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## An Update on USP Chapter <797> The New National Standard for Sterile Preparation

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The 2004 issue of the *United States Pharmacopeia—National Formulary (USP-NF)* contained the first enforceable USP chapter on the topic of compounded sterile preparations (CSPs) entitled “USP Tests and Assays Chapter <797>, *Pharmaceutical Compounding, Sterile Preparations*” (herein referred to as USP Chapter <797>).<sup>1</sup> The chapter—which applies to pharmacies, health care institutions, physician practices, and any other site or type of health care facility that prepares or compounds sterile preparations—outlined new requirements for the compounding, preparation, and labeling of sterile preparations. Unlike previous USP chapters on this subject and voluntary documents such as the ASHP guidelines on quality-assurance for pharmacy-prepared sterile products<sup>2</sup>, USP Chapter <797> is considered to be an official minimum standard for pharmacy sterile compounding, and it is therefore enforceable by the Food and Drug Administration (FDA), state boards of pharmacy, boards of health, and other regulatory agencies. Shortly after publication of the chapter, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) announced its intent to begin surveying health care facilities for compliance with this chapter on July 1, 2004.<sup>3</sup> Some state boards of pharmacy have also announced plans to revise their current regulations based on this chapter.

Given the high interest in the topic and pharmacists’ need for assistance in interpreting and applying the requirements of this chapter, an educational program entitled “Improving Quality Assurance in the Compounding of Sterile Preparations: An Update on USP Chapter <797>” was conducted during the 39th ASHP Midyear Clinical Meeting. This program was held on December 7, 2004, at the Orange County Convention Center in Orlando, Florida. It was supported by an educational grant from Hospira, Inc. The program was presented by Mr. Lawrence Trissel, FASHP, Director of Clinical Pharmaceuticals Research at the University of Texas M.D. Anderson Cancer Center. Mr. Trissel is one of the most widely recognized experts in the pharmacy community on the topic of sterile compounding and injectable drugs. He is the author of the *Handbook on Injectable Drugs*, a core reference currently in its thirteenth edition. This key publication is found in nearly every hospital and home care pharmacy in the United States and multiple foreign countries. Mr. Trissel currently serves as a member of the Sterile Compounding Committee of

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the Council of Experts of the United States Pharmacopeial Convention, Inc., the USP committee that drafted USP Chapter <797>. In addition, he was a member of the expert panel that drafted the original ASHP guidelines on quality assurance for pharmacy-prepared sterile products.<sup>4</sup>

### Background

Compounding is an integral part of pharmacy practice. However, incidences of patient morbidity and mortality associated with improperly prepared or contaminated pharmacy-prepared sterile preparations have prompted FDA to consider regulating or even banning pharmacy compounding. Until recently, the pharmacy community has been successful in convincing FDA to allow it to self-regulate pharmacy compounding. Attempts at self-regulation, however, have failed to *completely* eliminate the threat to patient safety caused by inadequate and inconsistent procedures in pharmacy compounding.

In the 1970s, the National Coordinating Committee on Large Volume Parenterals (NCCLVP), which was established by USP, attempted to set standards for sterile product preparation.<sup>5</sup> Following the dissolution of this group in the early 1980s and additional pressure by FDA, both USP and the American Society of Health-System Pharmacists (ASHP) developed guidance documents on the subject. In 1993, ASHP issued its Technical Assistance Bulletin (TAB) on quality assurance for pharmacy-prepared sterile products.<sup>6</sup> USP followed with its chapter <1206>, *Sterile Drug Products for Home Use*, an informational chapter aimed at home care pharmacy compounding.<sup>7</sup> The ASHP TAB was later revised and published as the ASHP guidelines on quality assurance for pharmacy-prepared sterile products.<sup>2</sup>

Although pharmacy has a long history with respect to its voluntary initiatives aimed at improving quality assurance in the compounding of sterile preparations, these efforts have fallen short of their goal of ensuring patient safety. History has

shown that compliance with voluntary guidelines is low. FDA eventually demanded that a meaningful, enforceable quality assurance standard along with an accreditation process for pharmacies be developed and implemented. As a result, USP announced its plans to develop enforceable standards for sterile compounding that would protect patients from erroneous or inadvertently contaminated preparations.

An expert committee was commissioned by USP to draft these standards. The committee was composed of pharmacists from various practice environments including academia, hospital practice, retail settings in which sterile preparations are prepared, and FDA. The committee developed USP Chapter <797> according to the standard USP process, which includes the following steps:

1. Expert committee develops a draft document, and the document is published in *Pharmacopeial Forum* for comment.
2. Committee meets to review comments.
3. Committee revises the chapter as needed, based on comments received.
4. Revised chapter is published.
5. The review and comment process continues indefinitely. USP chapters are dynamic documents that are always subject to revision.

The first draft of USP Chapter <797> drew numerous comments from the pharmaceutical industry as well as comments from practicing pharmacists. The revision of the chapter drew additional comments from compounding pharmacists, some of whom indicated that many pharmacists would be unable to meet the requirements of the chapter.

