as required by the laws and regulations of the applicable regulatory jurisdiction, whichever is longer.

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795 - FLAVORING

<795>: Adding Flavor to Conventionally Manufactured Nonsterile Products

November 1, 2022

Disclaimer: This document is intended to be a resource regarding adding flavor to conventionally manufactured nonsterile products. This informational document is intended to supplement *USP* General Chapter <795> *Pharmaceutical Compounding – Nonsterile Preparations*. This supplemental document is not part of the chapter, is not a comprehensive overview of the chapter, and is not intended to be used in place of the chapter. This document is not official *United States Pharmacopeia – National Formulary* (*USP–NF*) text and is not intended to be enforceable by regulatory authorities. Users must refer to the *USP–NF* for official text.

Questions may be sent to CompoundingSL@USP.org.

Background and Introduction

USP General Chapter <795> *Pharmaceutical Compounding — Nonsterile Preparations* provides official standards for compounding quality nonsterile preparations. Nonsterile compounding is defined as combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug product or bulk drug substance to create a nonsterile preparation.

Adding components (such as flavors) not stipulated in the labeling to conventionally manufactured products is compounding and has been within the scope of <795> since the chapter was first published in 2004. Flavors are organic chemicals with reactive functional groups including acids, alcohols, aldehydes, amides, amines, esters, ketones, and lactams. The effect of adding these substances, even in very small quantities or concentrations, to conventionally manufactured products is unpredictable due to the potential for a variety of chemical reactions.

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⟨797⟩ PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

Change to read:

▲1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed for the preparation of compounded sterile preparations (CSPs) for human and animal drugs. Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation.

The requirements in this chapter must be followed to minimize harm, including death, to human and animal patients that could result from 1) microbial contamination [nonsterility], 2) excessive bacterial endotoxins, 3) variability from the intended strength of correct ingredients, 4) physical and chemical incompatibilities, 5) chemical and physical contaminants, and/or 6) use of ingredients of inappropriate quality.

Aseptic techniques, processes, and procedures must be followed for preparing any sterile medication. Processes and procedures must be in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other products or CSPs.

The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* ⟨1223⟩ and *Validation of Compendial Procedures* ⟨1225⟩).

Unless otherwise specified in each section, the requirements of this chapter apply to compounding all categories of CSPs.

1.1 Scope

1.1.1 CSPs affected: The requirements in this chapter must be met to ensure the sterility of any CSP. Although the list below is not exhaustive, the following must be sterile:

- Injections, including infusions
- Irrigations for internal body cavities (i.e., any space that does not normally communicate with the environment outside of the body, such as the bladder cavity or peritoneal cavity). [NOTE—Irrigations for the mouth, rectal cavity, and sinus cavity are not required to be sterile.]
- Ophthalmic dosage forms
- Aqueous preparations for pulmonary inhalation. [NOTE—Nasal dosage forms intended for local application are not required to be sterile.]
- Baths and soaks for live organs and tissues
- Implants

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recommendations for the administration of hazardous drugs.

1.3 Immediate-Use CSPs

When all of the following conditions are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 CSPs:

1. Aseptic techniques, processes, and procedures are followed, and written SOPs are in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products or CSPs.
2. Personnel are trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs.
3. The preparation is performed in accordance with evidence-based information for physical and chemical compatibility of the drugs (e.g., approved labeling, stability and compatibility studies).
4. The preparation involves not more than 3 different sterile products.
5. Any unused starting component from a single-dose container must be discarded after preparation is complete. Single-dose containers must not be used for more than one patient.
6. Administration begins within 4 h following the start of preparation. If administration has not begun within 4 h following the start of preparation, it must be promptly, appropriately, and safely discarded.
7. Unless directly administered by the person who prepared it or administration is witnessed by the preparer, the CSP must be labeled with the names and amounts of all active ingredients, the name or initials of the person who prepared the preparation, and the 4-h time period within which administration must begin.

Handling of sterile hazardous drugs (HDs) must additionally comply with ⟨800⟩.

1.4 Preparation Per Approved Labeling

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer.

Preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of this chapter only if

1. The product is prepared as a single dose for an individual patient; and
2. The approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

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Low-Risk 12 hour BUD (segregated PEC-3 sterile products)

Low-Risk (3 sterile products) 48h/14d/45d

Medium-Risk (more than 3 sterile components)30h/9d/45d

High-Risk (non-sterile bulk) 24h/3d/45d

Category 1 CSPs	Category 2 CSPs	Category 3 CSPs
Sterile Products or nonsterile Bulk		
Must be prepared in a PEC that may be located in an unclassified segregated compounding area	**Must be prepared in a cleanroom suite-PEC inside a buffer room with ante room**	**Must be prepared in a cleanroom suite Head to toe skin coverage – must be tested for sterility**
Up to 12 hours at room temp Up to 24 hours refrigerated	Greater than 12 hours at room temp Greater than 24 hours refrigerated	Up to 180 days BUD frozen

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than those specified in the manufacturer's labeling.

1.5 CSP Categories

This chapter distinguishes three categories of CSPs: Category 1, Category 2, and Category 3, primarily based on the state of environmental control under which they are compounded, the probability for microbial growth during the time they will be stored, and the time period within which they must be used.

Category 1 CSPs are compounded under the least controlled environmental conditions and therefore are assigned a BUD of 12 h or less at controlled room temperature or 24 h or less when refrigerated, if compounded in accordance with all of the applicable requirements for Category 1 CSPs in this chapter.

Category 2 CSPs require more environmental controls and testing than Category 1 CSPs and may be assigned a BUD of greater than 12 h at controlled room temperature or more than 24 h if refrigerated, but not exceed the limits established in *Table 13* (see *14. Establishing Beyond-Use Dates*), if compounded in accordance with all of the applicable requirements for Category 2 CSPs in this chapter.

Category 3 CSPs undergo sterility testing, supplemented by endotoxin testing when applicable, and have more requirements than Category 2 CSPs for personnel qualification, use of sterile garb, use of sporicidal disinfectants, frequency of environmental monitoring, and stability determination. Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14* (see *14. Establishing Beyond-Use Dates*), if compounded in accordance with all applicable requirements for Category 3 CSPs in this chapter (see *14.4 Additional Requirements for Category 3 CSPs*).

The requirements that are not specifically described as applicable to Category 1, Category 2, or Category 3, are applicable to the compounding of all CSPs unless the CSP is otherwise described in *1.1 Scope*.

Category 1, Category 2, and Category 3 CSPs can be compounded by using only sterile starting ingredients, or by using some or all nonsterile starting ingredients. If all components used to compound are sterile from the start, the sterility of the components must be maintained during compounding to produce a CSP.

If one or more of the starting components being used to compound is not sterile, the sterility of the compounded preparation must be achieved through a sterilization process (e.g., terminal sterilization in the final sealed container) or sterilizing filtration, and then sterility must be maintained if the CSP is subsequently manipulated. When compounding with nonsterile starting components, supplies, or equipment, the quality of the components, the

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preparation that is free from excessive bacterial endotoxins.

2. PERSONNEL TRAINING AND EVALUATION

All personnel who compound or have direct oversight of compounding personnel must be initially trained and qualified by demonstrating knowledge and competency in compounding CSPs according to the requirements in this section before being allowed to perform their job functions independently. Designated person(s) are responsible for creating and implementing a training program for personnel and for ensuring that compounders, personnel who have direct oversight of compounders, and personnel who perform restocking or cleaning and disinfection duties are initially trained and qualified by demonstrating knowledge and competency in maintaining the quality of the sterile compounding environment before being allowed to perform their job functions independently. Training and observation may be performed by the designated person(s) or an assigned trainer. Personnel who compound or have direct oversight of compounding personnel must complete training initially and at least every 12 months in appropriate sterile compounding principles and practices as described below (see *2.1 Demonstrating Knowledge and Competency of Core Skills*). Personnel who only perform restocking or cleaning and disinfecting duties outside of the primary engineering control (PEC) must complete ongoing training as required by the facility's SOPs. Personnel compounding only immediate-use CSPs must complete training as required by the facility's SOPs (see *1.3 Immediate-Use CSPs*).

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 who compound, have direct oversight of compounding personnel, perform in-process checks, final verification, and dispensing of CSPs. This program must equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks, and SOPs should specify the training required for such tasks.

Training and evaluation of personnel must be documented (see *20. Documentation*).

