The ASHP Discussion Guide for

Compounding Sterile Preparations

SUMMARY AND IMPLEMENTATION OF USP CHAPTER <797>

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The ASHP Discussion Guide on USP Chapter <797>

Compounding Sterile Preparations

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The recently published *USP Chapter <797>, Pharmaceutical Compounding: Sterile Preparations,* became effective January 1, 2004. This discussion guide is intended to assist health-system pharmacists with implementation of USP Chapter <797> requirements.

The United States Pharmacopeia, 27th rev., and the National Formulary 22nd ed. USP General Information Chapter. Pharmaceutical Compounding–Sterile Preparations. Rockville, MD: The United States Pharmacopeial Convention, 2003.

Executive Summary

Over the past three decades, several pharmacy practice documents have been published in hopes of establishing a standard of practice for compounding sterile preparations that could be universally adopted. None of these documents was successful in achieving this goal. However, on January 1, 2004, USP Chapter <797>, Pharmaceutical Compounding: Sterile Preparations, which is published in USP 27/NF 22, came into effect. USP Chapter <797> 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. These standards may be adopted and enforced by state boards of pharmacy and surveyable by accreditation organizations. This discussion guide will provide important information about Chapter <797> and its procedures and requirements. As pharmacists, we have been given the right to compound, but as professionals, we have the obligation to compound right.

Chapter Overview and History

During the 1960s and 1970s, the practice of pharmacy was evolving and emphasis was placed on patient safety factors as a result of patient injuries and deaths that had occurred because of problems with medication delivery and sterile compounding. One of the first groups to address these patient safety issues was the National Coordinating Committee on Large Volume Parenterals (NCCLVP). NCCLVP was established by the US Pharmacopeial Convention, Inc., and subsequently developed and recommended standards of practice for the preparation, labeling, and quality assurance of hospital pharmacy admixture services.[1-7]

After the dissolution of NCCLVP in the 1980s, the profession of pharmacy was under pressure by the Food and Drug Administration (FDA) to address problems with contamination in hospitals in the United States.

In the early 1990s, several pharmacy organizations, including the American Society of Health-System Pharmacists (ASHP), United States Pharmacopeia (USP), and National Association of Boards of Pharmacy (NABP), issued practice recommendations in an effort to provide a professional mandate and practice assistance to pharmacists and technicians responsible for compounding sterile preparations.The central theme in each of the

documents was that the pharmacist was responsible for ensuring that compounded sterile preparations (CSPs) were properly prepared, labeled, stored, dispensed and delivered.

In 1992, the USP issued a draft recommendation entitled USP <1074>, Dispensing Practices for Sterile Drug Products Intended for Home Use. The intent of this general information chapter within the USP/NF was "to detail the various procedures necessary to prepare and dispense sterile drug preparations intended for home use: the validation of sterilization and aseptic processes, the quality and control of environmental conditions for aseptic operations, personnel training, aseptic techniques, finished product release testing, storage and expiration dating, the control of product quality beyond the pharmacy, patient or caregiver training, patient monitoring and complaints, and finally, a quality assurance program."[8] The United States Pharmacopeial Convention, Inc. adopted a finalized version of the draft and numbered it <1206>, Sterile Drug Products for Home Use, to provide specific practice standards and operating guidelines for CSPs.[9] The chapter was only a guideline and not enforceable; the pharmacy profession did not have any accountability to the USP as a regulatory agency.

In 1993, ASHP issued a Technical Assistance Bulletin (TAB) entitled "Quality Assurance for Pharmacy-Prepared Sterile Products."[10] This document defined the level and extent of recommended quality assurance measures that should be utilized by pharmacy operations when compounding sterile preparations. These recommendations also addressed operating parameters such as physical plant, types of products utilized, and length of product storage. This TAB was developed to be applicable in a variety of practice settings, including hospitals, community retail pharmacies, long-term-care facilities, and home care organizations. The TAB spawned the ASHP Risk Level categories (I-III) which, for some, have become the unofficial standard for the pharmacy profession. However, the recommendations in the TAB fell short with respect to the degree of specificity that most pharmacy practitioners wanted, which impeded its integration and general acceptance by the pharmacy community. Among the reasons for not following the recommendations in the TAB was the perception that they were unnecessary, excessive, costly, and too time-consuming. In addition, some practitioners did not think that the TAB added value to the process since there was insufficient evidence to support the recommended changes. As a result, the FDA's concerns were not alleviated by the ASHP QA TAB.

In 1998, former President Clinton signed into law the US Food and Drug Administration Modernization Act (FDAMA) of 1997. Section 503A of the FDAMA, which is titled "Pharmacy Compounding," defined the limits of legitimate compounding. This law limited the scope of pharmacy compounding and was designed to protect patients from the unnecessary use of extemporaneously compounded drugs by pharmacists. FDAMA granted FDA power to identify certain drug products that were difficult to compound and for which compounding could adversely affect safety or effectiveness. In 2001, the U.S. Supreme Court ruled that section 503A was unconstitutional, creating a vacuity of regulation for the pharmacy profession and the FDA.

