

Blueprint for implementing *USP* chapter 797 for compounding sterile preparations

ERIC S. KASTANGO

As the profession of pharmacy moves to meet the requirements of the new national standard of practice for compounding sterile preparations, published in chapter 797 in the *United States Pharmacopeia*,¹ identifying resources that can assist administrators, pharmacists, and technicians can seem like a monumental task. This article provides the information and resources needed to address this task and systematically implement the processes and procedures articulated in chapter 797. Pharmacists must keep in mind that *USP* requirements constantly evolve, and this chapter should be considered a document that is subject to change. The recommendations in this article are intended to meet or exceed *USP* requirements. The knowledge base and resources detailed in this article have been used by the author in both pharmacies and Food and Drug Administration (FDA)-regulated manufacturing operations. They are not, however, the only ways to address the *USP* requirements. There are many ways to create a controlled and consistent process whereby compounded preparations are prepared accurately and in a sterile environment.

Compliance with *USP* chapter 797 and applicable state board of phar-

Purpose. Guidelines for adopting and successfully implementing the requirements of the *United States Pharmacopeia (USP)* chapter 797 for compounding sterile preparations are presented.

Summary. The quality of a compounded sterile preparation (CSP) is directly related to the methods used to ensure that the CSP achieves the desired goal of purity, potency, and sterility. A properly designed, constructed, and maintained cleanroom contributes to the quality of CSPs. Design criteria of a sample cleanroom are supplied, as are a summary and comparison of the liquid disinfectants that can be used to clean and sanitize the facility and maintain environmental controls. All activities associated with cleaning the cleanroom, including air and surface sampling, must be properly documented in logs, examples of which are provided. A robust employee-training program for properly teaching aseptic technique and a method to verify that personnel have successfully completed the program are integral to compliance with chapter 797 and thoroughly discussed herein. Emerging

compounding and testing technology is also discussed.

Conclusion. Although the task of compliance with the requirements of *USP* chapter 797 may appear overwhelming, complicated, expensive, and even unattainable, quality can be established via a methodical and organized approach. After the systems have been implemented, maintaining them requires vigilance and follow-up. Compliance with chapter 797 involves upfront and ongoing costs associated with establishing these systems, but the time, energy, and cost required to maintain them are far less than those of retrospective or manual systems of collecting, reviewing, and collating quality assurance data on a monthly basis.

Index terms: Aseptic areas; Compliance; Compounding; Concentration; Control, quality; Costs; Disinfectants; Documentation; Economics; Education; Guidelines; Personnel; Planning and design; Purity; Standards; Sterile products; Sterility; Technology; *United States Pharmacopeia*

Am J Health-Syst Pharm. 2005; 62:1271-88

macy practice acts does not need to be complex or cumbersome, but it will require leadership, vigilance, and consistency from the pharmacists and the technicians who perform critical compounding activities on a daily basis, as well as their managers and supervisors.

In the *ASHP Discussion Guide for Compounding Sterile Preparations*, developed by the American Society of Health-System Pharmacists (ASHP) and Baxter Healthcare, several activities were identified as critical elements of a program for compliance with *USP* chapter 797, including

ERIC S. KASTANGO, M.B.A., B.S.PHARM., FASHP, is President, Clinical IQ, LLC, 184 Columbia Turnpike #282, Florham Park, NJ (ekastango@clinicaliq.com).

Copyright © 2005, American Society of Health-System Pharmacists, Inc. All rights reserved. 1079-2082/05/0602-1271\$06.00.

