Highlights of Changes: USP <797> Pharmaceutical Compounding Sterile Preparations

On November 1, 2022, USP released the official revision of *USP <795> Pharmaceutical Compounding-Non-Sterile Preparations.* The finalization of the revised chapter changes the status of *USP <800> Hazardous Drugs - Handling in Healthcare Settings* and *USP <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging* chapter from informational to compendial. USP standards represent the minimum practice standards for the safe compounding of pharmaceutical compounds for patients. The expected date of compliance is November 1, 2023; noting, states may vary on expected compliance.

The following briefings summarizes the work that must be completed as part of a compliance program.

USP <797> Pharmaceutical Compounding – Sterile Preparations Briefing

- Predecessor compendial chapter version: USP <797> v2008
- **Finalized and published November 1, 2022**
- **MUST** appears **617 times**, denoting **requirements**
- **SHOULD** appears **64 times**, denoting **recommendations**
- Noted major changes to USP <797> involve **Compounding Categories, Beyond Use Dates, Environmental Monitoring, Training and Facilities**
- **46 noted** Standard Operating Procedures
- 5 Programs defined and written: Training, Personal hygiene/garbing, Cleaning & Disinfecting, Sterilization & Depyrogenation, Quality Assurance & Quality Control

Compounded Sterile Preparations Categories and Beyond Use Dates (BUDs)

USP made a transition from the 'traditional' risk levels (Low-, Medium-, High-Risk) which was based on the number of sterile products and number of manipulations to the new compounding **Categories (1, 2, 3)** based on the **state of control of the environment where compounded sterile preparations (CSPs) are prepared.**

Immediate Use Compounded Sterile Preparations

The **Immediate-Use CSPs** category, with minor revisions, is consistent with v2008. All the noted limitations for the use of **Immediate Use sterile preparations** presented in the v2008 chapter are in place; with the significant modification from a 1-hour BUD to a **4-hour beyond use date (BUDs).** All staff that perform immediate use compounding **must** complete training as defined by site standard operating procedures.

NOTE refer to Section 1.3 Immediate-Use CSPs for complete guidance.

Category 1 Compounded Sterile Preparations

Category 1 CSPs aseptic manipulations **must** take place in an ISO 5 primary engineering control (PEC) that may be placed in an unclassified segregated compounding area (SCA) or a cleanroom suite.

Beyond Use Date Limits for Category 1 CSPs	
Storage Conditions	
Controlled Room Temperature (20°C-25°C)	Refrigeration (2°C-8°C)
≤ 12 hours	≤ 24 hours

Category 2 Compounded Sterile Preparations

Category 2 CSPs require compounding in a full cleanroom suite (separate anteroom and separate buffer room) with enhanced environmental controls and testing to meet the revised BUDs under section 14. *Establishing BUDs*. The BUDs criteria include the following criteria: sterile-to-sterile, non-sterile-to-sterile, terminal sterilization and sterility testing of the final preparations. **NOTE: BUDs must not exceed those listed.**

Preparation Characteristics		Storage Conditions		
Compounding Methodology	Sterility Testing Performed & Passed	Controlled Room Temperature (20°C -25°C)	Refrigeration (2°C -8°C)	Frozen (-25°C to -10°C)
Aseptically processed CSPs	No	Prepared from one or more non-sterile components **1 day**	Prepared from one or more non-sterile components **4 days**	Prepared from one or more non-sterile components **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	No	14 days	28 days	45 days
	Yes	45 days	60 days	**90 days**

Category 3 Compounded Sterile Preparations

Category 3 CSPs was introduced in the 2019 proposed revision to address extended dating of compounded preparations. To use this category, a more rigorous compounding program emulating that of current Good Manufacturing Processes (cGMP) must be continuously in place. Category 3 CSPs require additional training, use of **sterile garb**, no exposed skin during compounding, **final product testing to include sterility testing/endotoxin testing if applicable,** increased **environmental viable surface/air testing** including direct compounding areas after each compounded batch, enhanced cleaning requirements and enhanced quality assurance and documentation requirements. **NOTE: BUDs must not exceed those listed; Refer to section 14.4 *Additional Requirements for Category 3 CSPs.***

Beyond Use Date Limits for Category 3 CSPs			
Preparation Characteristics	Storage Conditions		
Compounding Method	Controlled Room Temperature (20°C-25°C)	Refrigeration (2°C-8°C)	Frozen (-25°C to -10°C)
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

Proprietary Bag and Vial Systems

Proprietary bag and vial systems **must** follow manufacturer's labeling and may be docked and activated outside of an ISO 5 PEC, if administered immediately to an individual patient. The chapter does state that docking of the proprietary bag and vial systems for future activation and administration **is considered compounding** and **must** be performed in accordance with manufacturer's labeling and not to exceed Section 14. Establishing Beyond-Use Dates.

