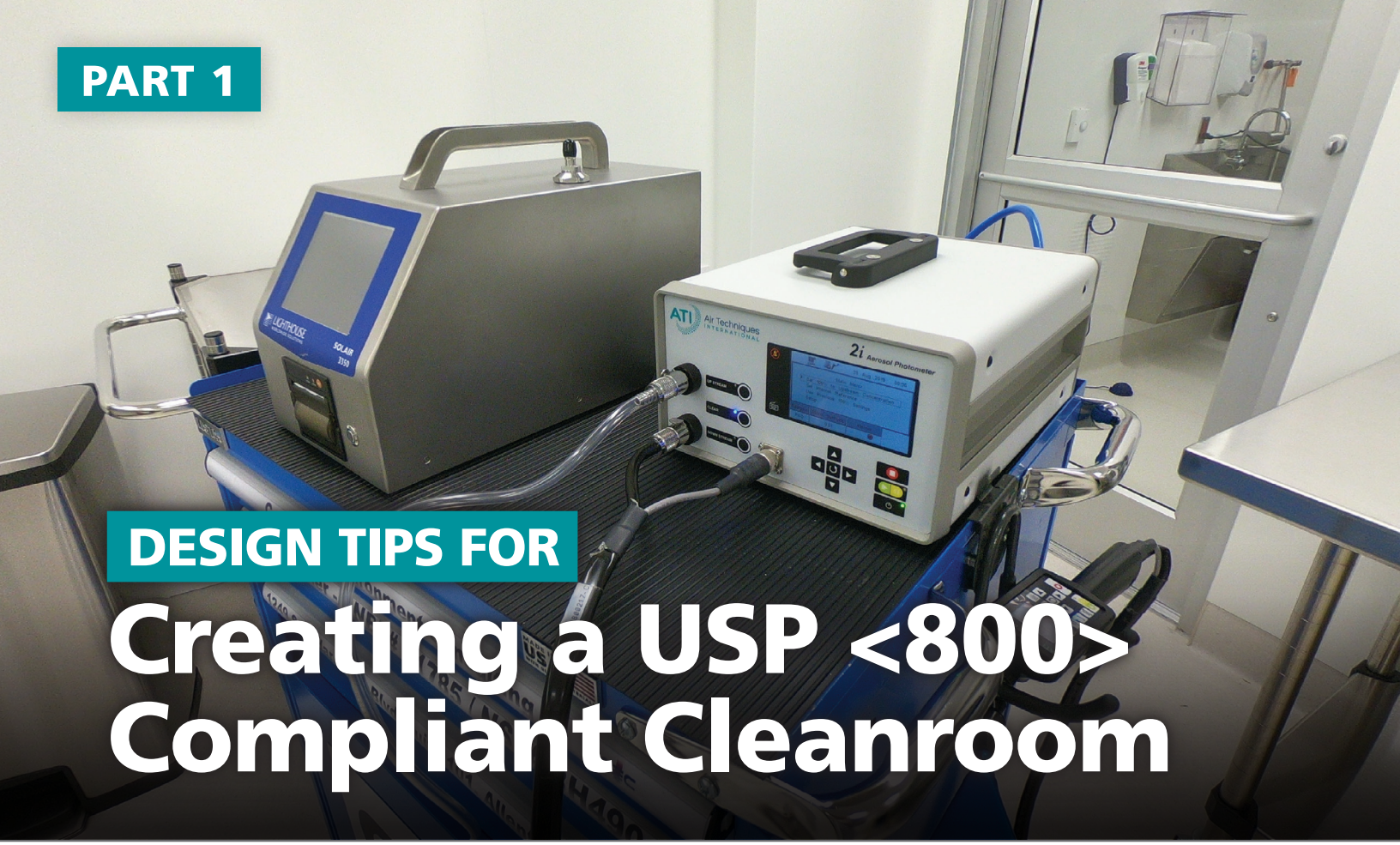
PART 1



DESIGN TIPS FOR Creating a USP <800> Compliant Cleanroom

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A well-designed hazardous drug (HD) cleanroom must account for a variety of factors. In addition to physical plant and equipment considerations, effective design must incorporate workflow requirements, such as gowning procedures and storage and receiving activity. While regulatory guidance is proscriptive, not all HD cleanrooms will be identical; rather, each will need to accommodate the various conditions and restrictions that are unique to the facility.