- Determine the pharmacy's compounding risk level (low, medium, or high risk) using a risk-level assessment checklist, chapter 797, and professional judgment,
- Perform a gap analysis by comparing chapter 797 requirements line by line with pharmacy operational procedures and facilities,
- Develop an action plan for compliance based on the prioritized gap analysis,
- Communicate the results of the gap analysis and action plan with pharmacy staff and the administrators and executives of the organization,
- Implement operational changes and revise policies and procedures for compounded sterile preparations (CSPs) and then address changes needed for facility and equipment compliance,
- Communicate the demonstrated improvements in patient care with staff,
- Evaluate the use of alternative products and reassess workload demands for all compounding sites, and
- Document all measures of quality performance and communicate improvements in compliance with staff, administration, and accreditation organizations.²

The best way to comply with chapter 797 is to be intimately familiar with it. Several tools and resources are available to assist pharmacy in conducting a gap analysis. ASHP offers a Web-based Chapter 797 compliance advisor and risk assessment-gap analysis tool, and the *International Journal of Pharmaceutical Compounding* is developing a similar tool. These tools can help build the foundation for a corrective action plan that details the activities and resources needed to comply with USP compounding requirements.

Understanding USP chapter 797

In an effort to clarify portions of chapter 797 that require action, several sections of the chapter are reviewed below, with suggestions to

assist the pharmacist in compliance efforts. Unless there are clear and concise understanding and agreement on the definitions, concepts, and objectives in the chapter, success cannot be reasonably achieved. This is why the chapter's first two sections are so important, as they clarify the depth and breadth of CSPs, the practice settings in which the chapter is applicable, and the importance of the personnel preparing the sterile preparations. The nature and critical relationship of the people involved in preparing CSPs are clearly defined: "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."¹ Several other responsibilities are listed and should be clearly understood by all personnel involved directly and indirectly with preparation of sterile compounds.

Microbial contamination risk levels. This section clarifies the differences in the risk levels. Risk levels are assigned to CSPs on the basis of their potential for microbial contamination. The more complex the procedure, inferior the environment, or longer the storage period, the greater the risk of the patient receiving a nonsterile preparation. Because it is the responsibility of the compounder to determine the compounding risk level, no single ironclad determination of risk exists with respect to specific practice settings or compounding procedures. Risk-level classification in chapter 797 is not prescriptive, with one exception: *Preparing CSPs from bulk, nonsterile components will always be a high-risk level procedure.*

This section of the USP chapter is most important, since the risk level determines how the pharmacist will design and build the compounding environment, how personnel are trained, the level of garbing used, the frequency of environmental moni-

toring, the aseptic technique media-fill verification used, the type of end-preparation evaluation tests performed, and the beyond-use date (formerly referred to as expiration dating) assigned. Expiration dates are assigned by the manufacturer to medications to show the time frame that the medication is expected to meet USP monograph standards. Beyond-use dates are assigned by a pharmacist to show the date after which a CSP should not be used. All of these factors are designed to ensure the chemical integrity and microbial sterility of CSPs. A quick way to define the risk level of compounding is to understand the relationship between the ingredients or components and the CSP (Table 1).

Verification of compounding quality. The quality (sterility and accuracy) of a CSP is directly related to the methods used to ensure that the CSP achieves the desired goal of purity, potency, and sterility. CSPs that require some form of terminal sterilization (i.e., filtration, steam, or ionizing radiation) have to be verified to ensure that each dose is devoid of microbial contamination. Chapter 797 predominately addresses the sterility of high-risk compounding of CSPs and does not include low- or medium-risk compounding activities. There must be proof that the CSP prepared under high-risk compounding conditions is accurate and sterile.

This domain on quality requires that the methods chosen to sterilize the CSP should not affect the chemical or physical properties of the CSP and that the preparation is sterile (devoid of living microorganisms) and nonpyrogenic. (Destructive testing would be required to show that the compounding processes produced a sterile and correct preparation.) Absolute sterility cannot be practically demonstrated without testing every unit within a batch.³

