NOVEMBER 2021

Bryan Prince, MBA

Owner and
Lead Consultant
Lab•Red Pharmacy
Consultants

Improve Workflow with Cleanroom Design

Designing a cleanroom requires a multifaceted process that should reflect the facility's compounding model—comprising drug volumes, types (hazardous or nonhazardous), etc—while also considering the pharmacists and technicians, equipment, workflow, and processes. Guidance from regulatory entities, such as state boards of pharmacy, accreditation organizations, the United States Pharmacopeia (USP), and the Federal Drug Administration (FDA) should closely be studied. This paper will focus mainly on 503A pharmacy requirements and the USP chapters <797> and <800>. It is important to recognize all of the above stakeholders during the cleanroom design process, not just to improve workflow, but also to optimize compliance.

Product Movement

Understanding the pharmacy's business model provides the foundation for determining product movement and workflow in order to optimize cleanroom design. The pharmacy should tabulate the average number of compounded prescriptions that are formulated and dispensed on a daily and weekly basis. Questions to ask during this initial phase include:

- **Business Model.** Does the volume of work primarily comprise batching or "one-offs" that require more compounding records and time/labor per compounded preparation?

Improve Workflow with Cleanroom Design

- **People.** How many technicians are needed for maximum production in the anteroom, sterile buffer rooms, and/or prep spaces?
- **Equipment.** What footprint is required for the large pieces of equipment? (eg, primary engineering controls, stainless tables)
- **Products.** Are products moved with carts and/or totes?
- **Storage.** What materials are stored inside of the cleanroom area, and what is stored outside?
  - Will hazardous drugs be stored inside the negative-pressure room?
  - Will bulk IV bags be stored outside the cleanroom and transferred in as needed?
- **Growth.** How does the previous year or 2-year compounding volume compare to the current year?
  - Was there growth year over year, and if so, in what product categories?
  - What growth is projected for the next 2 to 5 years?

The final three questions are essential, as the cleanroom should not be designed for today's business model; rather, it should serve your future business model. Outgrowing a new cleanroom in a short period of time is not financially wise, given the capital investment required. Nevertheless, it is not recommended to dramatically oversize the cleanroom in the initial build unless the business analysis predicts dramatic growth. Most pharmacies will want to account for the addition of at least one or two primary engineering controls (PECs) in a new cleanroom design project. PECs consume more space than any other equipment in the cleanroom, so their accommodation is essential to the design phase.

Use a Minimalist Approach

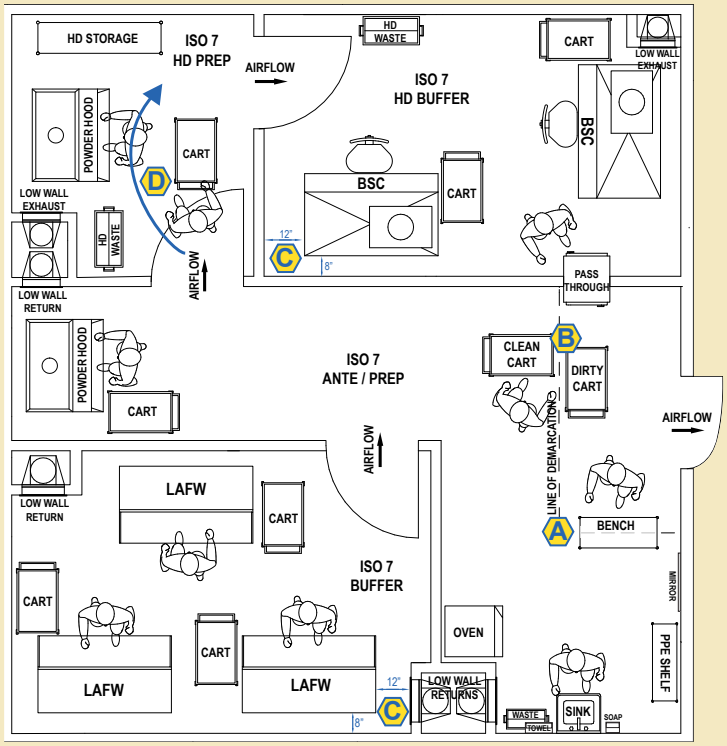
During the design and planning phase, account for everything that will be placed in the cleanroom suites. Remember that the more materials brought in from the unclassified space into the ISO rated cleanroom, the more opportunity there is for the introduction of bioburden. It is wise to accommodate mirrors, benches, personal protective equipment (PPE) dispensers/racks, trashcans, refrigerators, drug storage racks, and carts.

