CASE STUDY

Facility and Engineering Control Design Under USP <800>

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In light of the recently published versions of USP chapters <795>, <797>, and <800>, with the intention of creating cohesive alignment between nonsterile and sterile compounding, it is essential to consider engineering controls for HD handling with these two categories of compounding. Issues such as compounding volume, production downtime during renovations, air filtration, make up air units, and exhaust methods all factor into the design considerations for creating a compliant HD compounding operation.

DESIGN FOR THE FUTURE BUSINESS MODEL

To ensure a successful HD facility design, first consider the pharmacy's business model, with a focus on compounding volume. This is an important precursor to beginning the design process, as every design decision should be informed by the pharmacy's business trends. Examine the previous two years of compounding business evolution, taking into account factors such as patient demand, new providers, and the current landscape of state and federal regulations. Once you have quantified the business trends of the past few years, think ahead two to five years to consider potential growth, the competitive landscape, and projected patient trends. Given that quite a few pharmacies experience space constraints, it is understandable if future expansion seems daunting; however, the best approach is not to design your pharmacy for today's prescription volumes, but instead design with an eye towards the future, allowing room for growth.

MINIMIZE DOWNTIME

Losing production capacity during the remodeling process is a serious concern for pharmacies, so it is crucial to strategically plan the construction steps with the goal of averting downtime wherever possible. Have a frank discussion with the general contractor and the project team at the outset to help all parties understand that downtime is to be minimized. Whenever possible, it is recommended to utilize a phased approach to construction to minimize any negative impact on compounding production.

FRESH AIR VS. INDOOR CONDITIONED AIR

The heating, ventilation, and air conditioning (HVAC) system typically has the biggest financial impact on efforts to achieve USP <800> compliance. The chapter specifically states that the containment secondary engineering control (C-SEC) must be externally vented, meaning that the HD compounding room must have a system in place to direct air out of the building. While the chapter does not explicitly state what percentage of air from the C-SEC should be externally vented, it can be deduced that no recirculation of air from the HD room is to be introduced back into the air handler. When air is externally vented from the building, the source of the replacement air supply – which must satisfy the minimum number of air changes per hour (ACPH) – must be determined. Currently under debate is whether fresh air or indoor conditioned air should be used as the replacement air supply to satisfy the HD room's ACPH requirement.

A standard package air handling unit is not intended to consistently replace externally exhausted air. A standard package unit works on an 85% to 100%

recirculating model with little to no fresh air being introduced into the facility. In larger facilities, there may be an outdoor air damper on the air handler that allows for a small percentage of fresh air to be introduced into the system. In smaller facilities, it is not uncommon for fresh air to only be introduced into the building when the external building doors happen to open. Regardless of the package model type, in almost every case, the solution for replacing externally vented air is introducing a new makeup air unit (MAU) to satisfy the minimum ACPH requirement. The MAU draws in outside air, conditions it to appropriate temperature and humidity, and then supplies it to the HD compounding room.

Because conditioning air from outside can be costly, some pharmacies may consider whether it is appropriate to instead draw on already conditioned air within the building. Doing so would require taking a percentage of conditioned air from the hallway, retail area, or office area and recirculating it into the dedicated MAU for introduction into the sterile or nonsterile HD compounding room. The HD compounding room would then vent that air out of the building.

> *"HD cleanroom specifications and instruction should utilize the term air exhausts or low wall exhausts so that the architects, engineers, and contractors do not misinterpret the necessary direction of the air."*

There are multiple concerns with this approach; perhaps the most important is that the conditioned air from a common space may be above the temperature and humidity targets for the HD compounding room. Because of the operational simplicity of a standard commercial package/split system, an individual unit is not able to control temperature and humidity, which precludes it from being utilized to supply air to a controlled environment. A single pass of that common conditioned air through the dedicated MAU will not be enough to satisfy the HD compounding room targets, mainly because the setup makes the HD room parasitic to the space the air is being taken from.

A further concern is that the local HVAC contractor likely has a complex network of duct work, dampers, and controls to negotiate in order to determine the recirculation formula from common areas to HD compounding rooms. Most importantly, if air is redirected from any area (eg, retail, office, etc), that air then must be replaced, or the equation can cause the entire facility (or area) to become negatively pressurized, creating the potential for unhealthy interior conditions such as microbial growth and carbon dioxide buildup. Therefore, a dedicated MAU for the HD compounding rooms proves to be the most straight-forward mechanical solution.