2.1 Demonstrating Knowledge and Competency of Core Skills

Before beginning to compound CSPs independently or have direct oversight of compounding personnel, personnel must complete training and be able to demonstrate knowledge of principles and competency of skills for performing sterile manipulations and achieving and maintaining appropriate environmental conditions as applicable to their assigned job functions. This must be completed initially and at least every 12 months in at least the following:

- Hand hygiene
- Garbing
- Cleaning and disinfection
- Calculations, measuring, and mixing
- Aseptic technique
- Achieving and/or maintaining sterility (and apyrogenicity if compounding with nonsterile components)
- 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 PECs
- Principles of movement of materials and personnel within the compounding area

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training and demonstrated competency, and they must comply with the other requirements of this chapter.

2.2 Demonstrating Competency in Garbing and Hand Hygiene

Before beginning to compound Category 1, Category 2, or Category 3 CSPs or have direct oversight of compounding personnel, personnel must successfully complete an initial garbing competency evaluation no fewer than 3 separate times. The 3 successful completions must be in succession—failure of any of the 3 initial garbing competency evaluations requires repeat testing until personnel successfully complete 3 evaluations in a row. The garbing competency evaluation consists of a visual observation and gloved fingertip and thumb sampling (GFT) of both hands (see *Box 1*). Each of the 3 initial competency evaluations must occur after performing a separate and complete hand hygiene and full garbing procedure. All garbing competencies must be completed with gloved fingertip and thumb sampling after garbing (see *Box 1*) and a documented visual audit while performing hand hygiene and garbing procedures (see *3. Personal Hygiene and Garbing*). Gloved fingertip and thumb sampling after garbing, but before applying sterile 70% IPA to gloves, must be performed on donned sterile gloves on both hands in a classified area or segregated compounding area (SCA).

Failure is indicated by visual observation of improper hand hygiene and garbing procedures and/or gloved fingertip and thumb sampling results that exceed the action levels in *Table 1*. Results of the evaluation and corrective actions, in the event of failure, 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 and time; media and components used including manufacturer, expiration date, and lot number; starting temperature for each interval of incubation; dates of incubation; results and identification of the observer and personnel reading and documenting the results. Microbial identification of the colony-forming units (cfu) is not required for gloved fingertip and thumb sampling.

After the initial garbing competency evaluations, compounding personnel must successfully complete the garbing competency (see *Table 1*) at least one time every 6 months for personnel compounding Category 1 and Category 2 CSPs, and at least one time every 3 months for personnel compounding Category 3 CSPs. Personnel who have direct oversight of compounding personnel, but do not compound, must complete a garbing competency evaluation every 12 months. The evaluation should correspond to the type of garbing activities of the personnel they oversee. Personnel who have direct oversight of compounding personnel must not compound unless they successfully complete the garbing competency evaluation at the same intervals required for compounding personnel.

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2.3 Competency Testing in Aseptic Manipulation

Before beginning to compound Category 1, Category 2, or Category 3 CSPs independently or have direct oversight of compounding personnel, personnel must successfully complete an aseptic manipulation competency evaluation. The aseptic manipulation competency evaluation consists of a visual observation, media-fill testing, followed by a gloved fingertip and thumb sampling on both hands, and surface sampling of the direct compounding area to assess aseptic technique and related practices (see *Box 2*).

For personnel compounding Category 1 and Category 2 CSPs, the aseptic manipulation competency must occur initially and at least every 6 months thereafter. For personnel compounding Category 3 CSPs, the aseptic manipulation competency must occur initially and at least every 3 months thereafter. Personnel who have direct oversight of compounding personnel must complete an aseptic manipulation competency evaluation annually. The evaluation should correspond to the type of activities of the personnel they oversee but does not require the same quantities. Personnel who have direct oversight of compounding personnel must not compound unless they successfully complete the aseptic manipulation competency evaluation that simulates the most difficult and challenging aseptic compounding procedures encountered by the person at the same intervals required for compounding personnel.

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Table 8. Action Levels for Surface Sampling

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

6.3 Monitoring Surfaces for Viable Particles

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

For entities compounding Category 1 and Category 2 CSPs, surface sampling of all classified areas, and pass-through chambers connecting to classified areas, must be conducted at least monthly (see *Microbiological Control and Monitoring of Aseptic Processing Environments* ⟨1116⟩).

