CONSIDERATIONS *for* CHOOSING *a* PRIMARY ENGINEERING CONTROL *for* COMPOUNDING STERILE PRODUCTS

James T. Wagner
Controlled Environment Consulting · Bethlehem, Pennsylvania

The introduction of *United States Pharmacopeia* (*USP*) Chapter <797>[1] and the National Institute for Occupational Safety and Health (NIOSH) alert for preventing occupational exposure to hazardous drugs[2] have renewed interest in engineering controls used for compounding sterile drugs. Besides traditional equipment such as laminar airflow workstations and biological safety cabinets, cleanrooms and barrier isolators are beginning to take on more prominent roles.

Engineering controls are engineered equipment or machinery that eliminates or reduces the potential exposure of a preparation or personnel to contamination or a hazard. Primary engineering controls are employed directly at the point of use. Examples of primary engineering controls used in aseptic compounding are laminar airflow workstations, biological safety cabinets, and barrier isolators. The design and construction of a facility also contributes to protection of both the preparation and personnel, and thus is considered a secondary engineering control. Other secondary engineering controls include cleanrooms and negative-pressure containment rooms. This article reviews the primary engineering controls along with a rationale for choosing one type over another.

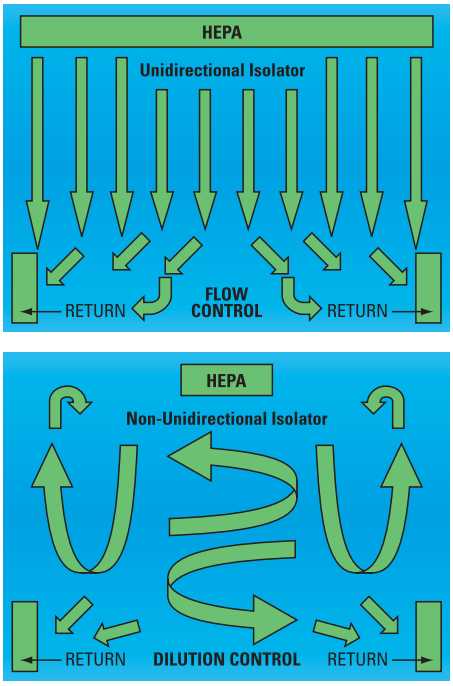

Figure 1. Unidirectional and turbulent airflow.

Basic Concepts

All of the engineering controls use airflow through high-efficiency particulate air (HEPA) filters to create air of an appropriate cleanliness for sterile compounding. This discussion begins with a review of these three basic concepts, then proceeds to how each device accomplishes its intended objective.

Airflow

Particulates in the air are managed by flow control using unidirectional airflow, dilution control using turbulent airflow, or some combination of the two. Generally, flow control is used for the primary or point-of-use engineering controls, and dilution control is used for the secondary engineering control, the cleanroom. While some cleanrooms do, in fact, employ unidirectional airflow, those used in compounding facilities tend to employ turbulent flow. Unidirectional airflow (sometimes referred to as "laminar airflow") showers the work zone with a continuous flow of HEPA-filtered air. By definition, unidirectional airflow is "air that flows in a single pass in a single direction through an air device or clean zone with generally parallel streamlines".[3] By showering the work area with air with relatively uniform airflow and using well-placed air returns, process-generated contamination can be controlled and environmental contamination eliminated from the work area.

Turbulent airflow cleans an environment by diluting dirty room air with clean, HEPA-filtered air.

