

USP <797> Pharmaceutical Compounding – Sterile Preparations

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Summary

USP <797> addresses policies and practices for preparing, packaging, and storing CSPs. The intent of USP <797> is to reduce the potential for contamination caused by an unclean environment, pharmacist error, lack of quality assurance, incorrect beyond-use dating, and other factors. Some specific issues USP <797> address include

- The responsibility of compounding personnel to ensure that CSPs are prepared, stored, dispensed, and distributed safely
- Contamination risk levels
- Procedures to verify the accuracy and sterility of CSPs
- Personnel training and evaluation
- Verification of Automated Compounding Devices (ACDs)
- Environmental quality and control
- Checks and tests of finished preparations before dispensing
- Storage and beyond-use dating
- Product quality and control after the CSP leaves the pharmacy
- Patient or caregiver training so they can store, administer, and dispose of the CSP
- Patient monitoring to track their response to the therapy
- The need for a feedback mechanism so patients and caregivers can report concerns about CSPs
- A quality assurance program that documents CSP policies, processes, and procedures

Enforceability

The effective “Standard of Practice” date is June 1st, 2008. Currently as of May, 2008 the Joint Commission and the Food and Drug Administration (FDA) has no plans or comments on any future adoption of USP <797>. U.S. Pharmacopeia acknowledges that the document has no authority until specifically adopted by the States Boards of Pharmacies. However, USP states that the standard should be followed voluntarily by pharmacies to avoid potential liability issues. USP <797> will be the industries standard of practice.

The Standard

There are two primary focuses of USP <797>. The first and perhaps the primary emphasis is to reduce the risk of contact contamination. Proper hand hygiene seems to have been a practice that has fallen to the wayside in typical pharmacy practice, sterile compounding being no exception. Contact is the most likely source of clinically significant microbial contamination.

The second goal of <797> is to provide more environmental controls.

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Additional specialty compounded Sterile preparations are addressed in <797>. They include Hazardous Drugs, Allergen Extracts and Radiopharmaceuticals.

Chapter <797> applies to pre-clinical administration manipulations of compounded sterile preparations including compounding, transportation, and storage.

Chapter <797> applies to all persons, regardless of profession, who prepare CSPs and all places where CSPs are prepared, such as institutions, clinics and emergency rooms.

The new chapter <797> places much more emphasis on the individual training and evaluation of those who compound sterile preparations. Environmental sampling must occur as part of a comprehensive quality management.

Sterilization methods in the chapter apply only to sterilizations of high risk preparations.

Determination of CSP Risk Levels

- There are three contamination levels for Compounded Sterile Preparations (CSPs); Low, medium and high risk levels.
- In addition to the three levels, there are two exceptions to the low risk level; Immediate Use and Low Risk with 12 hr or less BUD
- The licensed healthcare professional who supervises compounding is responsible for determining the risk level of each compounded sterile preparation.
- All compounded sterile preparations are assigned a risk level.

Low Risk Levels

Low Risk CSP are compounded with **aseptic** manipulations using only **sterile ingredients**. The compounding only involves transfer, measuring, and mixing using not more than **three** commercially manufactured products. The manipulations with low risk CSP's are limited opening, penetrating stoppers, transferring and packaging for storage and dispensing.

BUD limits of; 48 hours (at room temperature), 14 Days (refrigerated), 45 days Frozen

Low Risk Level with 12hr or less BUD

Intended to accommodate satellite pharmacies compounding **only** low risk level CSP's. Compounding of Hazardous Drugs are not permitted. These low risk level CSPs do not require the ISO class 7 clean room or buffer area and only require an ISO Class 5 hood.

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In addition, these low risk level compounding areas need to be segregated from other parts of the pharmacy and designated for use as a compounding area. Personnel shall follow cleaning and garbing requirements. Sinks shall not be placed adjacent to the ISO Class 5 hood.

Medium Risk Level

Medium Risk Level CSP's are essentially the same as Low Risk CSPs but intended to be utilized in bulk quantities. CSPs are compounded with **aseptic** manipulations using only **sterile ingredients**. Medium Risk level CSPs are intended for multiple patients or one patient on multiple occasions. The compounding process may be more complex than low risk CSP's. The compounding process may require unusually long duration such as that required to complete dissolution or homogenous mixing. No bacteriostat and administered over several days.

BUD limits of; 30 hours (at room temperature), 9 Days (refrigerated), 45 days Frozen.

High Risk Level

High Risk CSP's are prepared from non-sterile ingredients. These CSPs are either contaminated, or at high risk for being contaminated. Sterilization occurs after compounding. High Risk CSP's include compounds using nonsterile water that will not be sterilized within 6 hours of being compounded, sterile ingredients that are exposed to air quality that is worse than ISO Class 5 for more than 1 hour, CSPs compounded (or exposed to) personnel that are not properly garbed and gloved. Additionally, if the purity of components is assumed but not verified by documentation such as with bulk ingredients where a certificate of analysis is available.

BUD limits of; 24 hours (at room temperature), 3 Days (refrigerated), 45 days Frozen.

