

USP chapter 797: Establishing a practice standard for compounding sterile preparations in pharmacy

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No one single event is affecting the profession of pharmacy as is chapter 797 of *The United States Pharmacopeia and The National Formulary (USP)*, entitled *Pharmaceutical Compounding—Sterile Preparations*.¹ Pharmacists have been compounding for hundreds of years and take pride in being critical members of the patient care team. As a profession, however, we have failed to embrace the basic and fundamental principles of contamination control, aseptic processing, and quality assurance, despite the fact that several practice guidelines have been published over the past three decades establishing universal practice standards for compounding sterile preparations. None of these documents were completely successful in moving the profession forward to achieve the standards. Perhaps arrogance or ignorance has blinded us to the fact that we need to follow a uniform code of practice using evidence-based knowledge. On January 1, 2004, USP chapter 797 was published. It is enforceable by regulatory agencies and details the procedures and requirements with which pharma-

cists and other health care professionals must comply when they compound sterile preparations. The chapter establishes the practice standards that are applicable to all practice settings where sterile preparations are compounded (e.g., hospitals, community pharmacies, home infusion services, ambulatory care services, physician offices, nursing homes). As pharmacists, we have been given the right to compound; as professionals, we have the obligation to compound to the highest standards.

Chapter 797 overview and history

During the 1960s and 1970s, the practice of pharmacy was evolving. Emphasis was placed on patient safety after patient injuries and deaths related to medication delivery and sterile compounding issues were reported. One of the first professional groups to address these patient safety issues was the National Coordinating Committee on Large Volume Parenterals (NCCLVP). NCCLVP, established by the U.S. Pharmacopeial Convention, subsequently developed and recommended standards of practice for the preparation, labeling,

and quality assurance of hospital pharmacy admixture services.²⁻⁸

After the dissolution of NCCLVP in the 1980s, the profession of pharmacy received pressure from the Food and Drug Administration (FDA) to address microbial contamination of compounded products in U.S. hospitals.

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, issued practice recommendations in an effort to provide a professional mandate and practice assistance to pharmacists and technicians who compounded sterile preparations. Each document stated that the pharmacist was ultimately responsible for ensuring that compounded sterile preparations (CSPs) were properly prepared, labeled, stored, dispensed, and delivered.

In 1992, USP issued a draft recommendation, entitled *Dispensing Practices for Sterile Drug Products Intended for Home Use*. The intent of this document was

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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.⁹

USP adopted a final version of the draft, *USP* chapter 1206, entitled Sterile Drug Products for Home Use, to provide specific practice standards and operating guidelines for CSPs.¹⁰ Although the chapter was not enforceable by FDA, it provided excellent guidance for pharmacists who compound sterile preparations.

In 1993, ASHP issued a technical assistance bulletin (TAB) that further defined the level and extent of recommended quality assurance measures that should be used when compounding sterile preparations.¹¹ These recommendations also addressed operating issues, such as equipment and setup, compounding-personnel gowning procedures, cleaning procedures, types of products utilized, and the length of product storage. This TAB was developed to be applicable in a variety of practice settings, including hospitals, community pharmacies, long-term-care facilities, and home care organizations. It defined risk level categories (I–III), which have become the unofficial standard for some in the pharmacy profession. However, the TAB did not provide the degree of specificity that most pharmacy practitioners wanted, thereby impeding its integration and general acceptance by some pharmacists. Among the reasons for not following the TAB was the perception that the recom-

The Primer section covers basic information in various fields of knowledge of interest to pharmacists who practice in health systems. Within the scope of the section are reviews of fundamental concepts in, for example, pharmacy, pharmaceuticals, pharmacology, physiology, therapeutics, and health care technology. Also covered are topics somewhat out of the mainstream of pharmacy (e.g., advances in nondrug health care technology) but nevertheless of interest to practitioners.

mendations were unnecessary, excessive, costly, and time-consuming. In addition, some practitioners did not think that there was sufficient evidence to support the recommended changes. FDA's concerns for the safety of CSPs were not alleviated by this document.