Methods used to comply with this requirement must include the use of

Table 1.
Simplified Guidance to Determining Risk Levels of CSPs^a

Ingredient:CSP Ratio	Risk Level	Example(s)
1:1	Low	Reconstitution and transfer of a 1-g vial of cefazolin into a syringe or minibag
One to many (1:∞) or many to one (∞:1) (more than three ingredients)	Medium	Bulk 10-g vial of vancomycin distributed among several final doses; combination of three or more ingredients into one final dose
Any ingredient:CSP using nonsterile ingredients or devices or a CSP that requires terminal sterilization (filtration, steam, heat, gas, or ionizing radiation)	High	Alum bladder irrigation; PCA or epidural from powdered morphine; hydromorphone

^aAssumptions are that final CSPs are prepared in class 5 environment. Anytime that compounding occurs outside a class 5 environment, the CSP is classified as a high-risk preparation. Currently there is significant discussion in the USP Expert Committee on permitting bedside or immediate-use compounding under certain conditions. CSP = compounded sterile preparation, PCA = patient-controlled analgesia, USP = United States Pharmacopeia.

biological indicators (BIs) when using steam (autoclave), heat (dry-heat oven), or ionizing radiation (gamma radiation) to terminally sterilize the CSP. When compounding a sterile preparation, each batch must be handled and processed as a separate and discrete event. As such, each batch requires that the effectiveness (the capability to render the CSP sterile) of its sterilization cycle renders it sterile. BIs should be used to ensure that the autoclave is operating properly. BI ampuls contain spores of *Bacillus stearothermophilus* suspended in a colored culture medium. When exposed to the proper temperature and pressure for the proper period of time, the spores in the BI ampul will be killed. Autoclaved BI ampuls are incubated to ensure that the spores were killed and the autoclave functioned properly. An incubated BI ampul should not change color. If a color change, indicative of spore growth, occurs, the CSP is not sterile. Whenever BIs are used, a nonautoclaved BI should be incubated as a positive control to demonstrate that the spores in the ampul can grow.

Cold sterilization, or sterilization by filtration, is another way to terminally sterilize a CSP. The ultimate measure of a sterilizing filter's performance is bacterial retention. In

the Millipore bacterial retention test, 0.22- μ m filter disks and devices are challenged with a solution of culture medium containing bacteria (*Brevundimonas diminuta* ATCC 19146) in the range of 10⁷/cm² (just short of clogging the filter). The effluent is then passed through a 0.45- μ m filter disk which is placed on an agar plate and incubated. This test should be conducted in accordance with Health Industry Manufacturers Association methodology.⁴

When using a 0.22- μ m filter, the batch sterility can be verified through bubble-point or filter-integrity testing. Not all 0.22- μ m filters are the same; some are specifically designated as a sterilizing-grade filter and others are not. The sterilizing-grade filter is the ideal filter to use when preparing CSPs. The bubble-point test is a nondestructive, inprocess filter-integrity test that can be performed after filtering a batch of CSPs. This test operates on the principle that liquid is held in filter pores by surface tension and capillary forces. The bubble-point test detects the minimum pressure required to overcome these forces and force liquid out of the pores of a membrane filter. If pressure is released and air gets through the filter, it is indicative of a hole in the membrane.⁴ A "small vol-

ume device integrity tester kit" is available from Millipore and can be used to test filters with a filtration area of <15 cm².

Environmental quality and control. This section of the chapter specifies in great detail the physical plant and environmental requirements for compounding CSPs in each risk level. These requirements include

- Laminar-airflow workbenches (LAFWs) 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 (formerly class 100) environment for critical areas where CSPs are exposed to air in the physical environment,
- A class 7 (formerly class 10,000) 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,
- 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.

A major shift in the cleanroom classification schema occurred five years ago and was integrated into USP chapter 797. Until 2001, the United States used Federal Standard 209 as the benchmark for air quality and cleanliness. This standard was replaced by a classification system established by the Committee for European Normalization and the International Standards Organization (ISO). ISO 14644-1, "Classification of Airborne Cleanliness," is the first

of a family of worldwide standards for contamination control and air-borne cleanliness. ISO 14644-1 establishes the particle classification system to be applied to cleanrooms and clean-air devices (e.g., LAFWs, biosafety cabinets, isolators). ISO 14644-2, "Specification for Testing Cleanrooms and Associated Controlled Environments To Prove Continued Compliance," establishes the basic requirements for initial certification and monitoring and testing of cleanrooms to demonstrate and achieve continued compliance to the initial cleanliness classification specified in ISO 14644-1. A comparison of the particle counts defined by Federal Standard 209 and ISO 14644-1 can be found in *USP* chapter 797 and is summarized in Table 2.

