

## **Q&A on Proposed USP Chapter 797 Revisions with E. Clyde Buchanan**

E. Clyde Buchanan, MS, FASHP recently retired as Senior Director of Pharmaceutical Services for Emory Healthcare. He is Visiting Clinical Professor at the Mercer University, Southern School of Pharmacy and is an advisor to the Auburn University Facilities Design Research Program. Mr. Buchanan received his B.S. Pharmacy from the University of North Carolina and M.S. and residency training from The Ohio State University.

Mr. Buchanan has edited three books on compounded sterile preparations and numerous manuscripts and book chapters. He has been a frequent speaker for state and national conferences on United States Pharmacopeia (USP) Chapter 797. Most recently, Mr. Buchanan served as co-editor and contributing author for ASHP's *Compounding Sterile Preparations, second edition*, and the web-based *ASHP Self-Assessment Tool for Compounding Sterile Preparations*.

***All opinions expressed in the following interview are those of Mr. Buchanan. When evaluating specific recommendations regarding compounding practices, practitioners are strongly encouraged to rely on a wide array of sources, including state and local authorities, accrediting bodies such as the Joint Commission, and organizations such as the USP, as well as experts such as Mr. Buchanan.***

In May 2006, the USP published extensive proposed revisions to the original Chapter 797 that had become official in January 2004. Mr. Buchanan has fielded many questions about the proposed revisions to Chapter 797 and now replies to the most frequently asked of those questions here. Questions are grouped under section headings that appear in all capital letters.

### **USP REVISION PROCESS**

#### **How does USP revise chapters?**

All proposals for chapter revisions are published in the *Pharmacopeial Forum (PF)* for public review and comment. A period of at least 90 days from the date of publication in *PF* is allowed for public review and comment. USP's Scientific Liaison compiles the comments received for the appropriate Expert Committee (i.e., the Sterile Compounding Committee) to review the comments and accept or reject them, alter the text as deemed appropriate, and determine whether to proceed with the proposal. If the determination is made to proceed, the proposal must be approved by formal vote of the Expert Committee prior to publication in the USP/NF.

([www.usp.org/governance/policies/rulesAndProcedures/section09.html](http://www.usp.org/governance/policies/rulesAndProcedures/section09.html)) (accessed 12/09/06)

#### **Are USP chapters scientifically based?**

USP is an independent, science-based public health organization. In addition to scientific studies, USP expert committees use professional standards from relevant professional organizations and the input of experts in pertinent fields to develop USP proposed chapters. [www.usp.org/aboutUSP/](http://www.usp.org/aboutUSP/) (accessed 12/09/06) and Kastango E. Putting the science back into the "art and science" of compounding. *Int. J. Pharm. Comp.* 2006 (Jul/Aug); 10:263-8.

### **When will the final revision of Chapter 797 come out?**

No revision is final because USP chapters are under continual review. However, I believe that the next official version of USP Chapter 797 is likely to be published in mid-to-late 2007. Updates on the revision process can be found at: <http://www.usp.org/USPNF/pf/generalChapter797.html>.

## **DEFINITIONS OF CHAPTER TERMINOLOGY**

### **What is the difference between a primary engineering control and a secondary engineering control?**

The primary engineering control is the ISO Class 5 environment provided by a laminar airflow workbench (LAFW, a.k.a. “horizontal laminar flow hood”), a biological safety cabinet (BSC), or a compounding aseptic isolator (CAI, a.k.a. “barrier isolator” or “glove box”). (“ISO” is an abbreviation for the International Organization for Standardization, whose website is <http://www.iso.org/iso/en/ISOOnline.frontpage>.) A secondary engineering control is a controlled air environment like a buffer room (cleanroom) or anteroom. The buffer room enhances the ability of a primary engineering control to maintain its ISO Class 5 environment within the buffer room.

### **What is the difference between a sterile product and a sterile preparation?**

A sterile product is a commercially manufactured sterile drug or nutrient that has been approved by the Food and Drug Administration. A sterile preparation (a.k.a. “compounded sterile preparation,” abbreviated “CSP”) is a sterile drug or nutrient compounded in a licensed pharmacy or other healthcare-related facility pursuant to the order of a licensed prescriber.

### **What is the difference between an expiration date and a beyond-use date?**

An expiration date reflects the shelf-life of a commercially manufactured product when stored according to FDA-approved labeling, in its original container. The beyond-use date is the date or time after which a CSP must not be stored. The beyond-use date is determined from the date or time the preparation is compounded.