In 1995, ASHP conducted a national survey of quality assurance for pharmacy-prepared sterile preparations as a follow-up to the TAB.¹² The survey results indicated that very few pharmacies were equipped with adequately controlled compounding environments, which are essential for dispensing CSPs. The survey also showed that most pharmacists were not performing critical quality assurance checks, such as environmental monitoring, end-product testing, and process validation.¹³

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

In 2000, ASHP revised and published the aforementioned TAB as "Guidelines on Quality Assurance

for Pharmacy-Prepared Sterile Products."¹⁴ This revision expanded on the original document and provided further evidence that pharmacists and technicians should improve the safety and accuracy of CSPs.

Morris et al.¹⁵ conducted and published a national survey regarding pharmacy's compliance with these guidelines. The findings were similar to those of the 1995 survey, again demonstrating that the guidelines had not produced significant changes in sterile compounding practices in the 10 years since the publication of the first TAB.

Legal and regulatory issues

The genesis of chapter 797 is logical considering (1) USP's long history in setting drug and practice standards, (2) pharmacy had not widely adopted a practice standard, (3) the Supreme Court decision ruling section 503A of FDAMA unconstitutional, and (4) FDA's continued concerns over the quality of pharmacy-prepared sterile compounds. In 1906, the Food and Drugs Act was passed, and *USP* became the official standard for drugs in the United States. In 1938, Congress passed the Federal Food, Drug, and Cosmetic (FD&C) Act, a revision of the 1906 Food and Drugs Act. The FD&C Act, enforceable by FDA, recognized *USP* as the official compendia of drug standards.

Each chapter of *USP* is assigned a number, which appears in brackets along with the chapter name. Chapters 1–999 are requirements and official monographs and standards of *USP*, whereas chapters 1000–1999 are informational. Chapters 2000 and above apply to nutritional supplements.¹⁶ Since chapter 797 is considered a requirement, pharmacies

may be inspected for complicity with these standards by state boards of pharmacy, FDA, and accreditation organizations, such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), Accreditation Commission for Health Care, and Community Health Accreditation Program. FDA exercises enforcement discretion during routine inspections but will intervene when patient injuries or deaths associated with CSPs have occurred. Since 1990, FDA has become aware of more than 55 quality problems associated with CSPs, many of which have resulted in drug recalls, patient injuries, and deaths.¹⁷⁻³¹ The problems included grossly contaminated parenteral nutrient solutions, eye drops, histamine H₂-receptor antagonists, corticosteroids, and other CSPs. Common factors in most of these cases were poor employee training, lack of policy and procedure, poor aseptic technique, lack of validated sterility methods, and lack of properly designed and operating compounding facilities.

Chapter 797 summary

Each of the major areas within chapter 797 is discussed below. These summaries should not serve as a substitute for the actual text of the chapter.

Introduction. Sterile compounding is defined in the introduction of the chapter and clearly differs from nonsterile compounding, which is covered by *USP* chapters 795 and 1075. The intent of chapter 797 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.¹

This chapter applies to all health care settings where sterile preparations

are compounded. The introduction also defines CSP as a dosage unit of

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

The introduction to chapter 797 also discusses the three risk-level classifications (low, medium, and high) for CSPs, which are determined by the potential for microbial, chemical, and physical contamination.

Responsibility of compounding personnel. This section 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 responsibilities include maintaining appropriate cleanliness conditions and providing labeling and supplementary instructions for the proper clinical administration of CSPs. This section further discusses the responsibilities of the supervisor of compounding personnel to ensure that

- Personnel are adequately educated, instructed, and skilled to perform their functions,
- Ingredients have correct identity, quality, and amount,
- Open and partial containers are properly stored,
- Bacterial endotoxins are minimized,

- Proper and adequate sterilization is used,
- Equipment is clean, accurate, and appropriate,
- Potential harm from added substances is evaluated before dispensing,
- Packaging is appropriate for sterility and stability,
- Compounding environment maintains the sterility of presterilized items,
- Labels are appropriate and complete,
- Beyond-use dates are appropriate and based on valid scientific criteria,
- Correct compounding procedures are used,
- Deficiencies in compounding can be rapidly identified and corrected, and
- Compounding is separate from quality evaluation.

Microbial contamination risk levels. This section defines the three microbial contamination risk levels. The determination of compounding-risk levels is the responsibility of the compounder. Because this chapter was written in the broadest terms using general descriptive statements, no single ironclad determination of risk exists with respect to practice settings or compounding procedures. Risk-level classification is not prescriptive, with one exception: Preparing CSPs 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 class 5 (formerly known as class 100) environment at all times,
- Compounding procedures involve only a few closed-system, basic, simple aseptic transfers and manipulations,

- Routine disinfection and air-quality testing to maintain class 5 cleanroom,
- Adequate personnel garb for sterile preparation,
- Correct identity and amounts of components reviewed before and after compounding,
- Final visual inspection required for each CSP, and
- Annual media-fill test procedure for each person who compounds performed to validate proper aseptic technique.