Cleanrooms. Proper sterile compounding requires "a strict design regime, not only on the process area, but on the interactions with surrounding areas and the movement of people, materials and equipment so as not to compromise the aseptic conditions."⁵ Engineering controls (anterooms, cleanrooms, horizontal and vertical LAFWs, biological-safety cabinets, and isolators) and the associated controlled environments are designed to prevent, reduce, and control potential nonviable (e.g., dust, pollen, skin) and viable (e.g., mold, fungus, bacteria) contaminants from being introduced into CSPs and to support environmental control programs. A properly designed, constructed, and maintained cleanroom contributes to the quality of CSPs. It is unreasonable to believe

that proper aseptic technique alone can control contamination when LAFWs are placed in uncontrolled areas.⁶ It is very important to recognize that designing and building a pharmacy cleanroom without considering other critical quality system factors, like policies and procedures, employee training, aseptic technique and process validation, ongoing environmental monitoring, facility maintenance, and compliance auditing, will result in quality, operational, and maintenance problems in an operation.⁷

The procedures that will occur in the cleanroom should be understood before establishing and approving project budgets and starting construction. Cleanroom construction requires specialized knowledge, and choosing the most qualified individuals to manage the design, construction, and certification of the cleanroom is critical to the successful outcome of the cleanroom project.

The contractor and the person managing the construction project must work with the pharmacy department cooperatively to establish the best-cost design solution that will meet all applicable local, state, and federal standards (e.g., *USP*, ISO, state board of pharmacy) and day-to-day requirements based on the compounding activities that will occur (e.g., low-, medium-, or high-risk level). To demonstrate a clear understanding of cleanroom requirements, design criteria must be developed. An example of design criteria for a class 7 cleanroom is shown in Table 3.⁷

Isolators. For many pharmacy operations, isolators, also known as glove boxes, may be a viable option for meeting the compounding demand for sterile preparations. There is no universal definition of a barrier isolator and no uniform standard for the construction, operational requirements, or testing of barrier isolators. These operating standards vary by manufacturer, and no common performance attributes currently exist. Isolators are described in *USP* chapter 797 as an emerging alternative technology. The only criteria currently in place are that isolators be well designed, have positive pressure, and be supported by adequate procedures for maintenance, monitoring, and control by the manufacturer.

The differences among isolators should be considered before one is purchased. The isolator may not provide the required aseptic environment needed to prevent the need for a cleanroom. Some isolators create diluted or mixed air within the chamber and fail to provide unidirectional airflow to wash away contaminant buildup. This may result in contamination and cross-contamination during processing or when multiple products are compounded in this same equipment. More importantly is the design of the pass-through or antechamber of the barrier-isolator. Ideally, they should be pressurized and supplied with high-efficiency particulate air (HEPA)-filtered air to purge any particles or contaminants that may have been introduced into the chamber with the drugs and supplies. Also consider how the isolator can be cleaned and maintained safely, especially if it is used to prepare antineoplastics.⁸ Isolators should produce unidirectional airflow. However, an isolator does not currently obviate the need to gown properly. Operators must still wear hairnets, gowns, gloves, and shoe covers if the barrier isolator is in the same room as

Table 2.
Comparison of Particle Count Classifications in ISO 14644-1 and FS209^a

Variable	ISO 14644-1	FS209
No. cleanliness classes	9	6
No. class designations	9	100,000
Measurement units	Meters	Feet
Sample time (min)	1 minimum for all particles	>1 for smaller particles

^aISO = International Standards Organization, FS = Federal Standard.