### **What is the difference between a cleanroom and a buffer room?**

A buffer room is an ISO Class 7 area where the primary engineering control is physically located. For proposed USP Chapter 797, a cleanroom is the same as the buffer room.

### **What is the difference between a glove box and an isolator?**

The most current term for this primary engineering control is “compounding aseptic isolator” (CAI) or “compounding aseptic containment isolator” (CACI), which is a form of barrier isolator specifically designed for compounding pharmaceutical ingredients or preparations. Strictly speaking, a barrier isolator or a glove box may not provide an aseptic compounding environment; it may just separate the operator from a toxic substance.

## RESPONSIBILITY OF COMPOUNDING PERSONNEL

### **Are first doses of a new order exempted from USP 797 standards?**

Not unless they meet the criteria of CSPs for immediate use or are proprietary bag and vial systems (please see **Immediate Use CSPs** below).

### **Can nurses prepare first doses without fully garbing?**

Not unless the doses they prepare meet the criteria of CSPs for immediate use or are proprietary bag and vial systems (please see **Immediate Use CSPs** below).

### **Do proposed USP Chapter 797 standards require compounding external use extemporaneous preparations such as LAT (lidocaine-adrenoline-tetracaine) from nonsterile ingredients to be in a LAFW and cleanroom?**

No. Nonsterile preparations would be covered by USP Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations and Chapter <1075> Good Compounding Practice. USP Chapter 797 covers only sterile dosage forms, including the following preparations that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions, emulsions, solutions, and suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.

### **Allergists state that they adhere to practice parameters for the expiration dates for allergen dilutions and that nothing can grow in the allergy extract because of the high phenol content. What is your recommendation for the preparation of allergens given the above facts?**

Technically, the preparation of allergenic extracts and dilutions is covered by the standards set in USP Chapter 797. It is good compounding practice to assure that these products meet their purported characteristics of sterility, purity, accuracy of strengths, and non-pyrogenicity. I would recommend purchasing allergenic extracts from FDA-approved manufacturers or, if such extracts are not available, having a pharmacy compound the extracts according to USP Chapter 797 standards.

## COMPOUNDED STERILE PREPARATION MICROBIAL RISK LEVELS

### **Is a hazardous drug or a radiopharmaceutical a high-risk preparation?**

Risk levels refer to microbial risk levels, not the hazardous or radioactive nature of a CSP. Generally, microbial contamination risk levels are defined similarly for hazardous drugs as they are for other CSPs. However, a hazardous drug should not be handled as a CSP for immediate use; it must be prepared under the applicable USP 797 conditions. Radiopharmaceuticals for positron emission tomography must be prepared according to USP Chapter 823. For other types of radiopharmaceuticals, please see details in proposed Chapter 797 section on Radiopharmaceuticals as CSPs.

### **What is the storage period of a CSP?**

This is the time period after which the preparation is finished and administration of the dose begins. Pre-administration duration and temperature limits are specified for low-, medium- and high-risk CSPs in the absence of direct sterility testing that would justify different limits for specific CSPs. USP Chapter 797 does not intend to set standards for the time or duration of administration of a CSP.

### **What risk level is a CSP that contains preservatives?**

Proposed USP Chapter 797 has little to say about CSPs that incorporate preservatives, even though the chapter does give guidance about how multi-dose containers of commercially manufactured products may be used in compounding CSPs. Simply using a preserved diluent in a CSP may not prevent compounding risks like inaccurate measurements of additives, chemical or physical incompatibilities or even microbial contamination. Therefore, sterile compounding personnel should use USP Chapter 797 standards in compounding CSPs with preservatives.

### **IMMEDIATE-USE CSPs**

### **Is it necessary to go through the entire cleansing/gowning routine to prepare an emergency infusion like levarterenol?**

If the compounding process meets all six criteria below for the immediate use exemption, full cleansing/gowning would not be required. It is prudent to do immediate use compounding in an area that is kept clean and orderly, like a nursing station medication room or a pharmacy satellite.

1. Only simple aseptic measuring and transfer manipulations are performed with not more than three (3) sterile nonhazardous commercial drug and diagnostic radiopharmaceutical drug products, including an infusion or diluent solution.
2. Unless required for the preparation, the preparation procedure occurs continuously without delays or interruptions and does not exceed 1 hour.
3. At no point during preparation and prior to administration are critical surfaces and ingredients of the CSP directly exposed to contact contamination such as human touch, cosmetic flakes or particulates, blood, human body substances such as excretions and secretions (e.g., nasal and oral), and nonsterile inanimate sources.
4. Administration begins not later than one (1) hour following the start of preparing the CSP.
5. When the CSP is not administered by the person who prepared it, or its administration is not witnessed by the person who prepared it, the CSP shall bear a label listing patient identification information such as name and identification number(s), the names and amounts of all ingredients, the name or initials of the person who prepared the CSP, and the exact 1-hour beyond-use time and date.
6. If administration has not begun within one (1) hour following the start of preparing the CSP, the CSP is promptly and safely discarded. Immediate use CSPs must not be stored for later use.

