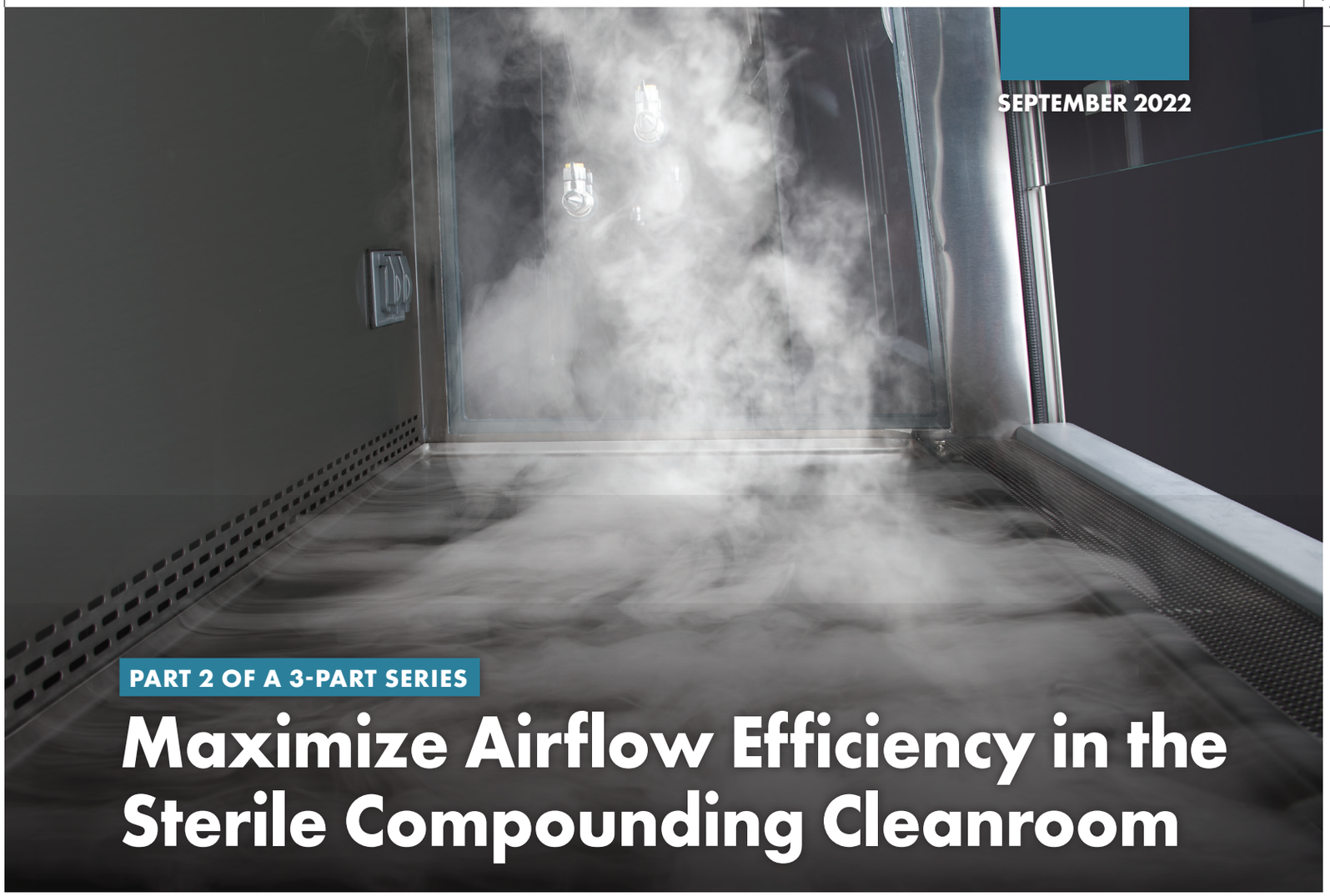

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PART 2 OF A 3-PART SERIES

Maximize Airflow Efficiency in the Sterile Compounding Cleanroom

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Airflow and exhaust must be carefully maintained in the pharmacy cleanroom to ensure the safe preparation of compounded sterile preparations (CSPs), along with staff and materials safety, while also allowing for an effective workflow. Further, airflow within the biological safety cabinet (BSC)—and any other PECs—is an important concern. Therefore, gaining a thorough understanding of heating, ventilation, and air conditioning (HVAC) systems, airflow, air changes per hour (ACPH), and the ideal work zone will support a state of control in which CSPs can be prepared safely.