Most pharmacists are quite familiar with *USP-NF*, as there are several chapters of interest to them (see Table 1). It is important for pharmacists to understand the intent of each chapter, which is signified by number. Chapters numbered 1–999 are considered to be U.S. medication standards and are therefore enforceable by the FDA under the Federal Food, Drug and Cosmetics Act. Chapters numbered 1000–1999 are considered to be advisory or informational, and those above 2000 apply to nutritional supplements. USP is a standard-setting organization and not an enforcement body. Its standards are enforceable by governmental agencies including FDA and state boards of pharmacy.

### Scope and Intent of USP Chapter <797>

As of January 2004, USP Chapter <797> is now the U.S. standard for preadministration manipulations of CSPs including the steps of compounding, transportation, and storage. USP Chapter <797> does not address administration of compounded sterile preparations. Because USP Chapter <797> focuses on protecting patients, it applies not only to pharmacies but to all sites where CSPs are compounded and to all personnel who compound sterile preparations, regardless of practice setting or profession.

TABLE 1

### USP chapters of interest to pharmacists:

- <1> Injections
- <71> Sterility Tests
- <85> Bacterial Endotoxin Test
- <795> Pharmaceutical Compounding—Non-Sterile
- <797> Pharmaceutical Compounding—Sterile
- <1075> Good Compounding Practices
- <1160> Pharmaceutical Calculations
- <1191> Stability Considerations in Dispensing
- <1211> Sterilization and Sterility Assurance

Because USP Chapter <797> focuses on protecting patients, it applies not only to pharmacies but to all sites where CSPs are compounded and to all personnel who compound sterile preparations, regardless of practice setting or profession.

Because USP Chapter <797> addresses only preadministration manipulations, it does not currently address manufactured products such as premixed intravenous drugs and delayed activation devices (e.g., ADD-Vantage®, Minibag Plus®). The proposed revisions to the chapter are expected to include a statement saying that the manufacturers' instructions for these products should be followed.

As noted previously, USP chapters are dynamic documents and are subject to continuous review and revision. This monograph describes several proposed revisions to the current chapter that are scheduled for publication in *Pharmacopeial Forum* in 2005. These proposed revisions are mainly clarifications and minor changes in language, and do not alter the essence of the chapter's requirements. In addition, JCAHO currently requires compliance with many of the chapter's requirements. Therefore, compounding personnel should proceed with their compliance efforts without delay. Pharmacists and other compounding personnel are encouraged to review these proposed revisions and provide any comments they believe are warranted.

### Responsibilities of Compounding Personnel According to USP Chapter <797>

USP Chapter <797> contains 13 major sections. The first section, which is one of the most important, outlines the responsibility of compounding personnel. Those responsibilities are listed in Table 2.

USP Chapter <797> requires that compounding personnel be adequately educated, instructed, and skilled to perform their functions. Meeting this standard is often a challenge, primarily because of issues related to training. Because most schools of pharmacy offer limited training in sterile com-

**TABLE 2****Responsibilities of Compounding Personnel**

- Personnel are adequately educated, instructed, and skilled to perform their functions
- Ingredients have correct identity, quality, amount
- Open/partial containers are properly stored
- Minimize bacterial endotoxins
- Proper and adequate sterilization is used
- Equipment is clean, accurate, appropriate
- Potential harm from added substances considered
- Packaging is appropriate for sterility, stability
- Compounding environment maintains the sterility of pre-sterilized items
- Labels are appropriate and complete
- Beyond-use dates are appropriate and based on valid scientific criteria
- Correct compounding procedures are used
- Deficiencies in compounding can be rapidly identified and corrected
- Separate compounding from quality evaluation

pounding, most of the training pharmacists receive takes place on the job. Obviously, there is a need for more training and resources in this area.

Compounding personnel are required to take on all responsibilities associated with sterile compounding, including making sure that the ingredients used are properly identified, of sufficient quality, and are in the proper amount. All ingredients should be stored properly and this applies to both open and partial containers. All preparations should be free of bacterial endotoxins. Compounding personnel must also ensure quality of the sterilization processes, equipment, packaging, and the compounding environment. Labeling, beyond-use dating, and compounding procedures also need to be addressed. Finally, compounding personnel need to be able to identify and correct any deficiencies in compounding, keeping in mind that compounding and evaluation of quality need to be separate whenever possible.

**Risk Levels**

USP Chapter <797> defines three levels of risk related to sterile preparations and includes quality assurance requirements for each risk level. These risk levels are based on the degree of risk that the preparation may become contaminated during the compounding and preadministration phases or remain contaminated in the case of high-risk compounding. The risk levels refer principally to microbial contamination (i.e., through microbial organisms, endotoxins, or spores), but the risk of physical or chemical contamination should be considered as well.

Compounding personnel need to be able to identify and correct any deficiencies in compounding, keeping in mind that compounding and evaluation of quality need to be separate whenever possible.