Table 3.
Design Criteria for a Class 7 Cleanroom^a

Element	Material Requirements	Recommended Design Specification
Ceilings	Epoxy-painted drywall; cleanroom ceiling tile with anodized aluminum T-bar grid	Cleanroom ceiling tile with anodized aluminum T-bar grid
Floors	Seamless vinyl sheet; monolithic epoxy	Seamless vinyl sheet with minimum 4–6" cove to the wall
Walls	Monolithic vinyl; FRP laminate panel; tempered glass; epoxy-painted drywall; melamine panel	FRP laminate panel
Doors	Stainless steel; anodized aluminum; epoxy-painted metal door	Anodized aluminum door frame
Light fixtures	Standard construction recessed cleanroom fixture; RTV sealed to anodized aluminum T-bar ceiling grid; acrylic lens with baked enamel finish	Standard construction recessed cleanroom fixture; RTV sealed to anodized aluminum T-bar ceiling grid; acrylic lens with baked enamel finish
Windows	Tempered safety glass with no sills and stainless steel or anodized aluminum frames	Tempered safety glass with no sills and stainless steel or anodized aluminum frames
Air changes	At least 20 per hour	40–60 per hour
Air pressure	Compounding room 0.05 inch WC to the anteroom	Compounding room 0.0 inch WC to the anteroom
Air filtration	99.97% or better HEPA filter with a 30% or better efficiency ASHRAE prefilter	99.97% or better HEPA filter with a 30% or better efficiency ASHRAE prefilter
Particulate control	Class 7	Class 7
Temperature	18–22 °C (64–72 °F)	18–22 °C (64–72 °F)
Relative humidity (%)	40–60	40–60

^aReprinted from reference 7, with permission. FRP = fiberglass-reinforced polyester, RTV = room-temperature vulcanizer, WC = water column, HEPA = high-efficiency particulate air, ASHRAE = American Society of Heating, Refrigerating and Air-Conditioning Engineers.

the LAFWs. Face masks are optional when using an isolator or biological-safety cabinet.¹

Cleaning and sanitizing. Personnel who work in controlled areas are the greatest source of viable and nonviable contamination.⁹ All pharmacy compounding areas and critical contact surfaces (class 5 LAFW or isolator), anteroom, and buffer or cleanroom compounding areas must be routinely cleaned and sanitized to maintain facility and environmental controls. Routine, ongoing, and consistently performed cleaning minimizes the overall viable microbial burden of the pharmacy compounding area. A sample cleaning plan that can be used as a model for any type of

pharmacy practice (community, hospital, or home care infusion) is presented in Table 4.¹⁰

Numerous cleaning agents must be used in the LAFW. In addition to using isopropyl alcohol as a routine cleaning agent during the compounding day and between batches in the class 5 LAFW or isolator, both 3% hydrogen peroxide and 1–2% bleach solution have been shown to be effective sanitizing agents.¹¹

Buckets and other cleaning equipment (mop handles, mop heads) should be dedicated to each area of use to prevent cross-contamination. Buckets used for cleaning the floors should never be used to clean LAFWs or walls.

It is critical that all activities associated with cleaning, such as the preparation of cleaning solutions, be properly documented in logs or notebooks. Special cleanings (e.g., at semiannual certification or after power loss), as well as routine daily, weekly, and monthly cleaning procedures, should be performed and documented consistently. It is essential to document the training of personnel other than pharmacy staff who perform cleaning procedures to ensure proper monitoring and compliance with policies on sterile compounding. A summary and comparison of liquid disinfectants are provided in Table 5.¹⁰

Environmental monitoring. Air and surface sampling is integral to ensuring that the microbiological integrity of controlled compounding environments is maintained. An environmental monitoring program should promptly detect shifts in microbiological conditions and allow for corrective action.

