



COMPOUNDING COMMITTEE: DRAFTED USP <797>

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Be Aware and Take Care: Talk to your Pharmacist!



Compounding Committee

- ▶ This presentation has been modified to ensure compliance with ADA provisions



United States Pharmacopeia (USP)

- ▶ General Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations
- ▶ General Chapter <797> Pharmaceutical Compounding – Sterile Preparations
- ▶ General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings
- ▶ General Chapter <825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging



USP Timeline

- ▶ Public comment period July 27, 2018 through November 30, 2018
- ▶ Open microphone session September 5, 2018
- ▶ Intended publication date June 1, 2019
- ▶ Intended official date of December 1, 2019



USP <797> Background

- ▶ 1996: First Chapter published for sterile compounding in <1206> Sterile Drug Products for Home Use
- ▶ 2004: Revised and renumbered chapter to <797>
- ▶ June 2008: First major revision to <797> became official
- ▶ July 2010: Newly formed EC began revisions to <797>
- ▶ September 25, 2015: Proposed major revision to <797> garnered more than 8000 comments
- ▶ July 27, 2018: Based on the public comments, <797> revised and republished for public comment
- ▶ June 2019: Revised <797> anticipated to be published in the USP-NF
- ▶ December 2019: Revised <797> anticipated to be official 6 months after publication in the USP-NF



General Chapter <797> Pharmaceutical Compounding – Sterile Preparations

- ▶ Open microphone session on September 5, 2018:
- ▶ Available
<http://www.usp.org/sites/default/files/usp/document/our-work/healthcare-quality-safety/797-open-microphone-presentation.pdf>
- ▶ Web recording:
<https://uspevents.webex.com/mw3300/mywebex/nbrshared.do>



USP <797> Overview: Sections

1. Introduction and Scope
2. Personnel Qualifications—Training, Evaluation, and Requalification
3. Personal Hygiene and Garbing
4. Facilities and Engineering Controls
5. Microbiological Air and Surface Monitoring
6. Cleaning and Disinfecting Compounding Areas
7. Equipment, Supplies, and Components
8. Sterilization and Depyrogenation



USP <797> Overview: Sections

9. SOPs and Master Formulation and Compounding Records
10. Release Testing
11. Labeling
12. Establishing Beyond-Use Dates
13. Use of Conventionally Manufactured Products
14. Use of CSPs As Components
15. Quality Assurance and Quality Control
16. CSP Storage, Handling, Packaging, Shipping, And Transport
17. Documentation
18. Compounding Allergenic Extracts



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Section 1. Introduction and Scope

- ▶ This chapter describes the minimum standards to be followed when preparing compounded sterile human and animal drugs based on current scientific information and best practices for sterile compounding.



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Section 1. Introduction and Scope

- ▶ **Sterile Compounding** is 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.
- ▶ **Administration** means the direct and immediate application of a conventionally manufactured product or CSP to a patient.
 - It is out of the scope of this chapter



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Section 1. Introduction and Scope

- ▶ **Reconstitution:** The process of adding a diluent to a solid conventionally manufactured product to prepare a sterile solution or suspension.
- ▶ **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.
- ▶ Proprietary bag and vial systems (e.g., ADD-Vantage, Mini Bag plus, addEASE):
 - Docking and activation in accordance with the manufacturer's instructions for immediate administration to an individual patient is **not** considered compounding.
 - Docking for future activation and administration is considered compounding.



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Section 1. Introduction and Scope

- ▶ Category is based on the conditions under which CSPs are made, the probability for microbial growth, and the time period within which they must be used.

Category 1:

- ▶ All PECs may be placed in an unclassified segregated compounding area (SCA)
- ▶ Beyond use date (BUD):
 - controlled room temperature: < 12 hours
 - Refrigerated: < 24 hours

Category 2:

- ▶ PECs (LAFS and RABS) must be placed in an ISO 7 positive pressure buffer room with an ISO 8 positive pressure ante-room.
- ▶ BUD:
 - controlled room temperature: > 12 hours
 - refrigerated > 24 hours



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Section 2. Personnel Qualifications Training, Evaluation, and Requalification

Personnel Qualifications:

- ▶ Visual observation of hand hygiene and garbing: every 6 months
- ▶ Gloved fingertip and thumb sampling: every 6 months, after media fill test
- ▶ Media fill testing: every 6 months

Core Competencies: 12 months (written and hands-on proficiency)

- ▶ 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 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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Section 2. Personnel Qualifications Training, Evaluation, and Requalification

- ▶ **Gloved fingertip and thumb sampling:**
 - Direct touch contamination is the most likely source of microorganisms.
 - Initial gloved fingertip and thumb sampling – before being allowed to compound.
 - Evaluates a compounder's competency in correctly performing hand hygiene and garbing.
 - No fewer than 3 separate times.
 - Must be performed on donned sterile gloves in the ISO 7 buffer room or SCA.
 - Action level ≥ 1 cfu (colony forming units) on both hands.
 - Then every 6 months after completing the media-fill test.
 - Must be performed on donned sterile gloves inside of an ISO 5 PEC.
 - Action level > 3 cfu (colony forming units) on both hands.