In 1995, ASHP conducted a national survey of quality assurance for pharmacy-prepared sterile preparations as a follow-up to ASHP QA TAB.[11,12] Results of the survey indicated that few pharmacies were equipped with adequately controlled compounding environments, which are essential for dispensing sterile preparations. The survey also documented that many pharmacists were not performing critical quality assurance checks, such as environmental monitoring, end-product testing, and process validation.[12]

Another national survey was conducted in 2002.[13] Unfortunately the findings were similar to the 1995 survey, demonstrating that ASHP's QA TAB guidelines had not produced significant changes in sterile compounding practices in the 10 years since publication of the document.[13]

Efforts to improve the quality of pharmacy-prepared sterile preparations have been ongoing. The first official and enforceable sterile preparation compounding requirement in the United States took effect on January 1, 2004, when USP published USP Chapter <797>.

Legal and Regulatory Basis

That USP would initiate a sterile preparation requirement is logical, considering its long history. In 1906, the Food and Drugs Act, passed by the US Congress and the US Pharmacopeia (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 the USP/NF as the official compendia of drug standards. The US Food and Drug Administration is responsible for the enforcement of the FD&C Act.

Each general 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 considered requirements and official monographs and standards of the USP/NF, whereas general chapters numbered from <1000> to <1999> are considered informational and chapters above <2000> apply to nutritional supplements.[14] Since USP Chapter <797> is considered a requirement, pharmacies may be subject to inspection against these standards by boards of pharmacy, FDA, and accreditation organizations, such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), Accreditation Commission for Health Care, Inc. (ACHC), and Community Health Accreditation Program (CHAP). Pharmacists are strongly encouraged to contact their respective boards of pharmacy for information on state enforcement criteria and activities. The FDA is exercising enforcement discretion during routine inspections but will intervene when patient injury or deaths associated with compounded sterile preparations have occurred. Since 1990, FDA has become aware of more than 55 quality problems associated with compounded preparations, many of which have resulted in recalls, patient injury, and deaths.[15–29]

Areas of Likely Concern

The following points review issues that are most likely to be of concern for pharmacy administrators, pharmacists and technicians:

- **Applicability in all healthcare settings:** The principles of contamination control and proper compounding procedures are not unique to the practice setting where sterile preparations are compounded. USP <797> requirements must be met in all healthcare settings that compound sterile preparations and by all disciplines associated with these settings; including physicians, nurses, and pharmacists in office practices, clinics, hospital care units, and main and satellite pharmacies. The enforcement of this chapter by boards of pharmacy is limited to licensed pharmacies.
- **Risk Levels Criteria:** The practices, policies, procedures and physical plant of pharmacies where sterile compounding occurs vary so widely that USP <797> was written to give the pharmacist, as the individual with the ultimate responsibility for sterility and accuracy of CSPs, flexibility in determining actual risk levels for preparations being compounded. The following examples better illustrate this point (See Table 1).

The checklist on page 4 provides an overview of the various factors that can be used when determining risk levels. The most important factor in determining risk level is sound professional judgment based on knowledge of aseptic compounding principles.

- **Environmental Quality Controls:** The cleanliness or quality of air in critical compounding areas is one factor influencing the likelihood of microbial contamination. The need to control the quality of critical operating environments dates back more than a century, when the etiologic role of bacteria in infection was discovered. Cleanrooms were developed to minimize or eliminate bacteria and to control

Table 1

Compounding Activity	Location	USP <797> Risk Level Determination
Reconstitution of several vials of lyophilized powder with a specific volume of sterile diluent for transfer to a small-volume minibag or large-volume parenteral solution *one at a time*	In the pharmacy using appropriate engineering controls (ISO Class 5 hood in an ISO Class 8 cleanroom)	Low-Risk Level
Reconstitution of several vials of lyophilized powder with a specific volume of sterile diluent; the resulting solution is then aggregated into an evacuated bottle for transfer to several small-volume minibags or large-volume parenteral solutions	In the pharmacy using appropriate engineering controls (ISO Class 5 hood in an ISO Class 8 cleanroom)	Medium-Risk Level
Reconstitution of a single vial of lyophilized powder with a specific volume of sterile diluent for transfer to a small-volume minibag or large-volume parenteral solution	Nursing station, ambulatory care center or at the patient bedside without any engineering controls	High-Risk Level

Pharmacy Compounding-USP <797> Risk Level Assessment

Classification	Requirements	Yes	No
Low-Risk Compounding	■ Simple admixtures compounded using closed system transfer methods ■ Prepared in International Organization for Standardization (ISO) Class 5 (Class 100) laminar airflow workbench (hood) ■ Located in ISO Class 8 (Class 100,000) buffer room (Cleanroom) with ante area ■ Examples include reconstitution of single-dose vials of antibiotics or other small-volume parenterals (SVPs), preparation of hydration solutions		
Medium-Risk Compounding	■ Admixtures compounded using multiple additives and/or small volumes ■ Batch preparations (e.g. syringes) ■ Complex manipulations (e.g. TPN) ■ Preparation for use over several days ■ Prepared in ISO Class 5 (Class 100) ■ Located in ISO Class 8 (Class 100,000) Cleanroom with ante area ■ Examples include pooled admixtures, parenteral nutrition solutions using automated compounders, batch-compounded preparations that do not contain bacteriostatic components		
High-Risk Compounding	■ Non-sterile (bulk powders) ingredients ■ Open system transfers ■ Prepared in ISO Class 5 (Class 100) ■ Located in ISO Class 8 (Class 100,000) Cleanroom with separate ante area ■ Examples include CSPs prepared from bulk, nonsterile components (morphine or other narcotics) or final containers that are nonsterile and must be terminally-sterilized (nuclear pharmaceuticals)		