For entities compounding any Category 3 CSPs, surface sampling of all classified areas, and pass-through chambers connecting to classified areas, must be completed prior to assigning a BUD longer than the limits established in *Table 13*, and at least weekly (see ⟨1116⟩) on a regularly scheduled basis regardless of the frequency of compounding Category 3 CSPs. Additionally, surface sampling must be conducted within the PEC used to prepare Category 3 CSPs, at the end of each batch before cleaning and disinfection occurs, unless a self-enclosed robotic device is used. When a self-enclosed robotic device is used as the PEC to prepare Category 3 CSPs, surface sampling must be conducted at least once daily at the end of compounding operations, before cleaning and disinfection occurs.

- Frequently touched surfaces

Surface sampling in the DCA must also be conducted in conjunction with media-fill testing to assess aseptic manipulation competency (see *2.3 Competency Testing in Aseptic Manipulation*)

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

4.2 Facility Design and Environmental Controls

In 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 maintained at a temperature of 20° or cooler and a relative humidity of 60% or below to minimize the risk of microbial proliferation and to provide comfortable conditions for compounding personnel attired in the required garb. The temperature and humidity must be monitored in each room of the cleanroom suite each day that compounding is performed, either manually or by a continuous recording device. The results of the temperature and humidity readings must be documented at least once daily or stored in the continuous recording device and must be retrievable. The temperature and humidity readings must be reviewed as described in the facility's SOPs. Temperature and humidity in the cleanroom suite must be controlled through a heating, ventilation, and air conditioning (HVAC) system. Free-standing air conditioners, humidifiers, and dehumidifiers must not be used within the classified area or the SCA. Temperature and humidity monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.

The designated person(s) is responsible for ensuring that each area related to CSP preparation meets the classified air

particle-generating activity must not be performed when sterile compounding is in process.

Segregated compounding area (SCA): A PEC may be located within an unclassified area without an anteroom or buffer room. This type of design is called an SCA. Only Category 1 CSPs may 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 where environmental control challenges (e.g., restrooms, warehouses, or food preparation areas) could negatively affect the air quality of the PEC within the SCA. The impact of activities (e.g., patient care activities) that will be conducted around or adjacent to the SCA must be considered carefully when designing such an area. The area within 1 m of the PEC should be dedicated only for sterile compounding (e.g., not storage, hand hygiene, donning and doffing garb, or other highly particle-generating activities such as patient care).

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monitor the pressure differential. The quantitative results from the pressure monitoring device must be reviewed and documented at least daily on the days when compounding is occurring.

4.2.6 Facilities preparing Category 2 or Category 3 CSPs from nonsterile starting components: Weighing, measuring, or otherwise manipulating components could generate airborne chemical particles (e.g., API or added substances). If preparing Category 2 or Category 3 CSP from nonsterile component(s), presterilization procedures, such as weighing and mixing, must be completed in an ISO Class 8 or better environment (e.g., anteroom or buffer room). Presterilization procedures must be performed in single-use containment glove bags, containment ventilated enclosures (CVEs), BSCs, or CACIs to minimize the risk of airborne contamination. CVEs, BSCs, or CACIs used for presterilization procedures must be certified at least every 6 months.

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.

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7. CLEANING, DISINFECTING, AND APPLYING SPORICIDAL DISINFECTANTS AND STERILE 70% IPA

Surfaces in classified areas used to prepare Category 1, Category 2, and Category 3 CSPs must be:

- Cleaned
- Disinfected

Table 10. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidal Disinfectants in Classified Areas and in the SCA[a]

Site	Cleaning	Disinfecting[b]	Applying Sporicidal Disinfectant
PEC(s) and equipment inside the PEC(s)	• Equipment and all interior surfaces of the PEC daily on days when compounding occurs and when surface contamination is known or suspected	• Equipment and all interior surfaces of the PEC daily on days when compounding occurs and when surface contamination is known or suspected	• Monthly for entities compounding Category 1 and/or Category 2 CSPs • Weekly for entities compounding Category 3 CSPs
Removable work tray of the PEC, when applicable	• Work surface of the tray daily on days when compounding occurs • All surfaces and the area underneath the work tray monthly	• Work surface of the tray on days when compounding occurs • All surfaces and the area underneath the work tray monthly	• Work surfaces of the tray monthly • All surfaces and the area underneath the work tray monthly
Pass-through chambers	• Daily on days when compounding occurs	• Daily on days when compounding occurs	• Monthly for entities compounding Category 1 and/or Category 2 CSPs • Weekly for entities compounding Category 3 CSPs
Work surface(s) outside the PEC	• Daily on days when compounding occurs	• Daily on days when compounding occurs	
Floor(s)	• Daily on days when compounding occurs	• Daily on days when compounding occurs	
Wall(s), door(s), and door frame(s)	• Monthly	• Monthly	• Monthly
Ceiling(s)[c]			
Storage shelving and bin(s)			
Equipment outside the PEC(s)			

[a] Cleaning of sinks is described in *4.4 Water Sources*.