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Section 3. Personal Hygiene and Garbing

Before entering a compounding area, at a minimum, individuals must:

- ▶ Remove personal outer garments.
- ▶ Remove all cosmetics.
- ▶ Remove all hand, wrist, and other exposed jewelry including piercings that could interfere with the effectiveness of garbing.
- ▶ 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.



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Section 3. Personal Hygiene and Garbing

Hand Hygiene:

- ▶ Must be performed before entering a compounding area
- ▶ Alcohol hand sanitizers alone are **not** sufficient
- ▶ Brushes must **not** be used for hand hygiene (potential skin irritation)
- ▶ Hand driers must **not** be used (air turbulence and contamination)
- ▶ Perform **after** donning shoe covers, head and facial hair covers, and a face mask.
 - The order of garbing must be determined by the facility
- ▶ 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.



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Section 3. Personal Hygiene and Garbing

- ▶ Hand Hygiene is required

Box 3-1 within the proposed revised chapter provides hand hygiene procedures



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Section 3. Personal Hygiene and Garbing

To enter a buffer room or SCA must be properly garbed.

Garbing Requirements:

- ▶ Gown (non-cotton, low-lint, sleeves that snugly fit, enclosed at the neck)
- ▶ Disposable covers for shoes (low-lint)
- ▶ Disposable covers for head and facial hair (low-lint)
- ▶ Face mask
- ▶ Sterile gloves (powder free)
- ▶ If using RABS (CAI or CACI) → disposable gloves (either nonsterile or sterile) inside of gauntlet gloves, and sterile gloves over gauntlet gloves.



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Section 4. Facilities and Engineering Controls

Cleanroom suite:

- All surfaces must be smooth, non-shedding, resistant to damage.
- HEPA filters must be located in the ceiling of the buffer and ante-rooms.
- Returns must be low on the wall.
- Pressure –differential monitoring systems must continuously monitor the pressure differentials. A minimum differential positive pressure of 0.02-inch water column is required between each ISO classified area.
- Line of demarcation in the ante-room.
- No tacky surfaces.
- Access doors should be hands-free.
- Sink may be placed inside or outside of ante-room.
- Buffer room must not contain water sources.
- Microbiological incubator (if used) must be placed outside of the classified areas.
- Temperature of 20° (68 F) or cooler and a relative humidity below 60%.



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Section 4. Facilities and Engineering Controls

SCA:

- All surfaces must be smooth, non-shedding, resistant to damage.
- Must be located away from:
 - Unsealed windows, doors that connect to the outdoors, and traffic flow.
 - Environmental control challenges (restrooms, warehouses, cafeterias, etc.)
- A visible perimeter must establish the boundaries.
- Sink at least 1 meter from the PEC, outside of the perimeter.



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Section 4. Facilities and Engineering Controls

PECs:

- Placement must allow for cleaning around all PECs.
- Smoke pattern test (under dynamic operating conditions) must be performed initially and every 6 months.
- LAFS (Laminar Airflow Systems) - must be located out of traffic patterns and away from room air currents that could disrupt airflow pattern inside the PEC.
- RABS (Restricted – Access Barrier System) (CAI and CACI) – the recovery time after opening to achieve ISO 5 air must be documented and followed.



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Section 4. Facilities and Engineering Controls

- Added clarifications on **Air Exchange Requirements**

Compounding Area

Unclassified SCA

ISO Class 7 room(s)

ISO Class 8 room(s)

ACPH Requirement

No requirement

≥ 30 ACPH (at least 15 from HVAC)

≥ 20 ACPH



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Section 4. Facilities and Engineering Controls

► **Certification:**

- During dynamic operating conditions
- Required every 6 months
- Certification needs to include:
 - Airflow testing (air velocity/volume, ACPH (from HVAC/PEC), pressure cascade etc.)
 - HEPA filter integrity testing (PEC and SEC)
 - Total particle count testing (all classified areas)
 - Smoke visualization studies

► **Recertification:**

- When 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.



