By Carl J. LaBella, BS, MBA

Making Sense of Engineering Controls:
The Proposed Changes to USP Chapter <797>

When published in 2004, the engineering control requirements under USP Chapter <797> led to confusion for many hospital pharmacists, as the requirements did little to provide definitive guidance for engineering control performance. The proposed changes to USP <797>, published in May 2006, expanded upon the original document's engineering control requirements and provided much needed detail regarding the requirements for establishing a sterile compounding environment. The proposed changes reduced ambiguity over the needs for air movement in controlled environments, pressure relationships between engineering controls, HEPA filtration, and testing engineering control performance during operations. The proposed changes also detail the necessary engineering controls for hazardous drug preparation and include employee safety as a sterile compounding goal.

Photo courtesy of IsoTech Design

CAIs and CACIs use a combination of air movement, filtration, pressure, and physical separation to provide a sterile compounding environment.

Primary and Secondary Engineering Controls

In order to grasp the complexity of the proposed changes, you should first understand the terms *primary* and *secondary engineering controls*.

- **Primary controls** for non-hazardous sterile drug compounding include ISO Class 5 laminar air flow workstations (LAWFs) and compounding aseptic isolators (CAIs). A CAI is an isolator that meets the definitions and performance attributes described by the Controlled Environment Testing Association (CETA) as suitable for sterile compounding. An ISO Class 5 cleanroom may also be used as a primary control for non-hazardous drug preparation.

Primary controls for hazardous drug compounding include Class II and III biological safety cabinets (BSCs) and compounding aseptic containment isolators (CACIs) designed to provide operator protection through containment, while providing ISO Class 5 air cleanliness. Exhaust air from hazardous drug compounding primary controls should be vented 100% from the building, because HEPA filters are not capable of capturing volatile fumes associated with certain hazardous drugs. Recirculation of these hazardous fumes within the BSC or isolator should be avoided.

LAFWs, CAIs, BSCs, and CACIs maintain control over the sterile compounding worksite through HEPA-filtered air, the velocity and direction of air movement, air pressure, and a partial or full enclosure of the critical worksite. The proposed changes to <797> require that ISO Class 5 air cleanliness be maintained throughout the compounding process within the primary control.

Pharmacists should recognize that no primary control is infallible on its own and can be defeated by inappropriate operator behavior, improper location within the room environment, equipment system failures, or poor design. Primary controls are considered open devices. LAWFs and BSCs are obviously open, but use specific design elements to provide product protection. When properly used and placed within the room, they use the unidirectional first air from the HEPA-filtered supply to maintain the compounding environment.

CAIs and CACIs use a combination of air movement, filtration, pressure, and physical separation (enclosure, view window, and gloves) to provide the desired sterile environment. Although perceived of as closed systems, sterile compounding isolators are also open to the surrounding environment because they use pass-through systems to introduce and extract preparations. According to CETA, air exchange into the isolator from the surrounding environment should not occur unless it has first passed through a microbial-retentive filter (HEPA minimum). Properly designed pass-through chambers, using HEPA filtration, air movement, and pressurization to provide separation between the main chamber and surrounding room environment, can provide adequate separation. The proposed changes define CAIs as isolators designed to maintain an aseptic environment throughout the compounding and material-transfer process. Air entering the isolator must first pass through a HEPA filter to prevent and reduce the infiltration of unwanted particles to the isolator's main chamber.