Note that the American Society for Microbiology is concerned that personnel preparing immediate use CSPs are not subject to a reasonable requirement for personal protective equipment use. At a minimum, personnel preparing immediate use CSPs should be required to wear sterile gloves. In addition, all personnel involved in CSP preparation should not be permitted to eat, drink, apply cosmetics, or smoke in the area in which the compounding occurs ([www.asm.org/Policy/index.asp?bid=44533](http://www.asm.org/Policy/index.asp?bid=44533)) (Accessed 12/11/06). Joint Commission Medication Management standard 4.20 Element of Performance 6 says:

Wherever medications are prepared, staff follow techniques to avoid contamination during medication preparation, which include but are not limited to the following: Using clean or sterile technique; maintaining clean, uncluttered, and functionally separate areas for product preparation to minimize the possibility of contamination; using a laminar airflow hood or other class 100 environment while preparing any intravenous (IV) admixture in the pharmacy, any sterile product made from non-sterile ingredients, or any sterile product that will not be used within 24 hours; and visually inspecting the integrity of the medications.

**Regarding preparing medications on a nursing unit, must administration begin within 1 hour of preparation and then administration be no longer than 12 hours?**

Although interim communications from USP mentioned an administration period no longer than 12 hours, proposed Chapter 797 does not. This is because USP 797 is not intended to govern drug administration, only sterile drug preparation and storage before medication administration begins.

**SINGLE-DOSE AND MULTIPLE-DOSE CONTAINERS**

**Can a single-dose container be used for more than one dose if it is used in an ISO Class 5 environment?**

Opened or needle-punctured single-dose containers such as ampuls, bags, bottles, syringes, and vials of sterile products and CSPs must be used within 1 hour if opened in worse than ISO Class 5 air quality, and any remaining contents must be discarded. Single-dose vials exposed to ISO Class 5 or cleaner air may be used up to 6 hours after initial needle puncture, unless package labeling provides other information. However, opened single-dose ampuls are not to be stored for any time period.

**What is the expiration date we should use on commercial multidose vials?**

USP Chapter 51 - Antimicrobial Effectiveness Testing requires that commercial sterile multidose product manufacturers do **no** sterility and stability testing beyond 28 days after the vial has been punctured with a needle. USP chapters, like Chapter 797, must agree with other USP chapters. Manufacturers do have the option of testing their products' sterility and stability beyond 28 days. If their FDA-approved labeling specifies a beyond-use date longer than 28 days, you may adhere to the manufacturer's labeling and use the longer date, provided the labeled storage conditions (e.g., temperature) are maintained. Adhering to the 28 day beyond-use date means that some expensive multidose drugs, like insulin, may have to be wasted.

**If we store a multidose vial (e.g., insulin) in a refrigerator, can it be used for longer than 28 days?**

While the drug may be stable chemically and physically longer than 28 days, the manufacturer does not guarantee that the product's preservative system will maintain sterility longer than 28 days – unless explicitly stated in the product's FDA-approved labeling.

**HAZARDOUS DRUGS AS CSPs**

**Are many medications, other than chemotherapy, considered hazardous (e.g., oxytocin)?**

There are many drugs considered hazardous besides antineoplastics, including several hormones like oxytocin, and some antivirals. For a good list of hazardous drugs see the sample list of drugs at the end of the National Institute for Occupational Safety and Health (NIOSH) Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings ([www.cdc.gov/niosh/docs/2004-165/](http://www.cdc.gov/niosh/docs/2004-165/)). Each health care organization should identify its own list of hazardous drugs.

**Is storing chemotherapy on a separate shelving unit sufficient to prevent mix-ups?**

While storing hazardous drugs like antineoplastics on separate shelving may reduce medication picking errors, it would do little to reduce hazardous drug contamination to the environment and personnel who handle stored products. Proposed Chapter 797 prefers a separate storage area such as a negative pressure room that has sufficient general exhaust ventilation (i.e., at least 12 air changes per hour) to dilute and remove airborne contamination. Additionally, hazardous drugs must be handled with caution, with handlers using chemotherapy gloves during distribution, receiving, stocking, inventorying, preparation and disposal of these drugs.

