Complying With USP 797

Designing Hospital Pharmacy HVAC Systems

By Christopher P. Rousseau, P.E., Member ASHRAE; and **Adam R. Bare, P.E.,** Associate Member ASHRAE

The furor over compliance with United States Pharmacopoeia (USP) General Chapter 797, Pharmaceutical Compounding—Sterile Preparations,[1] has somewhat subsided with the Joint Commission for Accreditation of Healthcare Organizations' decision not to enforce its requirements. As of this writing, at least 10 states require compliance (in whole or in part). However, many facilities may desire to comply now to prepare for future federal, state or industry regulations. Operational modifications are the primary means of compliance, but the pharmacy's HVAC system also must be evaluated. USP 797 offers some confusing requirements for HVAC system designers, but compliance in an existing facility is not as difficult as it may seem.

Definitions

Several terms in USP 797 are unusual, or are used in a different manner than is normal in the HVAC industry. A brief overview of some of these terms provides better understanding of the standard and a common vocabulary for discussion.

Laminar Airflow Workbench (LAFW) can be either a laminar flow clean bench or a biological safety cabinet.

Anteroom is a clean space located between the entrance to the buffer room and other spaces, with a wall separating it from the buffer room.

Ante Space is a clean space in the pharmacy, logistically, but not physically, separated from the buffer room.

About the Authors

Christopher P. Rousseau, P.E., is a partner and **Adam R. Bare, P.E.,** is a senior associate at Newcomb & Boyd in Atlanta.