The assignment of risk levels for sterile compounding is not a new concept; it was first introduced to pharmacists in 1992 in the ASHP draft guidelines for quality assurance for pharmacy-prepared sterile products.<sup>4</sup> In this document and in its subsequent revisions, the risk levels are defined as 1, 2, and 3. The parameters defining the three risk levels in USP Chapter <797> are essentially the same as those in the ASHP guidelines, but USP Chapter <797> refers to the risk levels as low, medium, or high.

While risk-level assignment for CSPs has not been a common practice among pharmacists, most practitioners recognize that added safety measures are warranted for more complex CSPs in which the risk of contamination may be high. For example, compounding a batch of 25 or more CSPs from non-sterile ingredients would clearly call for a more stringent set of procedures and quality assurance measures than compounding a single CSP in which one sterile commercial ingredient was added to an i.v. bag. The purpose of assigning risk levels is to ensure that compounding personnel consider the potential risks associated with sterile preparations and evaluate the need for additional precautions with preparations that are deemed to be of greater risk to patients.

USP Chapter <797> provides general guidance on risk-level assignment based upon compounding manipulations, types of ingredients and equipment used, compounding environment, and storage and use of the resulting preparation. However, it emphasizes that the ultimate determination of risk level is the responsibility of the "licensed health care professionals who supervise compounding." There is one situation, however, in which risk level determination is predetermined: compounding sterile preparations from non-sterile ingredients is always categorized as high-risk compounding.

*Low-Risk CSPs.* In general, low-risk CSPs are those that are prepared from sterile commercial ingredients using sterile commercial devices, maintained in an ISO Class 5 environment (formerly referred to as Class 100) at all times, and require only a few closed-system, basic aseptic transfers and manipulations. One example of low-risk compounding is reconstituting a vial and injecting the contents into an i.v. bag within a laminar-airflow workbench (LAFW).

Quality assurance procedures recommended for low-risk compounding include:

- Routine disinfection and air quality testing to maintain ISO Class 5
- Adequate personnel garb for sterile preparation
- Review for correct identity and amounts of components

- Visual inspection of the preparation
- Annual media-fill test of aseptic technique of each person who compounds

Contrary to some interpretations, USP Chapter <797> does not require chemical analysis or pyrogen testing for CSPs, regardless of the risk level. However, it does not preclude such testing either.

**Medium-Risk CSPs.** Medium-risk sterile preparations include those preparations that are compounded from multiple pooled sterile commercial products for use by multiple patients or one patient multiple times. They also include preparations that require complex aseptic manipulations (e.g., multiple transfers) or preparations that take significant time to make. Preparations that include no bacteriostat and are administered over several days are also considered medium-risk. USP Chapter <797> specifies maximum storage periods for medium-risk CSPs that do not undergo sterility testing. A typical total parenteral nutrition solution that is compounded by admixing four or more sterile commercial ingredients is one example of a medium-risk CSP.

Quality assurance requirements for medium-risk compounding include all of those specified for low-risk compounding in addition to a more stringent annual media-fill test for personnel representative of the complexities of medium risk-level compounding.

At one large institution, all pharmacy staff who are involved in sterile compounding undergo an annual media-fill test that involves a 10-step process of complex manipulations. Staff must complete the process successfully with no growth in the media in order to receive approval for preparation of CSPs. Over the last two years, 539 staff members were tested, and the initial contamination rate was 5.2%.<sup>8</sup> Staff who failed the validation process initially were allowed to retake the examination; all staff members passed the validation process on their second try. As a result of these data, the department is revising certain procedures used for medium-risk compounding in an effort to minimize the potential for contamination.

**High-Risk CSPs.** High-risk CSPs are those that are either contaminated or considered to be at high risk for becoming contaminated with microorganisms. High-risk compounding should be reserved for situations in which the therapeutic needs of the patient cannot be met in a safer manner. Examples of high-risk compounding include:

- Sterile preparations prepared from non-sterile ingredients.
- Preparations using sterile ingredients in an environment that is inferior to ISO Class 5 (e.g., open countertop).
- Sterile preparations in which there is an extended delay (more than 6 hours) between compounding and sterilization.
- Preparations in which the purity of components is assumed but cannot be verified by documentation (i.e., no certificate of analysis is available).

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All compounding personnel, including pharmacists, should be required to pass written and media-fill examinations before being allowed to compound CSPs.

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It is important to recognize that if touch contamination occurs during low- or medium-risk compounding, the resulting preparation would be considered high-risk and would require sterilization.

While the preparation of sterile products from non-sterile ingredients is typically associated with large-scale pharmaceutical manufacturing, there are some situations in which a pharmacy may be required to perform this type of compounding in order to meet the needs of the patient. For example, a pharmacist may receive an order for a high-potency morphine solution for intravenous administration that can only be compounded from non-sterile morphine powder.