**With a CAI, is the surrounding area required to be ISO Class 7?**

Proposed Chapter 797 specifies that isolators be placed in a buffer room (ISO Class 7) unless the isolator manufacturer documents that the isolator provides isolation from the room and maintains ISO Class 5 air quality during dynamic operation – including transferring ingredients, components, and devices into and out of the isolator during preparation of CSPs.

**If we use a closed-system vial-transfer device (CSTD) (e.g., PhaSeal), must we have a BSC or a CAI?**

When a CSTD is used, this must be within the BSC or CAI to provide backup containment and an ISO Class 5 environment.

**If we use a CSTD in a CAI must we place the CAI in a cleanroom?**

The ISO Class 5 CAI must be placed in an ISO Class 7 room that is physically separated (i.e., a different room) from other preparation areas, and optimally has no less than 0.01-inch water column negative pressure to the adjacent positive pressure ISO Class 7 anteroom, thus providing inward airflow to the buffer room to contain any airborne drug.

As proposed in USP 797, in facilities that prepare a very low volume of hazardous drugs (e.g., less than 5 preparations/week), the use of two tiers of containment (i.e., a CSTD within a CAI) that is located in a non-negative pressure room is acceptable. In addition, containment of the finished hazardous product must be maintained throughout the administration/disposal phase utilizing needleless or closed administration systems.

**Can we continue to use our BSC for compounding chemotherapy if we do not vent it 100% to the outside?**

Both NIOSH and proposed USP Chapter 797 strongly recommend 100% venting to the outside air through high-efficiency particulate air (HEPA) filtration ([www.cdc.gov/niosh/docs/2004-165/](http://www.cdc.gov/niosh/docs/2004-165/)). It is now recognized that several hazardous drugs can vaporize and are therefore not retained by HEPA filters inside the BSC or CAI. There does not appear to be a “grandfathering” clause for older facilities.

**Which hazardous drugs vaporize?**

German authors Kiffmeyer et al. (Vapor pressures, evaporation behavior and airborne concentrations of hazardous drugs: implications for occupational safety. *The Pharmaceutical Journal*, 2002 (Mar 9), 268:331-7) found that all five hazardous drugs tested (carmustine, cisplatin, cyclophosphamide, etoposide, and fluorouracil) may evaporate from solid to gaseous forms under normal working conditions. It is likely that many more hazardous drugs evaporate directly from the solid to the gaseous state.

**What is the best way to remove hazardous drugs from the outside of a vial? Is this done at the time of reconstitution (i.e., inside the BSC or CAI)? Could cleaning be done by the receiving technician?**

My recommendation is to use sterile water and a clean swab to scrub the outside of hazardous drug vials. Of course, personnel cleaning the outside of a vial of hazardous drugs would need to wear full personal protective equipment as defined in proposed USP Chapter 797. My recommendation is scrub the vials just before they are placed into the BSC or CAI, although pharmacy personnel could scrub the vials at the time they are received into pharmacy storage.

**How do we perform surface wipe sampling for hazardous drug contamination?**

The monitoring method for surface contamination is described by Larson et al. (*Am. J. Health-Syst Pharm.* 2002; 59:270-7). The method requires a sophisticated analytical method called reverse-phase high-performance liquid chromatography. Proposed Chapter 797 states, “Because standards of assay and unacceptable quantities of contamination of each [hazardous] drug have not been established in the literature, the following paragraph (surface wipe sampling for hazardous drug contamination) is a recommendation only. Future standards will be adopted as these assay methods are developed and proven.”

**PERSONNEL TRAINING AND EVALUATION IN ASEPTIC MANIPULATION SKILLS**

**Regarding media fills, is an incubator required for completed media fills?**

Yes. According to proposed USP Chapter 797, media-filled vials are generally incubated within a range of 20 to 35 degrees C. for 14 days. The American Society for

Microbiology says that an incubation temperature range of 32 degrees C +/- 2 degrees C covers the broadest range of potential contaminants and pathogens ([www.asm.org/Policy/index.asp=bid?38804](http://www.asm.org/Policy/index.asp=bid?38804)). (Accessed 12/11/06).