the incidence of infection in hospitals (especially in operating rooms). It was realized that by providing proper ventilation to critical areas in hospitals, the incidence of airborne infections could be greatly reduced. Another observation was that the airborne particles generated from the environment (dust, dirt, pollen, viable and nonviable microorganisms) and from people (skin flakes, lint, cosmetics, and respiratory gases) negatively influenced patient outcomes.[30] Compounding areas must be routinely monitored to determine the level of cleanliness. The appropriate combination of work areas, "cleanrooms", ante rooms, LAFW (laminar airflow workbenches), or the use of barrier-isolators to achieve desired cleanliness levels based on risk classification and work loads need to be determined. The costs associated with correcting or achieving appropriate levels of cleanliness in accordance with USP <797> can be significant (in the tens of thousands of dollars). Guidance from qualified persons who have experience and expertise with cleanrooms should be sought prior to "fixing the problem." A variety of facility/engineering controls can be employed to ensure that the proper environmental controls are in place, such as installing integrated high efficiency particulate air (HEPA) filters in the ceiling fans, replacing current ceiling tiles with plastic covered "clean room grade" tiles, removing refrigerators, computers, and printers from the compounding area, and replacing existing flooring with seamless vinyl floor covering (e.g., Medintech by Armstrong).

- **Process and Preparation Quality Controls:** Pharmacists and technicians must understand that compounding processes and personnel who perform the compounding (and whether they are following appropriate written policies and procedures) have an impact on the quality assurance of the final compounded sterile preparation. These controls are the cornerstone in ensuring CSP sterility and accuracy. The desired outcome of USP <797> is being able to determine where failures can occur in a process, followed by implementation of methods to control and monitor these critical points of failure, thereby increasing the likelihood of *consistently* producing a quality CSP. Quality cannot be inspected into the final product; it must be built into CSP through process and preparation quality controls. Many resources and guidance documents are available and should be used in order to better understand appropriate aseptic techniques, process validation procedures, and methods for end-process content accuracy, sterility, and other quality measures.
- **Sterility and Beyond-Use Dating:** Two factors are critical in establishing beyond-use dating (formerly known as expiration dating) for CSPs. The first is the chemical stability of the chemical entity in solution. A number of textbook references are available and should be consulted to demonstrate the chemical stability of medications in solution. The second factor is the sterility of the CSP. By definition, sterility is the absence of viable microorganisms in the CSP. Unlike pyrogenicity, sterility is an absolute concept. A CSP is either sterile or it is not. There are acceptable levels of pyrogens permitted in CSPs although the desired goal is to compound a pyrogen-free preparation. Since patient injury and death following administration of CSPs have been associated with microbial contamination, the assignment of risk levels and operating principles outlined in USP Chapter <797> serves to prevent CSP microbial contamination. Unless sterility testing is performed for the CSP, the beyond-use dating of the preparation CANNOT exceed the published limits found in USP <797> (Table 2). If sterility testing is performed according to USP <71> Sterility Tests, the CSP can be assigned beyond-use dating based on the maximum chemical stability of the drug in solution as permitted by valid references.
- **Staff Training, Competency, and Performance:** Pharmacy administrators, pharmacists and technicians are being asked to do more with less every day. This vicious cycle takes a great toll on one of the most crucial aspects of ensuring sterility and accuracy of CSPs: formal training and periodic competency assessment. Properly trained employees are the foundation for ensuring that procedures are followed correctly when compounding sterile preparations.

Compounding Accuracy and Sterility to Ensure the Safety of Patients

There is ample evidence that improperly compounded sterile and nonsterile preparations injure and kill patients.[15-29] The references cited here are not all-inclusive on the subject. Several state boards of pharmacy have made significant revisions to their pharmacy practice acts by expanding regulatory provisions for oversight of compounding. In the United States, the practice of compounding sterile preparations is now dictated by requirements published as a component of the Federal Food, Drug and Cosmetic Act. Subsequently, boards of pharmacy, attorneys, accreditation organizations, and the FDA may utilize and reference these requirements during inspections, surveys, and enforcement actions.

If the profession of pharmacy continues on the path of not looking for problems, it won't find any. However, the fact is that pharmacists are making errors. There have been several studies that have demonstrated the prevalence of pharmacists' compounding errors.[25, 31] It is highly probable that the incidence of vascular access

Table 2

Risk Level	Room Temp	Refrigeration	Freezer (≤-20 °C)
Low	48 hours	14 days	45 days
Medium	30 hours	7 days	45 days
High	24 hours	3 days	45 days

Source: USP <797> Pharmaceutical Considerations: Sterile Preparations.

device phlebitis, septicemia, and other nosocomial infections has not been investigated by taking into account the microbial flora in the sterile compounding areas in pharmacies. Analyzing a potential relationship between hospital infections and the hospital pharmacy might result in a startling find.