Medium-risk level

- Involves pooling multiple sterile commercial products for multiple patients or one patient multiple times (batched antibiotics or other small-volume parenterals),
- Involves complex aseptic manipulations (total parenteral nutrient [TPN] solutions 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, and
- Requires more challenging annual media-fill evaluation of compounding personnel technique that simulates the most challenging or stressful conditions.

High-risk level

- Prepared from nonsterile ingredients,
- Preparation from sterile ingredients but exposed to less than class 5 cleanroom,
- More than six-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, and

- 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 how well the methods used to compound the sterile preparation achieve the desired goal of purity, potency, and sterility. CSPs that require some form of terminal sterilization, by filtration, steam, or ionizing radiation, have to be validated to ensure that each CSP is void of microbial contamination.

Personnel training and evaluation in aseptic manipulation skills. Many pharmacists and technicians have little or no didactic training in sterile compounding. All personnel must be properly trained through didactic instruction in the theory and practice of sterile preparation before commencing any compounding and evaluated annually in low- and medium-risk level compounding and semiannually for high-risk-level compounding. Further, compounder evaluations should include a formal written exam and practical evaluation of aseptic technique using growth media (i.e., the media-fill method).

Environmental quality and control. This section details the physical plant and environmental requirements for each CSP risk level. These include

- Laminar-airflow workbenches and cleanrooms or barrier isolators and their recertification every six months,
- A compounding area separate from the general pharmacy with a controlled (particle, temperature, humidity) environment,

- A class 5 environment for critical areas where CSPs are exposed to air in the physical environment,
- A class 8 (formerly class 100,000) environment for the buffer zone or cleanroom (the terms cleanroom and buffer zone are interchangeable),
- Detailed cleaning and sanitizing procedures to maintain the cleanliness of the compounding environment,
- Properly garbed compounding personnel, in accordance with the risk level of compounding,
- Written, properly approved policies and procedures for the activities that occur in the compounding environment, and
- Routine environmental monitoring and documentation to prove that the compounding environment is properly maintained.

Processing. This section calls for a written employee-training and evaluation program specific to the preparation of CSPs in each health care setting to ensure that compounding personnel are knowledgeable and properly trained. It cannot be over-emphasized that training is the cornerstone for ensuring the quality and safety of CSPs.

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

Finished-preparation release checks and tests. All finished CSPs must be checked by a pharmacist before they are dispensed to ensure that the preparation is sterile and accu-

rate. There are several methods that can be employed to meet this requirement.

- Physical visual inspection for preparation integrity (e.g., absence of cores, other particulate matter, phase changes, discoloration).
- Verification of compounding accuracy by someone other than the compounding to ensure proper measurement, reconstitution, and component usage.
- Testing of high-risk CSPs in groups of over 25 in accordance with *USP* chapters 71 and 85.
- Testing of low- and medium-risk CSPs that exceeds chapter guidelines for beyond-use dating (formerly called expiration dating) in accordance with chapter 71.

Storage and beyond-use dating.

In many health care settings, CSPs are often prepared in anticipation of use and, as such, may be stored for extended periods of time. This section 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 before use, there is potential for microbial growth and pyrogen formation. Expiration limits based on risk level (Table 1) and chemical stability limits obtained from literature or testing using validated equipment (e.g., high-performance liquid chromatography, thin-layer chromatography, and flame spectrophotometry) are described.

USP chapter 795 provides the following guidance for instances when bulk nonsterile components do not have expiration dates:

- **Solids and nonaqueous liquids:** 25% of the remaining expiration period of the source ingredient or chemical, or six months, whichever is less.
- **USP standard bulk, nonsterile components:** no more than six months.
- **Aqueous formulations:** 14 days refrigerated.

Table 1.

Beyond-Use Dating Guidelines Based on Risk Level¹

Risk Level	Storage Temperature		
	Room (20–25 °C)	Refrigeration (2–8 °C)	Frozen (≤–20 °C)
Low	48 hr	14 days	45 days
Medium	30 hr	7 days	45 days
High	24 hr	3 days	45 days

- **All others:** no more than 30 days or the intended duration of therapy.