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Section 5. Microbiological Air and Surface Monitoring

- ▶ Microbiological Air and Surface Monitoring:
 - Under dynamic operating conditions
- ▶ Viable air sampling (each classified area): Initially and Every 6 months
- ▶ Surface sampling (each classified area): Initially and Monthly
 - Flat Surface Sampling
 - Irregular Surface Sampling
- ▶ And when:
 - New facility and equipment certification
 - After any servicing of facilities or equipment
 - Identified problems/trends

Action Levels

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



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Section 6. Cleaning and Disinfecting Compounding Areas

- **Cleaning and Disinfecting Compounding Areas.**
 - Classified area and within SCA Perimeter.
- **Cleaning** - removing organic and inorganic materials from surfaces, usually with a manual or mechanical process and a cleaning agent.
- **Disinfecting** - involves destruction of microorganisms, usually with a chemical agent.
- Surfaces must be cleaned prior to being disinfected, unless have an EPA registered one-step disinfectant cleaner.
- **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.



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Section 6. Cleaning and Disinfecting Compounding Areas

- Must be performed by trained and appropriately garbed personnel using facility-approved agents and procedures, which must be described in written SOPs.
- Minimum Contact Time - the manufacturer's directions or published data for the minimum contact time must be followed for the cleaning, disinfecting, and sporicidal agents used.
- 70 % IPA (Isopropyl Alcohol) must be sterile.



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Section 6. Cleaning and Disinfecting Compounding Areas

- ▶ Table 8 of the proposed revised changer provides the details the minimum frequency for cleaning and disinfecting surfaces and apply sporicidals in classified areas within the perimeter of the SCA.



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Section 6. Cleaning and Disinfecting Compounding Areas

- ▶ Cleaning supplies (e.g., wipers, sponges, mop heads)
 - Must be low-linting
 - Should be disposable
 - If reusable – must be made of cleanable material and cleaned before and after each use.
 - Must be dedicated for use in the classified areas or SCA, and must not be removed except for disposal.



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Section 7. Equipment, Supplies, and Components

- ▶ **Restricted-access barrier system (RABS):** enclosure that provides HEPA-filtered ISO Class 5 unidirectional air that allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations. Examples of RABS include CAIs and CACIs
 - **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.
- ▶ CAI or CACI - not an isolator.



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Section 7. Equipment, Supplies, and Components

- ▶ **Components:** 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.
 - Conventionally manufactured sterile products should be used when available and appropriate for the intended CSP.
 - Facility must establish the identity, strength, purity, and quality of the ingredients obtained.
 - Each lot of commercially available sterile, depyrogenated containers and container–closure systems must be accompanied by a COA .
 - Any ingredient lacking an expiration date shall not to exceed 1 year after receipt by the compounding facility. Date of receipt must be clearly marked.
 - Must be evaluated when received and before use.



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Section 7. Equipment, Supplies, and Components

- ▶ API (Active Pharmaceutical Ingredient):
 - Must be obtained from an FDA-registered facility
 - Must comply with *USP-NF* monograph if one exists.
 - Must be accompanied by a COA.
 - includes the specifications and test results and shows the API meets the specifications of the *USP-NF* monograph, if one exists.



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Section 8. Sterilization and Depyrogenation

Sterilization Methods

▶ Aseptic Preparation

- Compounding with only sterile ingredients
- Sterilization by filtration (not for a suspension)

▶ Terminal Sterilization is preferred, unless the CSP or container cannot tolerate (can achieve Sterility Assurance Level of 10^{-6}).

- Dry heat
- Steam autoclaving (not if moisture, pressure or temp would degrade CSP)
- Irradiation



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Section 9. SOPs and Master Formulation and Compounding Records

- ▶ Facilities that prepare CSPs, must develop SOPs
 - Must be reviewed every 12 months
 - Any revisions must be communicated to all personnel
- ▶ Master Formulation Record; required if:
 - CSP prepared in a batch for > 1 patient
 - CSPs prepared from nonsterile ingredient(s)

Box 9-1 provides the proposed details that must be included as part of the compounding record



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Section 9. SOPs and Master Formulation and Compounding Records

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

Box 9-2 provides the proposed details that must be included as part of the compounding record



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Section 10. Release Testing

- ▶ Visual Inspection required at the completion of compounding and before release
 - Check the physical appearance
 - Check that the CSP, its label and the prescription match
 - Container closure integrity (leakage, cracks, etc.)
- ▶ Sterility Testing (CAT 2 as required)
 - Units to be tested:
 - 1- 39 CSPs in a single batch: 10% of CSPs
 - > 40 CSPs in a single batch, follow USP<71>, Table 3
 - Must be performed according to:
 - USP Chapter <71>
 - Method Suitability Test must be performed
 - ✓ Membrane Filtration method: method of choice
 - A validated alternative method.
 - Validated per Validation of Alternative Microbiological Methods USP (1223)
 - And has been demonstrated to be suitable for that CSP formulation.



