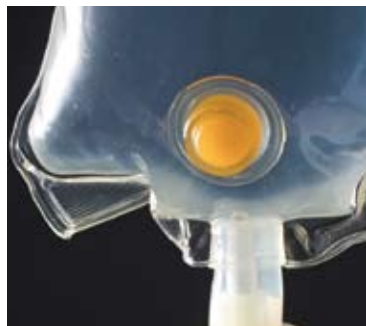


# The ASHP Discussion Guide on **USP CHAPTER <797>**



## for **COMPOUNDING** Sterile Preparations

### SUMMARY OF REVISIONS TO USP CHAPTER <797>

Developed by the American Society of Health-System Pharmacists  
in collaboration with Baxter Healthcare Corporation



American Society of  
Health-System Pharmacists®

Medication Delivery

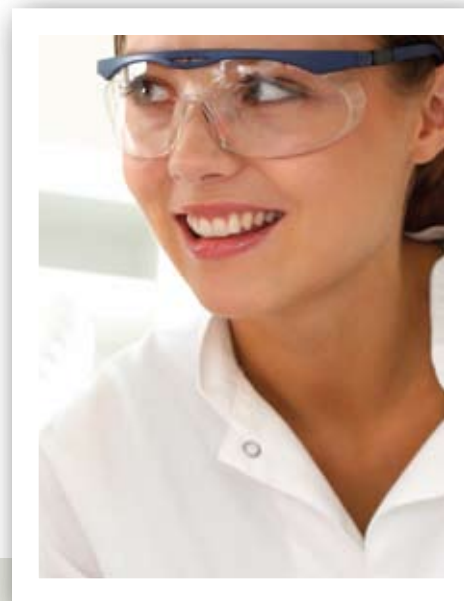
**Baxter**

**T**he Revision Bulletin to USP Chapter <797>, Pharmaceutical Compounding: Sterile Preparations, was released in late 2007 and will become official on June 1, 2008. This discussion guide is a follow-up to a discussion guide that was developed when the original chapter became official. This updated guide is intended to assist health-system pharmacists with implementation of revised USP Chapter <797> requirements. The revised chapter is currently posted on the USP website ([www.usp.org](http://www.usp.org)) as a Revision Bulletin for practitioners to review the chapter before it becomes official. The chapter will be published in the Second Supplement to USP 31-NF 26 and in the Pharmacists' Pharmacopeia.

The information and its applications contained in this guidance document are constantly evolving because of ongoing research and improvements in technology, and are subject to the professional judgment and interpretation of the practitioner due to the uniqueness of each pharmacy's role in compounding sterile preparations. The writers, reviewers, editors, ASHP, and Baxter have made reasonable efforts to ensure the accuracy and appropriateness of the information presented in this document. However, any reader of this information is advised that the writers, reviewers, editors, ASHP, and Baxter are not responsible for the continued accuracy of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the document in any and all practice settings. Any reader of this document is cautioned that ASHP, the writers, reviewers, and Baxter make no representation, guarantee, or warranty, express or implied as to the accuracy and appropriateness of the information contained in this document, and will bear no responsibility or liability for the results or consequences of its use.

# The ASHP Discussion Guide on **USP CHAPTER <797>** for **COMPOUNDING** Sterile Preparations

*The assistance of E. Clyde Buchanan, M.S, FASHP and Angela T. Cassano, Pharm.D., BCPS in preparing and reviewing the Discussion Guide is gratefully acknowledged.*



## Executive Summary

On January 1, 2004, the first version of USP Chapter <797>, Pharmaceutical Compounding: Sterile Preparations became official,<sup>1</sup> which details the procedures and requirements for compounding sterile preparations and sets standards that are applicable to all practice settings in which sterile preparations are compounded. Since the standards became official, they have been widely adopted, are enforced by many state boards of pharmacy, and may be surveyable by accreditation organizations. On June 1, 2008, the revisions to USP Chapter <797> will become the official standard and will be published in the Second Supplement to USP 31-NF 26 and in the Pharmacists' Pharmacopeia. While the intent of the standards has not changed, the revision includes important additions and clarifications that are intended to further the efforts to prevent patient harm from inaccurate or contaminated compounded sterile products (CSPs). This updated discussion guide will explain key changes in procedures and requirements in the revised USP Chapter <797>.

## Chapter Overview and History

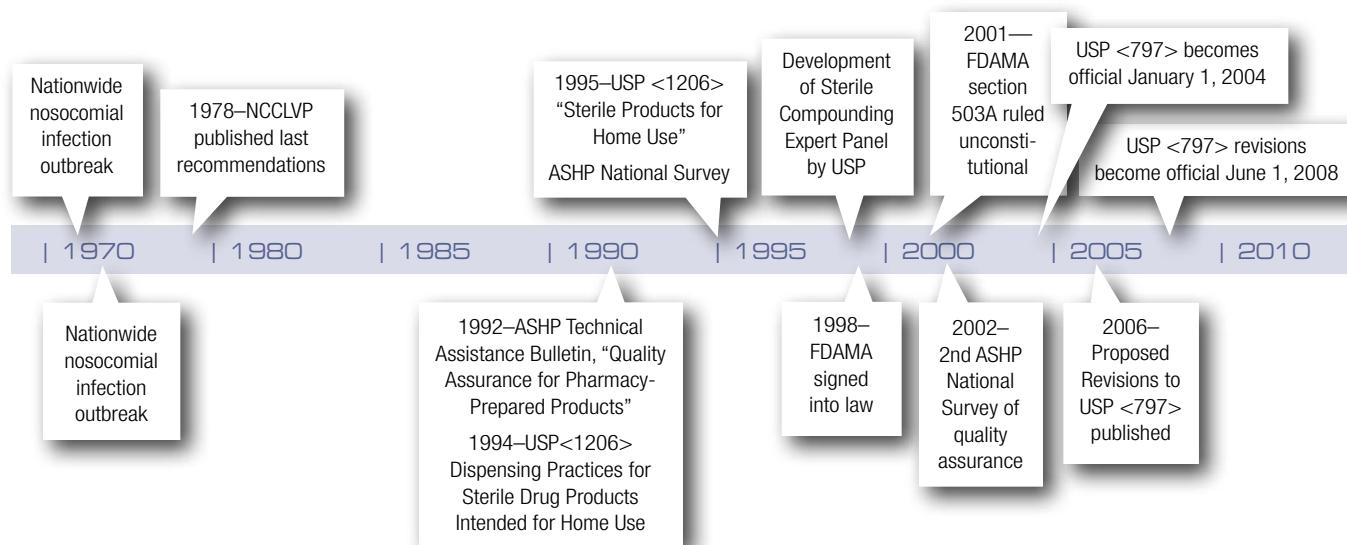
USP, along with many other organizations, has long been concerned with the quality and integrity of CSPs. In the early 1970s, thousands of cases of sepsis and hundreds of deaths occurred as a result of bacterial contamination of parenteral products,<sup>2,3</sup> exposing an immediate need for hospitals to implement a higher standard of compounding quality. During the 1970s and early 1980s, the National Coordinating Committee on Large Volume Parenterals (NCCLVP) of the US Pharmacopeial Convention, Inc. emerged as a driving force behind the call for the profession of pharmacy to ensure high quality of CSPs. Recommended standards of practice for the preparation, labeling, and quality assurance of hospital pharmacy admixture services were set forth by NCCLVP.<sup>4-11</sup> The Food and Drug

Administration (FDA) has also had a long-standing mission to protect the public's health where drug products of any type are concerned. With the dissolution of NCCLVP in the 1980s, the FDA turned to the profession of pharmacy to address problems with contamination in sterile preparations in the United States.

The body of literature and development of committees to address the growing concerns about sterility of compounded products skyrocketed in the 1990s (Figure 1). Organizations such as the American Society of Health-System Pharmacists (ASHP) and USP issued practice recommendations centered on the pharmacist's responsibility for ensuring proper preparation, labeling, storage, dispensing, and delivery of CSPs.<sup>12,13</sup> While the recommendations addressed many of the concerns of the profession, there was no formal

**FIGURE 1**

## Evolution of Sterile Compounding Standards



accountability to any regulatory agency other than ASHP's Residency and Technician Training Accreditation Program. Therefore, there was no enforcement and likewise, little monetary support for pharmacists and pharmacies wanting to improve their sterile compounding processes. Even with the emphasis on best practices, two national surveys conducted by ASHP in 1995 and 2002, found few changes in sterile compounding practices.<sup>14,15</sup> These results were particularly concerning because improvements in the handling and preparation of CSPs were not occurring despite the availability of formal guidelines for over a decade in the form of a Technical Assistance Bulletin (TAB) entitled "Quality Assurance for Pharmacy-Prepared Sterile Products."<sup>13</sup> Again, the pharmacy profession failed to take the lead in addressing FDA's concerns about CSPs.

