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Designing a Cleanroom to Meet the Updated USP <797> Requirements

Since July 2004, USP Chapter <797> had been laboring under continuous scrutiny, the perception of wavering deadlines, and open forum review. This period has come to a close, with the updated version of the chapter posted on www.usp.org on December 3, 2007, and scheduled to become official on June 1, 2008. The revised chapter is based on thousands of comments received during 30 months of open review and is the result of countless hours of work on the part of the USP Sterile Compounding Expert Committee (2005-2010). The Joint Commission's deadline for the completion of a facility action plan to achieve USP <797> compliance is January 1, 2008.

Now that the chapter is finalized, what do we do next? A good first step is to appropriately classify your compounding area, based on the risk level – low, medium, or high – of the CSPs you will prepare. For those unfamiliar with the terminology, thorough definitions of each of these risk levels are available in the updated chapter. Then, look to your procedures, your staff's techniques, and the consistency of staff discipline. Effective staff training is your first and best line of defense against compounded sterile preparation (CSP) contamination. No amount of environmental controls can overcome an individual's ability to knowingly or unknowingly circumvent the system and contaminate your CSPs. Of course, it is then vital to develop the proper environment in which your staff can perfect their technique and remain dedicated to the ultimate safety of the patients they serve.

Developing the Physical Environment

There are several steps to developing an appropriate compounding environment, outlined as follows:

STEP 1: Understand the Definitions

It is crucial to understand the terms presented in USP Chapter <797>. The chapter itself contains detailed definitions, paraphrased as follows:

Anteroom: An ISO Class 8 or better area where personnel perform hand hygiene and garbing procedures, stage components, perform order entry, label CSPs, and complete other high-particulate-generating activities. Also a transition area that constantly maintains pressure relationships, ensuring air flows from clean to dirty areas and reducing the need for the HVAC control system to respond to significant disturbances.

Biological Safety Cabinet (BSC) Class II: A ventilated cabinet for personnel, product, and environmental protection, having an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection.

Buffer Area or Cleanroom: An ISO Class 7 area in which the primary engineering control is physically located and the concentration of airborne particles is controlled. Microorganisms in the environment are monitored so that ISO Class 7 microbial levels for air, surface, and personnel are not exceeded. Activities in this area include the preparation of CSPs and the staging of compounding components and supplies.

Compounding Aseptic Isolator (CAI): A barrier isolator specifically designed for compounding pharmaceutical ingredients or preparations that provides unidirectional airflow and maintains an aseptic environment throughout the compounding and material-transfer processes. Air should not enter the isolator from the surrounding environment unless it has first passed through a HEPA filter.

Critical Area: An ISO Class 5 environment.

Critical Site: The sterile CSP ingredients and locations on devices and components used to prepare, package, and transfer CSPs that can be exposed to contamination.

Negative-Pressure Room: A room at a lower pressure compared to adjacent spaces. The net flow of air is into the room.

Primary Engineering Control: A device or room that provides an ISO Class 5 environment for compounding, including, but not limited to, laminar airflow workbenches (LAFWs), BSCs, and CAIs.

Positive-Pressure Room: A room at a higher pressure compared to adjacent spaces. The net airflow is out of the room.

Unidirectional Flow: Airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to sweep particles away from critical sites.

STEP 2: Understand Critical Physical Relationships

Everything starts with the ISO Class 5 primary engineering control or critical area where the sterile compounding process occurs. Primary engineering controls located within an ISO Class 7 buffer area or cleanroom should be placed away from traffic patterns (i.e., door openings) and room air currents (i.e., cross drafts from the HVAC system) which could disrupt your intended airflow patterns. CAIs may be placed outside of the ISO Class 7 buffer area/cleanroom as long as they are certified to maintain ISO Class 5 conditions under dynamic working conditions. For hazardous drug compounding, appropriate ISO Class 5 devices, such a BSCs and CACIs (compounding aseptic containment isolators), can be used to protect personnel from exposure to hazardous agents. CACIs must be placed within a negative-pressure room when not in an ISO Class 7 area. For low-volume hazardous drug compounding, a BSC, along with a closed-system drug transfer device, may be used in a positive-pressure cleanroom.