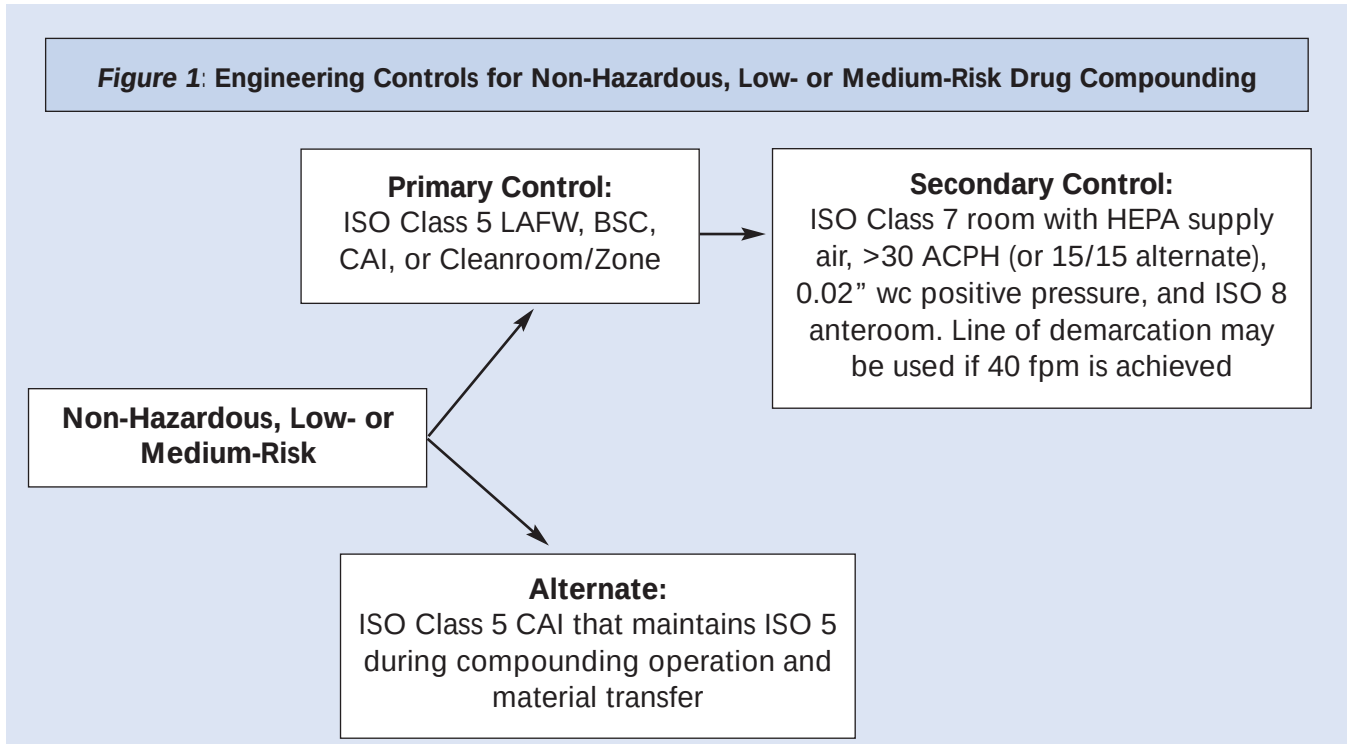
In 2005, CETA participated in a CAI review project along with NIOSH. The team reviewed CAIs sold for sterile compounding and found that certain isolator pass-through/transfer chamber designs failed to provide separation between the room and main chamber. In some cases, these pass-through chambers lacked HEPA filtration, appropriate pressurization, or sufficient purge times to protect the main chamber from particle incursion. Some failed to maintain desirable pressure relationships during routine operations, and some did not provide hazardous drug containment.

As a result, CETA developed definitions for isolators used in sterile compounding, along with independent test methods for both manufacturers and certifiers to verify isolator performance. These guidelines (available at

Testing will establish that your cleanroom engineering controls **meet requirements** under operating conditions and perform predictably and as designed.

www.cetainternational.org) can also aid pharmacists in developing procedures for isolator use, such as the appropriate wait time between transferring product into the main chamber and beginning preparation, the placement of the isolator inside or outside a cleanroom, and whether the isolator can be used for hazardous drug compounding.

■ **Secondary controls** are the environments leading to and including the ISO Class 5 primary controls, or more simply put, the cleanroom and anteroom. The proposed changes to <797> detail the specific criteria for secondary control environments. Cleanrooms, by definition, must control the generation and



introduction of airborne contamination, using HEPA-filtered supply air at a sufficient volume and air pressurization, as well appropriate materials and construction for its walls, ceiling, doors, etc. In some cases the room may use a line of demarcation instead of walls, doors, and pressurization. In this scenario, properly engineered displacement airflow at a sufficient velocity is required to protect the preparation area.