## ENVIRONMENTAL QUALITY AND CONTROL

### **Air particulates in our cleanroom have been measured and are fewer than 10,000 particles per cubic foot; are we required to HEPA-filter the air coming into the cleanroom?**

Yes. A cleanroom is defined as a compounding environment that is supplied with HEPA-filtered air, that meets ISO Class 7 (formerly Class 10,000). Additionally, the room should be segregated from surrounding, unclassified spaces to reduce the risk of contaminants being blown, dragged, or otherwise introduced into the filtered unidirectional airflow environment, and this segregation should be continuously monitored. For rooms providing a physical separation, through the use of walls, doors, and pass-throughs, a minimum differential positive pressure of 0.02 to 0.05 inches water column is required. For cleanrooms or buffer zones not physically separated from the anteroom, the principle of displacement airflow should be employed. This concept utilizes a low-pressure differential, high-airflow principle. Using displacement airflow typically requires an air velocity of 40 feet per minute (fpm) or more from the buffer zone across the line of demarcation into the ante-area. Other specifications for cleanrooms include temperature and humidity control and other indicators of quality (“CETA Certification Guide for Sterile Compounding Facilities CAG-003-2006” at [www.cetainternational.org/](http://www.cetainternational.org/)).

### **If we perform only low-risk sterile compounding, is a separate ante room required? Can the ante room be separate from the rest of the pharmacy?**

For low- and medium-risk sterile compounding, the ante area can be separated from the buffer zone by a simple line of demarcation (i.e., not a separate room). This is often referred to as an “open” cleanroom design and is permitted by both the USP and ISO. The ante area must physically be separate from the rest of the pharmacy. In other words, the “rest of the pharmacy” cannot serve as the ante room. See Proposed USP Chapter 797 definition of an ante room as to purposes of the ante room and its ISO Class 8 environment.

### **What specifications should I use in planning the construction of a buffer room?**

Required specifications are ISO documents 14644-1 “Cleanrooms and associated controlled environments Part 1: Classification of air cleanliness” and 14644-4 “Part 4: Design, construction and start-up”. Another good reference is the Controlled Environment Testing Association document, “CETA Certification Guide for Sterile Compounding Facilities CAG-003-2006” at [www.cetainternational.org/](http://www.cetainternational.org/).

### **Can a horizontal hood and a vertical hood be located in the same cleanroom?**

A horizontal hood (the preferred term is “laminar airflow workbench,” abbreviated “LAFW”) can be located in the same positive pressure cleanroom with a vertical hood (preferred term “biological safety cabinet”, abbreviated “BSC”) if both primary

engineering controls are used to compound non-hazardous CSPs. Hazardous drugs must be compounded in a separate negative pressure cleanroom as described above. It is virtually impossible to have both controlled positive pressure and negative pressure air supplied to the same cleanroom.

**Can we perform hazardous and non-hazardous drug compounding in the same cleanroom?**

No. The reason is explained in the question above. Putting a negative pressure compounding isolator for compounding hazardous drugs in a positive pressure room is not likely to work because any hazardous drug that escapes the CAI would be pushed out into surrounding rooms by positive pressure.

**If we have separate cleanrooms for hazardous and non-hazardous compounding, how do we pressurize the anteroom?**

There are two possibilities. Have one ISO Class 7 positive pressure anteroom for the negative pressure cleanroom in which hazardous drugs are compounded and a separate ISO Class 8 anteroom for the cleanroom in which non-hazardous drugs are compounded. Alternatively, you could have one ISO Class 7 anteroom that is positive pressure to the negative pressure cleanroom for hazardous compounding and that is lower pressure than the positive pressure cleanroom for non-hazardous drug compounding.

**What "furniture" is allowed in the buffer room and how much storage is allowed in this space?**

Regarding the cleanroom (i.e., buffer room), the proposed USP 797 specifies, "Only the furniture, equipment, supplies, and other material required for the compounding activities to be performed should be brought into the room. They should be nonpermeable, nonshedding, cleanable, and resistant to disinfectants. Whenever such items are brought into the room, they should first be cleaned and disinfected." Further, "Activities that occur in this area include the preparation and staging of components and supplies used when compounding CSPs." In other words, storage space in the buffer room is limited to working components and supplies needed for active compounding. No long-term storage would be allowed.

**If I own a CAI, should this device be placed within a cleanroom?**

Proposed Chapter 797 specifies that isolators be placed in an ISO Class 7 buffer room unless the isolator manufacturer documents that the isolator provides isolation from the room and maintains ISO Class 5 during dynamic operation – including transferring ingredients, components, and devices into and out of the isolator during preparation of CSPs.

**Currently there do not appear to be uniform testing standards for compounding isolators. How is the consumer supposed to select one isolator from the other without relying totally upon manufacturers' own promotional literature and statements?**

The Controlled Environment Testing Association recently published guidelines for testing sterile compounding isolators (see [www.cetainternational.org/CETACompoundingIsolatorTestingGuide2006.pdf](http://www.cetainternational.org/CETACompoundingIsolatorTestingGuide2006.pdf).)