Maintaining product quality and control after dispensing from pharmacy.

Pharmacists are responsible for ensuring that the CSPs' quality and integrity are maintained during transit, regardless of the physical location within the health system (hospital, home, or ambulatory care infusion center). This responsibility includes the use of appropriate packaging (coolers, wet-ice blocks, dry ice) that can maintain the proper temperature and conditions (refrigerated or frozen) during shipment via a common carrier (Federal Express, United Parcel Service, or the U.S. Postal Service). Quality-control responsibilities during transit also include the delivery of CSPs within a health care organization via courier or pneumatic tube system. Specific considerations are also made for the following subsections:

- Packaging, handling, and transport,
- Use and storage,
- Administration,
- Redispensed CSPs,
- Education and training,
- Packing CSPs for transit, and
- Storage in locations outside CSP-preparation facilities.

Patient or caregiver training. The patient or caregiver (e.g., nurse, physician, spouse, parent) must clearly understand how to store, administer, and dispose of the CSP. 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-event 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 chapter 797 focus on formalizing the policies, processes, and procedures used in preparing CSPs. One element related to quality that may not be routinely performed in pharmacies is documentation that compounding personnel are trained, the equipment is maintained and calibrated routinely, the compounding environment is properly maintained and tested, and CSPs are prepared using the correct components in the correct ratios or volumes. The essence of quality assurance is proving that you are doing what you should be doing.

Concerns and considerations for pharmacies

The following points review issues that were consistently identified during site visits of several different pharmacy practice settings, including major metropolitan hospitals with and without compounding satellites, community-based hospitals, ambulatory care centers, community compounding pharmacies, and home

infusion pharmacies. Conversations with pharmacists in these settings revealed a consistent lack of understanding of chapter 797. Most pharmacists did not even have access to a copy of the chapter, which makes it difficult, if not impossible, to implement the requirements.

Applicability to all health care settings. The principles of contamination control and proper compounding procedures are not unique to the practice setting where sterile preparations are compounded. Chapter 797 requirements must be met in all health care settings where compounding of sterile preparations occurs and by all disciplines associated with these settings, including physicians, nurses, and pharmacists in office practices, clinics, hospital units, and central and satellite pharmacies. The enforcement of this chapter by state boards of pharmacy is limited to licensed pharmacies. Several pharmacists questioned the enforcement of the requirements in practice settings other than licensed pharmacies. Pharmacists' immediate responsibility today is to focus on the safety of their patients and to get their house in order. In time, other means of enforcement may be identified for all practice settings before additional patient injuries or deaths occur.

Criteria for risk levels. There is a fair amount of consternation over the establishing of risk levels for pharmacy practice settings. Since the practices, policies, procedures, and facilities of pharmacies where sterile compounding occurs vary so widely, chapter 797 was written to give the pharmacist, as the individual with the ultimate responsibility for sterility and accuracy of CSPs, flexibility in determining the actual risk levels for CSPs instead of using clear-cut templates.

We compiled a checklist to provide an overview of some of the various factors that can be used when determining risk levels (Table 2). The

most important factor in determining risk level is sound professional judgment based on the knowledge of aseptic compounding principles.

Environmental quality controls.

A majority of pharmacies do not have the appropriate facilities to meet the engineering quality controls mandated in chapter 797. There is a significant knowledge gap and misinformation about air quality classification and how it is achieved. To achieve a true cleanroom classification, one must consider particle counts, high-efficiency particulate air (HEPA) filters, room air changes, and room air-pressure differentials.^{32,33} The quality of air in critical compounding areas can contribute to the level of microbial contamination. The need to control the quality of critical operating environments has been known for more than a century, when the etiologic role of bacteria in infection was discovered.³² Cleanrooms were developed to minimize or eliminate bacteria and to control the incidence of infection in hospitals (i.e., operating rooms),

where the incidence of airborne infections could be greatly reduced by providing proper ventilation to critical areas. Airborne particles generated from the environment (dust, dirt, pollen, viable and nonviable microorganisms) and from people (skin flakes, lint, cosmetics, respiratory gases) were also found to negatively influence patient outcomes.³² Therefore, areas where sterile preparations are compounded must be routinely monitored. The appropriate combination of work areas, cleanrooms, ante rooms, laminar-airflow workbenches, and barrier isolators to achieve desired cleanliness levels based on risk classification and workloads must be determined. The costs associated with achieving appropriate levels of cleanliness in accordance with chapter 797 can be significant, requiring institutional executives, administrators, and risk managers to realize that correcting this deficiency is no longer optional but is as fundamental as ensuring that operating rooms are properly designed, built, and maintained.