The cleanroom fixtures must have smooth, impervious, seamless, non-shedding, and cleanable surfaces. Fixtures should be constructed of materials such as stainless steel or plastic, which enable cleaning and resist contamination. Floors should be made of continuous sheet vinyl with welded seams and coved joints at the base of the walls. Walls should be smoothly sealed with minimal vertical and horizontal edge breaks. To promote and withstand frequent cleaning, walls should be constructed of epoxy-finished gypsum board. Ceilings should be smooth and designed for cleaning; any tiles should be caulked in place. Room enclosure penetrations caused by electrical and plumbing runs should be sealed at the edges.

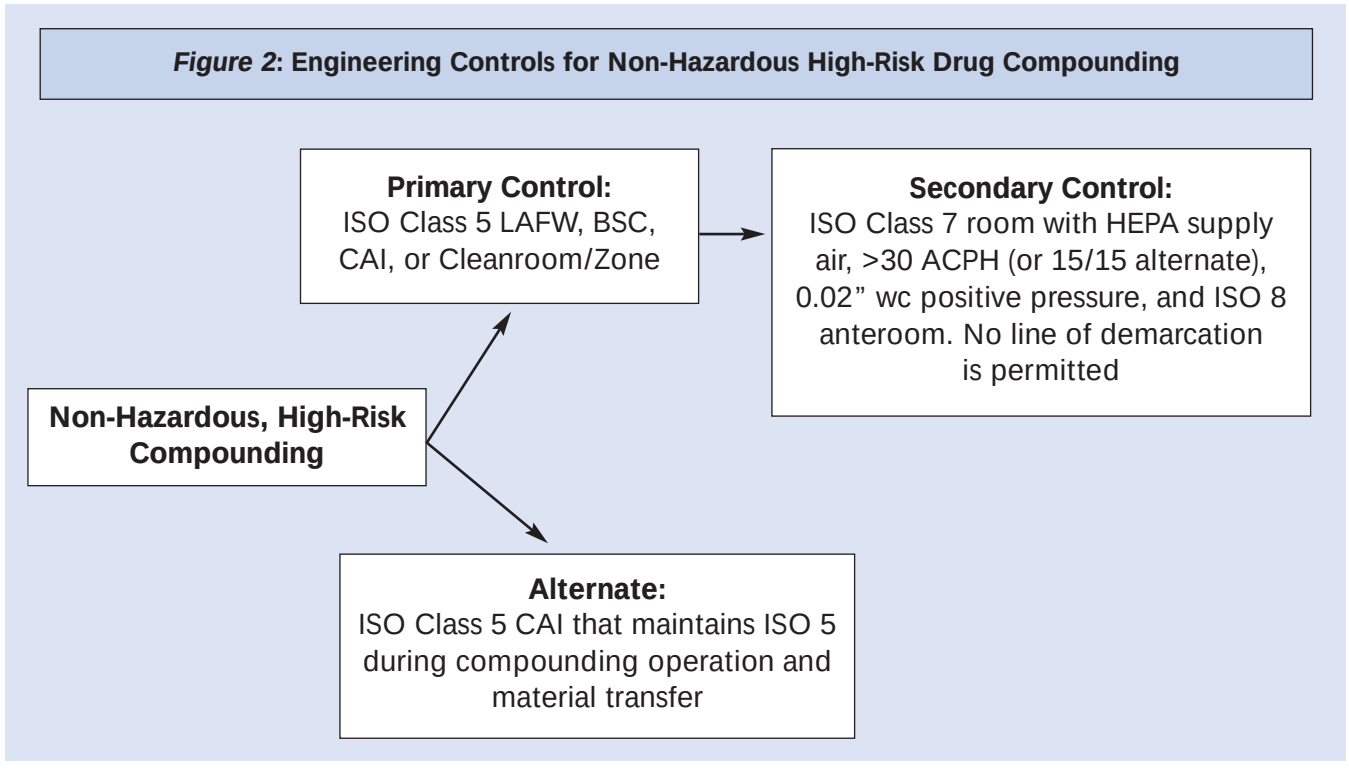
What Controls Do I Need?