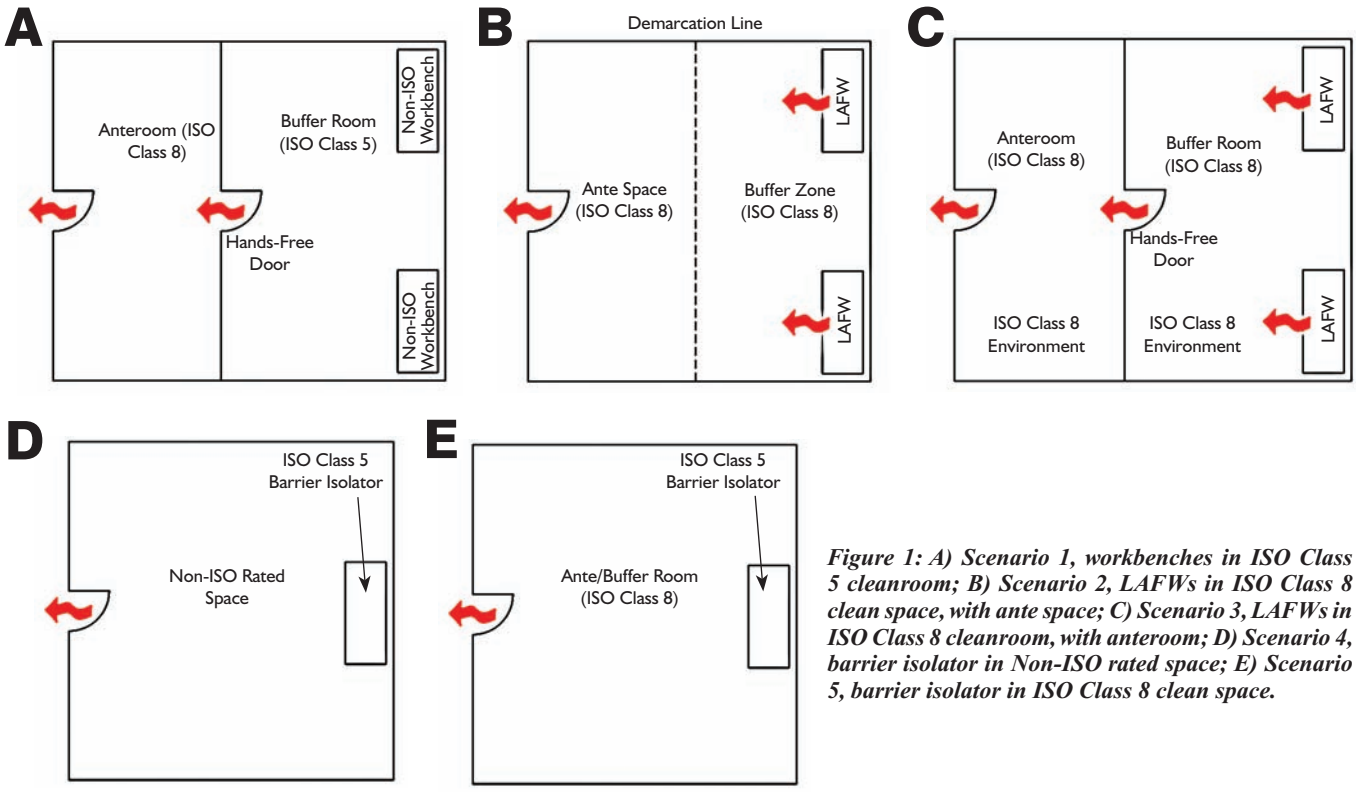

Figure 1: A) Scenario 1, workbenches in ISO Class 5 cleanroom; B) Scenario 2, LAFWs in ISO Class 8 clean space, with ante space; C) Scenario 3, LAFWs in ISO Class 8 cleanroom, with anteroom; D) Scenario 4, barrier isolator in Non-ISO rated space; E) Scenario 5, barrier isolator in ISO Class 8 clean space.

Barrier Isolator (a glove box) is designed to provide clean makeup air to the workspace and a seamless barrier between the workspace and the operator.

Buffer Area/Zone/Room is a clean space containing the primary engineering control equipment, and to which the secondary engineering controls are applied.

Cleanroom is any space where provisions are made to control particulates and/or microbes concentrations at or below specified limits (typically the buffer area, antespace, or anteroom). It corresponds to ASHRAE's definition of "clean space."

Compounded Sterile Preparations (CSP) are products administered to patients that require some type of manipulation prior to administration.

ISO Class[2] is a measurement of room air cleanliness. ISO Class 5 corresponds to Class 100; ISO Class 7 to Class 10,000; and ISO Class 8 to Class 100,000. Class numbers correspond to the number of particles per ft^3 at 0.5 microns or larger.

Primary Engineering Controls are measures taken to produce the environment in a LAFW or barrier isolator.

Risk Level (low, medium or high) pertains to the risk of the product becoming contaminated, not to a danger presented to the operator.

Secondary Engineering Controls are measures taken to produce the environment in the spaces occupied by staff and the LAFW or barrier isolator.

Space Configuration

Several ways exist to configure the pharmacy, equipment and the HVAC system to meet USP 797 requirements. The specific configuration has a significant impact on the HVAC system. The variables involved are risk level, type of equipment used (LAFW, vs. barrier isolator), and the cleanliness classification of the pharmacy. The basic configurations are:

- An ISO Class 5 clean space, with no LAFW or barrier isolator equipment (*Figure 1a*);
- An LAFW located in an ISO Class 8 clean space with an ante space, but without an anteroom (*Figure 1b*);
- An LAFW located in an ISO Class 8 clean space with an anteroom (*Figure 1c*);
- A barrier isolator located in a non-ISO rated space (*Figure 1d*); and
- A barrier isolator located in an ISO Class 8 space (*Figure 1e*).

Scenario 1 (*Figure 1a*) is unlikely to be implemented. This arrangement is expensive initially from the standpoint of finishes, and operationally from the standpoint of cleaning the space and controlling operator-generated particulates. Laminar flow clean benches, biological safety cabinets and barrier isolators are all specifically designed to provide the required ISO Class 5 space, and can minimize the impact of the room finishes and operator procedures on the sterile processes. This option does provide the most flexibility in that low, medium and high-risk procedures can all be performed on the benchtop without the spatial limitations of an LAFW or barrier isolator.

Scenario 2 (*Figure 1b*) is probably the best option for most existing facilities. Modifications can be made to the HVAC system to achieve the ISO Class 8 classification, and

the room can be configured to provide a buffer space for the actual preparation work, and an ante space for storage and product organization work. This scenario will work for low and medium risk CSPs.

Scenario 3 (*Figure 1c*) is the same as Scenario 2 except a wall is added to physically separate the buffer space from the ante space. This would allow the performance of high-risk procedures. However, as can be determined from the operational sections of USP 797, most high-risk procedures can be avoided with procedural modifications.

Scenario 4 (*Figure 1d*) makes use of a barrier isolator to compensate for the lack of an ISO Class 8 room. This would be an advantageous option if it were cost prohibitive to achieve an ISO Class 8 space with the existing room configuration or HVAC system. Another advantage is that procedures at all three risk levels can be performed. The disadvantage is the limitation on throughput caused by the additional operator time required to perform procedures in a glovebox.

Scenario 5 (*Figure 1e*) is basically the same as Scenario 4, but the room is arranged to have an ISO Class 8 classification. This arrangement is recommended (but not required) by USP 797 when a barrier isolator is used. However, this scenario is unlikely because, once the expense of an ISO Class 8 room is incurred, a need no longer exists to use a barrier isolator, unless it is required for personnel protection from hazardous or infectious agents. An LAFW will allow compliance at a lower cost.