Table 2. Pharmacy Compounding Risk-Level Assessment

Risk Level	Requirements
Low	<ul style="list-style-type: none"> Simple admixtures compounded using closed-system transfer methods Prepared in class 5 laminar-airflow workbench (hood) Located in class 8 buffer room (cleanroom) with ante area Examples: reconstitution of single-dose vials of antibiotics or other small-volume parenterals, preparation of hydration solutions
Medium	<ul style="list-style-type: none"> Admixtures compounded using multiple additives or small volumes Batch preparations (e.g., syringes) Complex manipulations (e.g., total parenteral nutrition) Preparation for use over several days Prepared in class 5 area Located in class 8 cleanroom with ante area Examples: pooled admixtures, parenteral nutrient solutions using automated compounders, batch-compounded preparations that do not contain bacteriostatic components
High	<ul style="list-style-type: none"> Nonsterile (bulk powders) ingredients Open-system transfers Prepared in class 5 area Located in class 8 cleanroom with separate ante area Examples: CSPs prepared from bulk, nonsterile components (morphine or other narcotics), or final containers that are nonsterile and must be terminally sterilized (nuclear pharmaceuticals)^a

^aCSP = compounded sterile preparations.

Guidance from qualified and certified persons who have experience and expertise with cleanrooms should be sought before modifying current facilities. To find qualified individuals who can design, build, and validate a cleanroom environment, the buyer must understand the design requirements and functional specifications necessary. This requires some research and self-education.

A variety of facility and engineering controls can be used to ensure that the proper environmental controls are in place, such as installing integrated HEPA filters in ceiling fans; replacing current ceiling tiles with plastic-covered, cleanroom-grade tiles; removing refrigerators, computers, and printers from the compounding area; and replacing existing flooring with seamless vinyl flooring (e.g., Medintech by Armstrong).

Process and preparation quality controls. Historically, few if any controls have been enforced for those personnel who compound sterile preparations. Rather, these individuals have been trusted to maintain professionalism in their preparation of CSPs. Much of the reason for this is the lack of understanding in key quality concepts, such as adherence to policies and procedures, proper documentation, and a lack of supervisory oversight. Amplifying this problem is the fact that supervisors do not realize the importance of quality systems and processes. Pharmacists and technicians must understand that compounding processes and the person who compounds contribute to the quality of the final CSP. As such, compounding must be done consistently. Compounding is no different than production lines in which process consistency, predictability, and repeatability are designed and controlled. These controls are cornerstones in ensuring CSP sterility and accuracy. The desired outcome of chapter 797 requirements is to proactively determine where fail-

ures may occur in a process and implement methods to control and monitor these critical points, thereby increasing the likelihood of consistently producing a quality CSP. Quality cannot be maintained by random, arbitrary, and retrospective checks of the final product, but must be designed into the system using quality-control measures.³⁴ Many resources and guidance documents are available to better understand appropriate aseptic techniques, process validation procedures, and methods for end-process content accuracy, sterility, and other quality-control measures.

Sterility and beyond-use dating. Another area of concern involves the assignment of beyond-use dating and determination of CSP sterility, two critical factors in establishing CSP beyond-use dating. First, the chemical stability of the drug or chemical entity in a given solution must be determined. Second, a CSP must be sterile. By definition, sterility is the absence of viable microorganisms in a CSP. Unlike pyrogenicity, sterility is an absolute concept. There are acceptable levels of pyrogens permitted in CSPs, although the desired goal is to compound a pyrogen-free preparation. Patient injury and death have occurred following the administration of CSPs contaminated with pyrogens and microbes. Proper assignment of risk levels and operating principles outlined in chapter 797 serves to help prevent microbial contamination of CSPs. Unless sterility testing is performed, the beyond-use dating of the preparation cannot exceed the published limits found in chapter 797 (Table 1). If sterility testing is performed in accordance with chapter 71, beyond-use dating of the CSP can be based on the maximum chemical stability of the drug in solution as permitted by valid references. Most of pharmacy's experience with end-product testing procedures involves methodologies that do not comply with chapter 71.