HEPA Filters

The HEPA filter is the cornerstone of any effective engineering control. Unfortunately, quite a bit of the pharmacy literature misrepresents how HEPA filters are rated. The Institute of Environmental Sciences and Technology (IEST) publishes a series of recommended practices, of which IEST-RP-CC001.3 is the current national guide for purchasing and specifying HEPA filters.[4] This document defines a HEPA filter as "a throwaway, extended-medium, dry-type filter in a rigid frame, having a minimum particle collection efficiency of 99.97% (that is, a maximum particle penetration of 0.03%) for 0.3-µm particles of thermally generated DOP or specified alternative aerosol." It is important to understand that the 0.3-µm size rating is for a "mass median" diameter particle. Traditionally, HEPA filters have been tested with mass-concentration devices (photometers). Some European filter manufacturers

and, recently, some domestic manufacturers have rated HEPA filters with discrete particle counters. When particle counters are used, a "count median" particle size should be referred to. HEPA filters are rated for their ability to filter out the most penetrating particle.

When filter manufacturers efficiency-test their filters, they test at what is referred to as the most penetrating particle size (MPPS). The MPPS when using particle counter technology is generally referred to as being "between 0.1- and 0.2-µm count median diameter" (compared to 0.3-µm mass median diameter for filters tested with a photometer). It is easy to envision how particles larger than the MPPS are filtered more effectively through impaction, interception, and sieving. What is generally not understood is that particle collection through diffusion actually favors particles smaller than the MPPS. Therefore, HEPA filters are rated at the size where penetration is at its worst (ie, the MPPS). It is not accurate to state that the filter removes particles "down to 0.3-µm," because particles smaller than that are generally removed at a higher efficiency than the filter rating.

HEPA filters have been proven effective in removing almost any particulate contamination. As an example, they have been demonstrated to be very effective in removing virus particles, which are smaller than 0.3-µm. They are not effective, however, at filtering gases and vapors. This is why NIOSH requires that volatile drugs be processed in biological safety cabinets and isolators that are vented outdoors.

The only reference I can point to in which a specific filter is specified for engineering controls is NSF/ANSI Standard 49, the industry standard for class II biological safety cabinets.[5] NSF Standard 49 specifies the use of either a type "C" or "F" filter per the IEST-RP-CC001 document. The current version of IEST-RP-CC001 lists six filter types, "A" through "F." For compounding pharmacies purchasing an engineering control, I strongly recommend assuring the device comes with at least the type "C" filter per IEST-RP-CC001.

The type "C" filter is 99.99% efficient against particles of 0.3-µm mass median diameter and is also leak-tested by applying a polydispersed aerosol. The efficiency test determines the overall efficiency at the MPPS, while the leak test is intended to find individual points of penetration at all sizes. Properly specifying the HEPA filter type, which is the cornerstone of an engineering control, may prevent potential problems down the road. As an example, most standard industry practice dictates that the HEPA filter in a primary engineering control be leak-tested to no more than 0.01% penetration. Since, by definition, a HEPA filter is "at least 99.97% efficient on 0.3-µm particles," this allows up to 0.03% penetration. Moreover, a HEPA filter does not necessarily have to be leak free. A filter can have multiple leaks and the overall efficiency still be within 99.97%. By specifying a type "C" filter, you are guaranteed both an overall efficiency of 99.99% and no individual leaks exceeding 0.01%.

If you plan to import equipment, note that some manufacturers specify HEPA filters using the European standard, EN 1822.[6] The closest thing to an equivalent to a type "C" filter for this standard would be an H14. When using this standard, it is even more important to properly designate the filter because the standard specifies an H10 filter, which is only 85% efficient but under EN 1822 is still classified as a HEPA filter. If you received a device with that filter, you would most likely never pass the required HEPA filter integrity leak test when you attempt to get the device certified. Certification in the US generally requires a HEPA filter leak rate of no more than 0.01%.

Air Cleanliness Classification

Classification of air cleanliness is described in the International Standard Organization (ISO) 14644-1:1999.[7] This standard has replaced the recently "sunsetted" Federal Standard 209E.