Air and surface sampling assesses the effectiveness of cleaning and sanitizing procedures and personnel that could affect the bioburden (total number of viable microorganisms) within pharmacy compounding areas. Weekly and monthly environmental microbial sampling procedures can also monitor the functionality of environmental control systems (HEPA filters, room air changes, and pressure differentials). The results of environmental sampling aid in the determination of the bioburden within controlled pharmacy areas and may provide information to help identify the species and origin of specific environmental microbial isolates.

Air and surface sampling involves collecting environmental “snapshots” on tryptic soy broth (TSB) or agar (TSA) plates, or both, that support the growth of many types of microorganisms. Air sampling is accomplished by placing air-settling plates at various locations through-

Table 4.
Sample Cleaning Plan for Class 5 or 7 Pharmacy Compounding Area^a

Area	Day of Week (Cleaning Agent)						
	Monday (Vesphene LpH or Equivalent)	Tuesday (Bleach)	Wednesday (Vesphene LpH)	Thursday (Vesphene LpH)	Friday (Vesphene LpH)	Saturday (Vesphene LpH)	Sunday (Vesphene LpH)
Aseptic compounding area, LAFWs	Wipe down equipment, ^b mop floor	Wipe down equipment, mop floor	Wipe down equipment, mop floor	Wipe down equipment, mop floor	Wipe down equipment, mop floor, mop walls, mop ceilings ^c	Wipe down equipment, mop floor	Wipe down equipment, mop floor
Anteroom, gowning room	Wipe down equipment, mop floor	Wipe down equipment, mop floor	Wipe down equipment, mop floor	Wipe down equipment, mop floor	Wipe down equipment, mop floor, mop walls, mop ceilings ^c	Wipe down equipment, mop floor	Wipe down equipment, mop floor

^aReprinted from reference 10, with permission. LAFW = laminar-airflow workbench.

^bEquipment includes interior surfaces of LAFWs, chairs, workstations, pumps, wire storage carts, garbage cans, and benches.

^cPerformed monthly.

out the controlled environment based on the types of activities performed or the number of personnel and extent of product movement in the area. The various locations in which environmental samples can be collected are illustrated in Figure 1.¹⁰

Each location is assigned three values: baseline (ideal), alert limit, and action limit (Table 6). Before the baseline is determined, the controlled work area should be thoroughly cleaned with a disinfecting detergent. After the cleaned areas are dry, samples from various locations are obtained and tested. In class 5 (class 100) environments (LAFWs or clean zones), the ideal baseline should be zero. The integrity of ISO classified environments is closely correlated with the sterility of pharmacy-prepared sterile products.

Air sampling is performed using 100-mm TSA plates. They should be exposed to cleanroom air for at least three but not more than eight hours. Exposure exceeding three hours causes the agar to dry out. Air sampling is a cost-effective way of obtaining quantitative data relative to the viable microbial particles expected to settle from the air at each sampling site. Other volume-of-air samplers, such as the slit-to-agar sampler and the Reuter Centrifugal Air Sampler (Biotest Hycon Corporation, Denville, NJ), can also be used to collect air samples. These sampling devices operate on the impaction principle. A volume of air is drawn into the sampler by means of an impeller, and particles are impacted onto the sampling strip. The medium on the strip is incubated, and any viable airborne particles (microorganisms) that form colonies are counted.

When using impaction sampling, the impeller blades used to generate and create the air vortex must be properly cleaned. This sampling method requires the purchase of expensive collection devices; however, the method provides quantitative sampling data.¹²