Staff training, competency, and performance. Many pharmacy practice settings have attempted to adopt and administer training programs in aseptic technique to meet the requirements for accreditation. There is no consistent, universally adopted, formalized, evidence-based training and education program for pharmacists and technicians in the area of contamination control, aseptic processing, and quality assurance. Several factors directly affect the sterility and accuracy of CSPs, including formal training, objective aseptic technique validation, and ongoing and periodic competency assessment. Properly trained employees and supervisors are of the utmost importance in ensuring the accuracy and sterility of CSPs.

Proper compounding documentation. Very few pharmacy practice settings generate the necessary documentation to allow for product tracking and recall and proof that policies and procedures were properly followed. Proper documentation practices are fostered only by active participation and review from management. Documentation can be used to not only assess quality but also proactively identify problems and correct them. Documentation of past events does not prevent future errors. Documentation serves as a means of detecting and correcting conditions or situations that affect quality.

Personnel garbing. The lack of proper garbing, especially with hand washing, has been consistently observed.¹⁴ There is overwhelming evidence that good personal hygiene habits and adherence to garbing procedures are critical to the asepsis of CSPs. This evidence dates back to 1847, when Ignaz Semmelweis, a Hungarian physician, demonstrated that the incidence of puerperal fever was related to hand washing. If food service personnel are expected to wear gloves while handling food, pharmacy personnel compounding

sterile preparations cannot claim that wearing gloves is not necessary. This is a guideline that a conscientious pharmacist or technician can institute immediately. Tables 3 and 4 detail the amount of inherent particles and particles emitted from personnel, even when garbed, in the environment.

Patient safety

There is ample evidence that improperly compounded sterile and nonsterile preparations injure and kill patients.¹⁷⁻³¹ Several state boards of pharmacy have significantly revised their pharmacy practice acts by expanding regulatory provisions to include the oversight of compounding. The practice of compounding sterile preparations is now dictated by requirements published as a component of the FD&C Act. State boards of pharmacy, attorneys, accreditation organizations, and FDA use and reference these requirements during inspections, surveys, and enforcement actions.

Several studies have demonstrated the prevalence of pharmacists' com-

pounding errors.^{27,35} It is highly probable that most investigations of vascular-access-device phlebitis, septicemia, and other nosocomial infections have not taken into account the microbial flora in the sterile compounding areas in pharmacies.

Careful supervision and the double-checking of calculations, measurements, and compounding policies and procedures are necessary to reduce the risk of medication errors. In 2002, a study of medication errors in U.S. hospitals revealed that serious mistakes involving prescription drugs occur in 3–7% of hospital inpatients, suggesting that more than 90,000 inpatients are harmed by medication errors each year.³⁶ State boards of pharmacy are citing pharmacists for their failure to comply with existing sterile compounding regulations and assessing significant financial penalties. Further, lawyers have successfully quoted USP chapters as evidence of standards of practice during lawsuits (Allen Loyd, *International Journal of Pharmaceutical Compounding*, personal communication, 2003 Oct).³⁷

Pharmacists must accept the responsibilities and comply with the new quality-control standards. If we look at W. Edwards Deming's red bead experiment³⁸ and apply it to the practice of pharmacy compounding, there appears to be a significant parallel. In this experiment, Deming proved that the only way to improve a product or service is for management to improve the system that creates that product or service. This experiment demonstrates that the inherent variation in systems causes a wide range of results. To reduce the variation in the quality of CSPs within an organization, system variation should be a primary focus of attention rather than individual efforts. Systems failures include inadequate facilities, poor or nonexistent plans, inadequate employee training, robust validated procedures, measurable performance criteria, and difficult work processes.

There are a number of pharmacists still waiting to see what happens next before they feel compelled to act. Many wonder who will enforce chapter 797. We must choose to address the underlying issues and voluntarily comply with the standards rather than wait for FDA to enforce the standard. Many pharmacists are taking this matter very seriously and, despite institutional financial deficits and other seemingly daunting obstacles, embracing and working toward compliance. There is clear and compelling evidence that the old ways of compounding sterile preparations are no longer scientifically, morally,

Table 3. Inherent Particles Present in Cleanrooms^a

Activity	No. Particles ≥0.3 μm
Person emits during garmenting process	3,000,000/min
Cleanest skin (hands)	10,000,000/ft ²
Employee street clothes	10,000,000–30,000,000/ft ²
Floor and bench surfaces	>10,000,000/ft ²
Garments supplied by cleanroom laundry	1,000,000/ft ²

^aAdapted from Austin PR. Encyclopedia of cleanrooms, bio-cleanrooms, and aseptic areas. Boca Raton, FL: CRC; 2000, with permission.