A minimalist approach is best practice for both storage and workflow activities inside the cleanroom. Multiple weeks' worth of PPE should not be stored inside the cleanroom, even if located on the dirty side of the demarcation. Bulk syringes or IV bags do not have to be stored in the ISO 7 buffer rooms, even if inside plastic bins. In a minimalist workflow, only the necessary materials for that formulation or that shift are brought into the cleanroom. This approach streamlines cleaning at the end of the shift.

Addressing these issues is not only important for establishing optimal workflow, but also for consideration of the appropriate number of air changes per hour (ACPH) to maintain air quality throughout the cleanroom. USP <797> states that "The design of the facility should take into account the number of personnel and their movement, and the equipment, supplies, and components to maintain and facilitate maintenance of air

FIGURE 1

Sample Workflow Diagram



In this sample cleanroom layout, **areas A and B** indicate the line of demarcation between the clean and dirty sides of the cleanroom, each with its own cart. **Area C** shows proper PEC placement away from the wall to allow for cleaning behind the cabinets. **Area D** demonstrates staff movement around the PEC that could affect airflow.

quality."[1] It is recommended the ACPH be designed beyond the USP minimum (20 ACPH for ISO 8; 30 ACPH for ISO 7), because people and processes generate particles and heat. Further, in areas where seasons change dramatically, strain is increased on the air handling unit that serves the cleanroom.

If the HVAC system is designed to meet the lowest ACPH standard, during dynamic operating conditions the cleanroom may fail particle counts, viable air sampling, viable surface sampling, temperature (recommended below 20ºC), or humidity control (recommended below 60% RH). Typically, the main reason for these failures is insufficient dilution of HEPA-filtered air in the cleanroom around people and processes. This may be the most essential design factor, because the HVAC system is typically the most expensive component of cleanroom design and directly correlates to workflow activity.

Dirty Side vs. Clean Side

The terms *dirty side* and *clean side* are used to identify each side of the line of demarcation, typically located just inside the anteroom door (see **FIGURE 1**, **area A**). The line of demarcation provides both a visible and process barrier to prevent people and material flow from introducing outside particles into critical areas inside the cleanroom. The perception of one side being dirty and the other being clean can be misleading, because both sides are wiped and mopped with cleaning agents and disinfectants.

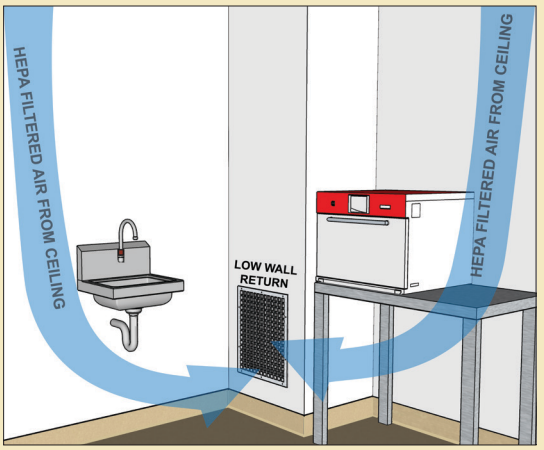
Materials such as carts, IV bags, and totes should be thoroughly wiped prior to crossing from the dirty side into the clean side. People are known to be the dirtiest objects in a cleanroom, but carts are a close second. For this reason, USP <797> states, "In a cleanroom suite, carts must not be moved from the dirty side to the clean side of the ante-room unless the entire cart, including casters, are cleaned and disinfected."[1] Best practice is to have carts designated as dirty and clean so that technicians do not have to dedicate time to wiping cart casters, which can be difficult to accomplish (see **FIGURE 1, area B**).

Environmental Monitoring

Because environmental monitoring is an extremely detailed topic, a few key points are addressed herein. Heavy equipment, such as PECs, cannot be easily moved in and out of a cleanroom, so they are precluded from the previously mentioned minimalist approach, instead requiring specific

FIGURE 2

Low-Wall Return for HEPA Filtered Airflow



Because air follows the path of least resistance, the HEPA filtered air in the cleanroom should flow past vapor- and heat-producing equipment, creating effective dilution while being swept into the low wall grille.

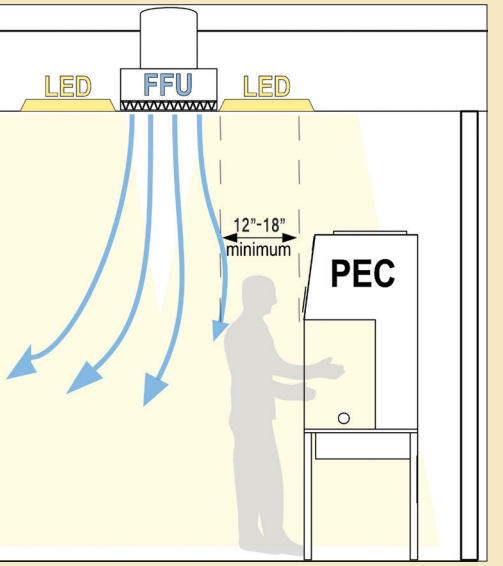
care and cleaning practices. Careful placement of heat-generating equipment must be considered in the cleanroom design as the heat gain will need to be accounted for in the ACPH calculations. For optimal design, place heat- or vapor-producing equipment near a low wall return grille. Air follows the path of least resistance, which in a cleanroom is from the ceiling down to the low wall returns. Theoretically, the HEPA filtered air sweeps down and flows past the equipment, creating effective dilution while being swept into the low wall grille (see **FIGURE 2**).