Similar to air sampling, surface sampling involves the collection of microbial data at specific locations. Each location is assigned three values: baseline, alert limit, and action limit. Before the baseline is determined, the controlled work area should be thoroughly cleaned with a disinfecting detergent. Surface sampling is performed with raised 60-mm TSA plates, called replicate organism detection and counting (RODAC) plates. The TSA in RODAC plates is mixed with polysorbate 80 and lecithin, which inactivate many residual disinfectants. Polysorbate 80 neutralizes phenols, hexachlorophene, and formalin, and lecithin inactivates quaternary ammonium compounds. During sampling, a RODAC plate is pressed onto the area to be tested. Any microorganisms on the surface of the area tested (which ideally should be flat) are transferred onto the RODAC plate. After the sample has been obtained, the area tested should be wiped down with isopropyl alcohol to remove any residue left by the RODAC plate. While the sample is being obtained, testing conditions should be rotated between production (dynamic) and nonproduction (static) times. Testing under dynamic conditions monitors the effectiveness of hand washing, garbing, and gloving by personnel. It also records the microbial condition of the controlled work area when staff are present. Testing under static conditions provides information about the function of HEPA filters and controls for pressure differentials, air exchanges, temperature, and humidity and the effectiveness of cleaning and sanitizing procedures.

The sampling plates are incubated for 48 hours at 30–35 °C (86–95 °F). Any discrete colonies, known as colony-forming units (CFUs), that grow on the plates are counted after the incubation period and are noted on a collection form (Appendix A). Ideally, the plates with CFUs should

be analyzed to identify the microorganism species.

Observing the trends in the microbial bioburden over time is key to establishing an effective environmental monitoring program. Any sudden increase in established action limits or trended increases in environmental bioburden (the absolute number of CFUs) over time are signals that an investigation should occur and that possible intervention may be necessary. Potential interventions include

- Retesting sampling areas if alert limits are breached,
- Reassessing cleaning procedures, which may include a review of cleaning documentation and the training of personnel,
- Examining recent production activities for changes (e.g., construction activity in or around the compounding area), the arrival of new compounding equipment in the controlled work area, or irregularities in employee performance,
- Cleaning the controlled work area three times,
- Using a different cleaning agent (other than the ones used on a rotational basis),
- Reviewing other validation outcomes to determine whether they indicate an increase in the bioburden, and
- Retraining staff members responsible for cleaning and compounding.¹⁰

Personnel training and evaluation. Most colleges of pharmacy do not have sterile compounding laboratories or adequate didactic teaching on contamination control and sterile preparation. As a result, most pharmacists and technicians have little or no evidence-based didactic training in sterile compounding. This section of the chapter requires that all personnel compounding sterile preparations are adequately educated, instructed, and skilled to perform their functions. Proper aseptic technique is a learned skill. The three

phases of a robust employee-training program include

1. A didactic program with an examination that an employee must pass as determined by pharmacy administration,
2. A psychomotor skills assessment checklist used by a supervisor when conducting direct observation of employee technique, and
3. An aseptic media-fill assessment.

The knowledge base and the skills of each compounder should be evaluated when hired (regardless of previous experience) and at least annually thereafter. A number of training resources and tools are available regarding the compounding of sterile preparations.^{13–16} The skills assessment checklist shown in Appendix B is an example of an assessment tool that can be used to evaluate the employees' actual ability to perform the compounding procedures expected of them.

Aseptic-technique verification. A media-fill or process-simulation test mimics an actual and entire compounding procedure, using a suitable growth medium (e.g., TSB) in place of the typical ingredients, to prepare a finished compounded preparation. Process-simulation testing can be used to evaluate the capabilities of aseptic compounding procedures and identify any weaknesses in the process that could negatively contribute to the inaccuracy or contamination of the CSP.¹⁷ A properly designed process-simulation test will be able to

- Demonstrate the capability of the aseptic procedures to produce CSPs,
- Qualify, certify, and verify the aseptic technique of all pharmacy compounding personnel including pharmacists and technicians, and
- Meet the verification and sterility testing requirements for CSPs as detailed in *USP* chapter 797.¹⁸