To determine the engineering controls needed per the proposed changes to <797>, use the hazard level of the drugs to be compounded as a foundation, and then consider both compounding volume and risk level.

Non-Hazardous, Low- and Medium-Risk CSPs

Non-hazardous drugs at all compounding volumes are identified by low-, medium-, or high-risk levels. For low- and medium-risk compounding, the primary control is the ISO Class 5 LAFW, CAI, BSC, or other ISO Class 5 zone used within an ISO Class 7 cleanroom. The primary control has HEPA-filtered supply air and positive pressure to adjacent spaces at a minimum of 0.02 inches of water column. The HEPA-filtered air entering the space must be at a sufficient volume to provide for adequate filtration and dilution, achieving at least 30 air changes per hour (ACPH). In some cases, this air change requirement can be reduced to no less than 15 ACPH from the room HEPA filter, where re-circulating primary control devices provide added filtration of the room air and make up the remaining 15 ACPH.

The preparation room must be accessed using an anteroom for gowning, hand-washing, and some storage. The anteroom must be at a positive pressure to the main pharmacy, and a wall or door must separate the anteroom and cleanroom. A line of demarcation may provide separation and control contamination



movement toward the primary control devices, but only if the displacement airflow provides adequate HEPA-filtered air flow (at least 40 feet per minute) from the preparation side of the line to the anteroom side.

As an alternative to a cleanroom, the proposed changes to <797> allow for the use of a CAI outside of a cleanroom, but only if it maintains an aseptic environment during compounding operations and material transfer. Pharmacists should require their certifier to field test the isolator while in operation (or pseudo-operation) and during material transfer to establish that ISO Class 5 levels are continually met throughout the compounding process. (*See Figure 1.*)

■ Non-Hazardous, High-Risk CSPs

For compounding non-hazardous, high-risk CSPs, all requirements for low- and medium-risk level compounding must be met. In addition, a wall with a door must separate the anteroom from the cleanroom, and there must be positive air pressure from the preparation room to the anteroom of at least 0.02 inches of water column. Use of a line of demarcation and displacement airflow is not allowed. The anteroom must have positive pressure in relation to non-controlled adjacent space.

As an alternative to a cleanroom, the proposed changes allow for the use of a CAI outside a cleanroom. Once again, this is an option only if the isolator maintains ISO 5 continually during compounding and material transfer operations. (*See Figure 2.*)

Hazardous Drug Compounding

Hazardous drug compounding must be performed in an environment that protects health care workers from harm. Consequently, there is no immediate-use provision in the proposed changes to allow for compounding hazardous drugs outside a primary control environment. Compounding of hazardous drugs must be performed within an ISO Class 5 primary control that is properly designed for such activity.

■ Five or More Preparations Per Week

Proposed hazardous drug compounding engineering controls vary according to the facility's weekly preparation volume, not by its risk level. For facilities preparing five or more CSPs per week, the primary control can either be a BSC or CACI vented 100% to the outside of the building, where feasible. The BSC or CACI must be located within an ISO Class 7 prepara-

tion cleanroom that has HEPA-filtered supply air and negative pressure relationships to adjacent spaces at a minimum of 0.01 inches of water column. The room must achieve at least 30 HEPA-filtered ACPH. This air change requirement can be reduced to no less than 15 ACPH from the room supply HEPA filter, if one or more re-circulating primary control devices make up the remaining 15 ACPH. Because the use of re-circulating primary control devices for hazardous drug compounding is not recommended by NIOSH, it is not likely that the 15 ACPH make-up allowance would be applied to hazardous drug secondary controls.

Unlike non-hazardous drug compounding, the preparation room for hazardous compounding must be accessed using an ISO Class 7 anteroom for gowning and hand-washing. The anteroom must be at a positive pressure to all adjacent areas, including the preparation room. A wall and door must separate the anteroom from the preparation room. No line of demarcation may be used to separate the spaces, regardless of risk level.

Pharmacists should **recognize** that no primary control is infallible on its own and **can be defeated** by inappropriate operator behavior, improper location within the room environment, equipment system failures, or poor design.