In addition to the quality assurance measures for low- and medium-risk compounding, USP Chapter <797> requires that all personnel who perform high-risk compounding complete semi-annual media fill validation for each type of compounding manipulation they perform.

## Verification of Compounding Accuracy and Sterilization

USP Chapter <797> requires that all compounding processes and sterilization procedures be correctly designed, documented, and verified. Finished CSPs should be visually inspected to ensure that the appearance and fill amount are consistent with expectations.

The health care professional who supervises compounding is responsible for determining the appropriate sterilization method—filtration, heat, or steam sterilization—for CSPs that require sterilization. USP <1211>, *Sterility Assurance of Compendial Articles*, provides detailed information on sterilization methods. In order to sterilize a product using steam sterilization or autoclaving, the material must be exposed to steam (121 °C) at a pressure of 15 p.s.i. for 20 to 60 minutes. Dry heat sterilization, typically used for glass and metal implement sterilization, requires that the items be heated to a mean temperature of 250 °C for two hours. When sterilizing a CSP using filtration, the compounding professional must use commercial 0.2-micron filters that are disposable, sterile, pyrogen-free, and certified to retain  $1 \times 10^7$  *Brevundimonas (Pseudomonas) diminuta* per cm<sup>2</sup> of filter surface.

USP Chapter <797> requires that sterilization procedures be verified. Sterilization is verified by preparing a solution using contaminated powdered growth media, sterilizing the solution, and then testing the sterility of the resulting solution to document that the process worked.

## Assignment of Risk Levels

As noted previously, the responsibility for risk-level determination lies with the health care professional who supervises sterile compounding. While USP Chapter <797> provides some general guidance, risk-level determination requires the professional judgment of the pharmacist or other compounding professional.

Below are several examples of typical compounding processes and their respective risk levels.

### Example 1.

**Cefazolin 1 g, reconstituted and added to 50 mL of D5W for IV use**

*Risk Level:* If this manipulation is performed in an ISO Class 5 environment, it is considered *low risk*.

### Example 2.

**Diphenhydramine 10 mg/0.2 mL drawn into tuberculin syringes for pediatric IM use**

*Risk Level:* If performed in an ISO Class 5 environment, this would be considered *low risk*.

### Example 3.

**TPN solution prepared from 4.5% amino acid solution and 22% dextrose, with 4 electrolytes, multiple vitamins, trace elements, insulin, and ranitidine added.**

*Risk Level:* This procedure would be classified as *medium risk*.

### Example 4.

**TPN solution prepared from powdered amino acids and 22% dextrose, with 4 electrolytes, multiple vitamins, trace elements, insulin, and ranitidine added.**

*Risk Level:* Because this TPN solution is being prepared using non-sterile ingredients, it would be classified as *high risk*.

### Example 5.

**Morphine 50 mg/mL + Bupivacaine 10 mg/mL in NS for use in a SynchroMed® pump for intrathecal use**

*Risk Level:* Because this preparation would require the use of nonsterile morphine powder, this preparation would be classified as *high risk*.

### Example 6.

**Cefazolin 1 g ADD-Vantage® vial attached to i.v. bag but not activated.**

*Risk Level:* Commercial premixed products and systems like ADD-Vantage® do not fall within the purview of USP Chapter <797> because they do not require compounding. The proposed revisions are expected to include a recommendation that the manufacturers' directions be followed when using commercial premixed products or commercial systems like ADD-Vantage®.

### Example 7.

**Fortified gentamicin 12 mg/mL ophthalmic solution (Genoptic® + gentamicin)**

*Risk Level:* If compounded in an ISO Class 5 environment using sterile components, this would be considered *low risk*.

### Example 8.

**"TriMix" for intracavernosal injection containing:**

**Alprostadil 12.5 mcg/mL**

**Papaverine HCl 4.5 mg/mL**

**Phentolamine mesylate 0.125 mg/mL**

*Risk Level:* If sterile commercial ingredients are used in this preparation and the preparation is being compounded for a single patient, this would be considered a *low-risk* preparation. However, if the preparation is compounded as a batch that will be dispensed to multiple patients, it would be considered *medium risk*. If compounded from nonsterile drug powders, it would be considered a *high-risk* preparation.

## Personnel Training

Training for personnel who compound sterile preparations is mandatory and should include thorough didactic and experiential training and testing. Because undergraduate pharmacy education often does not include in-depth training in sterile compounding, it should not be assumed that all licensed pharmacists are qualified to compound CSPs. All compounding personnel, including pharmacists, should be required to pass written and media-fill examinations before being allowed to compound CSPs.

Media-fill verification of technique, also referred to as media-fill challenge testing, is used to verify that personnel have mastered the skill of aseptic compounding. This testing should represent the most challenging conditions in which

personnel will be required to compound CSPs and should include all types of manipulations that personnel will be required to perform. During media-fill verification, personnel are instructed to prepare a CSP using a sterile liquid culture medium. The resulting solution is then incubated at 25–35 °C for 14 days. The solution should be visually inspected for evidence of microbial growth, or turbidity, during incubation and at the end of the 14-day incubation period. If there is evidence of turbidity, retesting, and possibly additional training, is required. All personnel who compound CSPs must complete media-fill challenge testing before they are allowed to compound CSPs. The testing should take place at least annually for low- and medium-risk CSPs and semi-annually for high-risk CSPs.