Most existing hospital pharmacies are served by central air-handling systems. If the system also serves patient care space, the air-handling unit probably already has high-efficiency final filters. Even if it does not serve patient care areas, it probably already has a higher than normal level of filtration. Therefore, for most healthcare applications, Scenarios 2 and 3 are the most technically feasible and affordable, while still yielding an efficient workspace. Therefore, the remainder of this article will focus on how to achieve compliance with USP 797 assuming that the intended result is an ISO Class 8 clean space, with LAFWs providing the ISO Class 5 compounding environment.

How to Achieve an ISO Class 8 Clean Space

Once the decision has been made that the pharmacy should meet a cleanliness level that meets or exceeds ISO Class 8, the design team must consider many factors. One might assume that, since the ISO standard applies to concentrations of particulates in the air, this must be primarily an HVAC engineering issue. To the contrary, the necessary provisions to achieve ISO Class 8 affect the pharmacy staff first, and the facility's architecture (i.e., space planning, finishes, etc.) second.

To yield an ISO Class 8 clean space, all sources of particulates must be controlled. Examples of these sources are the workers, any shedding surfaces (permanent or mobile), the compounding process itself, the supply air to the pharmacy, and infiltration through doors, cracks and penetrations. The following are some measures (both HVAC-related and not) that are used to control these sources of particulates.

Control Measures (Non-HVAC)

Operator Procedures. While not the focus of this article, the standard operating procedures (SOPs) that the pharmacy operators follow must be carefully assessed, and periodically reassessed to ensure that the worker's particulate generation is minimized as much as possible. USP 797 includes recommended SOPs that pharmacies should use as a baseline. Some activities yield increased particulate generation rates, such as gowning and writing.[3] Those types of activities should be confined to the antearea, or outside of the pharmacy altogether. For worker activities that must occur within the clean space, the operations should be configured so as to minimize the particulate generation to the maximum extent possible.

USP 797 requires that the air quality, on a particulate count basis, be checked in the LAFWs, barrier isolators, buffer rooms, anteareas, and anterooms at least every six months. Airborne microorganisms are required to be evaluated monthly at various locations (weekly for high risk). When the results from the environmental monitoring indicate that the counts of particulates are too high, or that the colony-forming units are trending upwards, the SOPs are often the first place to look for resolution.

Surfaces and Materials. All permanent surfaces, including ceilings, walls and floors, should be monolithic, nonshedding, and washable. All penetrations through the room barrier by conduits, lights, diffusers, sprinkler heads, etc., should be completely sealed. The devices themselves should be sealed and washable. All mobile materials and equipment in the clean space, such as supply carts and workers' garments, need to be nonshedding.

Cleaning Procedures. The cleaning supplies and procedures that are used to sterilize the clean areas must be closely reviewed to minimize any particulate or microbial generation during the cleaning procedure, and any residual generation that occurs after (i.e., such as from off-gassing). The processes should be reviewed thoroughly and coordinated with the facility's environmental systems department. In many cases it is determined that low-shedding type mop heads need to be used to maintain an ISO Class 8 environment. As with the operator SOPs, cleaning procedures often are reassessed when the results from the environmental monitoring indicate increased particulate or microorganism levels.

Control Measures (HVAC)

Supply Air Quality. The air being supplied to the pharmacy must be cleaner than the desired air quality of the room itself to mitigate the generation of particulates inside of the room (e.g., by workers). Means of calculating the required level of filtration exist that would be required for the supply air given a room change rate, a particulate concentration of the air entering the filters, an internal particulate generation rate, and a desired room air quality. However, since the internal particulate genera-

tion rates are difficult to predict, 99.97% efficient HEPA filters typically are used since they are known to successfully yield ISO Class 8 spaces for most applications. The HEPA filters can be located centrally, such as in the air-handling unit, or locally, such as at the pharmacy supply diffusers. Twenty-five percent efficient prefilters should be located somewhere upstream of the HEPA filters to increase the usable life of the more expensive HEPA filters. Also, the conditions of the HEPA filters need to be routinely checked for loading; the increased air pressure drop caused by the loading of HEPA filters can have a profound impact on the supply air volume, which in turn can impact room pressurization levels.

