Tech Talk provides a medium for industry professionals to share ideas about trends, new methods, and cost-saving techniques. Tech Talk articles are not peer-reviewed, but are selected for general interest and timeliness.

Industry Responds to Proposed Changes to USP Sterile Compounding Rules

Journal of the IEST News Report

Revisions would clarify and toughen USP cleanroom requirements for facilities that prepare, store, or transport compounded sterile preparations.

Keywords
Sterile compounding, CSP, USP Chapter 797

The pharmaceutical industry is striving to comply with requirements for safe compounding of sterile preparations set out in the 2004 edition of *United States Pharmacopeia–National Formulary (USP–NF)*. USP Chapter 797, "Pharmaceutical Compounding: Sterile Preparations," which requires compounded sterile preparations (CSPs) to be processed in a cleanroom environment, is the industry's first enforceable standard governing sterile compounding practices.

The standards apply to all facilities that prepare, store, or transport CSPs, including hospitals, treatment clinics, pharmacies, physician practice facilities, and other services. The stated objective of Chapter 797 is to prevent harm and fatality to patients that could result from microbial contamination and excessive bacterial endotoxins.

In May 2006 USP issued and distributed for public comment proposed revisions to USP 797 that would clarify requirements for facility design and environmental control. By the August 15, 2006, deadline for comments, USP had received approximately 2500 pages of comments from more than 300 hospitals, professional associations, vendors, practitioners, and other stakeholders.

As of April 2007, the USP 797 Expert Committee is still reviewing the public comments, many of which center on potential difficulties in meeting the requirements. Due to the volume and critical substance of the comments, USP has not projected when the proposed revisions will be finalized. Some observers have estimated the review may not be completed before late 2007.

Until any revisions are incorporated, the existing edition of Chapter 797 is in effect and facilities are required to comply by January 2008. A seminar and panel discussion, to be presented at ESTECH 2007 by members of the USP 797 committee and *CleanRooms* magazine, will help registrants interpret the new regulations. Panelists will discuss the provisions of the standard and explore the issues affecting industry compliance.

Required environmental controls

The current edition of Chapter 797 requires that CSPs be processed in controlled environments such as laminar airflow workbenches (LAFWs) or biological safety cabinets (BSCs) with air quality of Class 5 or better, as defined by the International Organization for Standardization (ISO) in *ISO 14644-1 Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness*. USP 797 also cites barrier isolators as an "emerging alternative technology" that "may offer an acceptable alternative" as a primary engineering control. Some observers have

objected that the document provides no definition or performance criteria for barrier isolators, and that approval of the new technology may be premature. The proposed revision to Chapter 797 would eliminate references to barrier isolators and accept compounding aseptic isolators (CAIs) in addition to LAFWs and BSCs.

According to the current edition, these isolators, or primary engineering controls, should be placed within an ISO Class 8 buffer zone. The document does not specify conditions for meeting this air quality standard—at rest, as built, or in operation. An anteroom for gowning and hand washing should precede the buffer area.

The revision would change the ISO Class 8 buffer zone requirement to the more stringent ISO Class 7 and would require the use of high-efficiency particulate air (HEPA) filters. The pressure-controlled anteroom preceding the ISO Class 7 zone would be required to meet at least ISO Class 8 conditions. All ISO air quality classes are specified for dynamic (operational) conditions.

Facilities that prepare high-risk CSPs would be required to separate the anteroom and buffer zone by physical means, such as walls, doors, and pass-throughs, with a minimum differential positive pressure of 0.02 to 0.05 inches of water column (in. w.c.). Where low- and medium-risk CSPs are prepared, a displacement airflow concept would be permitted for segregating the anteroom and buffer zone. This system would use a low-pressure differential with a typical air velocity of 40 feet per minute (fpm) or more from the buffer zone across the line of demarcation into the anteroom.

Handling hazardous drugs

A proposed new section of USP 797 stipulates safety precautions and practices to follow when hazardous drugs are ingredients in CSPs. This section would require hazardous drugs to be stored separately from other inventory in a manner to prevent contamination and personnel exposure, such as a negative pressure room with at least 12 air changes per hour (acph). According to the proposal, hazardous drugs should be prepared in an ISO Class 5 BSC or CAI placed in an ISO Class 7 room that is physically separated and has a minimum negative pressure of 0.01 in. w.c. to adjacent rooms. The BSC or CAI should be 100% vented to the outside air through HEPA filtration. An anteroom serving an ISO Class 7 negative pressure hazard containment cleanroom should meet ISO Class 7 conditions. These provisions have raised concern about retrofitting or replacing older facilities designed to comply with earlier standards that did not require ventilation to the outside. An exemption is made for facilities that prepare a very low volume of hazardous drugs and use two tiers of containment.

