PART 1 OF A 3-PART SERIES

Design Tomorrow's Cleanroom Today

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When designing a cleanroom for a health facility that compounds sterile drugs, two main drivers must be considered: the business model and compliance standards. As a cleanroom must be a controlled space to accommodate specific engineering controls and ensure a clean environment for sterile compounding, these drivers can be utilized to ensure success, as they will continue to prove as valid in years to come as they are today.

To gain an understanding of the pharmacy's business model, it is recommended to perform an analysis of compounded products over the previous 2 to 5 years. This will reveal business trends that may then be projected into the future. Consideration must be given to evolving compliance regulations—specifically state, federal, accreditation, and other applicable compliance standards—as these will directly impact the workflow, and therefore influence cleanroom design. Although the future is unpredictable, it is likely that coming years will continue to bear witness to changes to the regulatory environment in which sterile compounding is conducted.

A Deep Dive into the Business Model

It is important to collaborate with design experts who have a conceptual understanding of the health system's business goals. Although it is not the responsibility of the architect or contractor to determine the inner workings of the pharmacy's business, continual communication between the pharmacy team and the design team is essential. The facility's management team must own the process of the business analysis and needs assessment. Problems occur when the architect's design team is

tasked with designing a sterile controlled environment for a pharmacy team with whom they have little to no interaction. To that end, simply asking the design team to provide "a two-room positive-pressure cleanroom for two hoods" is grossly insufficient and leaves substantial subjectivity in the design criteria.

Reflecting on the business model analysis can reveal projected growth in future compounding volume that warrants specific design considerations. Pharmacy should determine how its growth is projected to trend over the next 2 to 5 years, and also identify new market opportunities that may influence cleanroom design parameters. If the design team is told to create two positive pressure rooms, this implies that the cleanroom will handle only nonhazardous drugs now and in the future. In addition to considering whether there may be a future demand for hazardous drugs (HDs), consult the NIOSH HD list to verify whether the facility is currently handling HDs. Asking thoughtful questions and critically looking to the future can guide the design of the cleanroom space, and impact the incorporation of engineering controls, which drive temperature and humidity compliance standards.

The Future of Compliance

There is no certain way to predict how compounding regulations will evolve over the next 5 to 10 years, just as few would have predicted 10 years ago that USP chapter <797> would see multiple proposed revisions for sterile preparations. In 2014, USP introduced chapter <800>, and yet this chapter on handling HDs still is not yet fully enforced as of the time of this writing 8 years later. Due to the unpredictability of federal and state enforcement, it is advantageous to adopt a mantra of "more is better." This rule of thumb encourages a deep dive into best practices, especially with consideration to engineering controls, digital environmental monitoring, and construction materials.

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Engineering Controls

While there is no established methodology for anticipating the degree of stringency that will define future regulations, there is one constant in that a key contributor to contamination control in the cleanroom is the use of engineering controls. Per USP chapter <797> (Sept 2021 proposed), 30 total HEPA-filtered air changes per hour (ACPH) must be supplied to ISO Class 7 rooms for compliance.[1] It is important to note that this minimum standard may not account for the particle counts and heat gain generated by people and equipment in the cleanroom. Consider whether automated equipment or other heat-generating devices will likely be integrated into the cleanroom in the future. Forward-looking equipment planning is important because these decisions directly influence the engineer's ACPH calculations and sizing of the air handling equipment. To mitigate the potential for future critical failures, engineers are advised to design the HVAC system with up to 45 ACPH to account for the heat gain and particle counts generated by people and processes. Note that there can be a point of diminishing return by aggressively increasing airflows. For example, doubling the minimum ACPH (ie, to 60+ ACPH) would potentially create turbulence within the cleanroom, making it difficult to demonstrate an effective visual smoke study.