ISO 14644-1 defines the level of airborne particulate cleanliness applicable to a cleanroom or clean zone, expressed in terms of ISO class *N*, which represents maximum allowable concentrations (in particles per cubic meter of air) for considered sizes of particles. Table 1 lists the class limits of the two standards. When specifying a cleanliness class, it is important to specify the appropriate particle size. Clean zones can be classified by particle sizes ranging from 0.1 -µm to 5.0 -µm. For the purposes of *USP* Chapter <797> classification, use 0.5 -µm particles.

The primary engineering controls (point-of-use) need to meet ISO Class 5. While the current version of *USP* Chapter <797> states ISO Class 8 for the secondary engineering controls, the draft for the proposed revision states ISO Class 7.

Summary of Primary Engineering Controls

The choices for point-of-use engineering controls can be broken down into three categories: laminar airflow workstations, biological safety cabinets, and barrier isolators. Each of the three is described here, followed by an explanation of the process of applying the appropriate control to a particular scenario.

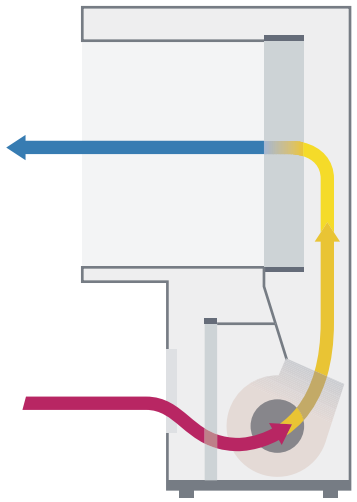

Figure 2. Laminar airflow workstation
Courtesy of the Baker Company

Laminar Airflow Workstation

This is the simplest of all the primary engineering control devices. Air is drawn through a prefilter into a blower, then blown into a plenum where the air finally passes through a HEPA filter across a partially enclosed work surface. Using unidirectional airflow, the filtered air sweeps across the work area, providing an ISO Class 5 environment. The air washes across the preparation, then around the operator before discharging into the room. This has been the cornerstone of contamination control since development of the HEPA filter.

The use of a laminar airflow workstation must be limited to nonhazardous applications. The airflow blows directly into the operator's face, making it the worst possible choice for compounding anything remotely hazardous to the operator.

Class II Biological Safety Cabinets

The industry standard for biological safety cabinets is NSF/ANSI standard 49. Standard 49 describes a class II biological safety cabinet as "a ventilated cabinet for personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward HEPA-filtered airflow for product protection, and HEPA-filtered exhausted air for environmental protection." Class II comprises four types of cabinets. The need for different types lies primarily in the limitation of the HEPA filter combined with the desire to provide the most energy-efficient configuration the contamination source allows. Some designs allow the cabinets to be vented directly into the room; others must be vented to the outside. There are obvious operating cost advantages to venting back into the room, so that should always be the first choice. As mentioned previously, the HEPA filter does not filter out gases and vapors. In the event the hazardous drug volatilizes, it must vent to the outside. The following is a description of each cabinet type along with its potential application.

Class II Type A1

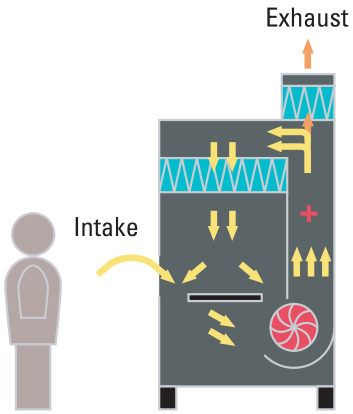

Figure 3. Class II Type A1 (A)
Courtesy of the Baker Company

This design is mostly intended for recirculation back into the room. While it can be exhausted outdoors through a canopy connection, it is not to be used with any volatile materials. This cabinet has HEPA-filtered downflow air that is a portion of the mixed downflow and inflow air from a common plenum. The fact that it may have positive-pressure contaminated ducts and plenums that are not surrounded by negative-pressure plenums make this design a poor choice for most hazardous applications. In the event there is a leak in the cabinet itself, material will leak into the room. The minimum intake velocity for this cabinet is 75 feet per minute (fpm), while all cabinets intended for use with toxic or volatile materials have a minimum intake velocity of 100 fpm. I do not consider this cabinet to be a good choice for many compounding applications.