Impact of HVAC on Cleanroom Control

The HVAC system is a major component of the cleanroom and has strong influence on the effectiveness of sterile compounding. Supply air is delivered to the cleanroom through terminal HEPA filters located in the ceiling. The supply airflow is utilized to calculate the air exchange rate, where minimum requirements for an ISO Class 7 room are 30 ACPH and 20 ACPH for an ISO Class 8 room. While minimum values meet the chapter requirements, they do not necessarily guarantee an environmental state of control.

Many factors can contribute to contamination in the cleanroom, so keep in mind that engineering controls alone do not provide a panacea for preventing contamination. Workflow, material ingress/egress, personnel behavior, and activity levels must also be considered when designing the cleanroom HVAC system and determining an appropriate supply air volume. As such, an air exchange rate that exceeds the chapter requirements is recommended (see the **Table**).

Air exchange rates in the cleanroom are calculated by taking air volume measurements with a capture hood at each terminal HEPA filter. The total volume of the

TABLE

Best Practice Recommendations for Airflow Design

Higher air change rates have shown to be more successful at sustaining a microbial state of control in cleanroom suites versus airflow parameters designed simply to meet the minimum requirements of USP <797>. This recommendation to increase air exchange rates is not intended to combat poor cleanroom behavior or the lack of proper PPE practices.

Area	USP <797> and <800> Minimum Required ACPH	Recommended ACPH
Anteroom (ISO 7)	30	60 (serves negative HD buffer room, has a sink, and hand hygiene and garbing activities occur)
Anteroom (ISO 8)	20	30-45 (has sink and hand hygiene and garbing activities occur)
Non-HD Buffer Room	30 (at least 15 from HVAC, other 15 may be from PECs)	30 HVAC plus PECs (provides a buffer)
HD Buffer Room	30	60 (under negative pressure - air drawn in from anteroom and other cracks and crevices)
HD Storage Room	12	15 (slight buffer in case exhaust flow decreases)

measured airflow for each individual room is then divided by the room volume, and then multiplied by 60 to determine the room air changes per hour (ACPH). For example, if you have three filters and the total volume of the three equals 1200 cfm and the room volume is 1500 cu ft, then 1200 cfm divided by 1500 cu ft times 60 equals 48 ACPH.

Key Factors Affecting Cleanroom Airflow

Many factors impact the cleanroom's airflow, such as air supply and return/exhaust, the type and placement of PECs, technology and accessories housed within the PECs, workflow, ergonomics, temperature, and humidity. Each of these concepts requires due diligence to ensure a properly run cleanroom.

Location of Return Grilles

The current iteration of USP General Chapter <797> (last revised in 2008) states: "returns should be mounted low on the wall."[1] The 2021 proposed revision of USP <797> provides further detail: "Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates the absence of stagnant airflow where particulate will accumulate."[2] Notably, the subjectivity of airflow visualization results is not explained in the chapter. Regardless, CETA Application Guide CAG-014:2022, *Airflow Visualization Study* provides details on how the testing can be performed and the expectations for acceptance.[3] Taking all of this into consideration, the best option to support a state of control is to have low-mounted returns. Although every cleanroom design is unique, placing the returns approximately 6 inches from the floor is the best place to start.

Ideally, place any particle generating equipment (eg, refrigerators, printers, waste bins, etc) close to a return or exhaust grille to evacuate any generated particulates as quickly as possible. That said, it is important not to block these grilles, as this will negatively affect the airflow. Consider placing this equipment at least 6 inches away from the grille.

Placement of PECs

Terminal HEPA filters located in the ceiling directly above the work opening of a PEC can impede the cabinet's intake airflow if the velocity from the ceiling HEPA filter is greater than the intake velocity of the cabinet. Turbulence and refluxing of air at the work opening can occur, potentially leading to ingress of lesser quality air into the PEC. Additional considerations must include staff traffic patterns and door placements, as cross drafts can be generated from personnel movement and the opening/closing of doors in close proximity.

PEC Airflow Dynamics

The airflow in each type of device discussed ahead serves the same purpose of minimizing exposure of the critical sites to potential contamination. A laminar airflow workstation (LAFW) or compounding aseptic isolator (CAI) utilized for non-HD compounding will not protect the end user from exposure to HDs, yet are simpler to integrate into the facility, as they do not require any external exhaust.