Along the way, the US Food and Drug Administration Modernization Act (FDAMA) of 1997 was signed into law. Section 503A of the FDAMA, which is titled "Pharmacy Compounding," defined the limits of legitimate compounding.<sup>16</sup> The law was designed to protect patients from the unnecessary use of extemporaneously compounded drugs by pharmacists and gave FDA the power to delineate certain drugs that were difficult to compound and for which compounding could adversely affect safety or effectiveness. In 2001, the U.S. Supreme Court ruled section 503A unconstitutional, creating a void of federal regulation for the pharmacy profession and the FDA.<sup>17,18</sup>

All of the various quality assurance measures culminated on January 1, 2004, when the first official and enforceable sterile preparation compounding standard in the United States was published as USP Chapter <797>.<sup>1</sup> The expert committee responsible for writing USP Chapter <797> received considerable feedback and comments after the chapter was published. Based on many of these comments, the committee proposed revisions to USP Chapter <797> in the *Pharmaceutical Forum* 32(3), May–June 2006. The revision process included a call for public comments on the proposed revisions. The response was overwhelming. More than 500 individuals, hospitals, pharmaceutical companies, and professional organizations responded, amassing over 1000 pages of comments.<sup>19</sup> USP posted a commentary document, which provides insight and background on the comments and the subsequent revision process. After careful deliberation and consideration of these comments, a revised standard was developed and released in December 2007. The revised standard becomes official on June 1, 2008.

## Chapter Justification and Enforceability

### Justification: Impact on Public Health

Practitioners often have questions about the scientific background and supporting evidence for USP Chapter <797>. Clinicians who have not had any bad experiences with CSPs have questioned the need to fix the

system. USP Chapter <797> evolved over a number of years as a means of addressing compounding practices as sources of infections.<sup>2,20</sup> Since the early 1990s, FDA has become aware of numerous problems associated with compounded preparations, many of which have resulted in recalls, patient injuries, and deaths.<sup>21-36</sup>

While information about the impact of sterile compounding procedures is widely available, devastating infections from contamination of CSPs continue to occur. Microorganisms such as *Enterobacter cloacae*, *Exophiala*, and *Pseudomonas fluorescens* have been found in products that were considered to be sterile, such as intravenous and epidural preparations.<sup>29,31-34</sup> To illustrate this point, a *Serratia marcescens* outbreak from contaminated magnesium sulfate injections recently affected patients in California and New Jersey.<sup>33,34</sup>

Cleanroom environments are known to reduce airborne particles and contamination rates. However, studies have shown that contamination cannot be eliminated by having a cleanroom environment or proper garbing alone, emphasizing the need for a multi-factorial approach to sterile compounding.<sup>37,38</sup> Trissel et al. evaluated microbial contamination rates for both low- and medium-risk compounding procedures; they determined that the contamination rate for medium-risk preparations compounded in a

cleanroom environment was 5.2%.<sup>39,40</sup> In a follow-up evaluation, additional changes, such as requiring sterile chemotherapy gloves and repeatedly disinfecting with isopropyl alcohol (IPA), were employed, resulting in a drop in the medium-risk contamination rate to 0.34%.<sup>41</sup> These results underscore the importance of the human element as a factor in safe compounding practices (e.g., cleansing, garbing, or aseptic technique) and that employee adherence to, and acceptance of sterile compounding standards are imperative.

## Enforcement

In 1906, the Food and Drugs Act and the USP/NF became the official standard for drugs in the United States. In 1938, Congress passed the Federal Food, Drug, and Cosmetic (FD&C) Act, which was a revision of the 1906 Act. The FD&C Act recognized USP/NF as the official compendia of drug standards. The FDA is responsible for the enforcement of the FD&C Act.

Each chapter of the USP/NF is assigned a number, which appears in brackets along with the chapter name. The general chapters numbered <1> to <999> are enforceable by the FDA and official monographs and standards of the USP/NF; general chapters numbered from <1000> to <1999> are considered informational and not enforceable, and chapters above <2000> apply to nutritional supplements. FDA defers to the states to regulate the practice of pharmacy and to perform inspections.<sup>17</sup> However, the FDA does have the authority to inspect pharmacies and enforce USP Chapter <797> in the interest of public health.

The National Association of Boards of Pharmacy (NABP) has shown support of the USP <797> chapter by incorporating the requirements into its Model State Pharmacy Act and Model Rules. In addition to Rules for Sterile Compounding outlined in the Model State Pharmacy Act, “the Board’s Good Compounding Practices Applicable to State Licensed Pharmacies, and the current USP-NF chapters on compounding and sterile pharmaceutical preparations,” are to be adhered to by compounding pharmacies and pharmacists.<sup>42</sup> All Model Rules or requirements of the State Pharmacy Model Act are enforced to the extent that they are adopted by individual states.

Individual states vary in the positions they have taken with respect to USP Chapter <797>. Some states have adopted the chapter in its entirety, while most have chosen to incorporate portions of the chapter into laws or regulations.<sup>43</sup> Other states have not made regulatory changes, but instead developed official policies and procedures. A few states have taken no definitive

**TABLE 1**

## Compounded Sterile Products

### Any compounded:

- Biologic
- Diagnostic
- Drug
- Nutrient
- Radiopharmaceutical

### Any manufactured sterile product

Examples include, but not limited to:

- Aqueous bronchial inhalations
- Aqueous nasal inhalations
- Baths and soaks for live organs and tissues
- Injections of any type
- Irrigations for wounds and body cavities
- Ophthalmic preparations
- Tissue implants

action in terms of written changes to state statutes. Pharmacists in each state must be aware of how USP Chapter <797> is interpreted and enforced because this will impact how compounders must assess and document compliance with the chapter.

Shortly after the initial version of USP Chapter <797> became official, the Joint Commission announced that it would survey for compliance with the new chapter beginning on July 1, 2004.<sup>44</sup> Specific timelines and expectations for compliance were developed and communicated to organizations that were scheduled for surveys by the Joint Commission. In 2006, the Joint Commission revised how it would assess organizations' compliance with USP Chapter <797>. The Joint Commission recognized USP Chapter <797> as "a valuable set of guidelines—contemporary consensus-based safe practices—that describes a best practice for establishing safe processes in compounding sterile medications," but is no longer requiring organizations to implement the chapter as a condition of accreditation.<sup>45</sup> It is important to note that portions of the USP chapters are similar to the Joint Commission's regulations, and in such cases, must be followed for an organization to meet Joint Commission standards. For purposes of accreditation, the Joint Commission "will expect to see structures and processes that ensure safe practices for compounding sterile medication."<sup>45</sup> Organizations are required to review their policies and procedures and decide if any revisions are necessary as part of meeting Joint Commission requirements. The timeline and extent of compliance with USP Chapter <797> that an organization attempts to achieve, if any, will be left to the discretion of the institution and state regulations, not the Joint Commission.

The Pharmacy Compounding Accreditation Board (PCAB), a voluntary system of standards for compounding pharmacies, was established shortly after the initial version of USP Chapter <797> became official. PCAB was formed by eight national pharmacy organizations, including USP, to serve as a voluntary accrediting body for the practice of pharmacy compounding. The standards established by PCAB are similar to those in the USP chapters. Pharmacies that successfully meet PCAB's requirements receive the designation "PCAB Accredited™ compounding pharmacy" and are able to display the PCAB Seal of Accreditation. The accreditation and seal offer the public and prescribers a means of identifying pharmacies that satisfy compounding criteria.

USP Chapter <797> applies to all personnel participating in compounding and many non-pharmacy organizations have taken a position on the applicability and enforcement of the chapter. Statements and updates about the chapter can be found on websites for physicians, physician assistants, and microbiology laboratory personnel, among others. Some state regulatory agencies have adopted and enforced portions of USP Chapter <797>. For example, in Virginia physicians who "perform mixing, diluting, or reconstituting in their practices" are required to report such activities. In addition, the state board of medicine will begin inspecting physician practices on compliance with three statutes many of which address USP Chapter <797> requirements.<sup>46</sup>

## Costs of Compliance

From the beginning, health care practitioners have been concerned about the expense associated with compliance. A cottage industry aimed at assisting facilities and practitioners with USP Chapter <797> compliance has arisen. On the other hand, many institutions have been successful in using an "in-house" approach to reaching compliance. What hospitals and other health care facilities resist most have been physical changes to the work environment.

The new USP Chapter <797> allows several exemptions or exceptions to building full cleanrooms. The immediate-use exemption can eliminate facility upgrade costs in fast-paced treatment areas, such as emergency rooms, operating rooms, therapeutic radiology, cardiac catheterization, and respiratory therapy. The use of proprietary vial and bag systems allows front-line caregivers to activate many different drugs in facilities that need only meet Joint Commission requirements for clean, organized medication preparation areas. In pharmacy satellites and outpatient treatment centers, doing just low-risk up to 12 hour beyond-use dated preparations allows the use of segregated compounding areas without an ante-area. In allergy clinics, no special facilities are required as long as USP Chapter <797> requirements are met.