If the air-handling system is dedicated to the pharmacy, consideration should be given to locating the HEPA filters in the air-handling unit. This reduces maintenance cost (since filters are easier to change in a mechanical room than in a ceiling plenum or clean space and typically fewer filters are used when located centrally). Additionally, variable frequency drives on the supply fans can enhance system performance since a constant airflow can be delivered while compensating for the loading of the HEPA filters. When HEPA filters are centrally located, take care to ensure that contaminants are not introduced downstream of those filters. For example, duct lining and sound attenuators should not be used downstream of the filters. If humidification is required to be added to achieve design humidity levels, the humidifiers should use clean steam.

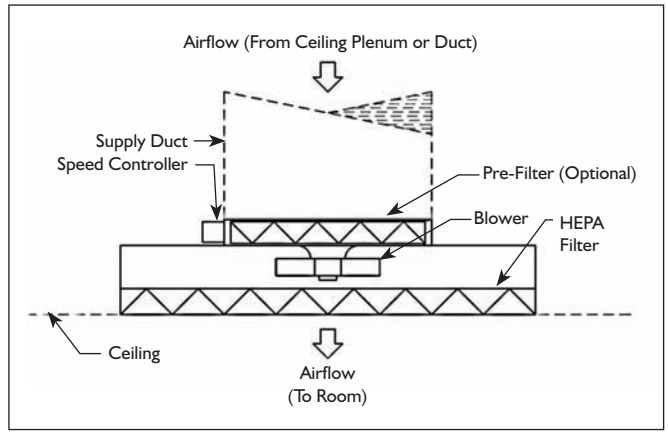

Figure 2: Fan/filter unit.

Room Air Changes. The number of air changes required to achieve ISO Class 8 can vary depending on room geometry, supply air quality, and the projected level of internal particulate generation. If the supply air passes through HEPA filters before being introduced into the space, then 20 to 30 air changes per hour is typically sufficient to achieve ISO Class 8.[4]

Room Airflow Distribution. The characteristics of the airflow within a pharmacy are an integral aspect of the clean space's performance. Airflow patterns are essential in keeping the particulate counts down throughout the space, and also help to effectively wash particulates away from the workers. Low velocity, non-aspirating-type diffusers and displacement ventilation design should be used to help prevent air turbulence in the room. The placement of LAFWs and diffusers is also important.

LAFWs should be located in non-traffic paths and away from doors to prevent movement of operators and the opening/closing of doors from influencing the airflow patterns at the face of the LAFW. Diffusers should be mounted away from LAFWs, such that the supply air velocity does not exceed 50 fpm (0.25 m/s) at the face of the LAFW.[5] In general, to maximize the room ventilation effectiveness the HVAC designer should take care in selecting diffuser locations in relation to where the air will be exhausted, and low exhaust is not normally necessary.

Room Pressurization. To prevent particulates from infiltrating through doors, cracks and penetrations, the clean spaces must be kept at positive pressure in relation to neighboring spaces. The ultimate intent is that the location where the sterile compounding occurs is at the highest pressure, and the room pressures cascade lower farther away from the most sterile location. The differential pressure across a room barrier causes airflow to move in the desired direction, which is from the cleaner space to the dirtier space. The target should be a minimum pressure differential across each room barrier of 0.01in. w.g. (2.5 Pa).[6]

Digital differential pressure monitors should be provided at the entrance to the buffer room and/or anteroom. These devices can send a signal to the building automation system, which enables the differential pressure to be trended over time, thereby highlighting a degrading differential pressure before it becomes an operational problem. Digital monitors with alarms are discouraged when there is not an anteroom before the buffer room, since whenever the door has been opened to the buffer room its pressure will equalize with the adjacent space, causing frequent alarms. If digital monitors are not preferred or applicable, designers might elect to provide physical indicators (i.e., ball-in-tubes, or flutter-strips), to signal pharmacy operators that there is a potential contamination problem.

Room Temperature and Humidity Control. Occupant comfort is always a concern, but the temperature and humidity must also be kept low enough to prevent workers from sweating, which increases human particulate and microbial generation rates. The garb that workers are projected to wear must be explored during design, since thicker garments will warrant lower room air temperatures. In the absence of specific design criteria, whenever possible, HVAC designers should ensure that the system can produce buffer room temperatures at least as low as 68°F (20°C), with the relative humidity maintained at or below 50% RH. These conditions are required due to the additional garb worn by workers, similar to that in an operating room.[7]

Implementation in Existing Facilities

Hospital renovations are inherently complicated. Maintenance of operations, infection control, and unknown existing conditions contribute to this complexity. A pharmacy renova-

Hospital renovations are inherently complicated. Maintenance of operations, infection control, and unknown existing conditions contribute to this complexity.

tion for USP 797 compliance involves these items, plus the additional technical challenges associated with higher levels of air filtration, higher air change rates, differential pressure, and additional exhaust requirements.