Careful supervision and double-checking of calculations, measurements, and compounding are necessary to reduce the risk of medication errors. In 2002, a study on medication errors in hospitals revealed that serious mistakes involving prescription drugs occur in 3% to 7% of hospital inpatients. These findings suggest that more than 90,000 patients are harmed by medication errors in our nation's hospitals each year.[32]

Since adverse events have not motivated significant change in how sterile preparations are compounded, there are three others—economics, publicity, and regulations—that could. Examples of how these three variables could initiate change follow:

Economics: At some point in the future, both payers and liability underwriters may demand evidence of compliance with the new USP chapter as a condition of continued coverage. For instance, insurance premiums could be increased solely on the basis that a facility prepares sterile compounds, making it high-risk. Liability coverage may be dropped altogether, resulting in difficulty obtaining insurance. Some liability underwriters have already begun assessing their tolerance of risk with respect to sterile compounding in certain pharmacy practice settings.[33] Accreditation organizations will survey pharmacies against USP Chapter <797>, and failure to comply may potentially affect accreditation status, subsequently limiting the ability of healthcare organizations to bill and collect from payers.[34]

Publicity: When problems occur, the media attention on such events damages the credibility of the profession and diminishes the confidence of regulators. As a result, additional regulatory actions by local, state and federal authorities may restrict compounding to specialty pharmacies and board certified pharmacists.

Regulations: Many states have changed their practice standards in response to the national publicity of pharmacy compounding errors. For example, Missouri has adopted standards that are more stringent than USP Chapter <797>. In fact, Missouri pharmacists will be conducting end-preparation evaluation for sterility, pyrogenicity, and potency on CSPs.

First Steps on the Road to Compliance

- Determine Risk Level of Compounding using Risk Level Assessment Checklist, Chapter <797> and professional judgment
- Perform Gap Analysis by comparing <797> requirements line by line with pharmacy operational procedures and facilities
- Develop action plan for <797> compliance from prioritized Gap Analysis (See Table 3)
- Communicate results of Gap Analysis and Action Plan with pharmacy staff
- Implement non-facility requirements and revise Policies and Procedures for CSPs, then address changes needed for facility and equipment compliance
- Communicate action plan and demonstrated improvements in patient care with staff
- Evaluate use of alternative products and reassess workload demands for all compounding sites
- Document all measures of quality performance and communicate improvements in <797> compliance with staff, administration, and accreditation organizations

State boards of pharmacy are citing pharmacies for failure to comply with existing sterile compounding regulations and are assessing significant financial penalties. Lawyers have successfully quoted USP/NF chapters as evidence of standards of practice during lawsuits.[34,35] From a professional standpoint, pharmacists should do the right thing because patients deserve our best efforts. There is clear and compelling evidence that the old ways of compounding sterile preparations must be changed to meet the requirements of USP Chapter <797>. The focus on developing, implementing, using and maintaining good compounding practices and quality systems continues to be critical in ensuring the health and well-being of patients as well as the professional enrichment of pharmacists and technicians. Now is the time for professionals working in the practice of pharmacy (pharmacists and technicians) to embrace the scientific facts that good compounding practices will yield quality preparations (accurate and sterile). This professional responsibility—to consistently meet or exceed state regulatory requirements when compounding sterile preparations—can be a matter of life and death.

First Steps on the Road to Compliance

Healthcare organizations that prepare CSPs may have significant practice standard gaps relative to compliance with USP Chapter <797> in several areas, particularly in regards to facility and equipment needs. As a first step, the risk level of the compounding that is being performed in the pharmacy needs to be determined. Most pharmacies perform low- and medium-risk level compounding. The checklist ("Pharmacy Compounding-USP <797> Risk Level Assessment") shown on page 4 of this guide can be used to identify and document the facility's risk level.

After the level of risk has been determined, the next step is to determine how current pharmacy compounding operations compare with those in USP Chapter <797>. This evaluation is known as a gap analysis. To perform a gap analysis, the requirements of <797> are compared line by line with current practices and operational facilities in order to identify differences or "gaps". The gap areas should be analyzed to identify specific practices causing the greatest risks or differences from <797> requirements, then these gaps should be prioritized by fiscal and human resource costs (Table 3). Developing an action plan from the prioritized gap list identifies options for immediately improving CSP practices, thus reducing vulnerability to microbial contamination and inaccurate compounded preparations.

Having a completed "Pharmacy Compounding-USP <797> Risk Level Assessment" and gap analysis can be used to demonstrate to accreditation organizations, boards of pharmacy and other regulatory authorities that current operating deficiencies are understood and corrective action is being taken to achieve compliance. The immediate corrective action plan should address all non-facility, low-cost requirements identified during the gap analysis. Revised policies and procedures should reflect *actual* day-to-day operations and practices, such as handwashing, gloving and gowning, didactic and skill-based training and competency of staff, aseptic technique media fill validation, proper housekeeping (cleaning and sanitizing), and microbial environmental monitoring. Non-facility issues can be addressed immediately after gap analysis and require little more than time, attention and vigilance. Large capital expenditures may require more time and planning to secure approval. By focusing on positive communication with pharmacy staff of improved quality and patient-care outcomes resulting from <797> requirements, procedural changes can be successfully achieved, establishing employee ownership and buy-in to change old habits.