## Environmental Quality and Control

One of the more controversial sections of the ASHP guidelines and USP Chapter <797> is environmental quality and control. While pharmacists and other compounding professionals have long recognized the importance of controlling the quality of the immediate environment in which the CSPs are prepared (referred to as the critical area, typically a laminar-airflow workbench), there have been questions regarding the need to control the environmental quality of the buffer area, or the area in which the LAFW is placed. Contrary to popular opinion, the LAFW is not a magic box that provides a suitable environment regardless of where it is placed. Because the airflow inside the LAFW is relatively slow, any movement in the buffer area can cause the area inside the LAFW to become contaminated. Moving items into the laminar flow hood causes the air from the buffer area to be swept inside the LAFW. Normal activity such as coughing, walking, or opening the door to the buffer area causes air from the buffer area to sweep organisms into the LAFW. Therefore, it is important to monitor and control the environmental quality of the buffer area or core room. In addition, traffic in the buffer area should be minimized.

The critical area should be ISO Class 5, which was formerly referred to as Class 100 (see Table 3). The buffer area should be ISO Class 7 and appropriate air conditioning and humidity controls must be in place in the buffer area. The current chapter erroneously states that the buffer area should be ISO Class 8 and will be corrected in the next revision. The anteroom or support area, which is outside the buffer area, should be ISO Class 8.

All surfaces in the buffer area should be smooth, impervious, non-shedding, and made of substances that are amenable to cleaning and sanitization. Cracks, crevices, and openings in these surfaces should be sealed. The buffer area should contain no sinks or floor drains. Personnel access to the buffer area should be limited, and only those tasks requiring a controlled environment should be carried out in the buffer area. Tasks that do not require a controlled environment, such as unpacking boxes, should not be carried out in the buffer area. Food and drink should not be introduced into the buffer area.

USP Chapter <797> briefly acknowledges the use of barrier isolators as an alternative to LAFWs for preparing CSPs. Barrier isolators are widely used outside the U.S. and have been gaining popularity in the U.S. over the past few years.

USP Chapter <797> includes requirements for cleaning and sanitizing the LAFW, buffer room, and anteroom, and requirements for environmental monitoring of these areas. Environmental monitoring is accomplished through air and surface sampling.

Requirements for personnel garb are also specified. Proper garb is essential for minimizing contamination of products from the skin, hair, and clothing. Standard operating procedures (SOPs) must be in place to ensure that proper

TABLE 3

### International Organization of Standardization (ISO) Classification of Particulate Matter in Room Air

ISO Class	Class Name		Particles	
	U.S. FS 209E		ISO, m <sup>3</sup>	FS 209E, ft. <sup>3</sup>
3	Class 1		35.2	1
4	Class 10		352	10
5	Class 100		3520	100
6	Class 1000		35,200	1000
7	Class 10,000		352,000	10,000
8	Class 100,000		3,520,000	100,000

Adapted from the Federal Standard No. 209E, Central Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO 14644-1: 1999 Clean rooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3520 particles of 0.5 µm per m<sup>3</sup> or larger (ISO Class 5) is equivalent to 100 particles per ft<sup>3</sup> (Class 100) (1 m<sup>3</sup> = 34.314 ft.<sup>3</sup>).

processes occur. USP Chapter <797> includes a list of recommended SOPs. The pharmacist-in-charge is responsible for ensuring that SOPs are followed.

One controversial aspect of USP Chapter <797> is the requirement to “control the dispersion of particles from body surfaces,” which some have interpreted to mean that personnel may not wear any cosmetics when compounding CSPs. The revised chapter is expected to include language clarifying that powdered or flaking cosmetics should not be worn. Similarly, finger nails should be short and clean. Long artificial nails should not be permitted.

## Finished Preparation Release

Finished CSPs should undergo visual inspection and verification of compounding accuracy prior to release. Ideally, someone other than the compounder should verify compounding accuracy whenever possible. Verification of compounding accuracy should include a double-check of the calculations as well as verification of the identity and quantity of ingredients used.

As an added safety measure to avoid overdoses or underdoses of chemotherapy drugs, the pharmacy department at M.D. Anderson implemented a process for verification of chemotherapeutic ingredients that requires weighing the final preparation and checking the weight against the calculated expected weight. Once verified, the weight of the final solution is documented in the compounding records. This process takes only a few seconds and it provides an objective, non-human method of verifying the amount of chemotherapy added to the admixture.<sup>9</sup>

USP Chapter <797> specifies additional testing requirements for batch preparation of high-risk CSPs. Batches of greater than 25 packages must be tested for sterility and

TABLE 4

Risk Level	Room Temp	Refrigeration	Freezer ( $\leq -20^{\circ}\text{C}$ )
Low	48 hours	14 days	45 days
Medium	30 hours	7 (9)* days	45 days
High	24 hours	3 days	45 days

\* The beyond-use dating will extend from seven to nine days in the proposed revisions.

pyrogen content according to the procedures outlined in USP <71> *Sterility Tests* and USP <85> *Bacterial Endotoxin Test*, respectively. These procedures have always been specified for batches of greater than 100 finished packages, but smaller quantities were not addressed previously.