Note that CETA is a private organization, not recognized by government agencies. Perhaps the group purchasing organization to which your institution belongs has researched compounding isolators and selected a vendor.

#### **CLEANING AND DISINFECTING THE STERILE COMPOUNDING AREAS**

**Proposed Chapter 797 mentions only isopropyl alcohol as a disinfectant. How do we find the best cleaning agent for floors, walls, and ceilings?**

The best option would be to work with your Environmental Services Department to select disinfectant(s) that suit proposed Chapter 797 cleaning schedules and EPA requirements. In its “Guidance for Industry Sterile Drug Products Produced by Aseptic Processing” (<http://www.fda.gov/cber/gdlns/steraseptic.pdf>), the FDA says:

To prevent introduction of contamination, disinfectants should be sterile, appropriately handled in suitable (e.g., sterile) containers and used for no longer than the predefined period specified by written procedures. Routinely used disinfectants should be effective against the normal microbial vegetative flora recovered from the facility. Many common disinfectants are ineffective against spores. For example, 70 percent isopropyl alcohol is ineffective against *Bacillus* spp. spores. Therefore, a sound disinfectant program also includes a sporocidal agent, used according to a written schedule and when environmental data suggest the presence of spore-forming organisms.

Disinfection procedures should be described in sufficient detail (e.g., preparation, work sequence, contact time) to enable reproducibility. Once the procedures are established, their adequacy should be evaluated using a routine environmental monitoring program. If indicated, microorganisms associated with adverse trends can be investigated as to their sensitivity to the disinfectants employed in the cleanroom in which the organisms were isolated.

**Do cleaning agents and disinfectants have to be rotated?**

Proposed Chapter 797 is silent on the need to rotate cleaning agents and disinfectants. There is some controversy as to whether rotating disinfectants is rational. The Centers for Disease Control and Prevention (CDC) does not mention rotating disinfectants in its “Guidelines for Environmental Infection Control in Health-Care Facilities” ([www.cdc.gov/ncidod/dhqp/pdf/guidelines/Enviro\\_guide\\_03.pdf](http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/Enviro_guide_03.pdf)). Your environmental monitoring program should tell you whether your cleaning and disinfecting agents are working appropriately.

## PERSONNEL CLEANSING AND GARBING

### **Does proposed USP Chapter 797 affect gowning requirements for cleanrooms?**

Yes, the proposal is that personnel must don garb in the following order: dedicated shoes or shoe covers, head and facial hair covers and face masks. Eye shields are optional unless working with irritants like germicidal disinfecting agents. After this garb, personnel clean their nails and wash their hands and arms as described in the chapter, then dry hands with lint-free disposable towels or an electric hand dryer. After hands are dry, personnel don a non-shedding gown. Once inside the buffer room, prior to donning sterile, powder-free gloves, personnel clean hands with an alcohol-based surgical hand scrub per manufacturer's recommendations. Personnel allow hands to dry thoroughly before donning the sterile gloves.

### **Does active psoriasis preclude a pharmacist or technician from compounding sterile preparations, even if the psoriatic lesions are covered?**

In general I would say that having active psoriasis would preclude a person from compounding sterile preparations. However, depending on the location of psoriatic lesion, I think you could use professional judgment to determine whether a person could sufficiently cover a psoriatic lesion. For example, if the lesion were confined to the trunk of the body, it might successfully be covered by clothing and cleanroom garb.

### **Since a face mask is not required to work in a BSC when the shield is six or more inches below the operator's mouth, is a face mask required when the operator is working in a CAI?**

Proposed Chapter 797 says that when CAIs are the source of the ISO Class 5 environment, the garbing and gloving requirements for compounding personnel should include shoe covers, head and facial hair covers, face mask, non-shedding disposable gown and gloves - unless the isolator manufacturer can provide written documentation based on validated environmental testing that any component(s) of personal protective equipment or personnel cleansing are not required.

### **Do proposed USP Chapter 797 standards require sterile gloves?**

Yes. Certainly, gloves do become contaminated when they contact nonsterile surfaces during compounding activities. Disinfection of contaminated gloves may be accomplished by applying 70% isopropyl alcohol to all contact surface areas of the gloves and letting the gloves dry thoroughly. I recommend using only gloves that have been tested for compatibility with alcohol disinfection by the manufacturer. Routine application of 70% isopropyl alcohol to gloved hands should occur throughout the compounding day and whenever nonsterile surfaces (e.g., vials, counter tops, chairs, and carts) are touched.