Actually, the least expensive changes required by USP Chapter <797> tend to be the most effective in reducing CSP contamination and inaccuracy. Training personnel on aseptic technique, hand cleansing, and garbing is relatively inexpensive. Personnel evaluation through observation, testing, media-fills, and fingertip sampling is next most important. Monitoring the environment for surface microbial contamination,

temperature, and humidity is more expensive but effective and leads to more comfortable work environments. Next most important is a review of primary engineering controls, especially those used to protect personnel and the environment from handling hazardous drugs. Finally, remodeling facilities and updating cleaning and disinfection procedures should be accomplished. Remodeling facilities can be the most expensive part of compliance with USP Chapter <797>, although these capital costs can be amortized over many years.

## Getting Started

Many organizations have spent substantial time and resources on becoming compliant with USP Chapter <797>. Facilities that were not able to achieve full compliance with the original standard were still able to benefit from a heightened sense of awareness for proper technique and quality assurance with respect to CSPs. A national survey of the impact of USP Chapter <797> revealed that a few facilities are still unaware of the requirement but most have made attempts at improving training while others fully comply, having designed and built new i.v. admixture cleanrooms.<sup>47</sup> Regardless of changes made to date, the revisions to USP Chapter <797> may require additional modifications to protocols, policies, procedures, and physical layouts to be in compliance.

Key steps that need to be taken to achieve compliance are shown in Figure 2. Organizations that have not yet attempted to achieve compliance with the original standard or institutions attaining only minimal compliance need to establish a CSP risk level. It is critical that such facilities begin with the Pharmacy Compounding-USP <797> Risk Level Assessment (Figure 3).

Organizations that have established their CSP Risk Level can address the two additional risk levels that have been added to the revision. The revised chapter takes into account that different risk levels and beyond use dates (BUDs) may be assigned depending on where in the facility the CSPs are compounded. Standard operating procedures (SOPs) should be developed and are a good starting point when addressing USP Chapter <797> compliance. Facilities needing guidance on what to include in their policy and procedure manuals should consult chapter sections on Suggested SOPs, Elements of Quality Control, Environmental Quality and Control, and Quality Assurance Programs.

**FIGURE 2**

## Steps Toward Compliance

1. Educate yourself on the new standards
2. Determine CSP risk level
3. Complete revised gap analysis to determine level of current compliance
4. Develop action plan
5. Prioritize action items
6. Report gap analysis results and action plan to staff
7. Assign action plan items and timelines to specific employees
8. Document all action plan progress
9. Continually reassess for compliance

When the original standard was published, facilities were encouraged to perform a gap analysis. Organizations should update their gap analyses according to the revised standard. ASHP's "Self-Assessment Tool for Compounding Sterile Preparations" has been revised and may be helpful. If gaps are identified, it is important to develop an action plan to address them taking into consideration the resources necessary to achieve compliance. A reasonable timeline for achieving compliance should be developed and followed. Gap analyses and action plans are important because they can be used to demonstrate to state boards of pharmacy, regulatory agencies, and accrediting bodies that a facility is aware of certain deficiencies and that corrective action is being taken to achieve compliance.

The revised USP Chapter <797> includes a new appendix (appendix I) that explains which competencies, initiatives, practices, and quality assurances the chapter requires versus those that are recommended. It should be helpful when determining priorities. It is important for practitioners to realize that a best practices scenario would incorporate both the required and recommended items. This Discussion Guide provides another appendix (Appendix A) which should be helpful to facilities that have already achieved compliance with the original standard, or are progressing toward it. Appendix A outlines new sections and revisions and explains revisions that need to be addressed.

**FIGURE 3**

Pharmacy Compounding—USP <797> Risk Level Assessment

Classification	Requirements	Yes	No
<b>Immediate-Use Category</b>	<ul style="list-style-type: none"> <li>■ For emergent use, or situations where low-risk compounding would add risk due to delays</li> <li>■ No storage or batch compounding</li> <li>■ Continuous compounding process lasting less than one hour</li> <li>■ Aseptic technique utilized</li> <li>■ Administer less than 1 hour after preparation begins, or discard</li> <li>■ Simple transfer of sterile nonhazardous drugs or diagnostic radiopharmaceuticals</li> </ul>		
<b>Low-Risk Level</b>	<ul style="list-style-type: none"> <li>■ Simple admixtures compounded using closed system transfer methods</li> <li>■ Prepared in ISO Class 5 LAFW</li> <li>■ Located in ISO Class 7 buffer area with ISO Class 8 ante area</li> <li>■ Examples include reconstitution of single-dose vials of antibiotics or other small-volume parenterals, preparation of hydration solutions</li> </ul>		
<b>Low-Risk Level with &lt;12 Hour Beyond Use Date</b>	<ul style="list-style-type: none"> <li>■ Simple admixtures compounded using closed system transfer methods</li> <li>■ Prepared in ISO Class 5 PEC</li> <li>■ Compounding area is segregated from non-compounding areas</li> <li>■ Administration must start no later than 12 hours after preparation</li> </ul>		
<b>Medium-Risk Level</b>	<ul style="list-style-type: none"> <li>■ Admixtures compounded using multiple additives and/or small volumes</li> <li>■ Batch preparations (e.g., syringes)</li> <li>■ Complex manipulations (e.g., TPN)</li> <li>■ Preparation for use over several days</li> <li>■ Prepared in ISO Class 5</li> <li>■ Located in ISO Class 7 buffer area with ISO Class 8 ante area</li> <li>■ Examples include pooled admixtures, parenteral nutrition solutions using automated compounders, batch-compounded preparations that do not contain bacteriostatic components</li> </ul>		
<b>High-Risk Level</b>	<ul style="list-style-type: none"> <li>■ Non-sterile (bulk powders) ingredients</li> <li>■ Open system transfers</li> <li>■ Prepared in ISO Class 5</li> <li>■ Located in ISO Class 7 buffer area with separate ISO Class 8 ante area</li> <li>■ Examples include CSPs prepared from bulk, nonsterile components or final containers that are nonsterile and must be terminally sterilized</li> </ul>		

## USP Chapter <797> Summary

The following points highlight each of the major sections within USP Chapter <797>. These summaries should not serve as a substitute for the actual text of the USP Chapter. It is important that the revised chapter be obtained from USP, either in stand-alone format or as a component of the Second Supplement to USP 31-NF 26. Institutions are strongly encouraged to consult the entire USP 31/NF 26 reference book, including the supplement, or the 2nd Edition of USP Pharmacists' Pharmacopeia so that they will have access to other important chapters that are referenced in USP Chapter <797>.

### Introduction

Compounded sterile preparations extend beyond traditional intravenous admixture compounding programs (Table 1). The differences between sterile and nonsterile compounding, which are governed by USP Chapter <795>, Pharmaceutical Considerations: Nonsterile Preparations and <1075> Good Compounding Practices are explained in the introduction. The objective of USP Chapter <797> is to prevent harm to patients, including death, which could result from the following with respect to CSPs:

- Microbial contamination,
- Excessive bacterial endotoxins,
- Variability in the intended strength of correct ingredients,
- Unintended chemical and physical contaminants, and
- Ingredients of inappropriate quality.

The chapter provides specific ways to reduce any of the above from being incorporated into CSPs and highlights the importance of preventing contamination of CSPs.

Practitioners had many questions about the basis on which the original USP Chapter <797> was founded. Some of those questions have been answered in the introduction to the revision, which states that the chapter “provides minimum practice and quality standards for CSPs of drugs and nutrients based on current scientific information and best sterile compounding practices.” Chapter <797> says, “The use of technologies, techniques, materials, or procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or

superior with statistical significance to those described” in the Chapter. This places the onus on health care practitioners who use alternative technologies to have strong comparative evidence that the alternatives are as good as or better than practices described in USP Chapter <797>.

Readers will notice some changes in terminology. For example, pharmacists and pharmacies have been replaced by compounders, compounding personnel, and compounding facilities. The standards in USP Chapter <797> apply to “all persons who prepare CSPs and all places where CSPs are prepared.” This means that pharmacists and pharmacies are not the only practitioners and departments held accountable to these standards. The introduction also makes a point of explaining that clinical administration of CSPs by any route from the standard is excluded.

### Definitions

Learning the terminology in the original USP Chapter <797> was a challenge for many compounding personnel. To make the process easier, the terms used in the chapter have been standardized, and definitions for 29 terms have been included in this new section. The Expert Committee decided to include this information to decrease confusion so that practitioners could focus on implementation.