Class II Type A2

This design is very similar to the A1 design. Like the A1, this cabinet has HEPA-filtered downflow air that is a portion of the mixed downflow and inflow air from a common plenum. The A2, however, requires all biologically contaminated ducts and plenums to be under negative pressure or surrounded by negative-pressure ducts and plenums. In the event of a leak in the cabinet itself, material will leak into the cabinet and not into the room. It may exhaust HEPA-filtered air into the room or to the outside environment. With a minimum intake velocity of 100 fpm, this cabinet can be used with minute quantities of volatile toxic chemicals if it is exhausted through a properly functioning exhaust canopy.

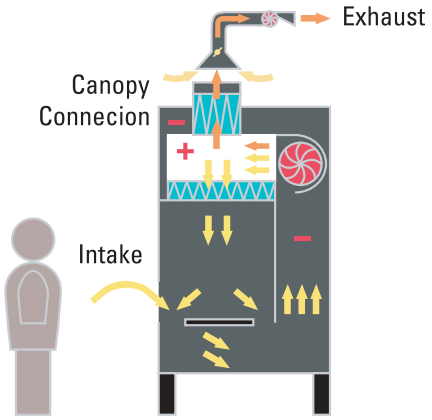

Figure 4. Class II Type A2 (A/B3)
Courtesy of the Baker Company

When properly vented, this cabinet is an acceptable choice for compounding hazardous drugs only if there is no concern that the drugs being processed may volatilize. Because the HEPA filters do not remove them, any volatilized materials are recirculated within the cabinet.

Class II Type B1

This design differs from the A1 and the A2 in that the HEPA-filtered downflow air is composed largely of uncontaminated recirculated inflow air. It exhausts most of the contaminated downflow air through a dedicated duct to the outside atmosphere after passing through a HEPA filter. When operating in the front half of the work surface, all the air that passes over the product is drawn into the front grille and recirculated. The supposed advantage to this cabinet design is that all of the air that enters the rear grille is vented directly to the outside atmosphere without recirculation. If you work in the back half of the cabinet, therefore, you do not have to worry about recirculation of volatile materials. The problem, however, is that the average person cannot work effectively in the back half of the cabinet; the average human arms simply are not long enough.

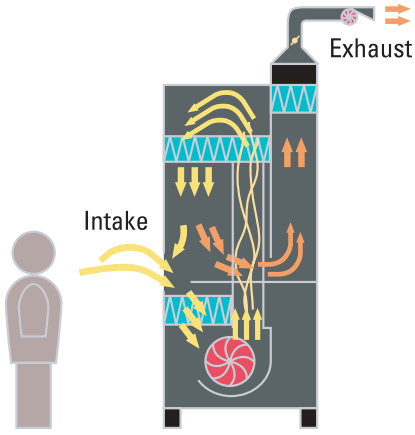

Figure 5. Class II Type B1
Courtesy of the Baker Company

This cabinet must be vented to the outside and has a minimum intake velocity of 100 fpm, making it an acceptable choice for volatile materials in certain circumstances. This design is acceptable if recirculation of the volatile will not interfere with the product or create a potential for cross-contamination. It would even be capable of preventing volatile recirculation if the work is done in the back half, though I believe that to be improbable.

Class II Type B2

This type of cabinet is referred to as a total exhaust biological safety cabinet. It draws HEPA-filtered downflow air directly from the room along with the front access inflow air. Both the downflow air and inflow air are exhausted to the outside atmosphere after filtering through a HEPA filter without recirculation in the cabinet or return to the room. All contaminated ducts and plenums are under negative pressure or surrounded by directly exhausted negative-pressure ducts and plenums.