### **Are sterile gloves needed in a CAI?**

It is understood that the gloves used in an isolator may not be sterile at the start of a compounding process but these gloves must be disinfected by applying 70% isopropyl alcohol to all contact surfaces of the gloves and letting the gloves dry thoroughly. Like

gloves in other primary engineering controls, the isolator gloves that separate the outside from the inside of the isolator should be cleansed frequently with isopropyl alcohol. Isolator gloves may need to be changed more often during the compounding of hazardous drugs as compared to non-hazardous drug compounding.

## ENVIRONMENTAL MONITORING

### **What is the difference between air particulate monitoring and air microbial monitoring?**

Monitoring the particulate matter above a certain size in a certain volume of air is the internationally accepted method of determining the cleanliness of a work area. For example, ISO Class 5 quality air has fewer than 3520 particles 0.5 microns and larger per cubic meter of air. The particulate quality of ISO classified areas must be certified every six months. Not all particles in the air carry microbes like bacteria, fungi, mold and viruses. In order to determine the number of viable microbes in the air, microbial air sampling must be done every month for low- and medium-risk compounding operations and every week for high-risk compounding operations.

### **Are settling plates still acceptable for microbial air sampling?**

No. Samples collected by gravity on settling plates are not suitable substitutes for volumetric air samples and should not be used to determine the relative air concentrations of different microorganisms because of the method's collection bias. The settling of particles by gravity onto culture plates is highly dependent on the particle size and is strongly influenced by air movement. Given the unpredictable and uncontrollable nature of ambient particle movement, pharmacists or technicians cannot directly relate the number of colony-forming units (cfu) on a settling plate to the concentrations of the corresponding particles in the sampled air environment.

### **Regarding environmental monitoring, if the facility buys the air sampling device, who operates the device?**

I recommend that a certified air particulate quality testing company do the semiannual testing for ISO Class 5, 7, and 8 environments, using their own instruments. But I recommend pharmacy buy the microbial air sampling device and that one or two pharmacy personnel learn to use the device because air microbial sampling has to be done at least monthly, depending on the risk level of sterile compounding. Proposed USP Chapter 797 recommends an impaction type of microbial air sampling device.

### **How do you find someone who is qualified to certify buffer rooms and ante rooms?**

My first recommendation is to ask the company that certifies your laminar airflow work benches (hoods, LAFWs) and BSCs if they are qualified to certify your buffer room and ante room to ISO Class 7 and 8 respectively. If they are not, you might find someone in your area by visiting the web sites for the International Air Filtration Certifiers Association ([www.iafca.com](http://www.iafca.com)) or the National Environmental Balancing Bureau ([www.nebb.org](http://www.nebb.org)) or the Controlled Environment Testing Association .

## VERIFICATION OF AUTOMATED COMPOUNDING DEVICES

### **What is the difference between accuracy and precision?**

Accuracy in verification of automated compounding devices (ACDs) means that the correct quantity of each ingredient is delivered to the final infusion container. The precision of an ACD is based on the day-to-day variations in performance of the accuracy measures, such as weights and volumes.

## FINISHED PREPARATION RELEASE CHECKS AND TESTS

### **Do we have to perform sterility tests on all high-risk preparations?**

No. Just high-risk level CSPs that are prepared in groups of more than 25 identical individual single-dose packages (such as ampuls, bags, syringes, vials), or in multiple-dose vials for administration to multiple patients, or exposed longer than 12 hours at 2 to 8 degrees C and longer than 6 hours at warmer than 8 degrees C before they are sterilized must be tested to ensure that they are sterile before they are dispensed or administered.

### **Do we have to perform pyrogen testing for all high-risk compounding?**

No. All high-risk level CSPs, except those for inhalation and ophthalmic administration, that are prepared in groups of more than 25 identical individual single-dose packages (such as ampuls, bags, syringes, vials), or in multiple-dose vials for administration to multiple patients, or exposed longer than 12 hours at 2 to 8 degrees C and longer than 6 hours at warmer than 8 degrees C before they are sterilized must be tested to ensure that they do not contain excessive bacterial endotoxins (see USP Chapters on *Bacterial Endotoxins Test 85* and *Pyrogen Test 151*).

## STORAGE AND BEYOND-USE DATING

### **Are proprietary vial and bag systems (e.g., Add-Vantage) required to be “activated” in a Class 5 hood? Or just in the cleanroom?**

Attachment of the vial to the bag does not have to be done in an ISO Class 5 environment or in a cleanroom. Sterility and stability beyond-use times for attached and activated (activated is defined as allowing contact of the previously separate diluent and drug contents) container pairs of drug products are as indicated by the manufacturers’ package labeling. In other words, users of proprietary vial and bag systems (e.g., Add-Vantage, Mini-Bag Plus, Add-A-Vial, and Add-Ease) should follow the manufacturers’ labeling rather than the compounding standards in USP Chapter 797.