While most commercial spaces rely on the common HVAC concept of air tonnage (ie, the number of BTUs the AC unit can remove in one hour) to plan for their HVAC needs, this concept does not apply to externally vented rooms; rather, cubic feet per minute (CFM), temperature, and humidity targets are the key HVAC criteria for compounding spaces. As a general rule, one ton equals 400 CFM, but using that logic, the pharmacy would exceed tonnage trying to achieve adequate CFM coverage. Even then, there would not be sufficient cooling capacity to make a standard commercial package unit cool 100% outside air. Better logic for achieving the desired temperature and humidity in the HD compounding room is sizing a custom HVAC to the proper CFM. Pharmacies must select a mechanical engineer who understands these concepts.

ACPH: DESIGN TO A HIGHER STANDARD

When engineering an air handling system for HD rooms, it is advised to avoid designing to the lowest common denominator; rather, the design should exceed the minimum ACPH as defined by the USP chapter. If the air handling unit is engineered simply to meet USP's lowest design standard, it is likely that the air handling unit and HD room will fail to maintain design parameters for ACPH, temperature, and humidity in all situations.

The minimum design requirement for a hazardous nonsterile room, or unclassified containment segregated compounding area (C-SCA), is 12 ACPH. In the hazardous sterile buffer room, the minimum requirement is 30 ACPH. Special consideration must also be given to temperature, which should be maintained below 20°C, and humidity, which should be maintained below 60% relative humidity. An effective design must also take into account the fact that people, equipment, and processes generate additional heat gain in the room. Furthermore, in certain geographic areas, temperature and humidity may be more difficult to control. Therefore, designing the air handling system to meet the required ACPH will likely require adjustments to accommodate both compounding processes and local climate. As such, it is best practice to design the nonsterile HD room with up to 18 ACPH and the sterile HD buffer room with up to 45 ACPH. While more ACPH requires more energy, which equals higher costs, the alternative of a cleanroom that fails to achieve compliance is exceedingly expensive.

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The compounding room, whether modular or stick built, can be expected to experience some amount of air infiltration or exfiltration. For example, doors will leak air an average of 80 to 130 CFM, depending on factors such as how the door slab seats into the frame, the size of the gap between the slab and the floor, the presence of gaskets and sweeps, and the amount of room pressure. The greater the room pressure (eg, closer to .03" water column [WC]), the more air is being pulled around the door. It is recommended that the design of the negative pressure HD room stay as close to .01" of WC as possible. The greater the room pressure, the greater the rate of infiltration (for negative pressure).

CREATE A TIGHT ENVELOPE

Infiltration is an important design concept, as negative pressure sterile HD compounding rooms can experience failing viable counts during environmental monitoring due to moisture and bacteria being pulled into the room. Negative pressure rooms, by nature, allow air infiltration, which has the potential to introduce bacteria, moisture, and other unwanted sources of contamination around doors, light switches, electrical outlets, or other wall penetrations. To better seal the exterior of a stick-built room, include a vapor barrier around the structure. To seal the wall penetrations, spray foam (preferably with an antimicrobial cleaning agent) can be utilized, but be cautious around electrical wiring and ensure that local building codes do not prohibit this practice.

USP <797> states, "Seals and sweeps should not be installed at doors between buffer and ante-rooms."[1] The reasoning behind this is to promote ease of cleaning. Seals and sweeps are rarely cleaned in ISO-related environments and therefore may harbor bacteria. However, there is a downside to not using seals and sweeps in a negative pressure environment as this reduces the control over airflow. Nonetheless, it is more important to keep the sterile compounding environments clean and identify other means of controlling air infiltration.

Inlaid ceiling panels and grids are a subtle culprit of air infiltration in negative pressure rooms. The space above the ceiling is commonly referred to as the interstitial space and can be a relatively dirty area. If the ceiling is a source of air infiltration, the recommended best practice is to caulk the ceiling grid to the perimeter walls. USP <797> states the following as further justification: "Junctures between the ceiling and the walls and between the walls and floor must be sealed to eliminate cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels must be caulked around each panel to seal them to the support frame."[1] As a best practice, it is recommended that caulking be applied after construction is complete and the HD room has been thoroughly cleaned to remove all debris and dust. It is further recommended to use a cleanroom caulk, because other sealants may absorb dust and present challenges to proper cleaning.

LOW WALL EXHAUSTS

USP Chapter <800> does not detail how HD rooms are to be externally vented, but based on airflow patterns, best practice is to use a low wall exhaust. The recommended design is to supply the air from the ceiling and place the exhaust vents just above the finished floor. Because air takes the path of least resistance, circulating air will move from top to bottom, and essentially sweep the room. A low wall exhaust is typically a metal grill, square or rectangular depending on the amount of CFM, placed about 8" to 12" above the finished floor. USP <797> states, "Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate."[1] It is important to understand that this direction from USP <797> applies to USP <800> cleanroom suites as well; however, the air returns terminology implies air will be returned or recirculated back into the air handler. A better term to use for the HD cleanroom specifications and instruction is *air exhausts* or *low wall exhausts* so that the architects, engineers, and contractors do not misinterpret the necessary direction of the air.