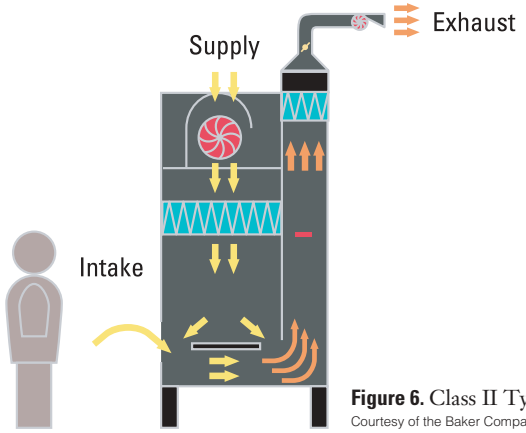

Figure 6. Class II Type B2
Courtesy of the Baker Company

This design may be used for work with volatile toxic chemicals without fear of recirculation. It is not clear to the author exactly how big of a concern drug volatility is. The best policy is to remain consistent with the intent of the NIOSH document. Specific applications are discussed later in this article, but this is the cabinet of choice if you are using a biological safety cabinet and are concerned about volatiles.

Class III Biological Safety Cabinet

This design is more typically associated with the highest levels of biological containment. It is listed here because it is mentioned in the NIOSH alert, but it is probably a bit of overkill for most facilities compounding sterile products. The class III biological safety cabinet is a totally enclosed, ventilated cabinet of leak-tight construction. Downflow air is drawn into the cabinet through HEPA filters. The exhaust air is treated by double filtration or by HEPA filtration and incineration. A minimum of 0.5" negative pressure is maintained.

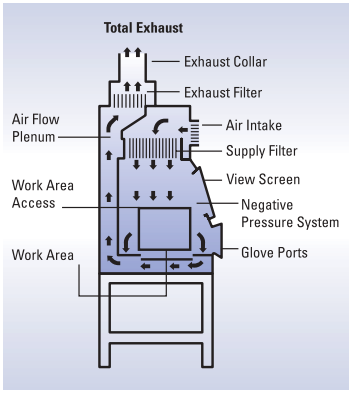

Figure 7. Class III biological safety cabinet airflow schematic
Courtesy of the Baker Company

Barrier Isolators

The use of barrier isolators for compounding sterile preparations is relatively new to the US. Unlike biological safety cabinets, barrier isolators have no industry standard available for reference for specific information. A good source of information is the Controlled Environment Testing Association (CETA) application guide for the use of barrier isolators in compounding sterile preparations in healthcare facilities.[8] This guide is available as a free download at www.cetainternational.org. Unfortunately, it covers only sterile compounding without regard to hazardous drugs. The following is a discussion of the fundamentals needed to make good purchasing decisions for both hazardous and nonhazardous applications.

Open System

When looking at an isolator, it appears to be a closed system. You work through gloves, and the enclosure is sealed to the environment. The weak point of the system, however, is how material is moved in and out. Compounding isolators all use pass-throughs

Table 1. Cleanliness Classification.[a]

Class Name ISO Class	US FS209E	Particle Size ISO, m^3	FS209e, ft^3
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3,520	100
6	Class 1,000	35,200	1,000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

[a]Classification of particulate matter in room air (Limits are in particles 0.5 µm and larger per cubic meter [current ISO] and per cubic foot [former Federal Standard Number 209E, FS209E]).

to move preparation. At some point the pass-through is open to the room, and then it is open to the isolator. When not carefully thought out and performed, the material-moving process provides a potential conduit for contamination to be brought into or out of the isolator. Thus, an isolator with a pass-through is considered an open system.

Material Transfer

The process of transferring materials into or out of the isolator is a very critical component of developing a good process flow scheme. To aid in this endeavor, pass-throughs are either attached or made an integral component of the isolator. A pass-through is basically a box with two doors; one door opens to the room and the other opens into the isolator. Product is brought into the isolator from the room by first placing it into the pass-through, then closing the outside door. Once the outside door is closed, the inside door can be opened and the product transferred from the pass-through to the isolator.