Table 4. Particles Emitted from Personnel Movement^a

Personnel Activity	No. Particles ≥0.3 μm Emitted per Minute in Garment Indicated				
	Snap Smock	Standard Overall	Two-Piece Overall	Tyvek Overall	Membrane Overall
No movement	100,000	10,000	4,000	1,000	10
Light movement	500,000	50,000	20,000	5,000	50
Heavy movement	1,000,000	100,000	40,000	10,000	100
Change position	2,500,000	250,000	100,000	25,000	250
Slow walk	5,000,000	500,000	200,000	50,000	500
Fast walk	10,000,000	1,000,000	400,000	100,000	1,000

^aLight and heavy movements refer to partial body movements (e.g., motioning with arm, tapping toes). Change of position refers to whole-body motion (e.g., standing up, sitting down). Adapted from Austin PR. Encyclopedia of cleanrooms, bio-cleanrooms, and aseptic areas. Boca Raton, FL: CRC; 2000, with permission.

or ethically acceptable. 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 pharmacists and technicians to embrace the scientific fact that good compounding practices will yield accurate and sterile preparations. 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 toward compliance

Most practice settings in which CSPs are prepared may have significant practice standard gaps relative to compliance with chapter 797 in multiple areas. Several steps must occur to comply with chapter 797.

Determine risk level of the compounding. Most pharmacies perform low- and medium-risk compounding. If bulk, nonsterile powders are used, high-risk compounding is being performed. Table 2 can help identify a facility’s risk level.

Perform gap analysis. After the level of risk has been determined, the next step is to compare current pharmacy compounding operations with those described in chapter 797. This evaluation is known as gap analysis. To perform gap analysis, the requirements of chapter 797 are compared line by line with current practices and operational facilities to identify differences, or “gaps.” The gaps should be analyzed to identify specific practices causing the greatest risks or differences from chapter requirements; then these gaps should be prioritized by fiscal and human resource costs (Table 5).

Develop an action plan. Developing an action plan from the prioritized gap list identifies options for immediately improving CSP practic-

es, thus reducing vulnerability to microbial contamination and inaccurate compounded preparations.

Completing the risk-level assessment and gap analysis can demonstrate to accreditation organizations, boards of pharmacy, and other regulatory authorities that the current operating deficiencies are identified and corrective action is being taken to achieve compliance. The immediate corrective action plan should address all nonfacility, low-cost requirements identified during the gap analysis. Revised policies and procedures should reflect actual day-to-day operations and practices, such as hand washing, gloving and gowning, didactic and skills-based training, competency of staff, aseptic technique, media-fill validation, proper housekeeping (cleaning and sanitizing), and environmental monitoring for microbes. Nonfacility issues can be addressed immediately after the gap analysis and will require little more than time and vigilance. Large capital expenditures may require more time and planning to secure approval and may require discus-

sions with administrators, risk managers, and environmental services.

Evaluate the use of alternative products. Another effective means of reducing the level of risk for CSPs is the use of alternative products or product configurations, such as frozen premixed medications and unit-of-use closed transfer packaging (e.g., Minibag Plus and Advantage). The Institute for Safe Medication Practices strongly recommends the use of prefilled or pre-made medication dosage forms as a means to improve patient safety.

Reassess workload of compounding personnel. Pharmacists should also reassess compounding demands based on risk-level requirements and by consolidating workloads from point-of-care locations, moving compounding to central pharmacies from satellite pharmacies. Centralizing compounding activities can improve CSP quality and consistency while reducing costs through ensuring employee competency and facility requirements. If compounding most often occurs at point-of-care locations, beyond-use

Table 5. **Costs and Significance of Addressing Compliance with USP Chapter 797 Domains^a**