### Responsibility of Compounding Personnel

This section, which outlines the responsibilities of personnel involved in compounding sterile preparations, is nearly identical to the original version. The section states, “compounding personnel are responsible for ensuring that CSPs are accurately identified, measured, diluted and mixed, and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed.” These performance responsibilities include maintaining appropriate cleanliness conditions and providing labeling and supplementary instructions for proper clinical administration of CSPs. The responsibilities of the compounding supervisor are also listed. Persons who supervise the compounding and dispensing of CSPs should be a “qualified licensed healthcare professional” and are responsible for ensuring that the following 14 objectives are achieved:

1. Personnel are adequately skilled, educated, instructed, and trained to perform and document their functions.
2. Ingredients have their correct identity, quality, and purity.

3. Open or partially used containers are properly stored.
4. Water-containing nonsterile CSPs are sterilized within 6 hours.
5. Proper and adequate sterilization is used.
6. Components are clean, accurate, and appropriate.
7. Potential harm from added substances is evaluated prior to dispensing.
8. Appropriate packaging is selected for sterility and stability.
9. Compounding environment maintains the sterility or purity of items.
10. Labels are appropriate and complete.
11. Beyond-use dates are appropriate and based on valid scientific criteria.
12. Correct compounding procedures are used.
13. Deficiencies in compounding can be rapidly identified and corrected.
14. Compounding is separate from quality evaluations.

Items in this above list have been abbreviated. Practitioners should consult the chapter for details and clarifications on each objective.

### CSP Microbial Contamination Risk Levels

Two new microbial contamination risk levels, immediate-use and the sub-level, low-risk level with <12-hour BUD, have been added to the revision. As before, compounding personnel are responsible for determining the appropriate compounding risk levels for CSPs. The three risk levels from the original standard are low risk, medium risk, and high risk. The revised chapter includes examples of compounds that could fall into each

category; however, the examples are provided as guidance only, with the understanding that the levels could change depending on circumstances in individual facilities. Beyond-use dating has been modified slightly as a direct result of feedback from practitioners (Table 2). Microbial contamination risk levels are defined as follows:

#### Immediate-Use CSPs

- Only for use in emergency situations or when preparation of the CSP under low-risk level conditions would subject patient to additional risk due to delays in therapy
- No storage or batch compounding
- Applies only to products that would otherwise be considered low-risk CSPs; medium- and high-risk level CSPs are not eligible for immediate use designation
- Exemption from low-risk level requirements, including ISO 5 conditions, if all of the following are met:
  - Simple transfer of not more than 3 commercially manufactured packages of sterile nonhazardous drugs or diagnostic radiopharmaceuticals
  - Compounding is a continuous process lasting less than one hour
  - Aseptic technique is utilized, and CSP is under constant surveillance to minimize contamination
  - Administration begins not later than 1 hour after preparation begins
  - If not administered immediately, CSP is labeled appropriately, including the exact 1-hour BUD and time
  - CSP will be discarded if administration has not begun within 1 hour

**TABLE 2**  
Beyond-Use Dates

Risk Category	Room Temperature	Refrigeration	Frozen ( $\leq 10^{\circ}\text{C}$ )
Immediate-Use	1 hour	1 hour	N/A
Low-Risk	48 hours	14 days	45 days
Low-Risk with 12-hour BUD	12 hours	12 hours	N/A
Medium-Risk	30 hours	9 days	45 days
High-Risk	24 hours	3 days	45 days

### Low-Risk Level CSPs

- CSPs compounded from sterile commercial drugs using commercial sterile devices
- Compounding occurs in ISO Class 5 environment at all times
- Compounding procedures involve only transferring, measuring, and mixing manipulations using not more than 3 sterile products and not more than 2 entries into each sterile container
- Involves only a few closed-system basic, simple aseptic transfers and manipulations
- ISO 5 engineering control must be located within an ISO 7 buffer area
- At a minimum, all quality assurance, garbing, and visual inspection release check procedures outlined by this section are followed
- Annual media-fill and other applicable competency testing completed for each person who compounds

### Low-Risk Level with 12-hour or Less BUD

- All procedures as outlined for low-risk level CSPs, except, ISO Class 5 primary engineering control (PEC) is not located within an ISO Class 7 buffer area
- Preparations must be patient specific, based on a prescriber's order
- Administration must start no later than 12 hours after preparation
- Compounding area is segregated from areas including, but not limited to: unsealed windows, high traffic areas, food service, or construction to decrease contamination risk
- Sinks should not be adjacent to ISO 5 PEC
- All quality assurance, garbing, aseptic technique procedures, competencies, and environmental testing outlined in the chapter apply to this risk level

### Medium-Risk Level

- Involves using multiple pooled sterile commercial products for multiple patients or one patient multiple times
- Involves complex aseptic manipulations (TPN or other multiple-ingredient CSPs)
- Compounding occurs over a prolonged period of time (complex procedures)

- No bacteriostatic agents are added to the preparation and it is administered over several days (chemotherapy or pain management administered via implanted infusion device)
- Environmental conditions and quality assurance procedures comply with low-risk guidelines
- Requires more challenging annual media-fill evaluation of compounding personnel technique that simulates the most challenging or stressful conditions

### High-Risk Level

- Prepared from non-sterile ingredients or with non-sterile devices
- Preparation from sterile ingredients but exposed to less than ISO Class 5 for greater than 1 hour, including sterile contents of commercial products, CSPs that lack effective antimicrobial preservatives and sterile surfaces of devices and containers used in compounding
- Improper garbed and gloved personnel
- More than 6-hour delay from compounding to sterilization of water-containing preparations
- Purity and content strength of components are assumed, but not verified by documentation or direct determination
- Quality assurance procedures comply with low-risk guidelines
- Requires a semiannual media-fill evaluation of compounding personnel technique that simulates the most challenging or stressful conditions using dry nonsterile media verification of compounding personnel technique
- Requires simulation of each high-risk level compounding sterilization process using dry nonsterile media verification

### Personnel Training and Evaluation in Aseptic Manipulation Skills

Very few revisions were made in this section. Compounding personnel need to perform didactic review and are required to pass written and media fill testing of their skills at least yearly for low-and medium-risk compounding and semiannually for high-risk level compounding. Personnel are referred to chapter <71> *Sterility Tests* and <1116> *Microbiological Evaluation of Clean Rooms and Other Controlled Environments* for more explicit guidance.

## Single-Dose and Multiple-Dose Containers

This is a new section and provides criteria for BUDs of single- and multiple-dose containers. If conditions are less than ISO Class 5, opened or needle-punctured single-dose containers are to be used within 1 hour. If conditions are ISO Class 5 or cleaner all single-dose containers may be used for up to 6 hours after needle punctures. Open ampuls should not be stored regardless of the environmental surroundings. Unless written documentation from the manufacturer specifies alternative dating, multiple-dose containers have a 28-day BUD after needle puncture of the vial diaphragm.

## Hazardous Drugs as CSPs

A major change in the standard is the separate category given to handling hazardous drugs. In 2004, the National Institute for Safety and Health (NIOSH) published a NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings.<sup>48</sup> The purpose of these guidelines was to prevent work-related injury and illness caused by exposure to hazardous drugs. The NIOSH guidelines are advisory unless they are adopted as regulations by the Occupational Safety and Health Administration (OSHA). The NIOSH standards and USP Chapter <797> are in close alignment.

The primary purpose of this section is to ensure the safety of personnel during the compounding and storage of hazardous drugs. Personnel are required to wear appropriate chemotherapy gloves during “receiving, distribution, stocking, inventorying, preparation for administration, and disposal.” Hazardous drugs must be stored and prepared within a negative pressure buffer area of ISO Class 7 or better. Caution is paramount during the preparation phase with the use of ISO Class 5 biological safety cabinets (BSCs) or compounding aseptic containment isolators (CACIs) being required. The ISO Class 7 buffer area must be physically separate from other areas, and hazardous drugs can be stored within the buffer area as long as the area passes certification. Any adjacent ante-areas must also be ISO Class 7 certified and can be a common ante-area servicing hazardous drugs and non-hazardous drugs buffer areas. The anteroom ISO level requirements for hazardous drugs must be ISO Class 7 because air from the anteroom will be drawn into the negative pressure buffer room. BSCs and CACIs optimally should be 100% vented to the outside air through HEPA filtration.

ISO Class 5 CACIs that cannot be located within an ISO Class 7 environment must still adhere to nega-

tive pressure specifications and the compounding area must have at least 12 air changes per hour (ACPH) to meet the specifications of the standard. Facilities that prepare low volumes of hazardous drugs are not required to have a buffer area as long as they adhere to a two-tier containment plan for preparation. Acceptable two tiers of containment could be a closed system transfer device (CTSD) within an ISO Class 5 BSC or CACI that is located in a non-negative pressure room

This section outlines in specific detail requirements for personnel protective equipment (PPE) (see Table 3) and training for personnel preparing hazardous drugs. The training must include didactic review of hazardous drugs, and the training must be ongoing (e.g., personnel should receive training for all new hazardous drugs that are marketed). Training should include the following:

- Didactic review of hazardous drugs and their properties,
- Proper aseptic manipulation techniques,
- Appropriate techniques for compounding within a BSC or CACI,
- Proper use of CTSD devices,
- Containment, cleanup, and disposal techniques for breakages and spills, and
- Procedures for treating personnel who have been exposed to hazardous drugs.