Table 1. ISO Classification of Particulate Matter in Room Air

(particles 0.5 µm and larger per cubic meter)

ISO Class	Particle Count
3	35.2
4	352
5	3,520
6	35,200
7	352,000
8	3,520,000

The buffer area is accessed through the positive-pressure ISO Class 8 anteroom or a negative-pressure/positive-and-negative-pressure ISO Class 7 anteroom. In a low- or medium-risk compounding environment, the anteroom and buffer area/cleanroom can be the same space. However, in a high-risk environment, a wall with a door must separate the anteroom and buffer area.

Anterooms are a necessary component of the cleanroom complex. For non-hazardous applications, an anteroom must maintain at least ISO Class 8 conditions and be at positive pressure to uncontrolled spaces and negative to the compounding room. Hazardous applications require an anteroom with at least ISO Class 7 conditions that is at positive pressure to both the general pharmacy and the cleanroom. **Figure 1** shows how a single ISO Class 7 anteroom can serve both positive- and negative-pressure compounding areas at the same time.

STEP 3: Meet the Performance Criteria

Next, it is important to understand the performance requirements for cleanrooms, and endeavor to meet them in your facility. For non-hazardous drug compounding, the positive-pressure cleanroom should achieve net displacement of air out of the space; in other words, the air should push against you as you enter the room. For hazardous drug compounding, the negative-pressure cleanroom should achieve net displacement of air into the space; the air should rush in with you, from behind, as you enter the room. The cleanroom must maintain at least ISO Class 7 conditions for particles 0.5µm and larger under dynamic operating conditions.

It is also vital to understand the chapter's requirements for airflow distribution in the cleanroom. The cleanroom should experience no less than 30 air changes per hour (ACPH). Cleanrooms for non-hazardous and non-radioactive CSPs are to be supplied with air through ceiling HEPA filters, with low wall-mounted return vents. The proper design and control of your buffer area's airflow distribution will prevent turbulence in critical areas, as well as pockets of stagnant air throughout the buffer area. For example, keep the ceiling supply air diffusers away from the front of your hoods to prevent air turbulence directly in front of the work site.

Conduct an in situ, air-pattern smoke study at your critical areas to determine that consistent unidirectional airflow is being achieved. In this vein, it is also important that all personnel gain a thorough understanding of "first air" and its proper use. All critical compounding manipulations must occur in unobstructed first air, exiting the primary engineering control's HEPA filter in a unidirectional stream. Proper product placement with respect to the critical area's air supply and discharge can provide a contamination-free compounding area and prevent cross contamination.

To meet USP <797>'s cleanroom pressure-differential guidelines, install a pressure gauge or velocity meter to monitor the pressure differential and airflow between the buffer area and anteroom/ante area, as well as the ante area and the general pharmacy environment outside of the compounding complex. The pressure difference between the ISO Class 7 area and the general pharmacy should not be less than 5 Pa (Pascal) or 0.02"wc. Meter readings should be reviewed and documented in a log during every work shift or collected by a continuous recording device. In addition, it is recommended to maintain a temperature of 20°C/68°F or cooler in the compounding facility in order to provide maximum comfort for your properly garbed personnel.

STEP 4: Incorporate Construction Details

There are several construction details to keep in mind when designing a cleanroom for USP <797> compliance. All surfaces, including ceilings, walls, and floors should be made of smooth, impervious, and non-shedding materials and free from cracks and crevices. The junctures of the ceiling to the walls should be coved. Walls should be constructed of epoxy-coated gypsum board, and floors should be made of sheet vinyl with heat-welded seams and a coved base. Any lighting fixtures should be flush-mounted with the ceiling and sealed. No sinks or floor drains should be present in the cleanroom.