In its most basic form, the isolator is equipped with a static pass-through without filtration or overpressure; it is simply a box with doors. The problem with static pass-throughs is that they introduce a very real source of potential contamination when moving materials in and out. As the outside door is opened, room air enters the pass-through, elevating particle levels; after the inside door is opened, the natural draft pulls air from the pass-through into the isolator, creating a high probability of contamination. The air in the pass-through is likely to be as dirty as the room air. Isolators equipped with static pass-throughs generally should be used only in carefully controlled environments such as a cleanroom.

Pass-throughs with HEPA-filtered air have been developed to reduce the likelihood of unfiltered room air being drawn into the isolator. Once the product is placed into the pass-through, the pass-through can be purged with HEPA-filtered air before the door to the isolator is opened. This greatly reduces the particle burden created by material transfer.

According to the *USP*, it is not necessary to place an isolator in a cleanroom. In fact, many isolators are being marketed as an alternative to a cleanroom. I suggest you seriously address how you are going to get materials in and out of the isolator as part of your purchasing decision. Especially where an isolator is used outside of a cleanroom, I suggest using a pressurized, filtered pass-through instead of a static pass-through. Also note that, as in the isolator itself, unidirectional flow pass-throughs clean up the air faster than turbulent flow pass-throughs.

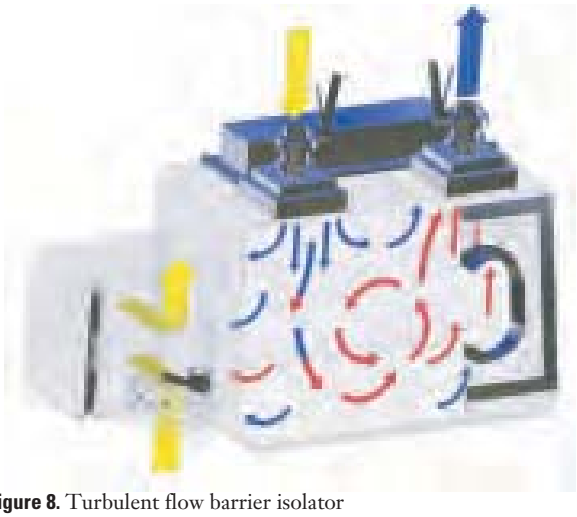

Figure 8. Turbulent flow barrier isolator
Courtesy of Germfree Laboratory

Figure 9. Unidirectional barrier isolator
Courtesy of Germfree Laboratory

Airflow

Unidirectional flow isolators provide a continuous flow of HEPA-filtered air across the work area. Particulates are removed prior to entry into the isolator by the HEPA filter. Process-generated contamination is swept away by the unidirectional airflow and removed by the air return. Turbulent flow isolators rely on dilution of the contaminants with clean, HEPA-filtered air. Process-generated particulates are diluted out and eventually carried to the returns as HEPA-filtered incoming air replaces the existing chamber air.

Unidirectional airflow isolators provide the additional benefit of preventing cross-contamination. Most compounding facilities do not compound the same preparation throughout the day. The sweeping action of the unidirectional airflow draws process-generated contamination immediately into the front or rear work area return grilles. By sweeping all contamination out of the isolator immediately, the potential for airborne preparation cross-contamination is virtually eliminated.

Recovery Time

Recovery time is the amount of time it takes for the air quality inside the isolator to recover to its operating level after an excursion. Transferring materials in and out of the isolator or a surge of process-generated contamination would potentially elevate the particle counts from operational levels. This is an extremely important concept with most engineering controls, but recovery time is even more important with isolators. In the enclosed environment of an isolator, any particles that enter the isolator are trapped until they are either removed by the returns or deposited on the product. In unidirectional flow isolators, the recovery time is a matter of seconds. While I have tested only a few turbulent flow designs, the units I have seen have had recovery times measured in minutes.