Optimally, environmental testing will include routine surface sampling to detect uncontained hazardous drugs. Exposure to these agents is potentially mutagenic, teratogenic, and carcinogenic; therefore, personnel capable of becoming parents must sign documentation that they understand the risks of compounding hazardous drugs. Personnel, including custodial staff, must be trained in appropriate disposal protocols as outlined by state and federal regulations.

## Radiopharmaceuticals as CSPs

The USP Expert Committee convened an ad hoc advisory panel of pharmacists and scientists for the express purpose of reviewing the radiopharmaceuticals section.<sup>19</sup> Guidelines for determining the specific compounding risk levels of radiopharmaceuticals are provided in this section. Specific attention is paid to positron emission tomography (PET) radiopharmaceuticals and technetium-99m generator systems. Standards for the production of PET drugs are addressed in USP Chapter <823> *Radiopharmaceuticals for Positron Emission Tomography—Compounding*, while USP

**TABLE 3.**  
**Personnel Cleansing and Garbing Order**

<b>Prior to entering buffer area or segregated compounding area</b>	<ul style="list-style-type: none"> <li>■ Remove all personal outer garments</li> <li>■ Remove cosmetics</li> <li>■ Remove jewelry from hands, wrists, or any other visible body parts</li> <li>■ No artificial nails allowed</li> <li>■ Don PPE in the following order:               <ol style="list-style-type: none"> <li>1–Dedicated shoes or shoe covers</li> <li>2–Head and facial hair covers</li> <li>3–Face masks/eye shields</li> <li>4–Perform hand cleansing procedures</li> <li>5–A non-shedding gown</li> </ol> </li> </ul>
<b>Upon entering buffer area or segregated compounding area</b>	<ul style="list-style-type: none"> <li>■ Antiseptic hand cleansing with surgical scrub</li> <li>■ Don sterile powder-free gloves</li> </ul>

PPE=personnel protective equipment.

Chapter <797> applies to “the further handling, manipulation, or use of the product” once it is released as a finished product from a production facility. According to USP Chapter <797> standards, technetium-99m/molybdenum-99 generator systems must be stored and operated in an ISO Class 8 environment. Procedures shall address ways to limit acute and chronic radioactivity exposure to as low as reasonably achievable (ALARA).

### Allergen Extracts as CSPs

Public comments in response to an article about the implications of regulatory guidelines on allergen vial mixing were instrumental in the development of this section.<sup>49</sup> Of 27,000 immunotherapy injections, none of which were prepared according to USP Chapter <797> specified controlled environments or garbing procedures, no infections were reported.<sup>49</sup> Allergen extracts as CSPs are excluded from the personnel, environmental, and storage standards as long as 11 criteria are met, including the use of sterile products and equipment and adherence of compounding personnel to many of the garbing, gloving, and handwashing requirements for low-risk level compounding. This section also outlines further requirements for aseptic technique, labeling, and storage procedures for allergen extracts.

### Verification of Compounding Accuracy and Sterility

The quality (sterility and accuracy) of the CSP is directly related to ensuring that methods used to compound the sterile preparation achieve the desired goal of purity, potency, and sterility. This section has been expanded to include additional terminal sterilization techniques. The revised section also refers the user to USP Chapters (<71>, <1035>, <731>, <1160>, <1211>) for guidance on methods of sterilization and compounding accuracy and validation. In the original chapter sterilization by filtration was described; this method has been expanded in the revision to include the requirement that filters used for sterilization must undergo integrity testing as specified by the manufacturer. Proof that the end-products are accurate and sterile is also required.

### Environmental Quality and Control

This section has been revised substantially and is nearly 15 pages in length. The section now provides detailed information on facility design, environmental, and engineering controls; environmental testing and cleaning procedures; and personnel garbing, training and testing requirements. Following are some of the requirements, which are dependent on CSP risk level.

## Facility Design

- Must have an ISO Class 5 environment as a PEC for critical site exposure. Laminar airflow workbenches (LAFW), BSCs, CAIs, and CACIs are common ISO Class 5 environments.
- The compounding area must be separated from activities not essential to CSP preparation and must be a controlled (particle, temperature) environment.
- Must have an ISO Class 7 environment for buffer area or cleanroom.
- Must have an ISO Class 8 environment for ante-areas.
- Buffer areas physically separated from ante areas must have a positive pressure differential; if no physical separation is present, displacement airflow principles must be used (high airflow velocity, low pressure differential).
- High-risk compounding is not eligible for displacement airflow; a physical separation must exist between buffer room and anteroom.
- Must have adequate ACPHs to maintain appropriate ISO Class, ACPH may be improved upon by PECs that re-circulate air between the room and the PEC itself.

## Environmental and Engineering Controls

- Placement of non-essential items within buffer and ante areas is determined by the impact on environmental quality as verified by monitoring.
- PECs must be physically located within an ISO Class 7 buffer area with two exceptions noted for CAIs or CACIs that meet specified conditions.

## Environmental Testing

- Environmental monitoring must be routinely performed to prove that the compounding environment is properly maintained. Documentation that proves control is required.
- Nonviable and viable airborne particle testing programs must be part of the facility's quality management program.
- Total particle counts must be conducted at a minimum of every 6 months for PECs, buffer areas, and ante-areas. Counts must also be obtained if the PEC is relocated or if physical alterations are made to the buffer or ante-areas.
- Viable airborne particle sampling plans of the PECs, buffer areas, ante-areas, and segregated

compounding areas at greatest risk of contamination must be developed and adhered to using electronic volumetric collection devices. Sampling should occur at least every 6 months.

- Must conduct regular surface sampling to test for adherence to cleaning and disinfecting procedures.
- Follow growth media specifications and incubation times specific to the type of sampling. Corrective actions should be based on microbial contamination action levels and microorganism identification.

## Cleaning Procedures

- There must be detailed cleaning and sanitizing procedures for ISO Class 5 PECs in order to maintain the cleanliness of the direct compounding area.
- Buffer area and ante-area ceilings, walls, and shelving must be cleaned monthly, while counters, work surfaces, and floors must be cleaned daily.
- Visual observation of cleaning and disinfecting techniques for all compounding and non-compounding personnel must occur at specified intervals.

## Personnel Cleansing and Garbing

- Compounding personnel will be properly garbed according to the risk level of compounding (Table 3).
- Policies and procedures addressing handwashing techniques shall exist.

## Personnel Training and Competency Testing

- In addition to media fill testing, subject matter areas of garbing, aseptic technique, achieving and maintaining various ISO Class conditions, and cleaning and disinfection techniques must be included in training procedures and competency evaluations.
- Gloved fingertip sampling and witnessed handwashing and garbing for all compounding personnel competency assessments.
- Completion and documentation must occur prior to compounding personnel preparing CSPs. Competencies, didactic training, written examinations, media fill testing, and gloved fingertip testing must be repeated on an annual or semi-annual basis for low- and medium-risk, and high-risk level compounding, respectively.

## Elements of Quality Control

The previous sections Processing, Aseptic Technique, Components, and Equipment have been incorporated into this new section. Training is the cornerstone of ensuring quality and safety of CSPs. This section calls for the development of a written employee-training and evaluation program for each site at which CSPs are prepared.

Particular attention is paid to the integrity of both sterile and nonsterile ingredients, with guidance given on how to inspect components as well as elements to be incorporated in written protocols. The section addresses the importance of using equipment that operates properly and within acceptable tolerance limits. A list of procedures that must be established for the proper use of compounding devices is also provided. The importance of adhering to policies and procedures as a means of ensuring quality and patient safety is also emphasized.

## Verification of Automated Compounding Devices (ACDs) for Parenteral Nutrition Compounding

The revisions to this section are mainly editorial and include the addition of suggested procedures for ensuring the accuracy and precision of ACDs. It is important that users be adequately trained, and the ACDs be properly calibrated, set up, and maintained.

## Finished Preparation Release Checks and Tests

All finished CSPs are required to be checked by a licensed healthcare person according to written policies and procedures prior to dispensing to ensure that the preparation is sterile and accurate. Several methods can be employed to meet this requirement and include:

- Physical visual inspection for preparation integrity (e.g., absence of cores, other particulate matter, phase changes, and discoloration).
- Verification of compounding accuracy conducted by someone other than the compounder to ensure proper measurement, reconstitution, and component usage.
- High-Risk Level CSPs in groups of >25 must be tested according to USP Chapter <71> Sterility Test and <85> Bacterial Endotoxin Test.
- Low-and Medium-Risk Level CSPs that exceed the USP chapter guidelines for beyond-use dating must be tested according to USP Chapter <71>.

- Accurate labeling and determination of correct fill volumes or quantities are outlined in written procedures.