On the other hand, BSCs and compounding aseptic containment isolators (CACIs) are more complex in that they must be exhausted, requiring an external exhaust system and additional supply air to make up for the exhausted air.

- **Laminar Airflow Workstations—** An LAFW is designed to produce a unidirectional airflow, either horizontally or vertically. Typical velocity set points are around 90 feet per minute (FPM), and these are usually determined by the manufacturer. LAFWs are designed to protect the product by providing HEPA filtered air to the work area which flows out of the LAFW into the buffer room. Since the airflow is HEPA filtered and the device is recirculating, the additional airflow can be used for air exchange calculations for the room.

FIGURE 1

Class II, Type A2 Airflow

Class II, Type A2 biosafety cabinets exhaust 70% of airflow. Approximately 30% of the air that passes through the work zone gets recirculated, which lessens the strain on the facility's ventilation system.

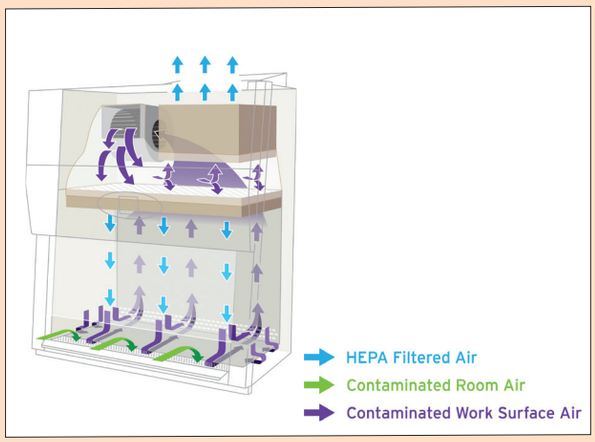
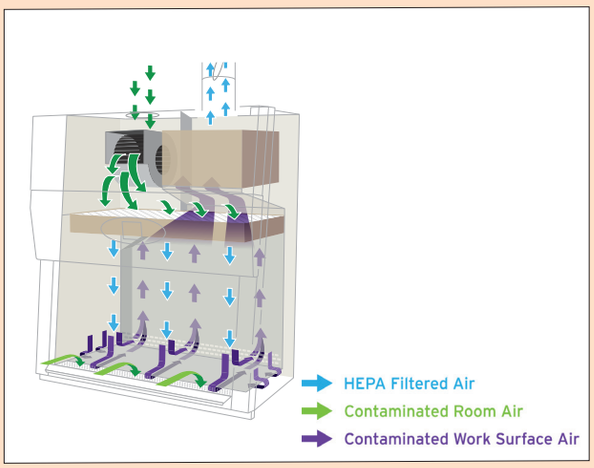


FIGURE 2

Class II, Type B2 Airflow

Class II, Type B2 biosafety cabinets recirculate 0% of the air passing through the work zone and must be connected to a dedicated ventilation system via a closed duct attachment.



- **Compounding Aseptic Isolators**—A CAI is a closed unit designed to produce a vertically unidirectional airflow. Typical velocity set points will vary depending upon the manufacturer. CAIs are designed to protect the product by providing HEPA filtered air to the work area, which flows down to the returns located on the work surface.
- **Biosafety Cabinets**—BSCs are designed to produce a vertical unidirectional airflow to the work surface while maintaining containment in the cabinet. USP General Chapter <800> requires that C-PECs utilized for sterile HD compounding are externally exhausted. This additional layer of the HVAC system must be carefully considered, as the BSC is integrated into the facility.

  Furthermore, the airflow will vary depending upon the cabinet type; an A2 BSC will recirculate airflow to the cabinet and out of the cabinet. A B2 BSC is different in that the airflow is not recirculated; rather, it is combined with the airflow from the work area and the front intake grilles as it mixes in the BSC plenum and then is completely exhausted from the unit (see **Figures 1** and **2**).
- **Compounding Aseptic Containment Isolators**—A CACI is a closed unit designed to produce a vertical unidirectional airflow to the work surface while maintaining containment within the unit. Since these are utilized for sterile HD compounding, they must be externally exhausted to comply with USP <800>. The various types of CACIs are similar to BSCs in that some units may recirculate some of the air while exhausting the rest, and others may completely exhaust all airflow.