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Section 10. Release Testing

- ▶ Bacterial Endotoxin Testing
 - Excludes:
 - inhalations
 - topical ophthalmics
 - Required for:
 - Category 2 CSPs:
 - If made from one or more nonsterile ingredient(s) or component(s) AND
 - If assigned a BUD that requires sterility testing



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Section 11. Labeling

- ▶ **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.
- ▶ 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



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Section 11. Labeling

- ▶ 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.
- ▶ The labeling of the CSP must provide any applicable special handling instructions or warning statements.



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Section 12. Establishing Beyond-Use Dates

- ▶ **Beyond-use date (BUD):** Either the date or hour and date after which a CSP must not be used or administration must not begin.
 - Is determined from the date/time that preparation of the CSP is initiated.
 - Not intended to limit the time during which the CSP is administered (e.g., infused).



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Section 12. Establishing Beyond-Use Dates

- ▶ Stability factors (not address in the BUD tables)
 - Chemical and physical properties of the drug and/or its formulations
 - Compatibility of the container-closure system with the finished CSP
- ▶ Sterility factors (related to the BUD tables)
 - Environment in which the CSP is prepared
 - Cleanroom suite or SCA
 - Aseptic preparation method and sterilization method
 - Components used: sterile or nonsterile starting ingredients
 - Sterility Testing
 - Storage conditions (e.g., packaging and temperature)



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Section 12. Establishing Beyond-Use Dates

► **Category 1 CSP:**

- PEC in a SCA

Table 11 provides Beyond Use Dates for Category 1 CSPs



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Section 12. Establishing Beyond-Use Dates

Category 2 CSP:

- ▶ Cleanroom suite
- ▶ Based on the following factors:
 - Aseptic preparation and sterilization method
 - Starting components
 - Sterility testing
 - Storage conditions

Table 12 provides Beyond Use Dates for Category 2 CSPs



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Section 12. Establishing Beyond-Use Dates

- ▶ **Multiple-dose container:** A container of sterile medication for parenteral administration 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. Intended to be entered or penetrated multiple times
 - Must be prepared as a Category 2 CSP.
 - Must pass antimicrobial effectiveness testing in accordance with *Antimicrobial Effectiveness Testing* (51).



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Section 12. Establishing Beyond-Use Dates

► Multiple-dose container:

- After initially entered or punctured, 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>).



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Section 13. Use of Conventionally Manufactured Products

- ▶ Conventionally Manufactured Product must be used by:

Type of Container	Time within which product must be used
Single-dose Container *not ampules	Iso Class 5: 6 hours Unclassified Air: 1 hour
Multiple-dose Container	28 days or per manufacturer
Pharmacy Bulk Package	As specified by the manufacturer



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Section 14. Use of CSPs As Components

- ▶ CSPs as Components :
 - Must be stored properly

Type of Container	Time within which product must be used
Single-dose Container	ISO Class 5: 6 hours
Stock Solutions	Must be entered or punctured in ISO 5 ISO Class 5: 6 hours
Multiple-dose Container	28 days or BUD assigned which ever is less



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Section 15. Quality Assurance and Quality Control

- ▶ Recall SOP must contain procedures:
 - To determine the severity and the urgency
 - To determine the distribution of any affected CSP
 - To identify patients who have received the CSP
 - For disposition and reconciliation of the recalled CSP
- ▶ Complaint handling:
 - Designated person must review all complaints
- ▶ Adverse Event Reporting:
 - Must be reported



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Section 16. CSP Storage, Handling, Packaging, Shipping and Transport

▶ Handling and Storing

- CSPs must be handled to maintain quality and package integrity.
- Personnel must monitor conditions in the storage areas.
- Temperature excursions must be detected and minimized.

▶ Packaging

- Packaging materials should protect CSPs from damage, leakage, contamination, degradation, and adsorption.
- Appropriate shipping containers and packaging materials must be selected.



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Section 16. CSP Storage, Handling, Packaging, Shipping and Transport

- ▶ Shipping and Transporting CSPs
 - Must select modes of transport that are expected to deliver properly packed CSPs in an undamaged, sterile and stable condition.
 - Consider exposure to heat, cold, light, physical shaking.
 - If special handling is required, instructions must be included on the exterior of the container.



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Section 17. Documentation

- ▶ The 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



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Section 17. Documentation

- ▶ 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.



References:

- ▶ <https://www.usp.org>
- ▶ <https://www.usp.org/compounding/general-chapter-797>
- ▶ <https://www.usp.org/sites/default/files/usp/document/our-work/compounding/797-open-microphone-presentation.pdf>
 - ▶ Web recording:
<https://uspevents.webex.com/mw3300/mywebex/nbrshared.do>
<https://www.usp.org/frequently-asked-questions/compounding>



Questions?