Immediate Use

Immediate use compounds are exempt from ALL requirements in <797> and is intended for situations where there is a need for emergency or immediate patient administration such as cardiopulmonary resuscitation, emergency room treatment, **preparation of diagnostic agents**. Low Risk, CSPs may qualify for immediate use when only simple aseptic measuring and transfer are needed, only non-hazardous products or diagnostic radiopharmaceutical products are used, not more than two entries into any one container or package are prepared, aseptic technique is followed during preparation, administration begins within 1 hour of the start of preparation. In addition, the intent of the immediate use provisions is that once the compounding begins that there are no delays or interruptions of the process all the way to administration to the patient.

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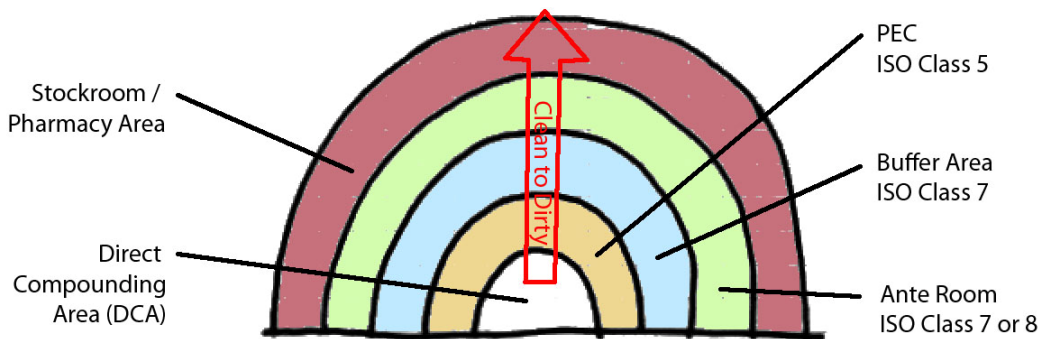
Other conditions of the immediate use category; the dose must be discarded if administration has not begun within 1 hour, the dose must be labeled if not administered by the preparer.

All CSPs must be prepared in an ISO class 5 environment except the immediate use category.

Environmental Quality and Control.

The primary environmental areas are: (from cleanest to dirtiest) **Direct Compounding Area (DCA) / Primary Engineering Control (PEC)**, **Buffer Area** and the **Ante Area**. These areas are separated from the rest of the pharmacy.

The concept of the environmental controls is to eliminate the number of particles in each area by properly cleaning and garbing as you go from a dirty areas to cleaner areas.

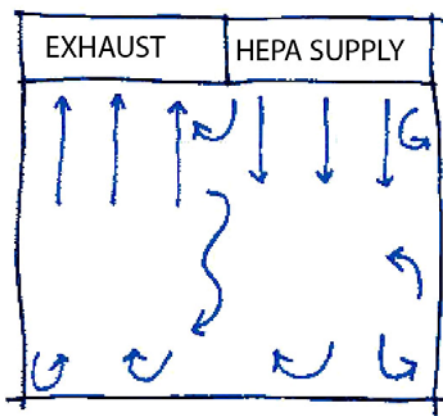


Direct Compounding Area (DCA) / Primary Engineering Control (PEC)

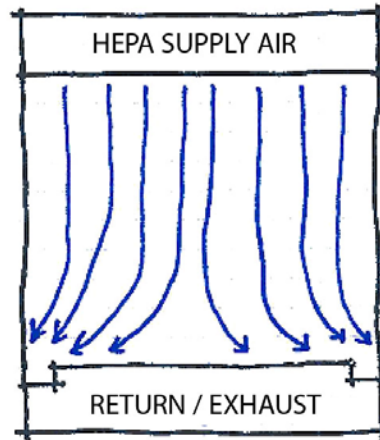
The Primary Engineering Control is typically a hood (such as LAFW, BSCs, CAIs, or CACIs) which is certified as an **ISO 5 environment**. Within the hood is an area where the compounding occurs referred to as the Direct Compounding Area. Proper design and control prevents turbulence and stagnant air in the PEC. The DCA is the critical area within the PEC and must be located to provide first air to the component, pathway, or opening.

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In situ air-pattern analysis via smoke studies should be conducted at the DCA to ensure that the system is installed and performing as it was designed. This is not a requirement of USP <797> but is highly recommended.



PEC with Turbulent Airflow



PEC WITH Unidirectional Airflow

Everything that enters the PEC must be sanitized. Likewise anything that is removed from the hood, no matter how brief, must not be taken back into the hood without being re-sanitized. This includes hands and arms of the staff. It is recommended that **sterile alcohol aerosol** be used over trigger spray bottles for sanitization of all items being taken into the hood.

Buffer Area

The area/room around the PEC is the Buffer area which is certified as an **ISO Class 7 environment**. The activities that occur in the buffer area are typically preparation and staging of components and supplies to be used when compounding.