### **What is the difference between stability and sterility of a CSP?**

Stability refers to chemical and physical characteristics of a CSP (e.g., lack of pH change, chemical degradation, precipitate formation, color change, etc.). Sterility refers to the CSP remaining free of viable microorganisms. Compounding personnel must consider stability and sterility separately when determining the beyond-use date of a CSP and use the shorter of the storage times that provide for both a stable and a sterile preparation.

**Can manufacturers' data on stability of reconstituted vials be used as a reference for beyond-use dating longer than that specified by USP Chapter 797 if it is not referenced in the package labeling?**

Manufacturer's data can be used but it is safest to do so only when it is included in the FDA-approved package labeling for stability of a CSP. Sterility beyond-use dating must not exceed that specified in USP Chapter 797 unless end product sterility testing justifies a longer storage time of a specific CSP.

**How do we determine whether an IV admixture that is within its beyond-use date can be redispensed?**

The pharmacy or other compounding facility must have the sole authority to determine when unopened, returned CSPs may be redispensed. Returned CSPs may be redispensed only when personnel responsible for sterile compounding can ensure that such CSPs are sterile, pure, and stable (contain labeled strength of ingredients). The following may provide such assurance: the CSP was maintained under continuous refrigeration and protected from light, if required; and no evidence of tampering or any readying for use outside the pharmacy exists. Assignment of new storage times and beyond-use dates that exceed the original dates for returned CSPs is permitted only when there is supporting evidence from sterility testing and quantitative assay of ingredients. Thus, initial preparation and thaw times should be documented and reliable measures should have been taken to prevent and detect tampering. Compliance with all procedures associated with maintaining product quality is essential. The CSP must not be redispensed if there is not adequate assurance that product quality and packaging integrity (including the connections of devices, where applicable) were continuously maintained between the time the CSP left and the time that it was returned.

**Does the beyond-use date for a multidose vial like insulin change depending on whether the opened vial is stored at refrigerator or room temperature?**

Storage temperature is specified by manufacturer's labeling after a multidose vial is punctured with a needle. Unless the manufacturer's labeling specifies a longer or shorter beyond-use date, the beyond-use date remains 28 days, as long as the manufacturer's storage requirements are met.

**Are we required to maintain temperature logs in the cleanroom?**

Yes, in the cleanroom and wherever sterile drug products and preparations are stored. To ensure that product potency is retained through the manufacturer's labeled expiration date, pharmacists must monitor the drug storage areas within the pharmacy. Any controlled temperature area should be monitored at least once daily and the results documented on a temperature log. Pharmacy personnel should note the storage temperature when placing the product into or removing the product from the storage unit in order to monitor any temperature aberrations. Suitable temperature recording devices may include a calibrated continuous recording device or a National Bureau of Standards calibrated thermometer that has adequate accuracy and sensitivity for the intended purpose and should be properly calibrated at suitable intervals. If the pharmacy uses a continuous temperature recording device, pharmacy personnel should verify at least once daily that the recording device itself is functioning properly. The temperature sensing

mechanisms should be suitably placed in the controlled temperature storage space to reflect accurately its true temperature. The Controlled Environment Testing Association (CETA) recommends that, for worker comfort, cleanrooms be kept between 66 and 70 degrees F (18.9-21.1 degrees C). (“CETA Certification Guide for Sterile Compounding Facilities CAG-003-2006” at [www.cetainternational.org/](http://www.cetainternational.org/) ).

**Are we required to monitor humidity in the cleanroom?**

I would recommend monitoring relative humidity for worker comfort. CETA recommends 35-60% relative humidity (“CETA Certification Guide for Sterile Compounding Facilities CAG-003-2006” at [www.cetainternational.org/](http://www.cetainternational.org/) ). Humidity that is too low may enhance static electricity mobilizing more particles into the air. High humidity makes temperatures feel hotter and may engender the growth of molds, mildew and fungi.

**THE OUALITY ASSURANCE PROGRAM**

**Where can we find sterile compounding policies and procedures?**

The *International Journal of Pharmaceutical Compounding* has numerous policies and procedures related to sterile compounding (<http://compoundingtoday.com/SOP/>). Also, many manufacturers of equipment and supplies offer standard procedures on how to use their products.