Another effective means of reducing the level of risk for CSPs is the use of alternative products or product configurations, such as manufacturer ready-to-use premixed medications and unit-of-use closed transfer packaging (Minibag Plus® and Add-Vantage®). Pharmacists can reassess compounding demands based on risk-level requirements and by consolidating workloads from point-of-care locations (main pharmacies versus satellite pharmacies). Questions such as "Could compounding responsibilities be centralized as a means of reducing costs (employee competency, facility requirements) and medium- or high-risk levels (eliminate or minimize decentralized compounding)?" need to be asked. In addition, all aspects of compounding sterile preparations need to be considered during the <797> compliance

Table 3

USP <797> Quality Domains	Impact to CSP Quality	Relative Cost
Compounding Conditions	N/A	N/A
QA Program	++++	$$
QA Practices	++++	$
Reports/Documents	++++	$
Outcomes (ADR) Monitoring	+++	$$
Patient Training	++++	$$
Maintaining Product Quality & Control	++++	$$$
Storage & Beyond Use Dating	+++	$$
Finished Product Release Checks & Tests	++++	$$
CSP Work Environment	+++	$$$$
Equipment and Supplies	++++	$$
Components	++++	$
Processing: Aseptic Technique	++++	$
Environmental Control	+++	$
Verification Processes		
Sterility Testing	+++	$$$
Environmental Monitoring	++++	$$
Personnel Training and Education	++++	$$

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evaluation, including personnel time, equipment and facility options (cleanrooms vs. barrier-isolators) for the central pharmacy, satellite pharmacies, clinics, procedure rooms, and nursing work stations.

The advice of W. Edwards Deming, one of the world's top quality experts, can be applied to compounded sterile preparations. Deming created the 85/15 Rule, a concept that attributes 85% of organizational problems to system failures, and 15% to human factors. Systems failures include poor or nonexistent plans, procedures, measurable performance criteria, and work processes. Deming and others established that the potential to eliminate mistakes and errors in the workplace lies mostly in improving the systems through which work is done, not in blaming the individual workers. These observations have evolved into the "rule of thumb" that approximately 85% of work problems can be corrected by changing the work system and less than 15% can be corrected by changing individual workers. Current research now indicates that the percent ratio leans even farther towards the system component. The rule might be restated as "95/5" or perhaps "97/3". Dr. Deming, through his famous Red Bead Experiment, proved that the only way to improve a product or service is for management to improve the system that creates that product or service.[36] Theodore Roosevelt's words also apply. Roosevelt said, *"In any moment of decision, the best thing you can do is the right thing. The worst thing you can do is nothing."*

USP Chapter <797> Summary

The following points highlight each of the major areas within USP Chapter <797>. These summaries should not serve as a substitute for the actual text of the USP chapter. It is imperative that this chapter be purchased from USP, either in stand-alone format or as a component of the new USP 27/NF 22. It is strongly encouraged that the entire USP 27/NF 22 reference book be purchased since several other important chapters are referenced in Chapter <797>.

Introduction

The definition of sterile compounding is placed in the introduction and is clearly different than nonsterile compounding, which falls under USP Chapters <795>, Pharmaceutical Considerations-Nonsterile Preparations and <1075>, Good Compounding Practices. The intent of Chapter <797> as written in the introduction is "to prevent harm and fatality to patients that could result from microbial contamination (nonsterility), excessive bacterial endotoxins, large content errors in strength of correct ingredients, and incorrect ingredients in CSPs." It is important to realize that this chapter applies to all healthcare settings where sterile preparations are compounded. The introduction also provides the definition of a CSP (compounded sterile preparation). According to Chapter <797>, a CSP is a dosage unit with any of the following characteristics:

- Preparations prepared according to manufacturer's labeled instructions
- Preparations containing nonsterile ingredients or employing nonsterile components and devices that must be sterilized before administration
- Biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that possess either of the above two characteristics and which include, but are not limited to, baths and soaks for live organs and tissues, implants, inhalations, injections, powder for injection, irrigations, metered sprays and ophthalmic and otic preparations

The introduction to Chapter <797> also discusses the three risk level classifications for CSPs, based on the potential for microbial, chemical and physical contamination (including low, medium and high-risk level compounding conditions).

Responsibility of Compounding Personnel

This section of the chapter details the responsibility of personnel involved in compounding sterile preparations. It states that "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 the proper clinical administration of CSPs. It further discusses the responsibilities of the compounding supervisor to ensure:

a. Personnel are adequately educated, instructed, and skilled to perform their functions
b. Ingredients have correct identity, quality, amount
c. Open/partial containers are properly stored
d. Bacterial endotoxins are minimized
e. Proper and adequate sterilization is used
f. Equipment is clean, accurate, and appropriate
g. Potential harm from added substances is evaluated prior to dispensing

h. Packaging is appropriate for sterility and stability

i. Compounding environment maintains the sterility of presterilized items

j. Labels are appropriate and complete

k. Beyond-use dates are appropriate and based on valid scientific criteria

l. Correct compounding procedures are used

m. Deficiencies in compounding can be rapidly identified and corrected

n. Compounding is separate from quality evaluation

Microbial Contamination Risk Levels

This section defines the three different microbial contamination risk levels. It is important to realize that the determination of compounding risk levels is the responsibility of the compounder. The chapter was written in the broadest terms using general descriptive states; therefore, no single "iron-clad" determination of risk exists with respect to practice settings or compounding procedures. Risk level classification in <797> is, in general, not prescriptive, with one exception: *CSPs prepared from bulk, nonsterile components will always be a high-risk level procedure*. Ultimately, assigning the appropriate risk level to a CSP requires the professional judgment of the pharmacist. Microbial contamination risk levels are defined as follows:

Low-Risk Level

- CSPs compounded from sterile commercial drugs using commercial sterile devices
- Compounding occurs in ISO Class 5 (formerly known as Class 100) environment at all times
- Compounding procedures involves only a few closed-system basic, simple aseptic transfers and manipulations
- Routine disinfection and air quality testing to maintain ISO Class 5 occurs
- There is adequate personnel garb for sterile preparation
- A review for correct identity and amounts of components occurs before and after compounding
- There is a final visual inspection of each sterile preparation
- Annual media-fill test procedure for each person who compounds is performed to validate proper aseptic technique

Medium-Risk Level

- Involves using multiple pooled sterile commercial products for multiple patients or one patient multiple times (batched antibiotics or other small volume parenterals)
- 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 infusion device)
- Quality assurance procedures include all steps for low-risk level
- 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
- Preparation from sterile ingredients but exposed to less than ISO Class 5
- More than 6-hour delay from compounding to sterilization
- Purity of components is assumed but not verified by documentation
- Quality assurance procedures include all steps for low-risk level
- 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

Verification of Compounding Accuracy and Sterilization

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. CSPs that require some form of terminal sterilization, either by filtration, steam or ionizing radiation have to be validated to ensure that each CSP is void of microbial contamination. There must be proof that the CSP is accurate and sterile.

Personnel Training and Evaluation in Aseptic Manipulation Skills

It is important to realize that many pharmacists and technicians have little or no didactic training in the area of sterile compounding. This section of the chapter requires that all personnel be properly trained by the following means:

- Prior to commencing any compounding, perform thorough didactic instruction in the theory and practice of sterile preparations, with evaluation of technique annually (for low- and medium-risk level) and semiannually (for high-risk level)
- Compounder evaluations should include a formal written exam and practical evaluation of aseptic technique using growth media (media fills)

Environmental Quality and Control

This section of the chapter specifies in great detail the physical plant and environmental requirements for each of the CSP risk levels. These requirements include:

- The need for laminar airflow workbenches (LAFW) and cleanrooms or barrier isolators
- The compounding area must be separated from the general pharmacy and must be a controlled (particle, temperature, humidity) environment.
- Must have an ISO Class 5 (formerly Class 100) environment for critical area where CSP is exposed to air in physical environment
- Must have an ISO Class 8 (formerly Class 100,000) environment for buffer zone or cleanroom (the terms cleanroom and buffer zone are interchangeable)
- There must be detailed cleaning and sanitizing procedures in order to maintain the cleanliness of the compounding environment.
- Compounding personnel must be properly garbed according to the risk level of compounding.
- There must be written, properly-approved policies and procedures for the activities that occur in the compounding environment.
- Environmental monitoring must be routinely performed in order to prove that the compounding environment is properly maintained. There must be documentation to prove control.

Processing

This section calls for a written employee-training and evaluation program specific to preparation of the CSP in each healthcare setting to ensure that compounding personnel are knowledgeable and properly trained. As discussed previously in this guide, training is the cornerstone of ensuring quality and safety of CSPs.

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

The complexity in preparing parenteral nutrition can be aided with automated compounding devices. It is important to recognize that in order for these devices to accurately deliver the desired volume of ingredients, users must be adequately trained, and the ACDs must be properly calibrated, setup (correct solution containers hung on the correct solution inlet tubing), verified and maintained. This section of the chapter details suggested procedures on ensuring the accuracy and precision of ACDs.

Finished Preparation Release Checks and Tests

All finished CSPs must be checked by a pharmacist prior to dispensing to ensure that the preparation is sterile and accurate. There are several methods that can be employed to meet this requirement. They 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 (formerly referred to as expiration dating) must be tested according to USP Chapter <71>.

Storage and Beyond-Use Dating

In many healthcare settings, CSPs are often prepared in anticipation of use and as such may be stored for extended periods of time. This section of the chapter focuses on the microbiological 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 (See Table 2)
- 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 (Alum)—no more than (NMT) 6 months.
- Aqueous formulations—14 days refrigerated
- All Others—NMT 30 days or intended duration of therapy

Maintaining Product Quality and Control After the CSP Leaves the Pharmacy

Pharmacists are responsible for ensuring that CSP quality and integrity are maintained during transit and regardless of physical location within the health system (hospital, home or ambulatory infusion center). This responsibility includes the use of appropriate packaging (coolers, wet ice blocks, dry ice) that is capable of maintaining proper temperature and conditions (refrigerated or frozen state) during shipment via common carrier (FedEx, UPS, or USPS). 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
- Administration
- Redispensed CSPs
- Education and Training
- Packing CSPs for Transit
- Storage in Locations Outside CSP 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.

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

Many of the elements of USP Chapter <797> focus on formalizing the policies, processes and procedures used in preparing CSPs. One element of quality that may not be routinely performed in pharmacies is documentation, or written "proof" that compounding personnel are trained, equipment is being maintained and calibrated routinely, the compounding environment is being properly maintained and tested, and CSPs are prepared using the correct components in the correct ratios/volumes. The essence of quality assurance is proving that you are really doing what you say you are doing.