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7.1 Agents and Supplies for Cleaning, Disinfecting, and Applying Sporicidal Disinfectants

7.1.1 Agents: Cleaning and disinfecting agents must be selected and used with careful consideration of compatibilities, effectiveness, and user safety. 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. After the disinfectant or sporicidal disinfectant is applied to the surface, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer.

Cleaning, disinfecting and sporicidal agents used within the PEC must be sterile. When diluting concentrated cleaning and disinfecting agents for use in the PEC, sterile water must be used. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used. When diluting concentrated cleaning and disinfecting agents for use outside of the PEC, sterile water should be used.

7.1.2 Supplies: All cleaning and disinfecting supplies (e.g., wipers, sponges, pads, and mop heads) with the exception of tool handles and holders must be low lint. In addition, cleaning and disinfecting supplies used in the PEC must be sterile with the exception of tool handles and holders, which must be cleaned and disinfected prior to use in a PEC. Wipers, sponges, pads, 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., handles should not be made of wood or any other porous material) and must be cleaned and disinfected 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 as determined based on the condition of the tools. Cleaning supplies used in the classified areas and SCAs must be disposed of in a manner that minimizes the potential for dispersing contaminants into the air (e.g., with minimal agitation, away from work surfaces).

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

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8. INTRODUCING ITEMS INTO THE SEC AND PEC

8.1 Introducing Items into the SEC

Before any item is introduced into the clean side of anteroom(s), placed into pass-through chamber(s), or brought into the SCA, providing that packaging integrity will not be compromised, it must be wiped with a sporicidal disinfectant, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers by personnel wearing gloves. If an EPA-registered disinfectant or sporicidal disinfectant is used, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer. If sterile 70% IPA is used, it must be allowed to dry. The wiping procedure should not compromise the packaging integrity or render the product label unreadable.

8.2 Introducing Items into the PEC

Just before any item is introduced into the PEC, it must be wiped with sterile 70% IPA using sterile low-lint wipers and allowed to dry before use. When sterile items are received in sealed containers designed to keep them sterile until opening, the sterile items may be removed from the covering as the supplies are introduced into the ISO Class 5 PEC without the need to wipe the individual sterile supply items with sterile 70% IPA. The wiping procedure must not render the product label unreadable.

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and depyrogenated.

9.3 Components

Compounding personnel must follow the facility's SOPs, which must address the selection, receipt, evaluation, handling, storage, and documentation of all CSP components, including all ingredients and container closures.

9.3.1 Component selection: Conventionally manufactured sterile products should be used when available and appropriate for the intended CSP.

When APIs are used:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must have a COA that includes the specifications (e.g., compendial requirements for quality) and that test results for the component show that the API meets expected quality
- In the United States, must be manufactured by an FDA-registered facility
- Outside of the United States, must comply with the laws and regulations of the applicable regulatory jurisdiction

For all components other than APIs:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must be accompanied by documentation (e.g., COA, labeling) that includes the specifications and test results and shows that the component meets the specifications
- In the US, should be manufactured by an FDA-registered facility
  - If a component cannot be obtained from an FDA-registered facility, the designated person(s) 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 but are not limited to 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.
- Outside of the US, must comply with the laws and regulations of the applicable regulatory jurisdiction

When CSPs are used as components, see *16. Use of CSPs as Components*. All APIs and other components used must be evaluated for suitability for use in sterile drug preparation. Components labeled with "not for pharmaceutical use", "not for injectable use", "not for human use" or an equivalent statement must not be used to compound for these purposes.

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⟩).

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by the manufacturer.

10. STERILIZATION AND DEPYROGENATION

When selecting the sterilization method for CSPs prepared from one or more nonsterile starting components or using nonsterile supplies or devices, 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, or quality) or the packaging integrity. (See also the ⟨1229⟩ series of chapters.)

The following must be considered when selecting an appropriate sterilization method:

- Terminal sterilization (e.g., steam, dry heat, 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
- Filtration may not be an option for some compounded preparations, for example preparations with suspended drug particles or emulsions with a significant droplet size.