USP 797 Enforcement

Pharmacy regulatory and accrediting bodies that support implementation of USP Chapter 797 include the following:

- The Food and Drug Administration (FDA) has the authority to enforce USP 797 and is pushing state agencies to adopt sterile compounding standards.
- The National Association of Boards of Pharmacy (NABP) endorses the USP standards for sterile compounding and recommends implementation by states.
- The Joint Commission on Accreditation of Health Care Organizations (JCAHO) references USP compliance as best practice.
- Many state boards of pharmacy have adopted provisions of Chapter 797 for enforcement in pharmacy inspections.

The revised document proposes the following new provisions regarding air supply to the clean zones:

- Airborne contamination control is achieved in the primary engineering control through the use of HEPA filters. The airflow in the primary engineering control is typically unidirectional and because of the particle collection efficiency of the filter, the "first air" at the face of the filter is, for the purposes of aseptic compounding, free from airborne particulate contamination.
- An ISO Class 7 cleanroom supplied with HEPA-filtered air should receive a minimum of 30 acph. The primary engineering control may supplement the air changes but may not be the sole source of HEPA-filtered air.
- In a room with an ISO Class 5 recirculating device, a minimum of 15 acph through the room supply HEPA filters is adequate providing the combined acph from the room supply and recirculating device is not less than 30.

Industry concerns

The pharmaceutical industry has raised concerns about the additional expense of meeting the more rigorous requirements, such as the proposed upgrade from ISO Class 8 to Class 7 buffer zones. In addition, some of the public comments contend that certain proposed design requirements, such as mandated use of HEPA filters, are excessively prescriptive, and that design engineers should have the discretion to select an appropriate means of meeting the ISO Class 7 performance standard.

The USP Expert Committee stated in a "Rationale for Major Changes" the belief that "the cost of building and operating a cleanroom at ISO Class 7, with allowance for internally generated HEPA filtration, should not be significantly greater than that of an ISO Class 8 cleanroom." Experts explain that allowing 15 acph to come from hoods within the room offsets the cost burden of the change from ISO Class 8 to Class 7 because industry guidelines typically recommend 20 acph of fresh air for Class 8 facilities.

USP 797 Timeline for Compliance

January 2004	Chapter 797 published as part of 2004 edition of *United States Pharmacopeia–National Formulary (USP-NF)*.
July 2004	JCAHO began surveying facilities for compliance with Chapter 797.
January 2005	Target date for organizations to have (1) performed a gap analysis to identify areas of non-compliance and (2) written an action plan with specific timeframes and funding approval for achieving compliance.
July 2005	Target date for organizations to implement standard operating procedures (SOPs) for personnel and equipment.
January 2006	Target date for organizations to implement formal quality assurance plan.
May 2006	Proposed revisions to USP Chapter 797 issued for public comment.
August 2006	Closing date for public comment on proposed revisions; 2500 pages of comments received from more than 300 sources.
January 2008	Target date for organizations to have completed all necessary physical site changes and to have sterile compounding in full compliance.
Current status (April 2007)	Public comments under review by the USP Expert Committee.

Hospital administrators are concerned about expending millions of dollars to meet the January 2008 deadline for compliance with an existing standard that may be extensively revised. The USP standards development process opens the general chapters annually to comments and proposed changes for evaluation by Expert Committees.

Sources

1. *United States Pharmacopeia–National Formulary (USP–NF)* Chapter <797>, Pharmaceutical Compounding: Sterile Preparations. (Current edition and proposed revisions).
2. USP (www.usp.org).
3. *CleanRooms* webcast. January 30, 2007. The Plain Truth about USP 797. (http://cr.pennnet.com/webcast/list_webcasts.cfm)
4. *CleanRooms* webcast. October 18, 2006. USP 797—Facts and Fallacies. (http://cr.pennnet.com/webcast/list_webcasts.cfm)
5. American Society for Healthcare Engineering (www.ashe.org).
6. Hurst, M. 2004. An overview of USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. Baxa Corporation (www.baxa.com).
7. *ISO 14644-1 Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness*. Available from IEST (www.iest.org; 847-255-1561).