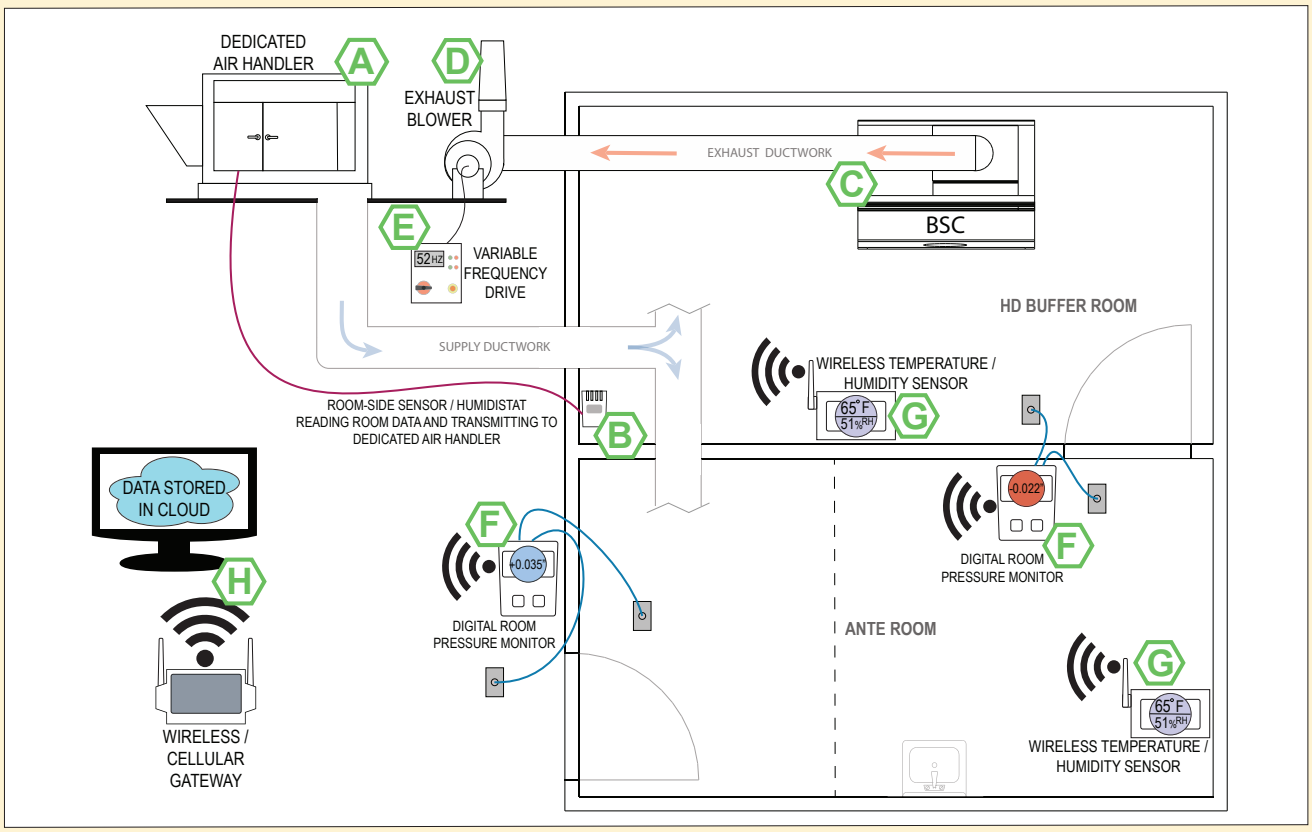
The proposed 2021 USP chapter <797> states that, "The cleanroom suite should be maintained at a temperature of 20°C or cooler with a relative humidity of 60% or below to minimize the risk of microbial proliferation and to provide comfortable conditions for compounding personnel attired in the required garb."[1] Be aware that if engineers design the air handling systems too close to the minimum requirement and do not exceed the American Society of Heating, Refrigerating and Air Conditioning (ASHRAE) table data to anticipate seasonal extremes or personal protective equipment (PPE) requirements, the cleanroom may not remain in compliance.

In light of unforeseen future conditions, it is recommended that engineers design the cleanroom with a target room temperature of 64°F and a target 45% to 50% relative humidity. While this may seem extreme, it will help account for increased future standards from USP chapter <800> for compliant HD handling. In the event that pharmacists and technicians are required to wear nonpermeable rear-tying gowns, double shoe covers, double gloves, hair bouffants, and masks, the temperature inside the cleanroom must be comfortable. Furthermore, to meet this design performance criteria, the air handling equipment must be more sophisticated.

To cool, heat, and dehumidify high percentages of outdoor air, dedicated,

FIGURE 1

Cleanroom Design Example



application-specific HVAC systems are being introduced. When USP <800> is fully implemented, dedicated air handling equipment to condition 100% outdoor air may be viable, as the chapter requires that the containment secondary engineering control (C-SEC) be externally vented (**Figure 1, Area A**). The International Mechanical Codes (IMC) and the ASHRAE now have minimum building requirements for the introduction of fresh air into buildings, and in recent years, facilities have been vigorously replacing old air handling equipment with application-specific HVAC systems to meet IMC and ASHRAE standards. When implementing new air handling equipment, it is strongly recommended that the cleanroom operate on its own dedicated system that is not shared with other rooms.