The following guidance for creating a USP <800>-compliant HD cleanroom includes direct reference to USP Chapters <797> and <795>.[1-3] Since this discussion focuses on compounding sterile preparations, Chapter <797> is the supporting reference. Note that the changes to <797> and <795> that were scheduled to take effect in December 2019 have been put on hold pending the outcome of appeals. The outstanding appeals may result in discrete changes to the chapters, but the facilities sections of the chapters will not be affected. Additionally, <800> is not under review; the published version is its final form. When designing a new facility, it makes sense to consider what is coming in the standards, not what was. As such, this paper focuses on the 2019 version of the chapters, where applicable.

Design

A cleanroom designed for compounding hazardous sterile preparations is typically, though not always, part of a three-room suite. Nevertheless, a USP compliant cleanroom will always have at least two rooms: an ISO Class 7 buffer room and an ISO Classified anteroom. For HD compounding, the anteroom must be ISO Class 7 because that air is drawn into the HD buffer room. In certain instances, a containment segregated compounding area (C-SCA) may be considered as a cleanroom alternative when the Category 1 classification per USP <797> is sufficient; however, since a C-SCA is not a cleanroom, that option will not be discussed herein.

USP Chapter <797> is referenced for general cleanroom criteria such as minimum air change rates, room pressures, architectural finishes, garbing area layout, certification criteria, ISO classification, pressure monitors, and other compounding-specific information. USP <800> is referenced for HD compounding-specific information such as requirements for negative pressure, external ventilation, and HD receiving and storage. It is important to note that there are areas where USP Chapters are silent; therefore we must rely on other standards and recommended practices to fill in those details.

Creating a USP <800> Compliant Cleanroom

Key guidance is available from:

- American Society of Heating, Refrigeration, and Air Conditioning Engineers (ASHRAE): ASHRAE Standard 170-2017, Ventilation of Health Care Facilities (tinyurl.com/t3t2vbl)
- Controlled Environment Testing Association (CETA): CAG-003 Certification Guide for Sterile Compounding Facilities (tinyurl.com/uqokehr)
- CETA Application Guide for the Exhaust System Requirements of Class II, Type B Biosafety Cabinets CAG-007 (tinyurl.com/t546o8z)

Anteroom Workflow

In addition to meeting USP standards, the cleanroom design must also accommodate the facility's workflow in order to achieve maximal effectiveness. Because each facility will have unique requirements, it is important to consult with the compounding team members during the design process to establish the key design considerations.

Gowning

Hand washing typically occurs in the anteroom. However, changes to Chapter <797> allow the sink to be placed immediately outside the anteroom. The design process must allow the pharmacy team's designated person to create the anteroom layout based on the intended gowning procedure. Once the sink is placed and the plumbing installed, the gowning procedure is determined. A line of demarcation (LOD) is required to separate the dirty side of the anteroom (no shoe covers) from the clean side (shoe covers required).[2] If the sink is placed in the anteroom, it can be positioned either on the clean or dirty side of the LOD, but is typically placed on the clean side so that hand-washing can occur after the donning of shoe covers, face masks, and head covers, but before the gown is donned.

If the sink is to be placed outside the anteroom, gowning process accommodations must be made. In this scenario, hand washing will occur before shoe covers are donned, so an alcohol-based hand rub must be used immediately after donning shoe covers and before any other gowning steps are performed. The hand-washing sink must be deep enough to contain splashing that results from washing up to the elbows.[2]

The anteroom should be limited to gowning activities with accommodations made for PPE storage.[1] Face masks, head covers, and shoe covers should be placed on the dirty side of the LOD near the gowning bench or stool.[2] Cleanroom gowns should be placed on the clean side of the LOD to be donned after hand washing if the sink is in the anteroom. Sterile gloves can be donned in the anteroom or buffer room with a sterile glove storage area and a flat work surface for laying out and donning gloves.

While often overlooked, waste disposal is essential in cleanroom design, as donning and doffing sterile garments results in a significant amount of waste. Be sure to allow space for appropriate waste containers at every location where wrappings are removed and garments are disposed.[1]

HD Buffer Room

The HD buffer room must be arranged to support the workflows specific to the hazardous sterile preparations compounded at the facility; there is no single layout that is applicable to all HD compounding operations. The following components must be accommodated in the facility design:

- HD receiving
- HD storage
- Material transfer
- Primary engineering control (PEC) placement
- PEC venting and room exhaust
- Heating, ventilation, air conditioning (HVAC)

HD Receiving

USP Chapter <800> requires HDs be received in neutral to negative pressure. If a separate unclassified room is provided for storing HDs, the drugs are typically received in that negative pressure room. If HDs are stored in the HD buffer room, they can be received in that room, but the exterior shipping container cannot be taken into the cleanroom.[1] The zip-lock bags must be removed from the tote and wiped down prior to being transferred into the buffer room where the drugs are removed from the bag and received into inventory.