## Storage and Beyond-Use Dating

In many healthcare settings, CSPs are prepared in anticipation of use and as such may be stored for extended periods of time. This section of the chapter focuses on the microbial limits of CSPs based on risk level and duration of storage. When a CSP is stored for a prolonged period of time prior to use, there is potential for microbial growth and pyrogen formation. As mentioned earlier in the discussion guide, two components—chemical stability and microbial sterility—are described.

- Microbiological limits based on risk level
- Chemical stability limits obtained from literature or testing using validated equipment (e.g., HPLC, TLC and flame spectrophotometry)
- USP Chapter <795> provides guidance for instances where bulk nonsterile components do not have expiration dates.
  - Solids and nonaqueous liquids—25% of the remaining expiration period or 6 months (whichever is less)
  - USP bulk nonsterile components—no more than (NMT) 6 months
  - Aqueous formulations—14 days refrigerated
  - All others—NMT 28 days or intended duration of therapy

## Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs

This section (formerly Maintaining Product Quality and Control After the CSP Leaves the Pharmacy) has been renamed. The section has undergone some revision although its intent has not changed. Compounding personnel are responsible for ensuring that the quality and integrity of CSPs are maintained during transit, regardless of physical location within the health system (hospital, home, or ambulatory infusion center). This responsibility includes the use of appropriate packaging that is capable of maintaining proper temperature and conditions (refrigerated or frozen state) during shipment via common carrier. Quality control responsibilities during transit also include the delivery of CSPs within a healthcare organization via courier or pneumatic tube system. Specific considerations in the following subsections are also covered:

- Packaging, Handling and Transport
- Use and Storage
- Ready for Administration
- Redispensed CSPs
- Education and Training
- Packing and Transporting CSPs
- Storage in Locations Outside Compounding Facilities

### **Patient or Caregiver Training**

It is crucial that the patient or caregiver (e.g., nurse, physician, spouse, and parent) clearly understands how to store, administer, and dispose of the CSP at all times. A formal training program is required to ensure that all persons involved in the handling and use of the CSP are knowledgeable and properly trained. For any facilities participating in home care dispensing, this section provides 12 objectives and competencies for patients and caregivers. This section also provides guidance on training and assessment programs, which can be used by facilities in the development of their own programs.

### **Patient Monitoring and Adverse Events Reporting**

A key component in the pharmaceutical care delivery model is monitoring the patient's response (appropriate and adverse) to therapy. This section focuses on ensuring that patients are clinically monitored when receiving CSPs. Also required is the provision of an effective feedback mechanism for patients and caregivers to report concerns regarding CSPs or administration devices. Review and evaluation of adverse event reports can serve as a quality indicator to improve patient care.

### **Quality Assurance Program**

This section is an excellent starting place for facilities that are attempting to put in place a formal quality assurance program. The section outlines six characteristics of a quality assurance program.

### **Appendices**

The original chapter included one appendix that outlined criteria based on risk levels. The revised chapter includes five appendices covering a variety of topics. Appendix I provides an overview of the principal competencies, conditions, practices, and quality assurances that are required and recommended in the chapter. Appendix II lists common disinfectants for inanimate surfaces and non-critical devices, while Appendices III–V are sample forms that can be used to assess compliance with compounding procedures.

## References

1. Pharmaceutical compounding-sterile preparations (general information chapter 797). In: The United States pharmacopeia, 27th rev., and The national formulary, 22nd ed. Rockville, MD: The United States Pharmacopeial Convention, 2004:2350-70.
2. Duma RJ, Warner JF, Dalton HP. Septicemia from intravenous infusions. *N Engl J Med.* 1971; 284:257-60.
3. Felts SK, Schaffner W, Melly Ma et al. Sepsis caused by contaminated intravenous fluids. Epidemiologic, clinical, and laboratory investigation of an outbreak in one hospital. *Ann Intern Med.* 1972; 77:881-90.
4. National Coordinating Committee on Large Volume Parenterals. Recommended methods for compounding intravenous admixture in hospitals. *Am J Hosp Pharm.* 1975; 32:261-70.
5. National Coordinating Committee on Large Volume Parenterals. Recommended system for surveillance and reporting of problems with large volume parenterals in hospitals. *Am J Hosp Pharm.* 1975; 34:1251-3.
6. National Coordinating Committee on Large Volume Parenterals. Recommendations for the labeling of large volume parenterals. *Am J Hosp Pharm.* 1978; 35:49-51.
7. National Coordinating Committee on Large Volume Parenterals. Recommended procedures for in-use testing of large volume parenterals suspected of contamination or of producing reactions in a patient. *Am J Hosp Pharm.* 1978;35:678-82.
8. National Coordinating Committee on Large Volume Parenterals. Recommended guidelines for quality assurance in hospital centralized admixtures in hospitals. *Am J Hosp Pharm.* 1980; 37:645-55.
9. National Coordinating Committee on Large Volume Parenterals. Recommended standard of practice, policies and procedures for intravenous therapy. *Am J Hosp Pharm.* 1980; 37:660-3.
10. National Coordinating Committee on Large Volume Parenterals. Recommendations to pharmacists for solving problems with large-volume parenterals—1979. *Am J Hosp Pharm.* 1980; 37:663-7.
11. Barker KN, ed. Recommendations of the NCCLVP for the compounding and administration of intravenous solutions. Bethesda, MD. American Society of Hospital Pharmacists;1981.
12. The United States Pharmacopeia, 23rd rev., and the National Formulary 19th ed. USP General Information Chapter <1206>. Sterile Drug Products for Home Use. Rockville, MD: The United State Pharmacopeial Convention, 1995.
13. American Society of Health-System Pharmacists. ASHP Technical Assistance Bulletin on Quality Assurance for Pharmacy-Prepared Sterile Products. *Am J Hosp Pharm.*1993; 50:2386-98.
14. Santell JP, Kamalich RF. National survey of quality assurance activities for pharmacy-prepared sterile products in hospitals and home infusion facilities-1995. *Am J Health-Syst Pharm.* 1996;53:2591-605.
15. Morris AM, Schneider PJ, Pedersen CA et al. National survey of quality assurance activities for pharmacy-compounded sterile preparations. *Am J Health-Syst Pharm.* 2003; 60:2567-76.
16. [No Author Listed.]US Food and Drug Administration.[US Food and Drug Administration Website.] Food and Drug Administration Modernization Act of 1997. Available at: <http://www.fda.gov/cber/genadmin/fdamod97.txt> Accessed April 8, 2008
17. US Food and Drug Administration. Compliance Policy Guides Manual. Sec. 460.200 Pharmacy Compounding. Reissued 5/29/02. Available at: [http://www.fda.gov/ora/compliance\\_ref/cpg/cpgdrg/cpg460-200.html](http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html). Accessed 2/28/2008
18. [No Author Listed.] US Food and Drug Administration.[US Food and Drug Administration Website.]Compliance Policy Guide. Sec.460.200 Pharmacy Compounding. Available at: [http://www.fda.gov/ora/compliance\\_ref/cpg/cpgdrg/cpg460-200.html](http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html) Accessed April 8, 2008.
19. United States Pharmacopeia. Commentary-To Revision Bulletin for General Chapter Pharmaceutical Compounding-Sterile Preparations <797>. Available at: <http://www.usp.org/pdf/EN/USPNF/general-Chapter797Commentary.pdf>. Accessed 2/13/08.
20. Arnold TR, Hepler CD. Bacterial contamination of intravenous fluids opened in unsterile air. *Am J Hosp Pharm.* 1971; 28:614-9.
21. Solomon SL, Khabbaz RF, Parker RH et al. An outbreak of *Candida parapsilosis* bloodstream infections in patients receiving parenteral nutrition. *J Infect Dis.* 1984; 149:98-102.
22. Hughes CF, Grant AF, Leckie BD et al. Cardioplegia solution: A contamination crisis. *J Thorac Cardiovasc Surg.* 1986; 91:296-302.
23. Associated Press. Pittsburgh woman loses eye to tainted drug;12 hurt. *Baltimore Sun.* November 9, 1990:3A.
24. Dugleaux G, Coutour XL, Hecquard C et al. Septicemia caused by contaminated parenteral nutrition pouches: The refrigerator as an unusual cause. *J Parenter Enteral Nutr.* 1991; 15:474-75.
25. Perrin J. Unsafe activities of compounding pharmacists. *Am J Health-Syst Pharm.* 1995; 52:2827-8.
26. Pierce LR, Gaines A, Varricchio R et al. Hemolysis and renal failure associated with use of sterile water for injection to dilute 25% human albumin solution. *Am J Health-Syst Pharm.* 1998; 55:1057-70.
27. Food and Drug Administration. Hazards of precipitation with parenteral nutrition. *Am J Health-Syst Pharm.* 1994; 51:427-428.
28. Hallissy E, Russell S. Who's mixing your drugs? Bad medicine: pharmacy mix-ups a recipe for misery; Some drugstores operate with very little oversight. *San Francisco Chronicle.* June 23, 2002.
29. Centers for Disease Control and Prevention. Exophiala infection from contaminated injectable steroids prepared by a compounding pharmacy—United States, July—November 2002. [www.cdc.gov/mmwr/preview/mmwrhtml/mm5149a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5149a1.htm) (Accessed 2008 Feb 26).
30. US Food and Drug Administration Website. Report: Limited FDA Survey of Compounded Drugs. Available online at <http://www.fda.gov/cder/pharmcomp/survey.htm>. (Accessed 2008 Feb 28).
31. Selenic D, Dodson DR, Jensen B et al. Enterobacter cloacae bloodstream infections in pediatric patients traced to a hospital pharmacy. *Am J Health-Syst Pharm.* 2003; 60:1440-6.
32. Centers for Disease Control and Prevention. Pseudomonas bloodstream infections associated with a heparin/saline flush—Missouri, New York, Texas, and Michigan, 2004—2005. [www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm). (Accessed 2008 Feb 26).
33. Compounded i.v. solution linked to sepsis cases. American Society of Health-System Pharmacists. Bethesda, MD. 21 March 2005. (Accessed Jan 6, 2008)
34. Pharmacy linked to multiple-state outbreak of *Serratia* infections. American Society of Health-System Pharmacists. Bethesda, MD, 21 October 2005. (Accessed 2008 Jan 6)
35. Tresoldi AT, Padoveze MC, Trabasso P et al. *Enterobacter cloacae* sepsis outbreak in a newborn unit caused by contaminated total parenteral nutrition solution. *Am J Infect Control.* 2000; 28:258-61.