CSPs that are terminally sterilized (e.g., steam, dry heat, or irradiation) must use a process intended to achieve a probability of a nonsterile unit (PNSU) of 10^{-6}. [NOTE—This is also called the sterility assurance level (SAL).] A PNSU of 10^{-6} is equivalent to a probability that 1 unit in a million is nonsterile. A PNSU 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.

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11. MASTER FORMULATION AND COMPOUNDING RECORDS

11.1 Creating Master Formulation Records

A master formulation record (MFR) is a detailed record of procedures that describes how the CSP is to be prepared. An MFR must be created for all CSPs prepared from nonsterile ingredient(s) or CSPs prepared for more than one patient. Any changes or alterations to the MFR must be approved and documented according to the facility's SOPs. *Box 9* lists the information that must be included in an MFR.

12. RELEASE INSPECTIONS AND TESTING

All release testing procedures (e.g., visual inspections and testing) must be included in the facility's documentation (see *11. Master Formulation and Compounding Records* and *17. SOPs*). Any out-of-specification results must be investigated, and a corrective action plan must be implemented and documented as part of the quality assurance (QA) and QC program (see *18. Quality Assurance and Quality Control*).

intrathecally administered CSPs. See also *Guidelines on the Endotoxins Test* ⟨1085⟩.

13. LABELING

Category 1, Category 2, and Category 3 CSPs must be labeled with appropriate, legible identifying information to prevent errors during storage, dispensing, and use. The term *labeling* designates all labels and other written, printed, or graphic matter on the immediate container or on or inside 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⟩.

All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction.

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14. ESTABLISHING BEYOND-USE DATES

14.2 Parameters to Consider in Establishing a BUD

BUDs for CSPs should be established conservatively to ensure that the drug maintains its required characteristics (i.e., stability and sterility) until its BUD.

When establishing a BUD for a CSP, compounders must consider parameters that may affect quality, including but not limited to:

- Chemical and physical stability properties of the drug and/or its formulation
- Materials of composition of the container closure system and compatibility of the container closure system with the final preparation (e.g., leachables, interactions, adsorption, and storage conditions)

The BUDs for CSPs are based primarily on factors that affect the achievement and maintenance of sterility, which include but are not limited to the following:

- Conditions of the environment in which the CSP is prepared
- Aseptic processing and sterilization method
- Starting components (e.g., sterile or nonsterile ingredients)
- Whether or not sterility testing is performed
- Storage conditions (e.g., packaging and temperature)

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

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

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

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

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

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

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18. QUALITY ASSURANCE AND QUALITY CONTROL

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 the facility's SOPs that ensure that all aspects of the preparation of CSPs are conducted in accordance with the requirements in this chapter (⟨797⟩) and the laws and regulations of the applicable regulatory jurisdiction. Designated person(s) 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 facility's SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. Designated person(s) responsible for the QA program must have the training, experience, responsibility, and authority to perform these duties. The overall QA and QC program must be reviewed at least once every 12 months by the designated person(s). The results of the review must be documented, and appropriate action must be taken if needed.

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

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19. CSP HANDLING, STORAGE, PACKAGING, SHIPPING, AND TRANSPORT

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

19.1 Handling and Storing CSPs

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. The temperature must be monitored each day, either manually or by a continuous recording device. The results of the temperature readings must be documented in a temperature log per facility SOPs or stored in the continuous temperature recording device and must be retrievable. Temperature monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.

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(s) 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.

19.2 Packaging of CSPs

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.

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.

19.3 Shipping and Transporting CSPs

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.

20. DOCUMENTATION

All 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, MFRs (if required), and CRs (if required)
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigations and corrective actions

Documentation must comply with all laws and regulations of the applicable regulatory jurisdiction. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required documentation for a particular CSP (e.g., MFR, CR, and release inspection and testing results) must be readily retrievable for at least 2 years after preparation or as required by laws and regulations of the applicable regulatory jurisdiction or accrediting organization(s), whichever is longer.