Staff comfort needs to be considered in the design which may include cooling of the room. The additional garbing that is required for staff needs to be taken into consideration. The working environment shall be designed to accommodate 68° F.

Airflow Displacement Method of Separation

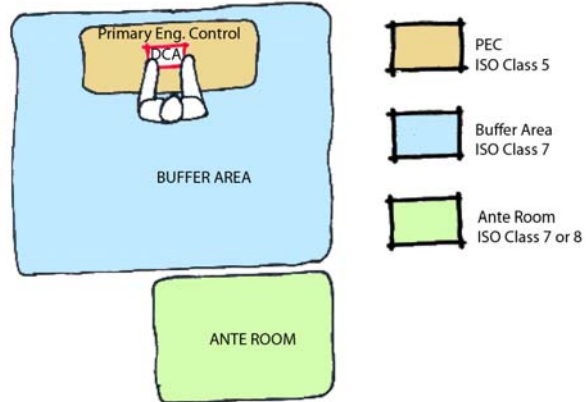
The Buffer area does not have to be physically separated from the ante room by a barrier for low and medium risk compounding areas. The displacement method can be used by creating an area of low pressure at the ante area and higher pressure at the buffer area. A line of demarcation must be designated where the air velocity across the line measures 40

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ft per minute. Although this is allowable by the standard, it may be too costly to be a practical solution.

Ante Room

The Ante Room is the area which is certified as an ISO 8. The activities that occur in the ante room are garbing, staging of components, labeling, or other high particulate generating activities. In addition the ante room serves as a transition space from uncontrolled dirty areas into the clean environment.



HVAC Design

The ante and buffer areas require **HEPA filtered** air of not less than **30 ACPH**. If the primary engineering control is a recalculating device the hood can augment the ACPH. The 30 ACPH can be reduced to 15 ACPH if hood can provide 15 ACPH. There have been many questions about the inclusion of HEPA filtered air as a prescriptive requirement. The intent of the section is to provide an ISO class 7 area, therefore it would seem that a space designed to meet that class should be able to comply with the standard. Clean rooms have effectively been designed to meet the ISO Class 7 certification using filter beds of MERV 16 and lower.

The Standard also requires that the supply air be introduced at the ceiling and recommends that the exhaust be through low wall returns creating a general to-down dilution of area air sweeping any particulate out of the area.

Gowning

Before Entering the ante or buffer area, personnel must remove street clothes, make-up and jewelry or piercing.

Personnel shall don the PPE in the order from dirtiest to cleanest. (e.g. shoe covers, head and facial hair covers, face masks/eye shields. After proper hand hygiene an nonshedding gown with sleeves that fit snugly around the wrists and an enclosed neck shall be donned. Disposable is preferred, but not required by USP <797>. Sterile gloves shall be the last item donned before compounding begins.

Plan Review Checklist

PEC

- The hood or area can be certified as ISO Class 5
- The hood is located in an area without traffic
- The proper hood is selected (i.e. vertical or horizontal LAFW, Isolator for hazardous)

Buffer Area

- The Buffer area can be certified as ISO Class 7
- HEPA filtered air is provided
- Proper Air Changes
 - 30 ACPH with isolator or non-recirculating
 - 15 ACPH with open recirculating hood, hood must provide 15 ACPH
- Separated from other areas with a minimum pressure differential of .02-.05-inch water column.
- No Sinks or floor drains are included in the buffer area
- Surfaces of ceilings walls, floors, fixtures, cabinets etc are impervious, free from cracks and crevices and non-shedding materials.
- Work surfaces are constructed of stainless steel or molded plastic
- Storage shelving, counters and cabinets are smooth, impervious, free from cracks and crevices, non-shedding, cleanable and disinfectable
- Junctures of ceilings to walls are coved or caulked
- Junctures of floors to walls are coved
- Ceiling surfaces are hydrophobic
- Walls are epoxy coated gypsum or heavy gauge polymer
- Penetrations through walls or ceilings sealed

Ante Room

- Room physically separated from the buffer area
 - Where displacement method is used,
 - Compounding only low and medium risks
 - Supply air located above buffer area
 - Return air located above ante room
 - Demarcation line indicated
 - Designed Air velocity of 40fpm across demarcation line
- Proper Air Changes
 - 30 ACPH
 - Uses displacement method with isolator or non-recirculating at buffer area
 - 15 ACPH with open recirculating hood, hood must provide 15 ACPH
- Separated from other areas with a minimum pressure differential of .02-.05-inch water column.
- Sink Provided with elec. Hand dryer or lint free disposable towels

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- Surfaces of ceilings walls, floors, are impervious, free from cracks and crevices and non-shedding materials.
- Work surfaces are constructed of stainless steel or molded plastic
- Storage shelving, counters and cabinets are smooth, impervious, free from cracks and crevices, non-shedding, cleanable and disinfectable
- Junctures of ceilings to walls are coved or caulked
- Junctures of floors to walls are coved
- Ceiling surfaces are hydrophobic
- Walls are epoxy coated gypsum or heavy gauge polymer
- Penetrations through walls or ceilings sealed