### Beyond-Use Dating

Beyond-use dating (BUD), or expiration dating, has been a controversial part of USP Chapter <797> because it incorporates potential microbial contamination of the CSP into the determination of BUD. Until recently, BUD was based solely on chemical stability. The rationale for including microbiological beyond-use dating is to reduce the potential for patient harm if the patient receives a contaminated CSP. According to USP Chapter <797>, BUD of the final CSP corresponds to either its microbiological BUD or chemical stability limit, whichever is shorter.

USP Chapter <795>, *Pharmaceutical Compounding—Nonsterile Preparations* provides guidance on determining chemical stability when specific published information is not available. For solids and non-aqueous liquids, the recommendation is 25% of the remaining expiration period or 6 months, whichever is less. For USP bulk substances, the recommended beyond-use date is not more than 6 months and for aqueous formulations, it is 14 days refrigerated. For all others not specified in the chapter, the recommended dating is not more than 30 days or the intended duration of therapy, whichever is less.

Microbiological beyond-use dating is based on the risk level of the CSP and the time and temperature at which the preparation is stored and used. For example, because warm temperatures promote microbial growth, preparations stored or administered over extended periods of time at or above room temperature will have shorter BUDs than those in the same risk level stored under refrigeration.

Table 4 lists the current guidelines for microbiological beyond-use dating. One proposed revision in the BUD section of the chapter is to extend from seven to nine days the BUD for medium-risk products stored under refrigeration. One reason for the change is that CSPs dispensed by home care pharmacies sometimes require two days for delivery. It is anticipated that this proposed change will be published for comment in *Pharmaceutical Forum* in spring 2005.

Beyond-use dating (BUD), or expiration dating, has been a controversial part of USP Chapter <797> because it incorporates potential microbial contamination of the CSP into the determination of BUD.

It is important to note that microbiological beyond-use dating applies only to preparations that are not tested for sterility. If preparation sterility is tested and verified, these limits do not apply. It is also important to realize that the BUD is the time from the end of the preparation to the beginning of administration and does not include “hang” time or administration of the product.

### Other Requirements of USP Chapter <797>

USP Chapter <797> contains additional requirements for:

- Verification of automated compounding devices
- Monitoring and maintaining product quality after the CSP leaves the pharmacy
- Patient or caregiver training
- Patient monitoring and adverse event reporting
- The pharmacy’s formal written quality assurance program

### Requirements for Quality Assurance Program

All employees must understand and follow the facility’s quality assurance program, and adherence to the quality assurance program must be documented. The phrase, “if it isn’t written, it didn’t happen” is the essence of a quality assurance program. Documentation is the only way to demonstrate compliance with regulatory requirements.

### Proposed Revisions and Clarifications

There are a number of proposed revisions and clarifications to the current chapter that will be published for comment in *Pharmaceutical Forum* in spring 2005.<sup>10</sup> Pharmacists are encouraged to review these proposed changes carefully and submit comments to USP during the comment period. Some of the more notable proposed changes and clarifications are listed below. Until the revision process is completed—probably in 2006—the current USP Chapter <797> remains official.

**Addition of definitions of CSP and product.** The term “compounded sterile preparation” (CSP) was introduced in USP Chapter <797>. The proposed revisions to the chapter will include a clarification of the differences between a *preparation* and a *product*. The following definitions are proposed for inclusion at the end of the introduction section:

**PREPARATION.** A preparation, or compounded sterile preparation, CSP, is a sterile drug or nutrient prepared in a licensed pharmacy or other health care related facility pursuant to the order of a licensed prescriber, which may or may not contain sterile *products*.

**PRODUCT.** A *product* is a commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the U.S. Food and Drug Administration, FDA. *Products* are accompanied by full prescribing information, which is commonly known as the FDA-approved manufacturer's labeling or *product* package insert.



**A revised order of garbing will be proposed.** The revised chapter will propose that the appropriate sequence of garbing be changed. The order of garbing remains the subject of debate. One proposed sequence is: shoe covers; head and facial hair covers; face masks; scrubbing of hands and arms; non-shedding coats, gowns, or coveralls; sterile gloves.

**A proposal to shorten the beyond-use period for multidose vials (MDVs) after initial puncture from 30 days to 28 days.** The current chapter calls for a beyond-use date of thirty days after initial puncture. The USP antimicrobial preservatives effectiveness test, the test used by manufacturers to assess the effectiveness of antimicrobial preservatives, is a 28-day test. Therefore, the effectiveness of antimicrobial preservatives cannot be ensured beyond 28 days.