Single Dose Vials

Single-dose containers entered or punctured within an ISO 5 PEC can now be assigned a **BUD of 12 hours** as long as the labeled storage requirements are maintained during that time. This is an increase from 6 hours in v2008.

Restricted Access Barrier Systems *(previously known as 'isolators', CAI and CACI)*

The location of the ISO 5 PEC, including restricted access barriers RABS (formally 'isolators'), must be in accordance with the environmental requirements of the Category, i.e., elimination of RABS exemptions from v2008

Garbing and Hand Hygiene

Sites **must** determine the sequence of donning garb and hand hygiene based on the placement of the sink and define in standard operating procedures.

- **Must not** wear earbuds/headphones into the cleanroom suite
- Eyeglasses **must** be wiped/cleaned
- Donning and doffing of garb **should** not take place at the same time
- Garb **must** be stored in manner to decrease contamination, i.e., away from sinks
- Scrub bushes and hand dryers **must not** be used for hand hygiene
- Disposable soap dispensers **must not** be refilled
- Skin **must not** be exposed in the ISO 5 PEC

NOTE: Category 3 requirements differ significantly, Refer to section 2. Personal Hygiene and Garbing

Microbiological Air and Surface Monitoring

Compounding locations commonly rely on third party certifying companies to manage the microbiological air and surface sampling processes.

Sites **must** develop and implement written procedures and training for microbiological air and surface monitoring denoting all sampling locations and all test results with corrective actions **must** be documented.

Viable sample media (i.e., tryptic soy agar; TSA) **must** have a certificate of analysis (COA) from the manufacturer that **must** verify that the media meets defined growth promotion, pH, and sterilization requirements, and, for surface sample media that the media (i.e., TSA) **must** be supplemented with neutralizing additives that neutralize the effects of potential residual disinfecting agents on surfaces; refer to Sections: *6.2.2 Viable air sampling procedures; 6.3.2 Surface sampling procedures*

If sites elect to incubate environmental growth sample plates note revised incubation standards:

- Dual media method for sampling is still allowed, same as v2008
- **NEW** allowance of using growth agar that supports both bacterial and fungal growth (single plate method)
  - **NEW** media **must** be incubated at **30˚C to 35˚C for 48 hours**, followed by incubation at **20˚C to 25˚C** for **5 days** (**must** be in an incubator)
- Incubators **must** be temperature controlled and documentation of temperatures daily
- Incubators **should** be on a cleaning schedule and **should** be placed on an annual calibration plan

Viable air sampling must use a volumetric, impaction active air sampling device of all classified areas during dynamic conditions (settling plate method not allowed). For Category 1 & Category 2 air sampling **must** be every **6 months.**

NOTE: more frequent may be required according to individual state requirements

Viable surface sampling must be conducted for Category 1 and Category 2 compounding where classified areas, including each room and the interior of each ISO Class 5 PEC and pass-through chambers connecting to classified areas and **must** be sampled **monthly.** Revised USP added new language, "Sampled areas **must** be thoroughly **cleaned** and **disinfected** post sampling", historically the process only involved disinfection. If samples are taken within the ISO5 workspace/PEC the cleaning and disinfecting solutions **must** be sterile

Environmental Viable Monitoring Requirements		
Category	Type of Sampling	Minimum Frequency & Location
Category 1 & 2	**Air** Sampling	All Classified Areas under dynamic operating conditions every **6 Months**
	Surface Sampling	All Classified Areas and Pass-through Chambers at least **MONTHLY**

NOTE: Category 3 requirements differ significantly, Refer to section 6. Microbiological Air and Surface Monitoring

Actionable Air and Surface Sample Growth

Actionable growth limits for air and surface samples updated the **surface sample ISO Class 8** surface samples with lowering the allowance from >100 CFU/media device (v2008) to **>50 CFU/Media Device.**

If the actionable limits are reached, the **cause must be investigated,** and **corrective action must be taken**. If actionable CFU levels are met, an attempt **must** be made to ID any microorganism recovered to the genus level with the assistance of a microbiologist. The corrective action plan **must** consider the CFU count and the microorganism. USP gives examples of corrective actions which include (but not limited to) processes, facility remediation, personnel re-training, enhanced cleaning, or secondary engineering control HEPA assessment and repairs.

The corrective action plan must be documented. Refer to section 6. Microbiological Air and Surface Monitoring

Personnel Training and Evaluation

Significant revisions are made to section 2. Training and Evaluation. The USP FAQ for USP <797> clearly states that any personnel who 'touch' a CSP must have training, but not all personnel require the same training.

USP clarified personnel involved with sterile compounding process from **Designated Person**, delegated **training oversight person,** to **compounding personnel.** Personnel who receive sterile preparations, enter orders but do not compound or **check CSPs preparations, clean compounding areas, transport CSPs**, or **other activities must** have documented competence as defined by the organization.

Training program **must** be documented with demonstrative knowledge and competency of core skills and **must** be completed and passed prior to compounding.