36. Patel PR, Larson AK, Castel AD et al. Hepatitis C virus infections from contaminated radiopharmaceuticals used in myocardial perfusion studies. *JAMA*. 2006; 296:2005-11.
37. Brier KL, Latiolais CJ, Schneider PJ et al. Effect of laminar airflow and cleanroom dress on contamination rates of intravenous admixture. *Am J Hosp Pharm*. 1981; 38:1144-7.
38. Thomas M, Sanborn MD, Couldry R. I.V admixture contamination rates: traditional practice site versus a class 1000 cleanroom. *Am J Health-Syst Pharm*. 2005; 62:2386-92.
39. Trissel LA, Ogundele AB, Ingram DS et al. Using medium-fill simulation to establish a benchmark microbiological contamination rate for low-risk-level compounding. *Am J Health-Syst Pharm*. 2003; 60:1853-5.
40. Trissel LA, Gentempo RW, Anderson RW et al. Using a medium-fill simulation to evaluate the microbial contamination rate for USP medium-risk-level compounding. *Am J Health-Syst Pharm*. 2005; 62:285-8.
41. Trissel LA, Gentempo JA, Saenz LM et al. Effect of two work practice changes on the microbial contamination rates of pharmacy-compounded sterile preparations. *Am J Health-Syst Pharm*. 2007; 64:837-41.
42. National Association of Boards of Pharmacy. Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy. Mount Prospect, IL. Aug 2007.
43. Clinical I.Q. Website. US Boards of Pharmacy, Sterile Compounding Laws, Regulations and CE Map. [http://www.clinicaliq.com/component?option=com\\_google\\_maps/Itemid,111/](http://www.clinicaliq.com/component?option=com_google_maps/Itemid,111/). (Accessed 2008 Feb 27).
44. Joint Commission on Accreditation of Healthcare Organizations. Time frames for completing the various sections of USP Chapter 797. *Jt Comm Perspect*. 2004; 24(10):13-4.
45. Clarification: Joint Commission expectations related to USP-NF Chapter 797 on Compounding Sterile Preparations. *Jt Comm Perspect*. 2006:26(5):
46. Virginia Board of Medicine Board Briefs. Mixing, diluting, and reconstituting. 2007;68. <http://www.dhp.virginia.gov/medicine/newsletters/BoardBrief68.doc> (Accessed 2008 Feb 26).
47. Candy TA, Schneider PJ, Pedersen CA. Impact of United States Pharmacopeia chapter 797: Results of a national survey. *Am J Health-Syst. Pharm*. 2006;63:1336-43.
48. NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings. 2004-165. <http://www.cdc.gov/niosh/docs/2004-165/#g> (Accessed 2008 Feb 19).
49. Lin SY, Houser SM, Rodriguez HP. The implications of regulatory guidelines on allergen vial mixing for the practicing otolaryngologist. *Otolaryngol Head Neck Surg*. 2007; 136(6):1017-8.

## APPENDIX A

### Comparison of Original and New USP Chapter <797>

USP Chapter <797> Section	Status	Revisions and Additions
<b>Introduction</b>	Revised	<ul style="list-style-type: none"> <li>■ More detailed introduction</li> <li>■ Identifies Direct Contact with critical sites as posing the “greatest probability of risk to patients”</li> <li>■ Alternative technologies, techniques, materials, and procedures may be utilized to achieve compliance IF they have been proven to be “equivalent or superior with statistical significance” to the ones outlined in the chapter</li> <li>■ Excludes clinical administration from this chapter</li> <li>■ Broadens and clarifies the types of CSPs</li> </ul>
<b>Definitions</b>	New	<ul style="list-style-type: none"> <li>■ 29 terms are defined by the chapter in this new section</li> </ul>
<b>Responsibility of Compounding Personnel</b>	Minor, Editorial Revisions	
<b>CSP Microbial Contamination Risk Levels</b>	Revised	<ul style="list-style-type: none"> <li>■ Low-risk category CSPs are limited to no more than 3 commercially manufactured packages of sterile products and no more than two entries into any sterile container or administration device</li> <li>■ New subcategory of low-risk level CSPs with 12-hour or less BUD added</li> <li>■ Medium-risk level CSPs may be stored under refrigeration for 9 days</li> <li>■ Medium-risk level CSPs drop the prior exception for sterile CSPs that contain broad-spectrum bacteriostatic substances (See section on single and multiple-dose containers).</li> <li>■ Media-Fill Test Procedures are expanded upon</li> <li>■ Incubation temperature ranges modified to 20–25 °C or 30–35 °C</li> <li>■ High-risk level CSP condition added for sterile surfaces of devices and containers exposed to air quality worse than ISO Class 5 for longer than one hour</li> <li>■ High-risk level CSP condition added for improperly garbed and gloved compounding personnel</li> <li>■ High-risk CSP condition changed from non-sterile preparations exposed for at least 6 hours before sterilization to just water-containing preparations exposed for at least 6 hours before sterilization.</li> </ul>
<b>Personnel Training and Evaluation of Aseptic Manipulation Skills</b>	Revised	<ul style="list-style-type: none"> <li>■ Incubation guidelines added for media-fills where 1 or temperature ranges can be used</li> </ul>
<b>Immediate-Use CSPs</b>	New	<ul style="list-style-type: none"> <li>■ New risk level, exempt from USP &lt;797&gt; requirements</li> <li>■ Only for emergency or immediate patient administration situations</li> <li>■ Not more than 3 sterile, non-hazardous drug products in the preparation</li> <li>■ Administration must begin within one hour after START of preparation</li> <li>■ Unless under continual, immediate supervision, each dose is labeled appropriately</li> <li>■ Unless administration begins within one hour of the start of preparations, the CSP is discarded appropriately</li> </ul>