Airflow Visualization Studies

Airflow visualization studies are the only way to prove that first air is delivered to critical areas and any areas of turbulence or eddy currents do not impact the critical area within the PEC. The following statement comes from FDA's Aseptic Processing Guide:[4]

"Proper design and control prevents turbulence and stagnant air in the critical area. Once relevant parameters are established, it is crucial that airflow patterns be evaluated for turbulence or eddy currents that can act as a channel or reservoir for air contaminants (eg, from an adjoining lower classified area). In situ air pattern analysis should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. The studies should be well documented with written conclusions, and include evaluation of the impact of aseptic manipulations (eg, interventions) and equipment design. Videotape or other recording mechanisms have been found to be useful aides in assessing airflow initially as well as facilitating evaluation of subsequent equipment configuration changes. It is important to note that even successfully qualified systems can be compromised by poor operational, maintenance, or personnel practices."

Maximize Airflow Efficiency in the Sterile Compounding Cleanroom

Airflow pattern analysis can be conducted by either pharmacy staff or the certifier, or as a joint effort. The current <797> (2008 version) does not specify a frequency for dynamic smoke studies; however, the revised <797> (2021) states, "A dynamic airflow smoke pattern test must be performed in the PEC initially and at least every 6 months to ensure that 1) the LAFW is properly placed into the facility and 2) compounders understand how to utilize the unidirectional airflow to maintain first air in the DCA."[2]

Impact of Equipment in the PEC

"Equipment should not obstruct airflow and, in critical areas its design should not disturb unidirectional airflow."
—FDA Aseptic Processing Guide[4]

Automated compounding devices (ACDs), especially PN compounding machines, have a large footprint within an LAFW, which raises the risk that they may block first air, thereby impacting unidirectional airflow and leading to turbulence. In recent years, there has been an increase in the use of automated IV workflow management systems (IV-WMS), which also require proper placement of the technology in the PEC working area. First air considerations likewise apply to accessories that may be stored in the PEC, such as cleaning tools or scanners. The use of these technologies and some accessories is encouraged; however, a smoke study is critical to not only document the proper placement of the technologies within the PECs, but also to ensure proper personnel workflow within the PECs. The ultimate goal is to prevent contamination from reaching critical sites by providing first air directly over them. In addition to the smoke studies conducted every 6 months, airflow pattern analysis should also be conducted anytime equipment is introduced or relocated within the PEC to ensure that first air reaches the critical site and to identify any changes that must be made by compounding personnel to achieve first air at the critical site.

Workflow Considerations

Supplies used in compounding often generate particulates, especially when they are opened within the PECs. With an overarching goal of setting up workflow in a way that minimizes risk to the CSP, it is recommended that the compounder consistently work either from left to right, or right to left when manipulating supplies. For example, when transferring materials into the PEC that have been wiped down, place them to the left of the direct compounding area. Once a component/supply is used for the preparation, it is then moved to the right side of the direct compounding area.

A common problem is the incorporation of too many components in the PEC at a time, which can compromise the delivery of first air over critical sites. This underscores the importance of simulating dynamic conditions when performing smoke studies, which helps ensure that the workflow does not impede first air to the critical sites during compounding.

Because workflow within the cleanroom may affect airflow efficiency, staff members should utilize the following procedures to minimize risk:

- Follow proper wipe-down procedures during material transfer into the cleanroom and into the PECs
- Perform appropriate hand hygiene and garbing procedures
- Limit talking and avoid fast movements
- Perform appropriate cleaning and disinfecting procedures
- Eliminate unnecessary items from ISO classified rooms/devices
- Limit personnel to those necessary for operations

When all of these activities are performed appropriately, they will support the airflow efficiency of the cleanroom and result in a slower loading of HEPA filters over time.

Control Temperature and Humidity

The control of temperature and humidity is an additional factor to consider when discussing airflow efficiency. The amount of equipment and number of personnel in the room must be factored into the design of temperature and humidity controls. If left uncontrolled, these elements will lead to increased particle release, thereby increasing the load on HEPA filters and decreasing their efficiency at a faster rate. In addition, temperature and humidity may affect many of the workflow items listed above, which in turn will contribute to reduced airflow efficiency. USP standards recommend maximum temperature/humidity setpoints of 20°C (68°F)/60% relative humidity (RH) or lower. Because staff are gowned, temperatures between 64° and 66°F will be more effective in providing comfort and reducing perspiration.

Conclusion

As detailed herein, there are many factors that affect airflow efficiency in a cleanroom. When thinking about maximizing energy efficiency, it is important to do so without compromising the safety and integrity of the sterile compounds being prepared or safety of the employees preparing them.

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