As an alternative, you can use an ISO Class 5 CACI in an unclassified room, as long as that room achieves at least 12 ACPH and negative pressure relationships to adjacent spaces at a minimum of 0.01 inches of water column. (*See Figure 3.*)

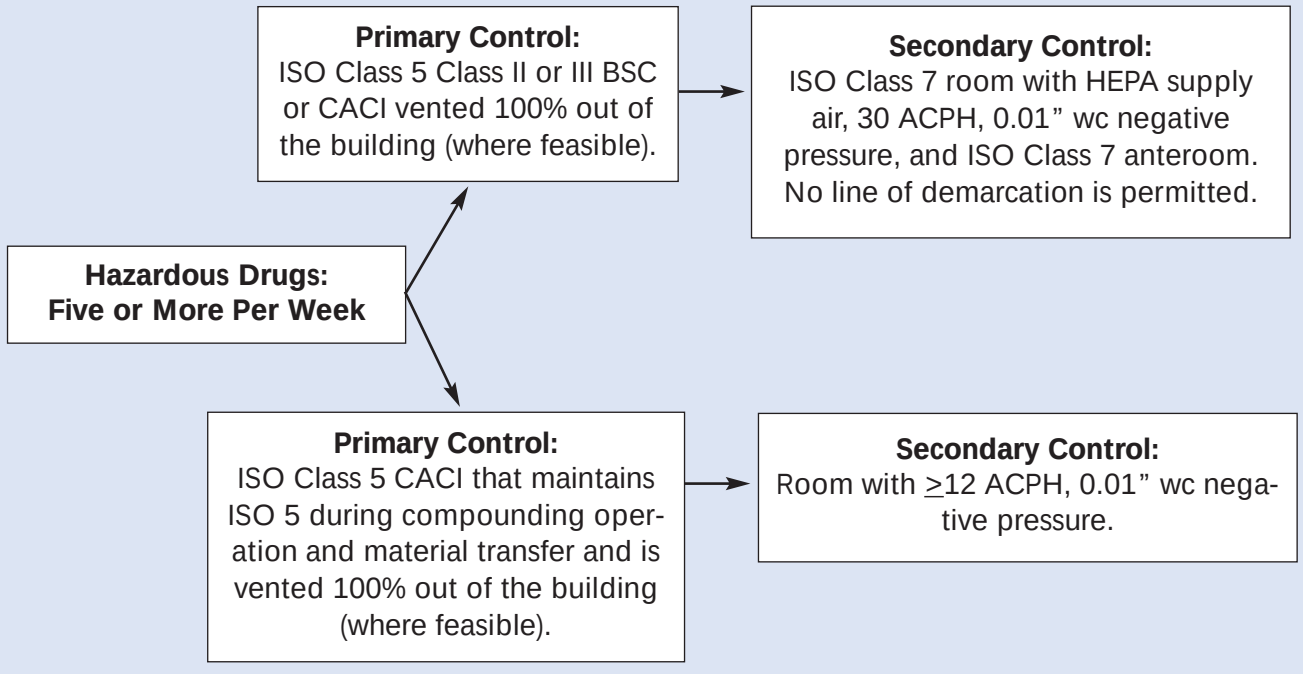
Fewer Than Five Preparations Per Week

For hazardous drug compounding volumes lower than five preparations per week, the proposed changes allow the facility to use a BSC or CACI outside a cleanroom. The isolator must maintain ISO Class 5 conditions during compounding operations and transfers. The BSC or CACI must be located within a separate room devoted to hazardous drug preparation. This room must provide at least 12 ACPH, but no negative room pressure is required. However, in order to meet this provision when using just a BSC or CACI, a second tier of containment through the use of a closed-system vial transfer device (CSTD) is required. (*See Figure 4.*)

Hazardous Drug Storage

Hazardous drugs, regardless of preparation volume or risk, must be stored in a room that is separate from non-hazardous drug storage. This room must provide at least 12 ACPH, be at a negative pressure of 0.01 inches of water column to adjacent areas, and provide continuous general exhaust to the outside of the building.