Quality Domains	Impact on CSP Quality	Relative Cost
Compounding conditions	NA	NA
Quality assurance program	++++	\$\$
Quality assurance practices	++++	\$
Reports and documents	++++	\$
Outcomes (ADR) monitoring	+++	\$\$
Patient training	++++	\$\$
Maintaining product quality and control	++++	\$\$\$
Storage and beyond-use dating	+++	\$\$
Finished product release checks and tests	++++	\$\$
CSP work environment	+++	\$\$\$\$
Equipment and supplies	++++	\$\$
Components	++++	\$
Processing: aseptic technique	++++	\$
Environmental control	+++	\$
<i>Verification processes</i>		
Sterility testing	+++	\$\$\$
Environmental monitoring	++++	\$\$
Personnel training and education	++++	\$\$

^aUSP = The United States Pharmacopeia and The National Formulary, CSP = compounded sterile preparations, NA = not applicable, ADR = adverse drug reaction. The + signs indicate the relative value of the quality domain, with + indicating the lowest value and ++++ indicating the greatest value. The \$ signs represent a relative cost to comply with the quality domain, with \$ indicating the least expensive and \$\$\$\$ being the most expensive. Reprinted from Clinical IQ, LLC, Florham Park, NJ, with permission.

dating should be limited to the shortest period of time necessary to meet the patients' needs, minimizing the potential of microbial growth.

Document performance and quality improvements. All measures of quality performance should be documented. Also, it is imperative to communicate improvements in compliance with chapter 797 with staff, administration, and accreditation organizations. By focusing on positive communication with pharmacy staff of improved quality and patient care outcomes related to chapter 797, procedural changes can be successfully achieved, establishing employee ownership and buy-in to change old habits. JCAHO will accept a documented gap analysis and action plan as an acceptable approach to meeting chapter 797 in 2004.³⁶

Conclusion

FDA is currently monitoring pharmacy's compliance with chapter 797. Additional regulatory promulgations could be made to restrict the practice of compounding to a select group of trained, qualified, and certified professionals. Pharmacists must now finally embrace their professional responsibility as patient care providers through compliance with chapter 797.

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Metabolic complications of parenteral nutrition in adults, part 1

IMAD F. BTAICHE AND NABIL KHALIDI

Parenteral nutrition (PN) therapy is the administration of nutritional support via the intravenous route when the gastrointestinal tract cannot or should not be used in patients who are malnourished or at risk for malnutrition.¹ Components of PN include macronutrients, or the energy-yielding substrates (amino acids, dextrose, lipids); micronutrients (vitamins, trace elements); fluids; and electrolytes. PN is a lifesaving therapy in patients with intestinal failure, but its use is not without complications. In a meta-analysis of studies that evaluated PN in critically ill patients, malnourished patients seemed to benefit most from PN and developed fewer complications than nonmalnourished patients who received PN.² Similarly, the Veterans Affairs Cooperative Study showed that perioperative PN increased complication rates in patients with low to moderate malnutrition but improved outcomes in certain high-risk, severely malnourished pa-

Purpose. Common metabolic complications associated with parenteral nutrition (PN) are reviewed, and the consequences of overfeeding and variables for patient monitoring are discussed.

Summary. Although PN is a lifesaving therapy in patients with gastrointestinal failure, its use may be associated with metabolic, infectious, and technical complications. The metabolic complications associated with PN in adult patients include hyperglycemia, hypoglycemia, hyperlipidemia, hypercapnia, refeeding syndrome, acid-base disturbances, liver complications, manganese toxicity, and metabolic bone disease. These complications may occur in the acute care or chronic care patient. The frequency and severity of these complications depend on patient- and PN-specific factors. Proper assessment of the patient's nutritional status; tailoring the macronutrient, micronutrient, fluid, and electrolyte requirements on the basis of the patient's underlying diseases, clinical status, and drug

therapy; and monitoring the patient's tolerance of and response to nutritional support are essential in avoiding these complications. Early recognition of the signs and symptoms of complications and knowledge of the available pharmacologic and nonpharmacologic therapies are essential to proper management. PN should be used for the shortest period possible, and oral or enteral feeding should be initiated as soon as is clinically feasible. The gastrointestinal route remains the most physiologically appropriate and cost-effective way of providing nutritional support.

Conclusion. PN can lead to serious complications, many of which are associated with overfeeding. Close management is necessary to recognize and manage these complications.

Index terms: Electrolytes; Manganese; Minerals; Nutrition; Toxicity

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tients.³ Any decision to use PN should be based on a risk-benefit analysis taking into consideration the associated complications and costs.

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