21. COMPOUNDING ALLERGENIC EXTRACTS

Licensed allergenic extracts are 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

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CONCLUSION AND CLINICAL PEARLS

- BUDs maximum is 180 days (6 months) for both 795 and 797; no exceptions for stability testing extensions
- Water activity is the determinant for nonsterile BUDs
- Cleaning and garbing are specified in greater detail in regard to agents, areas, and intervals for both chapters
- There is no limit to batch size for sterile category 1 & 2
- The batch size limit is 250 for sterile category 3

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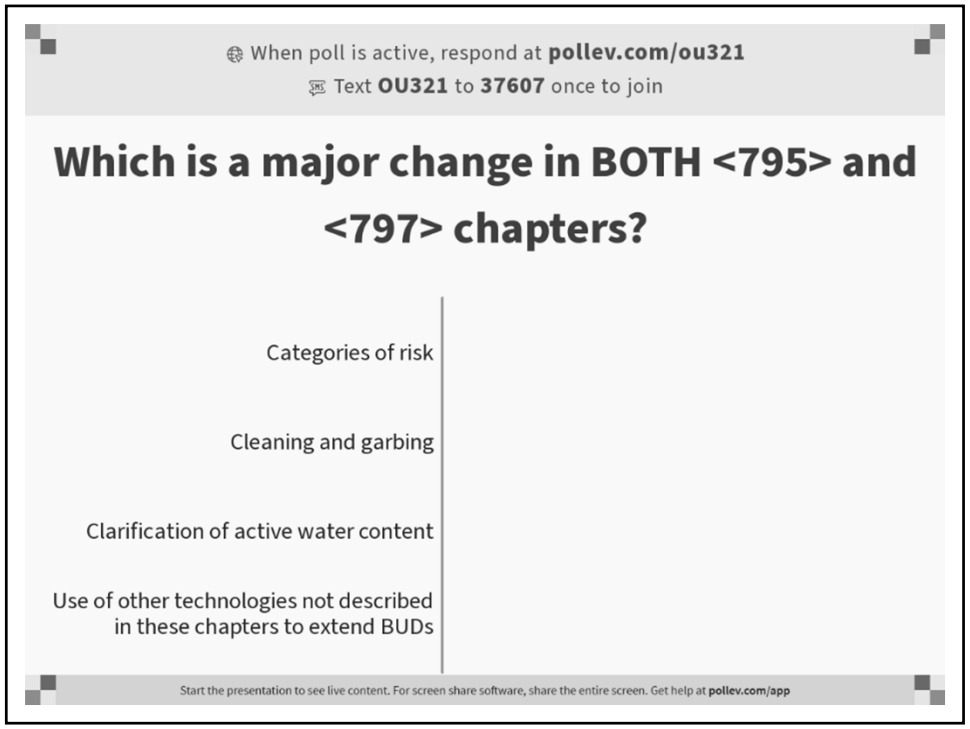
When poll is active, respond at pollev.com/ou321
Text OU321 to 37607 once to join
Which is a major change in BOTH <795> and <797> chapters?
Categories of risk
Cleaning and garbing
Clarification of active water content
Use of other technologies not described in these chapters to extend BUDs
Start the presentation to see live content. For screen share software, share the entire screen. Get help at pollev.com/app

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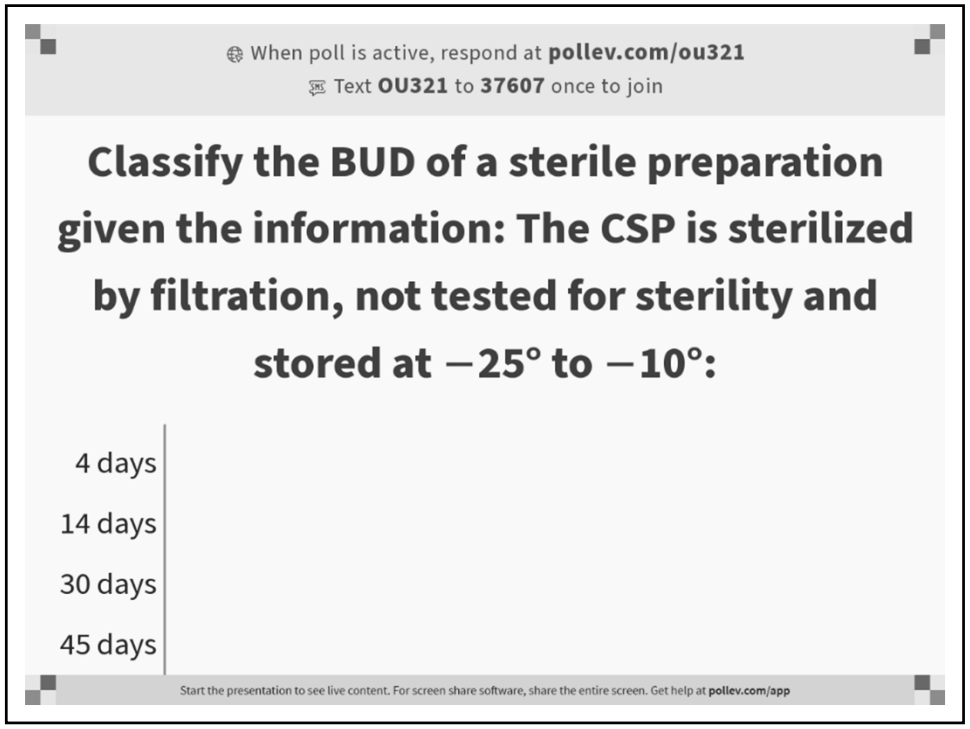
When poll is active, respond at pollev.com/ou321
Text OU321 to 37607 once to join
Classify the BUD of a sterile preparation given the information: The CSP is sterilized by filtration, not tested for sterility and stored at −25° to −10°:
4 days
14 days
30 days
45 days
Start the presentation to see live content. For screen share software, share the entire screen. Get help at pollev.com/app