***Figure 3*: Engineering Controls for Compounding Five or More Hazardous Drugs Per Week**

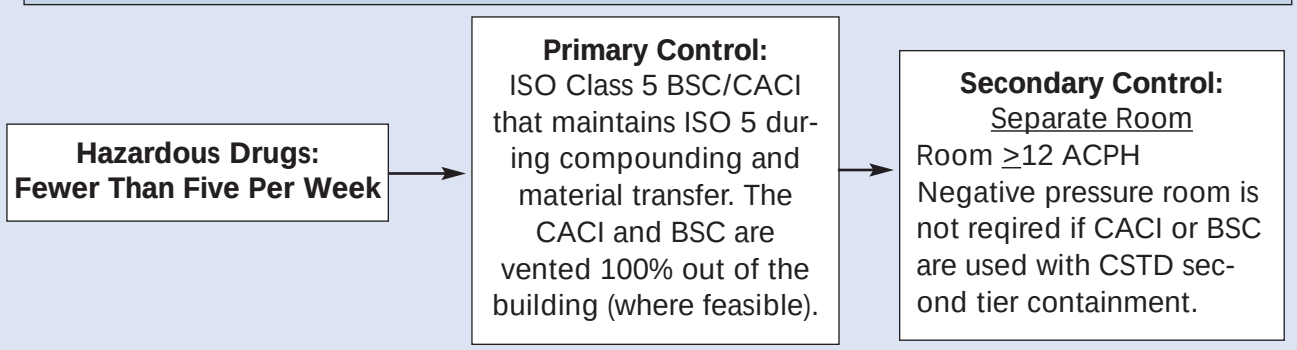


Testing and Verification

The proposed changes to <797> refer to published cleanroom industry guidelines and other guidance for testing cleanroom and engineering control performance verification. Testing will establish that your cleanroom engineering controls meet requirements under operating conditions and perform predictably and as designed. The proposed changes are prescriptive in nature, identifying the necessary controls and challenges that determine if the equipment actually works during

dynamic conditions. For example, isolators and cleanrooms should be tested during preparation and transfer conditions. Installed HEPA filters for both primary and secondary controls should be challenge tested to verify the filtration system is leak-free, rather than assuming they work based upon point-in-time particle levels. Testing during more stringent operational conditions will aid in verifying that the controls provide an environment that protects the compounding process.

***Figure 4*: Engineering Controls for Compounding Fewer than Five Hazardous Drugs Per Week**



Conclusion

With an understanding of engineering controls, pharmacists can avoid costly mistakes by specifying their needs up front, rather than discovering post-purchase that the controls in place fail to perform as required. After all, cost-effective alternatives are only a savings if they actually work. However, avoid being lulled into a false sense of security; even the best engineering controls will not overcome bad human practices. Aseptic technique, proper conduct, and employee training are critical to providing favorable sterile compounding outcomes. Relying exclusively on engineering controls without correcting bad practices is like expecting a good car design to fix a bad driver; it could be an accident waiting to happen. ■

Carl J. LaBella, BS, MBA, is president and chief operating officer of CSI Testing, Inc., a cleanroom and controlled environment testing firm based in Plymouth, Minnesota. LaBella is a board member of the Controlled Environment Testing Association, and a member of the American Biological Safety Association, Institute of Environmental Sciences and Technology, International Society of Pharmaceutical Engineering, and American Society of Health-System Pharmacists. He received a BS from the University of Wisconsin, Madison, and an MBA from the University of St. Thomas, in St. Paul, Minnesota.

WHERE TO FIND IT:
SOURCES FOR LAWs, BSCs, CAIs, AND CACIs

Vendor	Reader Service
The Baker Company	2
Comecer	10
Germfree	22
Innovative Technology	30
IsoTech Design	60
NuAire	72

WHERE TO FIND IT:
SOURCES FOR CLEANROOM DESIGN SERVICES

Vendor	Reader Service
Clean Air Technology, Inc.	70
Lasco Services	3
Liberty Industries	11
Modular Cleanrooms	31
Terra Universal	61
Travis Clean Air	73