Only the minimum amount of furniture, equipment, and supplies should be brought into the buffer room – just those items that are required for compounding activities. Furthermore, furniture and equipment placed in the compounding complex must be non-permeable, non-shedding, cleanable, and resistant to frequent cleaning and disinfecting. Items like printers, refrigerators, and other devices not essential to compounding should be carefully placed in the anteroom to establish their appropriate relationship with airflow patterns. In other words, the placement of these devices is dictated by their effect on the required environmental quality of the air and surfaces in the compounding complex. Proper placement of these devices should be verified by testing and monitoring, such as smoke tests, to ensure particles being emitted are pulled toward an air return.

Pharmacies should have their cleanrooms certified according to the guidelines set forth in CETA's Certification Guide for Sterile Compounding Facilities (CAG-003-2006). Certification is required every six months or whenever a device is relocated or altered or major service to the facility is performed.

Conclusion

This article is not intended to be a design manual. Instead, think of it as a Cliff Notes to the rules of cleanroom design. In order to fully grasp the requirements of USP <797> – as well as ensure your compliance with them – you must read the chapter itself. However, you can use these "rules of the road" to speed you on your journey toward a USP <797>-compliant compounding complex. ■

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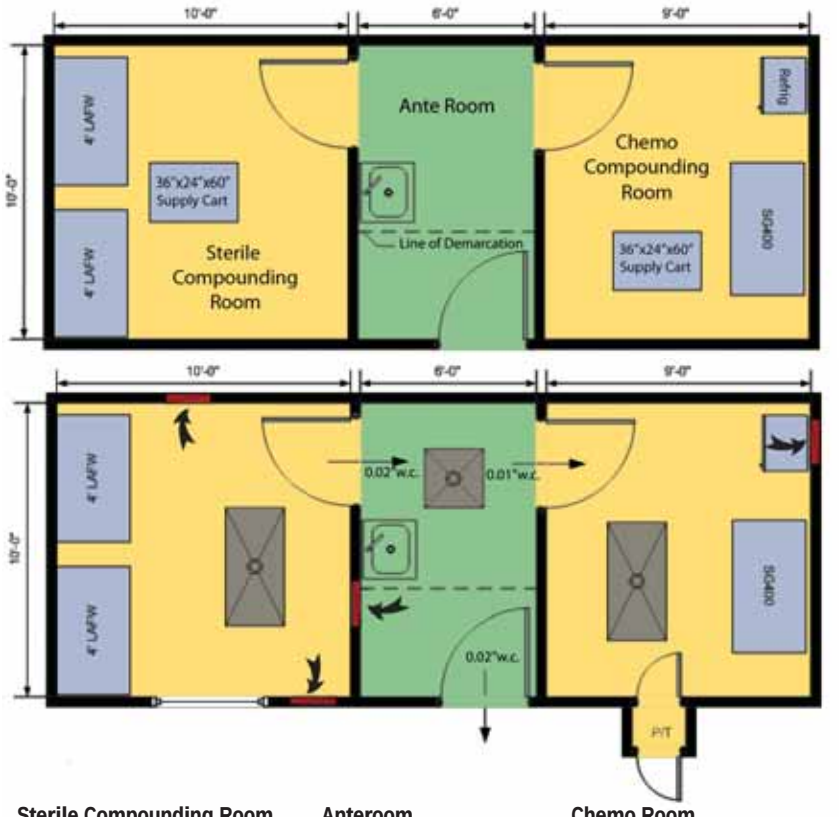
Figure 1. A Single ISO Class 7 Anteroom for Both Sterile & Chemo Compounding Rooms



Sterile Compounding Room
90 ft² w/ 8 ft ceiling
720 ft³
360 CFM at 30 ACPH
180 CFM at 15 ACPH

Anteroom
60 ft² w/ 8 ft ceiling
480 ft³
240 CFM at 30 ACPH

Chemo Room
90 ft² w/ 9 ft ceiling
810 ft³
450 CFM at 33 ACPH
RM. Ex. 700 CFM
350 CFM at BSC
350 CFM at low-wall
250 CFM displacement at door

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