The addition of a new air-handling unit is often the simplest solution, but for many facilities might not be the most cost-effective solution. In that case, perhaps the most difficult feature to include is HEPA filtration of the supply air. HEPA filters impose a significant air pressure drop on an existing air-handling unit. Many facilities may be tempted to merely install HEPA filter diffusers. However, this will cause either less-than-desired airflow in the pharmacy, or balancing problems in the remainder of the air-handling unit zone. A better approach is the use of fan/filter units (*Figure 2*). The fan provides the additional static pressure needed to compensate for filter air pressure drop. Ceiling plenum space and acoustical considerations will require evaluation. The integral blower generates a considerable amount of noise, particularly at the manufacturers' recommended maximum airflows (typically equivalent to 100 fpm [0.5 m/s] through the diffuser face), which can be mitigated by using more fan/filter units at lower face velocities.

Prefilters only should be provided with the fan/filter units if the inlet air has not already passed through roughing filters, such as if the air is being drawn directly from the plenum space,

since the prefilters present maintenance and access issues. For example, if a fan/filter unit has a prefilter that can only be accessed from an ISO Class 8 space (such as through a ceiling access panel or light fixture), the space will be briefly exposed to the dirty air in the ceiling plenum, and the pharmacy will have to be temporarily shut down for the amount of time needed to replace the filters and to bring the space particulate counts back down to ISO Class 8 levels. If HEPA filters are located at the air-handling unit, existing ductwork downstream of the filters should be cleaned and existing duct lining removed.

If the existing air-handling system cannot be rebalanced to provide additional airflow in the pharmacy, the challenge of providing additional air changes can be solved in much the same way as the filtration issues. The fan/filter units discussed previously also can provide the additional airflow recirculated from the space. Unlike most health-care applications where patient safety and infection control are the primary issues, the concern in the pharmacy is primarily particulate control. Therefore, ventilation air quantities are not as important, and the additional supply air can be recirculated through the local HEPA filters, and not through the central air-handling unit.

Maintaining the pharmacy at a positive pressure with respect to all adjacent spaces (not just the adjacent spaces with a communicating door) is typically just a matter of balancing the space for more supply air than return air. Some sealing of cracks in the room enclosure may be required. If any LAFWs are exhausted to the outside, obtaining positive pressure is more of a challenge.

The lower temperature and humidity requirements due to operator clothing can be a challenge for an existing air-handling system. The additional supply air changes provided for particulate control will help, but probably will not be sufficient. A lower supply air temperature will likely be required. This could possibly be achieved by rebalancing the chilled water flow to the cooling coil. If not, a new cooling coil may be required. If the supply air temperature is reduced, the impact on existing reheat coil capacity must also be evaluated.

Future Issues

Currently, a change to USP 797 has been proposed that would increase the buffer area requirements from ISO Class 8 to ISO Class 7.[8] This change would have a significant impact on the HVAC systems and would require different solutions than those outlined here. The two sources noted as the basis for this change deal primarily with the manufacturing process. It is not clear that this change would provide substantial improvement in protecting the sterility of CSPs.

Unlike most health-care applications where patient safety and infection control are the primary issues, the concern in the pharmacy is primarily particulate control.

Conclusion

While an initial reading of USP 797 might be intimidating, compliance is not that difficult. The ISO Class 8 requirements, while substantially cleaner than typical office space, are not that much cleaner than normal patient care spaces. Fortunately for HVAC system designers, with a little planning and attention to detail, an existing pharmacy facility may be brought into compliance. The pharmacy professionals have the more difficult task of complying with the new procedural issues.

References

1. *United States Pharmacopoeia*. 2004. USP General Chapter <797>, Pharmaceutical Compounding—Sterile Preparations.
2. ISO 14644-1-1999, *Classification of Air Cleanliness.*
3. *2003 ASHRAE Handbook—HVAC Applications,* Chapter 16, Clean Spaces, 3.
4. *2003 ASHRAE Handbook—HVAC Applications,* Chapter 16, Clean Spaces, 11.
5. *2003 ASHRAE Handbook—HVAC Applications,* Chapter 14, Laboratories, 5.
6. Bare, A.R. 2006. "Pressurization strategies for biocontainment." *2007 R&D Laboratory Design Handbook* (11):59–63.
7. American Institute of Architects. 2006. *AIA Guidelines for Design and Construction of Health Care Facilities.*
8. www.usp797.org.