HD Storage

Based on an assessment of risk, many HDs, including all antineoplastic drugs, must be stored in a negative pressure room separate from other inventory.[1] While a designated negative pressure HD storage room can be used, it is not uncommon to utilize the HD buffer room for storage, as it meets the criteria established by USP <797> and USP <800> for a negative pressure room. Select HDs require refrigeration; therefore, a refrigerator will need to be placed in the HD buffer room. To reduce the particulate burden generated by the compressors and the risk of microbial contamination from the condensation pan, an exhaust grille should be placed behind each refrigerator. Note that this exhaust should be positioned at a wall height appropriate to remove the particulate contamination caused by the refrigerator's compressors and condensers.[1] The actual height of the exhaust grille should be determined *after* the refrigerator is selected.

Definition of Terms

Anterooms: Cleanrooms must be supported with an anteroom that accommodates hand hygiene and gowning. For facilities compounding sterile hazardous preparations, all buffer and anterooms must be built to maintain ISO Class 7 under dynamic operating conditions.[1]

Buffer rooms: Per USP chapters, the cleanrooms where sterile compounding is performed.

Negative pressure: For sterile nonhazardous compounding, cleanrooms are designed to be under a positive pressure to adjacent rooms. Conversely, because hazardous compounding must be contained, sterile HD compounding is always conducted in negative pressure containment cleanrooms.[1]

Alternatively, a compressor-less refrigerator or a unit with an external compressor placed outside of the cleanroom can be utilized. Note that if a compressor-less refrigerator is used, condensation and cleaning issues must be addressed.

Pass-through Boxes

Materials and CSPs are often transferred into and out of the buffer rooms from the general pharmacy through wall mounted pass-through boxes. All pass-throughs should be equipped with sealed and interlocked doors,[1] and the interiors must be smooth, cleanable, and free from exposed fasteners and mechanical components, such as pass-throughs constructed of stainless steel.

The FDA and some state board of pharmacy inspectors have taken the position that pass-throughs from ISO classified rooms to unclassified rooms must be HEPA filter purged. HEPA purge on a pass-through is not mandated in USP chapters, and adding that option significantly increases the cost and complexity of the build-out. If a HEPA purge is used, the pass-through will need to be certified similar to a PEC.

Components transferred into the buffer room must be disinfected prior to placement in the pass-through from the general pharmacy. An area suitable for that purpose must be provided in the general pharmacy at the pass-through. This can either be a wipe-down counter or an open area that accommodates the tote transfer cart.

Primary Engineering Controls

The cornerstone of the HD buffer room is the PEC. Because compounding aseptic containment isolators (CACIs) now have the same facility requirements as Class II BSCs, many facilities are now using NSF International (www.NSF.org) listed Class II, Type A2 cabinets for their ease of use. NSF listing is recommended to ensure the cabinets are independently validated to meet robust industry-developed design and performance criteria.

USP Chapter <800> states, "For most known HDs, type A2 cabinets offer a simple and reliable integration with the ventilation and pressurization requirements of the C-SEC."[1] This is a change from older guidance documents such as the NIOSH Alert for the Prevention of Occupational Exposure to Antineoplastic and Other Hazardous Drugs. Previous industry guidance recommended Class II Type B2 BSCs; however, B2 BSCs can be more difficult to integrate into the facility than Class II Type A2 BSCs. Recent studies[4] have shown the Type A2 cabinet provides similar protection as the B2 cabinet against common HDs with much less complication, and therefore less risk.

The Class II Type A2 BSC must be connected to the building exhaust through a canopy connection.[1] All PECs must be equipped with an exhaust alarm. The canopies and exhaust alarms may be purchased as a system from the BSC manufacturer. The BSC must be strategically positioned in the buffer room to avoid cross drafts from the HVAC and must be out of the traffic patterns. Avoid placing the BSCs directly under a HEPA filter supply diffuser. Position BSCs 6 to 8 inches from the walls to permit cleaning behind and to the sides of the cabinet.

Physical Plant

Because the physical plant serves as the backbone of any design, the details are of crucial importance. If pharmacy is not fully experienced in this area, expertise may be brought in as necessary. Consultants should be knowledgeable in terms of building standards as well as the needs of the pharmacy.

External Venting

USP Chapter <800> requires that all PECs used for sterile HD compounding of antineoplastic agents be vented to the outside. CETA CAG-007[5] provides specific requirements for exhausting Class II BSCs. In addition to the air removed from the BSC, other wall-mounted exhaust grilles must be strategically located throughout the room. Ideally, air movement must be accounted for in each of the 4 corners of the room. If a refrigerator is present in the cleanroom, a grille should be positioned behind the refrigerator at a height convenient to the compressor. Exhaust grilles not positioned by a refrigerator should be mounted low on the wall. Air from a negative pressure HD buffer room should not be returned to the HVAC system.