Historically, there has been much debate over the placement of the cleanroom's hand hygiene sink. For years, the sink was placed on the dirty side of the demarcation line; then as PPE workflow processes evolved, the sink moved to the clean side. The proposed (2019) version of USP <797> states, "In facilities with a cleanroom suite, the sink used for hand hygiene may be placed either inside or outside of the anteroom."[1] If the hand hygiene sink is placed inside the anteroom, best practice is to place a low wall return beside the sink, so that HEPA filtered air from the ceiling sweeps across the sink into the low wall grille, minimizing the potential burden. For environmental monitoring, a viable surface sample should be conducted in close proximity to the sink to validate that there is no growth.

Improve Workflow with Cleanroom Design

FIGURE 3

Fan-Filtered Unit Airflow



FFUs should not be placed directly above the face opening of the PEC.

PEC Placement

Proper placement of PECs is a critical design consideration as it is impacted by the location of doors, fan-filter units (FFUs), lights, low wall returns, and workflow patterns. Avoid placing PECs flush against the wall, as this prohibits cleaning behind them and may allow viable bacteria to accumulate and grow. Rather, PECs should reside 6" to 12" away from the wall (see **FIGURE 1, area C**).

Maintaining proper airflow at the face opening of the PECs is crucial for both product and personnel protection. If the face opening of a laminar airflow workbench (LAFW) is disrupted by unnecessary air currents, it is possible that ISO 5 first air could be disrupted during aseptic technique. During the design phase, consider the traffic patterns of personnel through the sterile buffers. Excessive staff movement should be limited around PECs actively engaged in sterile compounding, because a cross draft caused by employees opening doors or walking through the sterile buffer may disrupt the proper airflow inside the PEC (see **FIGURE 1, area D**).

In addition, pay close attention to the placement of FFUs in the ceiling in relation to PECs. When designing the reflected ceiling plan, ensure the FFUs are not located directly above the face opening of the PEC, because the supply air from the FFU can shear the face opening of the PEC, which can create turbulence and circumvent the first air on an LAFW. The downward shear may also negatively influence inflow of air into the hazardous PEC (eg, biological safety cabinet), which impacts both personnel and product protection. The same principle is true for a Class I PEC. It is best practice to place the FFU at least 12" or more from the vertical plane of the PEC face opening (see **FIGURE 3**).

Lighting levels are another important consideration. USP Chapter <1066> *Physical Environments that Promote Safe Medication Use* is not an enforceable chapter but offers beneficial guidelines relating to sterile work area lighting levels. This short chapter states that lighting for the sterile compounding and preparation work area is recommended at 100 to 150 footcandles.[2] For best practice, the design sequence should begin with placement of PECs, followed by FFUs and then lighting.

Ongoing Training

The success of a cleanroom design is determined in the long term by the people working therein. The pharmacists and technicians must consistently engage in good practices such as hand hygiene, aseptic technique, thorough cleaning protocols, and deliberate/intentional movement through the cleanroom. While repetition can be the pathway to skill development, repetition in job function can put the subconscious on an autopilot mode; for this reason, training should not be a "one and done" effort. USP <800> states that personnel competency must be reassessed at least every 12 months; however, biannual or even quarterly refreshers can ensure consistency.[3] The adage of "fail to plan, plan to fail" is apt for managing technicians and pharmacists compounding drugs; therefore, ongoing training can ensure success for the cleanroom.

References

1. United States Pharmacopeial Convention. *USP General Chapter <797>. Pharmaceutical Compounding – Sterile Preparations.* Second Supplement to the United States Pharmacopeia and National Formulary (USP 42-NF37). June 3, 2019. www.usp.org/compounding/general-chapter-797. Accessed August 6, 2021.
2. United States Pharmacopeial Convention. *USP General Chapter <1066> Physical Environments that Promote Safe Medication Use.* United States Pharmacopeia. www.uspnf.com/notices/retired-compendial-notices/general-chapter-physical-environments-promote-safe-medication-use. Accessed August 6, 2021.
3. 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 August 6, 2021.