References

1. National Coordinating Committee on Large Volume Parenterals. Recommended methods for compounding intravenous admixture in hospitals. *Am J Hosp Pharm.* 1975; 32:261–70.
2. 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.
3. National Coordinating Committee on Large Volume Parenterals. Recommendations for the labeling of large volume parenterals. *Am J Hosp Pharm.* 1978; 35:49–51.
4. National Coordinating Committee on Large Volume Parenterals. Recommended procedures for in-use testing of large volume parenterals suspected or of producing reactions in a patient. *Am J Hosp Pharm.* 1978; 35:678–82.
5. 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.
6. 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.
7. Barker KN, ed. Recommendations of the NCCLVP for the compounding and administration of intravenous solutions. Bethesda, MD. American Society of Hospital Pharmacists; 1981.
8. Anon. Pharmacopeial Forum, Vol. 18, Number 2, Mar–Apr 1992, pages 3053.
9. 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 States Pharmacopeial Convention, 1995.
10. 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.
11. 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.
12. Myers CE. Needed: Serious attention to sterile products. *Am J Health Syst Pharm* 1996; 53:2582.
13. 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.
14. US Pharmacopeial Convention, Inc. General Notices. United States Pharmacopeia 27/National Formulary 22. Rockville, MD: US Pharmacopeial Convention, Inc; 2004, p. 4.
15. 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.
16. Hughes CF, Grant AF, Leckie BD, et al. Cardioplegia solution: A contamination crisis. *J Thorac Cardiovasc Surg* 1986; 91:296–302.
17. Associated Press. Pittsburgh woman loses eye to tainted drug; 12 hurt. *Baltimore Sun.* November 9, 1990:3A.
18. 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; 15:474–475.
19. Perrin J. Unsafe activities of compounding pharmacists. *Am J Health-Syst Pharm* 1995;52:2827–2828.
20. 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;55:1057–1070.
21. Food and Drug Administration. Hazards of precipitation with parenteral nutrition. *Am J Health-Syst Pharm* 1994; 51:427–428.
22. 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.
23. North Carolina Department of Health and Human Services. Painkiller suspected in fourth N.C. meningitis case. www.dhhs.state.nc.us/pressrel/10-18-02.htm (Accessed 2002 Nov 22).
24. 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 (Accessed 2003 Jan 8).
25. 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 on January 3, 2004.
26. United States Department of Justice, Federal Bureau of Investigation Website, April 22, 2002. Available online at: http://kansascity.fbi.gov/kcmostate042202.htm. Accessed on July 6, 2002.
27. Trissel LA. Compounding our problems-again. *Am J Health-Syst Pharm.* 2003; 60:432. Editorial.
28. 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.
29. Niedowski, E, Bor,J. State to probe Hopkins death: 2-year-old cancer patient died after receiving improper IV mixture. December 20, 2003. Baltimore Sun, Baltimore, MD.
30. Kastango, ES, DeMarco, S. Pharmacy Cleanroom Project Management Considerations: An Experience-Based Perspective. *Int J Pharm Compd.* 2001; 5: 221–225.
31. Flynn, EA, Pearson, RE, Barker, KN. Observational study of accuracy in compounding IV admixtures at five hospitals. *Am J Health-Syst Pharm.* 1997 Apr 15; 54: 904–912.
32. Bond, CA, et. al. Clinical Pharmacy Services, Hospital Pharmacy Staffing, and Medication Errors in the United States Hospitals, *Pharmacotherapy* 22(2): 134–147, 2002.
33. Personal conversation between Ken Baker, Vice President and General Counsel, Pharmacists Mutual, and Eric S. Kastango, Clinical IQ, LLC. January 2004.
34. Rich, DS. NHIA 13th Annual Conference: Sterile Product Preparations: Meeting New USP Guidelines, Regulations and Standards of Practice for Compounding Sterile Preparations. March 2004.
35. Personal correspondence between Loyd Allen, R.Ph., Ph.D., Oklahoma City, Oklahoma and Eric S. Kastango, Clinical IQ, LLC. October, 2003.
36. Barnes BJ, Van Wormer JM. *Process Thinking and the 85:15 Rule Applied to Education.* Available online at: http://www.grandblanc.k12.mi.us/qip/ProcessThinking.htm. Accessed on July 6, 2002.

Additional Resources

Accreditation Commission for Health Care, Inc. (ACHC) www.achc.org

American Society of Clinical Oncology (ASCO.) Criteria for Facilities and Personnel for the Administration of Parenteral Systemic Antineoplastic Therapy. Journal of Clinical Oncology 1997; 15(11): 3416–17.

American Society of Health-System Pharmacists (ASHP). www.ashp.org

Anon. New National Standards on Pharmaceutical Compounding. Infusion. 2003; 10(1):-20-22. (This article includes the full NHIA Position statement on USP <797>)

ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products. Am J Health-Syst Pharm. 2000; 57:1150–69.

ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033–49.

American Society for Parenteral and Enteral Nutrition (ASPEN). Safe Practices for Parenteral Nutrition Formulation. Journal of Parenteral and Enteral Nutrition. 1998 Vol. 22, No. 2.

Bing, C (ed.) Extended Stability for Parenteral Drugs, 2nd ed . Bethesda, MD: American Society of Health-System Pharmacists; 2003.

Buchanan EC, McKinnon BT, Scheckelhoff DJ, Schneider PJ. Principles of Sterile Product Preparation, revised first edition. Bethesda, MD: American Society of Health-System Pharmacists; 2002. (Second edition in production for 2004)

Centers for Disease Control. Guideline for Hand Hygiene in Health-Care Settings. Morbidity and Mortality Weekly Report. October 25, 2002 / Vol. 51 / No. RR-16. http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf

Community Health Accreditation Program (CHAP): www.chapinc.org

Cooper, JC, Thoma, LA. Screening Extemporaneously compounded intraspinal injections with bacterial endotoxins test. Am J Health-Syst Pharm. 2002; 59:2426–2433.