Notably, there is no airflow design reference in USP Chapter <795> for nonsterile compounding. Nonetheless, nonsterile compounding rooms typically experience heavy power handling. Should technicians breach containment with contaminated gloves or instruments, micron-size powders can aerosolize and become airborne, potentially entering the HD compounding room. To counteract this risk, the use of low wall exhausts in the nonsterile room is recommended to sweep the room with air and eliminate dead zones. Theoretically, any aerosolized powder in this situation would be forced down to the floor, where it can be cleaned during the daily cleaning routine or exhausted via the low wall exhaust.

AIR FILTRATION PRIOR TO EXTERNAL EXHAUST

USP Chapter <800> indicates that air exhausted from the HD compounding room should be filtered through HEPA filtration located inside the containment primary engineering controls (C-PECs). There are both sterile and nonsterile compounding room designs which include a low wall exhaust used either to supplement the exhaust CFM or to carry all the C-SEC exhaust as part of the ACPH calculations. If low wall exhausts are used as a means of externally exhausting all, or even a small percentage of, the C-SEC's air, then they must be HEPA filtered as well. In the event of a bulk powder spill in the HD room, airborne aerosolized particulates will be generated. In this situation, if the low wall exhaust is directly ducted to the external exhaust blower without any HEPA

filtration, this will release a potentially contaminated airstream directly to the outside atmosphere. For this reason, a HEPA filter module should be in line with the exhaust duct before the exhaust blower. It is strongly recommended that the HEPA filter module contain a "bag-in/bag-out" (BIBO) feature, which protects staff members from exposure to contamination while replacing HEPA filters.

BALANCING THE NEGATIVE PRESSURE ROOM

Occurring near the end of the design project, a third party sets the supply CFMs and makes adjustments on the exhaust blower to balance the negative pressure rooms to .01" WC to .03" WC, which may prove to be a tight parameter of balance. For this reason, it is imperative that engineering solutions are available to maintain absolute control over the negative pressure room. The totality of room variables such as wall/ceiling/door infiltration, supply diffuser type, and exhaust source (ie, via the C-PEC or low wall exhaust), combine to make the test and balance process imperative.

Per USP <797>, "Air supplied to the cleanroom suite must be introduced through HEPA filters that are located in the ceiling of the buffer and ante-rooms."[1] The most common way to introduce air into a cleanroom is with a fan filter unit (FFU), also known as a fan-powered HEPA. Since the tiles and ceiling grid must be caulked, the FFU should have a room-side accessible fan speed controller so that supply CFM can be accurately dialed. If the facility needs multiple FFUs, certain models can be wired together and centralized into a main control panel, allowing each FFU to be adjusted from the control panel. The goal is to simplify the process for the provider conducting the test and balance, as well as the cleanroom certification representatives, who also play a role in the balancing process.

Integrating the FFU as a supply source may be a reasonable strategy in the nonsterile HD room as well, not for an intended ISO room rating, but because the fan speed and supply CFM can be accurately dialed in during the room's test and balance process. The FFU supply strategy is more expensive than a traditional supply diffuser, but gaining absolute control over the supply CFM air is vital.

A best practice in HVAC design is utilizing dampers over the supply and exhaust, especially in negative pressure rooms. Dampers installed in the ductwork allow airflow to be manipulated in and out of the room; however, one challenge associated with damper control is access after the ceiling tiles have been caulked. It has been a common practice to refrain from sealing one ceiling tile to allow for future access, but if the supply and exhaust ducts are spread apart, it is unlikely that one ceiling tile will be sufficient. State boards of pharmacy do not typically support this approach, so caution is advised in this area. It is possible to cut the caulk seal with a utility blade to allow access, but then tiles must be caulked again, creating extraneous labor and downtime in the compounding rooms. One unique solution we recommend as a best practice is the integration of gear drive dampers. The gear drive damper allows for room-side access to the damper for manual adjustment of supply or exhaust airflow.

CONCLUSION

When updating a facility and engineering controls, it is essential to clarify the scope of the project, taking into account the many design choices, product options, and price points offered in the market. When assembling project teams that may include architect, mechanical engineer, structural engineer, electrical engineer, and various other general contractors, all parties must understand the full scope of your business model, and they should read the appropriate section in USP chapters <795>, <797>, and <800> to better conceptualize the goals of the project. Each step taken toward compliance ensures safety and productive workflow.

1. USP General Chapter <797>. Pharmaceutical Compounding - Sterile Preparations. Second Supplement to United States Pharmacopeia and National Formulary (USP 42-NF37). www.usp.org/compounding/general-chapter-797. Accessed October 3, 2019.

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