Qualification for Category 1 and Category 2	Process	Compounder	Oversight Person*
Visual observation of hand hygiene and garbing	Observation	Every 6 months	Ever 12 Months
Gloved fingertip and thumb sampling	Media Plate		
Media Fill testing	Media Fill		
Direct compounding area surface sample post-media fill	Media Plate		
Gloved fingertip and thumb sample post media fill	Media Plate		
Acceptable Qualification Limits			
Gloved fingertip and thumb	**Media Fill**	**Gloved fingertip and thumb post Media Fill**	**Direct Compounding Area post Media Fill**
0 CFU	No Turbidity	Less than 3 CFU	Less than 3 CFU

**Not allowed to compound Category 1, Category 2 and Category 3 Sterile Preparations.*

If sites elect to incubate media fill samples note standards

- Growth media **must** support the growth of microorganisms
- Following the media-fill test, gloved fingertip and thumb sampling **must** be performed on both hands inside of an ISO Class 5 PEC
- **NEW:** Surface sampling of the direct compounding area **must** occur immediately following the media-fill, gloved fingertip and thumb sampling
- Incubate the media-fill containers at 20°C–25°C for 7-days and then at 30°C–35°C for 7 days= **14 days**
- Incubate plates or paddles for gloved fingertip and thumb sampling and direct compounding area at 30°C–35°C for 48 h and followed by 20°C–25°C for 5 days
- Incubators **must** be temperature controlled and documentation of temperatures daily
- Incubators **should** be on a cleaning schedule and should be placed on an annual calibration plan

Qualification for Category 3 Sterile Compounded Preparations are more complicated. Refer to section 2. *Training and Evaluation.*

Facility

Restricted Access Barrier Systems *(previously known as 'isolators', CAI and CACI)*

The location of the ISO 5 primary engineering control, including restricted access barriers RABS (formally 'isolators'), **must** be in accordance with the environmental requirements of the desired compounding Category.

NOTE: Eliminates all RABS (CAI and CACAI) **exemptions from v2008**

Segregated Compounding Areas (SCA) for Category 1 compounding

- SCA can be in a room with non-classified air quality
- SCA **must** be clean, uncluttered, and dedicated to compounding
- Room **must** house an ISO 5 primary engineering control with visible perimeter area within 1 m of the PEC
- Compounding location **must** be separated from areas not directly related to compounding
- Sink **must** be no less than 1 meter from the ISO 5 primary engineering control

Cleanroom Suite for Category 2 and Category 3 compounding room

- Cleanroom **must** have a separate ISO classified anteroom and buffer room separated by walls and doors
- Anteroom **must** have a line of demarcation defining clean side from dirty side
- Tacky mats **must not** be placed within ISO-classified areas
- HEPA filters for the cleanroom suite **must** be in the ceiling
- Return vents for non-hazardous drug compounding **must** be low on a wall
- Lines of demarcation **must** be present in the flooring
- Hand dryers **must not** be used
- Anterooms not connected to a negative pressure room **must** be either ISO 8 with a minimum of 20 ACPH or ISO 7 with a minimum of 30 ACPH
- Buffer rooms **must** be ISO 7 with a minimum of 30 ACPH
- Cleanroom suite **should** be maintained at a temperature of 20° or cooler and a relative humidity of 60%
- Temperature and humidity devices **must** be calibrated every 12 months
- Pressure differentials for non-hazardous compounding **must** be at least 0.02-inch water column and must be continuously monitored
- Temperature, humidity, and pressures **must** be documented daily
- Sterile gloves **must** be donned in an ISO rated room or SCA but not in the Primary Engineering Controls
- Surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified area **must** be smooth, impervious, free from cracks and crevices, and non-shedding so they can be cleaned and disinfected: **NOTE: USP removed from v2008 the use of wire shelving**
- Ceilings consisting of panels **must** be caulked around each panel to seal to grid and wall
- Sink for hand hygiene may be placed inside or outside of the anteroom
- Buffer room **must not** contain plumbed water sources (e.g., sink, eyewash, shower, or floor drain)
- Anteroom **must not** contain a floor drain
- Blood-derived and biological materials (autologous serum) used during compounding **must** be clearly separated from other compounding activities

Refer to Section 4. Facilities and Engineering Controls the complete list of requirements and recommendations

References

USP <795> Pharmaceutical Compounding- Non-Sterile Preparations and *USP <797> Pharmaceutical Compounding- Sterile Preparations* now require a paid subscription to the USP Compounding Compendium

USP has published free references to assist with interpretation of new chapters

1. USP <800> Hazardous Drug Handling in Health Care Settings
2. USP <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging
3. NEW: USP <797> FAQs
4. NEW: USP <795> and <797> BUD FACT Sheet
5. NEW: USP <797> Commentary
6. https://go.usp.org/2022_Revisions_795_797

This guide is meant to present highlights of changes to *USP <797> Pharmaceutical Compounding- Sterile Preparations* and is not meant to be totally inclusive of all new and existing requirements and recommendations.