When designing a cleanroom, the goal is to create a "state of control" over the environment.

International and local building codes and ANSI/ASHRAE/ASHE Standard 170 – Ventilation of Health Care Facilities[6] should be consulted when positioning the exhaust fan and its discharge. Based on these guidance documents, discharge from the exhaust fan should extend at least 10 feet above the roof line. The exhaust blower should be placed on the roof to ensure that the ductwork is negative pressure throughout the building. The exhaust fan should be located at least 25 feet from air intakes so that the discharge from the exhaust does not get re-entrained back into the building through a supply air system.

HVAC

When designing a cleanroom, the goal is to create a "state of control" over the environment. The dominant priority is to establish and maintain a clean space appropriate for compounding hazardous sterile preparations. To achieve particle control in a room, the particle laden air is replaced with particle-free, HEPA filtered air from the HVAC.[2] *Air changes per hour* (ACPH) indicates the number

of times air is changed over in a room. When compounding HDs, the amount of air exhausted from the cleanroom will exceed the amount delivered to the room by the HVAC. Nevertheless, air cannot be returned to the HVAC from a room used to compound HDs. While this can be challenging for the HVAC engineer, should air be returned to the HVAC from an HD space and then distributed to other rooms, contamination could spread to those spaces.

The negative pressure buffer room must be balanced to 0.01-0.03" water column (w.c.) to adjacent rooms accessed by a door.[1] Typically, this is only the anteroom. Adjacent rooms not accessed by a door, such as the general pharmacy, will usually be neutral or negative to the HD buffer room (the negative pressure buffer room is not necessarily negative to ALL adjacent spaces). Note that room pressures in a suite of cleanrooms are additive: If the anteroom is 0.04" w.c. positive to the general pharmacy and the HD buffer room is 0.02" w.c. negative to the anteroom, the HD buffer room would then be 0.02" w.c. positive (-0.02 plus +0.04" w.c. = +0.02" w.c.) to the general pharmacy. If the negative pressure buffer room is negative to the ceiling space or to adjacent rooms, contamination could be drawn into the buffer room through sprinkler heads or cracks and crevices. Therefore, walls and ceilings must be sealed to ensure leakage from the buffer room is negligible.[2]

Cleanroom airflow design is based on strategically managing the air delivered into the room against the air removed from it. Stagnant airflow must be avoided to prevent pockets where microbes can accumulate. Air movement throughout the room and in all corners can be achieved through the effective placement of PECs, return vents, exhaust vents, and doors.[2] It is important to recognize that cleanrooms do not operate as a sealed box. There should be an undercut beneath the door to facilitate air movement. Absent that, the air transfer between ante- and buffer rooms would be minimal to nonexistent. The more air transfer at the door, the more control will be maintained when the door is opened. Air will transfer from the anteroom into the HD buffer room, which is why the anteroom must be the same ISO Class 7 as the HD buffer room. A higher transfer airflow is most important at the anteroom door to an unclassified general pharmacy or support area. A good cleanroom design ensures an air return/exhaust, door, or PEC at each of the room's four corners. Air returns should also be placed by particle generators.

HEPA Filters

Changes to <797> require all cleanrooms to be served by HEPA filters located in the ceiling of the cleanroom.[2] Remote HEPA filter banks are no longer allowed. The chapter also requires the HEPA filters to be certified leak-free at installation and then again at every 6-month certification.[2] Ideally, HEPA filter housings are equipped as follows to meet the requirements of the chapter:

- Room-Side-Replaceable (RSR): to ensure minimal disruption to the cleanroom when the HEPA filters must be replaced
- Room-Side-Challenge-Port (RSCP): to ensure minimal disruption to the cleanroom during certification
- Static Pressure/Challenge Port: to provide a means to measure the static pressure across the HEPA filters and to measure the upstream challenge for the HEPA filter integrity test

If HEPA filter housings are not set up to be integrity tested, alternative means to introduce a challenge and measure the upstream concentration will need to be provided. If a remote challenge is introduced, the smoke detector will need to be bypassed at each certification.[2] Properly specifying the HEPA filter housings during the design phase will eliminate headaches down the road.

Conclusion

A careful design is essential for an efficient, compliant cleanroom. By taking into account the variety of factors that contribute to an ideal cleanroom, pharmacy can ensure an effective and safe workflow in optimal conditions for all team members. Because a well-designed cleanroom requires significant expertise, the initial investment in developing this expertise will avert staff frustrations and the potential for regulatory challenges once the cleanroom is up and running.

References

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