The recovery time is a function of how often the air within the isolator is replaced with HEPA-filtered air. Air-exchange rates in a unidirectional flow isolator are typically in the range of 1,100 to 1,500 air changes per hour (ACPH). Turbulent flow isolators often provide as few as 250 ACPH.

Pressurization

The isolator chamber pressure relative to the room pressure is determined by the type of compounding to be done. Aseptic nonhazardous compounding is done in a positive-pressure isolator. In the event there is a leak in the unit, the material will leak into the room and not contaminate the work. Hazardous drug compounding is done in a negative-pressure isolator. In the event there is a leak in the unit, the hazardous material will leak into the isolator and not contaminate the room. Until a standard for compounding isolators is created, the US Food and Drug Administration (FDA) *Guide for Sterile Drugs Produced by Aseptic Processing—Current Good Manufacturing Practice* is an appropriate resource for specification guidance.[9] The FDA recommends maintaining a pressure of 0.07" to 0.20" water gauge for isolators used in aseptic processing.

Ergonomics

Comfortable working height varies among people of different sizes. Most isolators come with height adjustment mechanisms to accommodate personnel size differences. Another ergonomic factor is glove, sleeve, and collar configurations. Other decisions that must be made include the choice between round and elliptical collars, the orientation of the collars on the front view screen, the type of glove, and the type of sleeve. Think through the process of working in the isolator for the amount of time needed to accomplish all the work your facility needs to accomplish. What may allow acceptable worker comfort for 1 to 2 hours may not be acceptable for 6 to 8 hours.

Conclusion

Many different configurations of primary engineering controls are and have been available for years. The optimal configuration for your facility is dependent on many considerations, including facility limitations, work volume, ventilation limitations, personal preference, and budget. Careful consideration of all options should be made before making a final decision.

References

1. [No author listed.] US Pharmacopeial Convention, Inc. *United States Pharmacopeia 27-National Formulary 22*. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2003: 2350.
2. [No author listed.] National Institute for Occupational Safety and Health. *Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings*. Cincinnati, OH: Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2004. DHHS publication number 2004–165.
3. [No author listed.] Institute of Environmental Sciences and Technology. *IEST-RP-CC002.2: Unidirectional Flow Clean-Air Devices*. Rolling Meadows, IL: Institute of Environmental Sciences and Technology; 1999.
4. [No author listed.] Institute of Environmental Sciences and Technology. *IEST-RP-CC001.3: HEPA and ULPA Filters*. Rolling Meadows, IL: Institute of Environmental Sciences and Technology; 1993.
5. [No author listed.] NSF International. *NSF/ANSI Standard 49-2002: Class II (Laminar Flow) Biohazard Cabinetry*. Ann Arbor, MI: NSF International; 2002.
6. [No author listed.] European Committee for Standardization. *CEN EN 1822–1: High-efficiency Air Filters (HEPA and ULPA). Classification, Performance Testing, Marking*. Brussels, Belgium: European Committee for Standardization; 1998.
7. [No author listed.] International Organization for Standardization, Technical Committee 209. *ISO 14644-1: Cleanrooms and Associated Controlled Environments—Part 1: Classification of Air Cleanliness*. Geneva, Switzerland: International Organization for Standardization; 1999.
8. [No author listed.] Controlled Environment Testing Association. *CETA Applications Guide for the Use of Barrier Isolators in Compounding Sterile Preparations in Healthcare Facilities*. Raleigh, NC: CETA International; 2004.
9. [No author listed.] US Food and Drug Administration. *Guidance for Industry—Sterile Drugs Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. Rockville, MD: U.S. Food and Drug Administration; 2004.

Address correspondence to James T. Wagner, Controlled Environment Consulting, 2067 Hilltop Rd., Bethlehem, PA 18015. E-mail: jimwagner@fast.net ■