USP Chapter <797> Section	Status	Revisions and Additions
<b>Single-Dose and Multiple-Dose Containers</b>	New	<ul style="list-style-type: none"> <li>■ Must use single-dose containers within 1 hour if in less than ISO 5 conditions</li> <li>■ May use single-dose containers for up to 6 hours if in ISO 5 conditions</li> <li>■ After opening, ampuls may not be stored for any time period</li> <li>■ Unless otherwise stated by the manufacturer, multiple-dose containers have a BUD of 28 days</li> </ul>
<b>Hazardous Drugs as CSPs</b>	New	<ul style="list-style-type: none"> <li>■ Separate storage section dedicated to hazardous drugs, preferably in a negative pressure room</li> <li>■ Closely aligned with NIOSH guidelines</li> <li>■ Outlines the need for personnel safety in compounding and storing hazardous drugs</li> <li>■ Chemotherapy gloves required during all stages of drug manipulation, including receiving, distribution, stocking, inventory, preparation, and disposal</li> <li>■ Preparation of all hazardous drugs must take place in an ISO Class 5 BSC or CACI</li> <li>■ The BSC or CACI must be physically separated from other preparation areas, in a negative pressure ISO Class 7 buffer room adjacent to an ISO Class 7 ante-area</li> <li>■ Optimally, the BSC or CACI should be 100% vented to outside air</li> <li>■ CACIs not located in an ISO 7 environment, must be in a negative pressure room that undergoes at least 12 ACPH</li> <li>■ Closed-system transfer devices may be used, but only within an ISO Class 5 BSC or CACI</li> <li>■ Optimally, environmental work surface sampling to detect uncontained hazardous drugs should be performed at routinely</li> <li>■ Guidance for surface sampling and potential drug assay examples given</li> <li>■ Personnel protective equipment (PPE) and training guidelines outlined</li> <li>■ Disposal must comply with state and federal regulations</li> <li>■ Personnel, including custodial staff, must be trained to do appropriate disposal and cleaning</li> </ul>
<b>Radiopharmaceuticals as CSPs</b>	Revised	<ul style="list-style-type: none"> <li>■ Production of positron emission tomography (PET) radiopharmaceuticals is governed by USP chapter &lt;823&gt;, after PET drugs leave a production facility, USP chapter &lt;797&gt; applies</li> <li>■ Low-risk level radiopharmaceutical compounding must be in an ISO Class 5 PEC that is located in an ISO Class 8 or better buffer area or, if BUD is 12 hours or less, within a segregated compounding area</li> <li>■ Physical layout guidelines and environmental requirements are outlined</li> <li>■ Procedures should limit radioactivity exposure to as low as reasonably achievable (ALARA)</li> <li>■ A demarcation line segregating the compounding area must be present when radiopharmaceuticals are prepared as low-risk CSPs with &lt;12-hour BUDs</li> </ul>
<b>Allergen Extracts as CSPs</b>	New	<ul style="list-style-type: none"> <li>■ Exempts intradermal and subcutaneous single- and multi-dose vials with suitable preservatives, if ALL eleven compounding conditions outlined in the standards are met</li> <li>■ Any extract that does not contain preservatives must comply with USP &lt;797&gt;</li> </ul>

USP Chapter <797> Section	Status	Revisions and Additions
<b>Verification of Compounding and Sterility</b>	Revised	<ul style="list-style-type: none"> <li>■ Additional cross-referenced USP chapters added for further guidance: USP Chapters &lt;71&gt;, &lt;1035&gt;, &lt;731&gt;, &lt;1160&gt;, &lt;1211&gt;</li> <li>■ Sterilization by dry heat and depyrogenation by dry heat are added to the section</li> <li>■ Filter integrity testing, to manufacturers' specifications, required for high-risk level CSPs</li> <li>■ Recommendation for quantitative chemical assays for CSPs with narrow therapeutic plasma concentration range</li> </ul>
<b>Environmental Quality and Control</b>	Revised with new subsections added	<p><b>Facility Requirements</b></p> <ul style="list-style-type: none"> <li>■ ISO Class 5 PECs, buffer areas, and ante-areas sub section is completely revised, including less specific diagrams of facility requirements</li> <li>■ Facility requirements are outlined as being for either-low-risk level CSPs with &lt;12 hour BUD or low-, medium-, and high-risk level CSPs</li> <li>■ Placement of non-essential devices within buffer and ante-areas can occur, but must be based on their effect on environmental quality of the area as verified by monitoring</li> <li>■ A well-lighted, comfortable working environment is required for compounding personnel, including compounding area temperatures of 20 °C or cooler</li> <li>■ Buffer areas must maintain ISO 7 conditions, ante-areas are held to ISO 8 conditions</li> <li>■ If a buffer area is not physically separate from an ante-area, displacement airflow may be utilized; this is not an option in high-risk compounding</li> <li>■ High-risk compounding must be done in a buffer room that maintains a minimum positive pressure differential from the anteroom</li> <li>■ Guidelines for air exchanges per hour (ACPH) have been added</li> <li>■ Specifications for floors, walls, ceilings, work surfaces and furnishings have been clarified</li> </ul> <p><b>CAIs and CACIs</b></p> <ul style="list-style-type: none"> <li>■ CAIs and CACIs must be in an ISO Class 7 buffer area unless they comply with all outlined conditions and documentation can be provided; otherwise the CSPs prepared in such conditions must adhere to low-risk level CSP requirements with &lt;12 hour BUDs</li> </ul> <p><b>Environmental Sampling</b></p> <ul style="list-style-type: none"> <li>■ Environmental Sampling subsection significantly revised with updated requirements for when environmental sampling must occur</li> <li>■ Environmental nonviable particle testing program expanded upon, with more details included</li> <li>■ Pressure differential monitoring added to the section</li> <li>■ Environmental viable airborne particle testing program changed to require electronic volumetric air sampling decreased to every 6 months</li> <li>■ Settling plates no longer deemed sufficient for air quality testing</li> <li>■ Recommended action levels for microbial contamination table added</li> <li>■ The revisions of using sterile 70% IPA and sterile gloves are incorporated throughout this section</li> <li>■ In addition to counting colony forming units (cfus), identification of microorganisms is recommended for further evaluation</li> </ul> <p><b>Additional Personnel Requirements</b></p> <ul style="list-style-type: none"> <li>■ Manipulation of patient blood-derived or other biological materials must be separate from routine material handling and CSP activities</li> <li>■ Packaging for compounding supplies should be removed and components, wiped with a suitable disinfectant, preferably in the ante-area</li> </ul>

USP Chapter <797> Section	Status	Revisions and Additions
<b>Environmental Quality and Control (continued)</b>		<p><b>Cleaning and Disinfecting</b></p> <ul style="list-style-type: none"> <li>■ Cleaning and disinfecting subsection revised, intervals for cleaning modified and outlined in a table format</li> <li>■ Specifications for cleaning materials added</li> </ul> <p><b>Personnel Cleansing and Garbing</b></p> <ul style="list-style-type: none"> <li>■ Personnel Cleansing and Garbing subsection revised, specific order of donning PPE is changed and outlined</li> <li>■ Exclusion of cosmetics, artificial nails, visible jewelry and piercings</li> <li>■ Cleansing, garbing, and gloving requirements also apply to the CAI or CACI environment; unless the manufacturer provides validated testing results to show that any of the standard PPE are not required either to protect the product or, for CACIs, the operator</li> </ul> <p><b>Surface Cleaning and Disinfecting</b></p> <ul style="list-style-type: none"> <li>■ Surface cleaning and assessment subsection added</li> <li>■ Process for surface sampling is explained in detail; frequency of surface sampling is noted to be on a “routine basis”</li> </ul> <p><b>Competency Evaluations</b></p> <ul style="list-style-type: none"> <li>■ Competency evaluation subsection on garbing and aseptic work practice added which includes guidelines for personnel glove fingertip testing, garbing and gloving competency evaluation, and aseptic manipulation competency evaluation</li> <li>■ Competency evaluation required to assess cleaning and disinfecting methods</li> <li>■ These are all in addition to media fill testing, and should be completed on the same schedule as outlined for media fill testing based on CSP risk-level for the facility</li> <li>■ Appendices III-V provide sample assessment forms for these procedures</li> </ul>
<b>Suggested Standard Operating Procedures</b>	Editorial Revisions	<ul style="list-style-type: none"> <li>■ Two SOPs added</li> </ul>
<b>Elements of Quality Control</b>	Renamed Section	<ul style="list-style-type: none"> <li>■ Formerly Processing, Aseptic Technique, Components, and Equipment sections</li> <li>■ Otherwise, editorial revisions only</li> </ul>
<b>Verification of Automated Compounding Devices (ACDs) for Parenteral Nutrition Compounding</b>	Editorial Revisions	
<b>Finished Preparation Release Checks and Tests</b>	Editorial Revisions	
<b>Storage and Beyond-Use Dating</b>	Revised, New subsection added	<ul style="list-style-type: none"> <li>■ Expiration dating for MDVs used in compounding is 28 days unless specified in writing by the manufacturer</li> <li>■ Proprietary Bag and Vial Systems sub-section added</li> <li>■ Sterility and stability for these systems must follow manufacturer instructions</li> <li>■ Storage area temperature ranges modified</li> </ul>

USP Chapter <797> Section	Status	Revisions and Additions
<b>Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs</b>		<ul style="list-style-type: none"> <li>■ Transportation of any chemotoxic or hazardous drugs via pneumatic tube system is discouraged</li> <li>■ Confirm maintenance of sterility and stability of CSPs if they will be exposed to greater than 30 °C for greater than 1 hour during administration</li> </ul>
<b>Patient of Caregiver Training</b>	Editorial Revisions	
<b>Patient Monitoring and Adverse Events Reporting</b>	Editorial Revisions	
<b>Quality Assurance Program</b>		
<b>Appendices I-V</b>		<ul style="list-style-type: none"> <li>■ Appendix I: Delineates items that are required versus recommended in the chapter</li> <li>■ Appendix II: Chart of disinfectants and their microbial inactivation properties</li> <li>■ Appendix III: Provides a sample form for assessing hand hygiene and garbing practices</li> <li>■ Appendix IV: Provides a sample form for assessing aseptic technique</li> <li>■ Appendix V: Provides a sample form for assessing cleaning and disinfection procedures</li> </ul>