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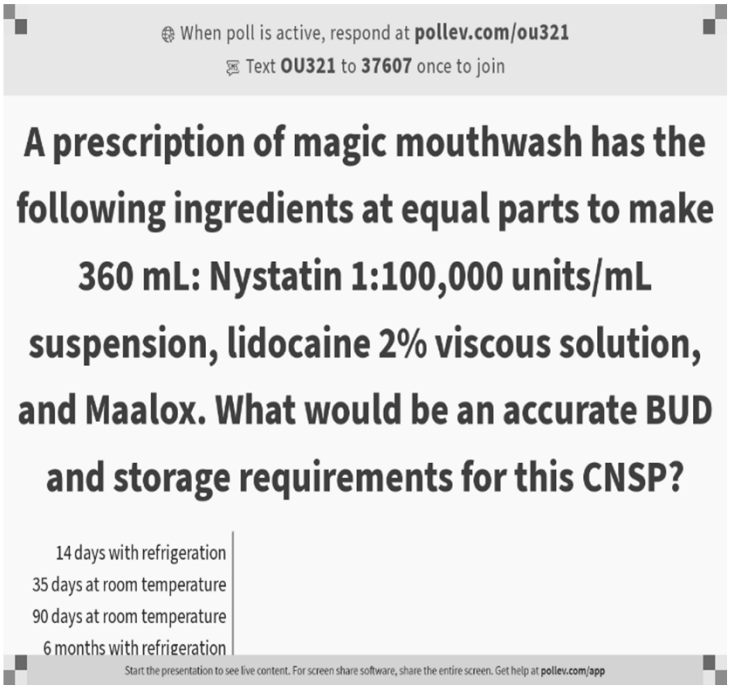
Identify the appropriate beyond-use date for acquired data:



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ADDITIONAL RESOURCES

- Stay informed on USP Compounding Standards and associated initiatives and educational materials by signing up for USP Healthcare Quality and Safety updates: https://go.usp.org/hqs-signup-form
- FAQs and other information on USP Compounding:
  - https://go.usp.org/USP_GC_795_FAQs
  - https://go.usp.org/USP_GC_797_FAQs
  - https://www.usp.org/frequently-asked-questions/hazardous-drugs-handling-healthcare-settings
  - https://go.usp.org/Compounded_Preparation_Monograph_Information

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REFERENCES

- USP43-NF38 <795> PHARMACEUTICAL COMPOUNDING-NONSTERILE PREPARATIONS; OFFICIAL 2014
- USP43-NF38 <797> PHARMACEUTICAL COMPOUNDING-STERILE PREPARATIONS; OFFICIAL 2008
- USP 2023 <795> PHARMACEUTICAL COMPOUNDING-NONSTERILE PREPARATIONS; DocId: GUID-98DCB48D-DC23-4A63-AD2E-01CA8979FB7E_6_en-US
- USP 2023 <797> PHARMACEUTICAL COMPOUNDING-STERILE PREPARATIONS; DocId: GUID-A4CAAA8B-6F02-4AB8-8628-09E102CBD703_7_en-US

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USP 795 AND 797 CHAPTER UPDATES

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