**A proposal to clarify the beyond-use dating for single-dose vials after initial puncture.** The revision will propose that single-dose vials shall be used within one hour if opened in an environment that is inferior to ISO Class 5 (such as an open counter) and within six hours if opened in ISO Class 5 conditions.

**An "immediate use" exemption from ISO Class 5 is proposed.** The proposed revisions will include an exemption for sterile preparations that are prepared outside a controlled environment such as in emergency settings (e.g., ambulance, emergency room), operating rooms, nursing units, and satellite pharmacies provided that administration is begun within one hour and completed within 12 hours of preparation of the CSP. This exemption is consistent with the Centers for Disease Control and Prevention (CDC) guidelines and the FDA's labeling for injections. This exemption is based on the premise that if the sterile preparation is inadvertently contaminated during preparation, the growth of organisms in this time period will not be sufficient to cause significant patient harm.

**Clarification of proprietary bag and vial systems (e.g., ADD-Vantage<sup>®</sup> and Mini-Bag Plus<sup>®</sup>).** The proposed revision will state that storage and beyond-use times for attached and activated vials are as stated in the manufacturers' FDA-approved labeling.

**Barrier isolator usage.** The proposed revision will clarify that barrier isolators should be used according to manufacturers' recommendations. There are a variety of barrier isolators currently on the market and the requirements vary among manufacturers.

**The revision will propose that use of non-sterile isopropyl alcohol is permitted.** The current chapter requires that sterile isopropyl alcohol be used.

**A requirement for microbial bioburden testing of ISO Class 5 surfaces will be proposed.** This step will measure the effectiveness of staff cleaning of LAFW surfaces.

**Proposed clarification of the scope of the requirements.** The proposed revision will clarify that sterile compounding pertains to preadministration manipulations of compounded sterile preparations including compounding, transportation, and storage, but not to administration. The chapter will also clarify the distinction between sterile and nonsterile compounding.

**Proposed clarification of compounding personnel.** The proposed revision will clarify that the standards apply to all compounding personnel without regard to site or profession.

**Proposed correction of the environmental quality of buffer area.** As stated previously, the buffer area should be ISO Class 7. The current chapter erroneously states that the buffer area should be ISO Class 8. This will be proposed for correction in the next revision.

**Proposed addition of new section on hazardous drugs.** A new section on hazardous and radioactive drugs is being proposed for the chapter. This section will refer compounding professionals to applicable state and federal standards and guidelines.

## JCAHO and USP Chapter <797>

In April 2004, JCAHO announced that it would begin surveying accredited organizations for compliance with USP Chapter <797> beginning July 1, 2004.<sup>3</sup> In October 2004, JCAHO clarified that surveyors would approach the new requirements in the following manner:

- For provisions of USP Chapter <797> that are equivalent to the current elements of performance (EP) of the 2004 Joint Commission standards, compliance will be evaluated and scored.
- Between July 1, 2004, and December 31, 2004, organizations were required to conduct a risk assessment (or gap analysis) of their compliance to all provisions of USP Chapter <797> and develop a plan for each section of the chapter with specific time frames.