FDA. Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice. DRAFT guidance issued August 2003 for comments, pending final release. http://www.fda.gov/cder/guidance/1874dft.htm

FDA. Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation — Small Entity Compliance Guide, November 2001. http://www.fda.gov/cder/guidance/4774fnl.pdf

Food and Drug Administration Modernization Act of 1997,£127. Application of Federal Law to Practice of Pharmacy Compounding. http://www.fda.gov/cdrh/modact97.pdf

Joint Commission on Accreditation of Healthcare Organizations (JCAHO): www.jcaho.org

Kastango, ES. USP <797> Gap Analysis Tool. Clinical IQ website: www.clinicaliq.com.

Kastango, ES, DeMarco, S. Pharmacy Cleanroom Project Management Considerations: An Experience-Based Perspective. Int J Pharm Compd. 2001; 5: 221–225.

Kastango, ES, Douglass, K. Improving the Management, Operations and Cost Effectiveness of Sterile-Product Compounding—Improve the ability to predict employee efficiency, cost of service and product wastage while simultaneously improving quality. Int J Pharm Compd. 1999; 3:253–258.

Kastango, ES, Bradshaw, B. Sterile Product Compounding: Developing Quality-Based Standards for Pharmacy Practice. Infusion. 2002; 8: 23–27.

Kastango, ES, Douglass, K. Quality Assurance for Sterile Products. Int J Pharm Compd. 2001; 5: 246–253.

Kastango, ES, Trissel, LA, Bradshaw, B. An Ounce of Prevention: Controlling Hazards in Extemporaneous Compounding Practices. Int J Pharm Compd. 2003; 5: 401–416.

Kastango, ES. Sterile Product Preparation: A Multimedia Learning Tool. Bethesda, MD: American Society of Health-System Pharmacists, 2002. (CD-ROM)

Kastango, ES. Compounding Containment Devices: Buyer Be Aware. Int J Pharm Compd. 2001; 5: 384–388.

Kastango, ES. The Cost of Quality for Sterile Products, Int J Pharm Compd. 2002; 6: 404–407.

Levy L. Get ready for new sterile compounding regulations. Drug Topics 2003; 147:41.

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.

National Association of Boards of Pharmacy. Model State Pharmacy Practice Act and Model Rules of the National Association of Boards of Pharmacy. Fall 2002. www.nabp.net

NHIA 12th Annual Conference Advanced Specialty Workshop Regulatory Issues Focus: Sterile Product Preparation (2 Tape Set) February 2003—120 minutes (2 cassettes) Speakers: Eric Kastango, RPh, MBA, FASHP and Gloria Lee Wilder, Pharm.D.

NHIA Audio Conference tape from October 22, 2003n"Meeting the Future Challenges in Sterile Product Compounding" Speaker: Eric Kastango, R.Ph., MBA, FASHP.

O'Neal BC, Schneider PJ, Pedersen, et al. Compliance with safe practices for preparing parenteral nutrition solutions. Am J Health-Syst Pharm. 2002; 59:264–9.

OSHA Technical Manual Section VI, Chapter 2. Controlling Occupational Exposure to Hazardous Drugs (HD's). www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

Pharmaceutical Compounding—Sterile Preparations (General Information Chapter 797) in United States Pharmacopeia, 27th rev., and the National Formulary 22nd ed, Rockville, MD: The United States Pharmacopeial Convention; 2003.

Quality Assurance for Pharmacy-Prepared Sterile Products. Videotape & Workbook. Bethesda, MD: American Society of Health-System Pharmacists; 1994.

Safe Handling of Cytotoxic and Hazardous Drugs Videotape. Bethesda, MD: American Society of Health-System Pharmacists; 1990.

Sterile Drug Products for Home Use, Chapter 1206. . USP 24–NF 19. Rockville, MD: USP Convention, Inc.; 1999. p. 2130–43.

Sterility Testing (General Information Chapter 71) in United States Pharmacopeia, 27th rev., and the National Formulary 22nd ed, Rockville, MD: The United States Pharmacopeial Convention; 2003.

Talley RC. Sterile compounding in hospital pharmacies. Am J Health-Syst Pharm. 2003; 60:2563. Editorial.

Tamer HR, Sweet BV. Management Consultation: Compounding pharmaceuticals for investigational use. Am J Health-Syst Pharm. 2002; 59:1716–19.

Thompson CA. News: USP publishes enforceable chapter on sterile compounding. Am J Health-Syst Pharm. 2003; 60:1814–17.

Trissel, LA. Compounding our problems—again. Am J Health-Syst Pharm. 2003; 60:432. Editorial.

Trissel, LA. Handbook on Injectable Drugs, 12th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2003.

Trissel LA, Ogundele AB, Ingram DS, et al. Using a media fill simulation to establish a benchmark microbiological contamination rate for low-risk-level compounding. Am J Health-Syst Pharm. 2003; 60:1853–5.

Trissel's 2 Clinical Pharmaceutics Database: www.trissels.info

United States Pharmacopeia (USP) web site: www.usp.org

Young D. News: Compounding sterile preparations raises informed consent issues. Am J Health-Syst Pharm. 2003; 60:1209–10.

Young D. News: Outsourced compounding can be problematic. Am J Health-Syst Pharm. 2002; 59:2261–4.