Energy Efficiency

To ensure protection against microorganism growth, air handling systems in sterile compounding cleanrooms must run 24/7. As such, energy efficiency is a priority. The newer, dedicated HVAC systems mentioned previously are energy efficient, as are direct expansion (DX) HVAC systems, which can monitor temperature and humidity as independent climate control parameters. A room-side sensor, sometimes called a humidistat, continuously transmits information from the cleanroom back to the HVAC system to adjust temperature and humidity control in real time (**Figure 1, Area B**). The system's modulating compressor technology provides precise temperature and humidity control, which is especially important for geographic areas that experience extreme high and low temperatures. While the integration of off-peak hour settings on general HVAC systems improve energy efficiency when parts of a building are not occupied, this strategy is not applicable for a cleanroom.

External ventilation presents further challenges for energy efficiency. Engineers must understand the mechanical demands of USP <800>, specifically *Table 3: Engineering Controls for Sterile HD Compounding* (**Figure 2**) in subsection 5.3.2 *Sterile Compounding*.[2] Both the containment primary engineering control (C-PEC) and the containment secondary engineering control (C-SEC) must be externally vented for sterile hazardous compounding (**Figure 1, Area C**). This compliance requirement does not contribute to energy efficiency, because a cleanroom could potentially send 400

FIGURE 2

External Ventilation Requirements

Per USP chapter <800>, C-PECs and C-SECs must be externally vented for an ISO Class 7 configuration. This requirement may create energy efficiency challenges.[2]

Table 3. Engineering Controls for Sterile HD Compounding

Configuration	C-PEC	C-SEC	Maximum BUD
ISO Class 7 buffer room with an ISO Class 7 ante-room	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 30 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in <797>
Unclassified C-SCA	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 12 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in <797> for CSPs prepared in a segregated compounding area

cubic feet per minute (CFM) or more of conditioned air out of the building 24/7. Externally venting this amount of air requires a separate exhaust blower (**Figure 1, Area D**), which is typically roof-mounted. Exhaust blowers are increasingly utilizing direct-drive electronically commutated motors (ECMs), which are energy efficient. A direct-drive motor does not utilize belts, as belts can break. The recommendation for the cleanroom of the future is to utilize a direct drive ECM or variable frequency drive (VFD) (**Figure 1, Area E**) controller for direct drive motors. The VFD must be easily accessible, as the pressure gradient in a negative pressure room can only be maintained with a controllable exhaust blower.

Digital Monitoring Technology

Pharmacy cleanrooms are beginning to adopt digital monitoring technology, one benefit of which is the ability to log real-time data into the facility's building information management system or the vendor's cloud storage (**Figure 1, Area H**). Integrating digital monitoring and logging reduces human error and removes the need for a paper-based system that risks duplicate reporting in a spreadsheet. The cleanroom of the future should be equipped with continuous monitoring systems for temperature, humidity, and pressure gauges to ensure compliance.

USP <797> states, "The temperature and humidity must be monitored in each room of the cleanroom suite each day that compounding is performed, either manually or by a continuous recording device. The results of the temperature and humidity readings must be documented at least once daily or stored in the continuous recording device and must be retrievable."[1] While the commonly used analog magnehelic gauge provides continuous monitoring, it relies on manual verification and documentation to record room pressure compliance data. Further, these gauges do not provide alarms when the pressure falls out of specification due to mechanical or electrical issues. A digital room pressure monitor (**Figure 1, Area F**) provides visual and/or audible alerts in the event of pressure failure. Both wired and wireless temperature/humidity monitoring technology (**Figure 1, Area G**) is becoming more affordable and widely available, allowing data to be digitally recorded and transmitted to a cloud-based software service (**Figure 1, Area H**) or to a local server. The hardware and software offer ease of integration and retrieval of cleanroom compliance data, which are especially valuable in anticipation of future evolution of regulations, for which real-time recording may become a *must* instead of a *should*.

Conclusion

While it is impossible to predict the future, regulatory compliance is an ever growing concern. Monitoring current and recent trends within the cleanroom can hold the key to long-term functionality and success. USP and local regulations are always subject to change; however, designing the cleanroom with an understanding of the pharmacy's business model and an eye toward energy efficiency, around-the-clock monitoring, and compounding capability is the best way to be prepared for tomorrow's cleanroom requirements.

References

1. United States Pharmacopeial Convention. USP General Chapter <797> *Pharmaceutical Compounding – Sterile Preparations*. www.usp.org/compounding/general-chapter-797. Accessed April 22, 2022.
2. United States Pharmacopeial Convention. USP General Chapter <800> *Hazardous Drugs – Handling in Healthcare Settings*. www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare. Accessed April 22, 2022.