**TABLE 5**

**Time Frames for Completing the Various Sections of USP Chapter <797>**

Compliance Areas	Specific Details to Consider	Recommended Completion Date
<b>Quality Assurance (QA) Program</b>	Formalized in writing	July 2005
	Describes specific monitoring and evaluation activities (measures identified)	July 2005
	Reporting and evaluation of results	January 2006
	Identification of follow-up activities when thresholds are exceeded	January 2006
	Delineation of individual responsibilities for each aspect of the program	January 2006
<b>QA Practices</b>	Routine disinfection of direct compounding environment	Current
	Quality testing of direct compounding environment	January 2006
	Visual confirmation of personnel processes regarding gowning, etc.	January 2005
	Review of orders and packages of ingredients to assure correct identity and amounts of ingredients	Current
	Visual inspection of compounding sterile products (CSP)	Current
<b>Reports/Documents</b>	Adverse event reporting	Current
	Complaint procedures	Current
	Periodic review of quality control documents	January 2005
<b>Patient and Caregiver Training (Home Care only)</b>	Formalized program that includes the following:	Current
	<ul style="list-style-type: none"> <li>• Understanding of the therapy provided</li> <li>• Handling and storage of the CSP</li> <li>• Appropriate administration techniques</li> <li>• Use and maintenance of any infusion device involved</li> <li>• Use of printed material</li> <li>• Appropriate follow-up</li> </ul>	
<b>Maintaining Product Quality and Control once the CSP leaves the Pharmacy (both institutional-based and NICPs)</b>	Packaging, handling, and transport	July 2005
	<ul style="list-style-type: none"> <li>• Policies and procedures including the packaging, handling, and transport of chemotoxic/hazardous CSPs</li> </ul>	
	Use and Storage	July 2005
	<ul style="list-style-type: none"> <li>• Policies and procedures</li> </ul>	
	Administration	Current
<ul style="list-style-type: none"> <li>• Policies and procedures dealing with such issues as hand washing, aseptic technique, site care, etc.</li> </ul>		
Education/Training	July 2005	
<ul style="list-style-type: none"> <li>• Policies and procedures dealing with proper education of patients and staff ensuring all of the above</li> </ul>		
<b>Storage Conditions and Beyond—Use Dating</b>	Specific labeling requirements	January 2005
	Specific beyond-use dating policies, procedures, and requirements	January 2005
	Policies regarding storage	July 2005
<b>Finished Product—Release Checks and Tests</b>	Policies and procedures that address the following:	July 2005
	<ul style="list-style-type: none"> <li>• Physical inspections</li> <li>• Compounding accuracy checks</li> </ul>	
<b>Finished Product—Release Checks and Tests</b>	Policies and procedures that address the following:	July 2005
	<ul style="list-style-type: none"> <li>• Sterility testing</li> <li>• Pyrogen testing</li> <li>• Potency testing</li> </ul>	
<b>CSP Work Environment</b>	Appropriate solid surfaces	Approved facility renovation plan by <b>January 2005</b> for completion in 3 years. Interim safety measures required by <b>July 2005</b>
	Limited (but necessary) furniture, fixtures, etc.	
	Anteroom area	
	Buffer zone	
<b>Equipment</b>	Policies and procedures that address calibration, routine maintenance, personnel training	July 2005
<b>Components</b>	Policies and procedures that address sterile components	July 2005
<b>Processing: Aseptic Technique</b>	Policies and procedures that address specific training and performance evaluation	July 2005
<b>Environmental Control</b>	Policies and procedures that address the following:	July 2005
<ul style="list-style-type: none"> <li>• Cleaning and sanitizing the workspaces (DCCA)</li> <li>• Personnel and gowning</li> <li>• Standard operating procedures</li> </ul>		
<b>Sterility Testing of Non-Sterile Products</b>	Sterility, pyrogen, and potency testing completed on sample from each batch	Current
<b>Verification Procedures—Environmental Monitoring</b>	Certification of laminar air flow workbench (hood) and barrier isolates every six (6) months	If new—before use, if current by January 2005
	Certification of the buffer room/zone and anteroom/zone every six (6) months	If new—before use, if current by January 2005
	Bacterial monitoring using an appropriate manner	January 2006
<b>Verification Procedures—Personnel Training and Education</b>	Initially and annually thereafter	January 2005
	<ul style="list-style-type: none"> <li>• Didactic review</li> <li>• Written testing</li> <li>• Media-fill testing</li> </ul>	

A crosswalk of JCAHO standards with USP Chapter <797> requirements was published in the April 2004 issue of *Perspectives*.

In June 2004, ASHP and JCAHO convened a 13-member expert panel to discuss the Joint Commission's plans to enforce USP Chapter <797>, develop the timeline, and determine which areas have the highest priority for compliance.<sup>11</sup> The resulting timeline (Table 5) included a target completion date of January 2005 for certain critical elements including certain education and training verification procedures and review of quality control documents. Items with a July 2005 suggested completion date include policies regarding the checking and release of finished products and equipment-maintenance policies. Other elements are targeted for compliance by January 2006. It is important to note that these time frames are only guidelines, and organizations will *not* be surveyed against them. The organization should select time frames based on its analysis of workload and sterile compounding risk levels and available resources, but the time frames should be realistic.

Starting in January 2005, the Joint Commission will be surveying for the presence of a gap analysis and action plan for compliance with the chapter. Failure to have one will be scored at standard MM.8.0, Element of Performance #2. In addition, the method used to conduct the gap analysis and develop the action plan will be evaluated. Joint Commission surveyors will not survey the specifics of USP Chapter <797>.

only that there is a sufficient action plan and that it is being implemented according to the plan.

A key part of the compliance process for hospitals and organizations involves performing a risk assessment to determine overall compliance with the compounding standards and develop a schedule for attaining full compliance. The schedule should take into account time needed to complete renovations involving the sterile compounding area and any plans for expansion of the facility.

## Conclusion

USP Tests and Assays Chapter <797>, *Pharmaceutical Compounding, Sterile Preparations* is now considered to be the minimum standard for pharmacy compounding of sterile preparations. While its content is similar to previous voluntary guidelines on the topic, the chapter is enforceable by the Food and Drug Administration (FDA) and state boards of pharmacy and compliance by pharmacies and other facilities where sterile preparations are compounded is mandatory. JCAHO has begun surveying accredited organizations for compliance with this chapter. Several revisions and clarifications to the chapter are scheduled for publication in the spring 2005 issue of *Pharmaceutical Forum*. Pharmacists and other stakeholders are encouraged to review these proposed changes and provide comments to USP where appropriate. The goal of USP Chapter <797> is to protect patients from harm associated with contaminated or improperly prepared compounded sterile preparations.

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