The number of media-fill tests and frequency of testing are contro-

Table 5.
Summary and Comparison of Liquid Disinfectants^a

Class	Recommended Uses	Activity	Advantage(s)
70% Isopropyl alcohol solution	Cleaning some instruments; cleaning skin	Changes protein structure of microorganism; presence of water assists with killing action	Fairly inexpensive
Chlorine compounds	Spills of human body fluids; good bactericidal; good fungicidal; good sporicidal at >1000 ppm sodium hypochlorite	Free available chlorine combines with contents within microorganism, reaction byproducts cause its death; need 500–5000 ppm; produce chemical combination with cell substances; dependent on release of hypochlorous acid	Kills hardy viruses (e.g., hepatitis) and a wide range of organisms; inexpensive; penetrates well; relatively quick microbial killing; may be used on food preparation surfaces
Glutaraldehyde	Good bactericidal; good fungicidal; excellent tuberculocidal; good viricidal; good sporicidal	Coagulates cellular proteins	Nonstaining; relatively noncorrosive; usable as a sterilant on plastics, rubber, lenses, stainless steel, and other items that cannot be autoclaved
Iodophors (iodine with carrier)	Disinfecting some semicritical medical equipment; very good bactericidal; excellent fungicidal; excellent viricidal	Free iodine enters microorganism and binds with cellular components; carrier helps penetrate soil and fat; need 30–50 ppm; probably by disorder of protein synthesis due to hindrance or blocking of hydrogen bonding	Kills wide range of organisms; highly reactive; low tissue toxicity; kills immediately rather than by prolonged period of stasis; not affected by hard water; may be used on food preparation surfaces
Phenolic compounds	Excellent bactericidal; excellent fungicidal; excellent tuberculocidal; excellent viricidal	Gross protoplasmic poison; disrupts cell walls; precipitates cell proteins; low concentrations inactivate essential enzyme systems	Nonspecific concerning bactericidal and fungicidal activity; when boiling water would cause rusting, the presence of phenolic substances produces an antirusting effect
Quaternary ammonium compounds (QUATS)	Ordinary housekeeping (e.g., floors, furniture, walls); excellent bactericidal; good fungicidal; good viricidal (not as effective as phenols)	Affects proteins and cell membrane of microorganism; releases nitrogen and phosphorus from cells	Contain a detergent to help loosen soil; rapid action; colorless; odorless; nontoxic; less corrosive; highly stable; may be used on food preparation surfaces

^aReprinted from reference 10, with permission. EPA = Environmental Protection Agency.

versial topics. Currently, *USP* chapter 797 does not specify the number of media-fill units (MFUs) required. The only stipulation is that testing has to occur at least once yearly for low- and medium-risk compounding and at least twice yearly for high-risk compounding. The volume of CSPs being prepared for each compounding procedure, the number of patients that may receive CSPs prepared from the same batch, the complexity of the compounding procedure, the equipment being used, and the physical environment where the compounding is conducted must be considered when conducting media-fill tests.

Best practices, as adopted from those performed by pharmaceutical manufacturers, involve verification procedures that are conducted over three consecutive batches or days. The initial media-fill verification could be performed daily for three days. This will test the operator's technique for consistency and reproducibility and eliminate results skewed by chance. It may be reasonable to consider additional (e.g., quarterly) media-fill runs. The frequency, number, and results of MFUs must be documented. Media fills should not be performed during normal production, but immediately after daily production activity under

worst-case conditions when microbial bioburden is at the highest level. TSB should not be used while sterile preparations are being compounded because of the potential for cross-contamination and dispensing errors (such as in cases where MFUs are accidentally labeled and sent to patients for infusion). Several aseptic technique verification kits are currently available or the individual components can be purchased and used to verify the aseptic ability of the compounding personnel, procedure, or compounding devices. Some are limited only to the use of ampuls, vials, and syringes. Although these kits produce a valid

Table 5 (continued)

Disadvantages	Comments and Hazards	Examples
<50% solution not very effective; not active when organic matter present; not active against certain types of viruses; evaporates quickly; contact time not sufficient for killing	Flammable; eye irritant; toxic	...
Corrodes metals such as stainless aluminum; organics may reduce activity; increase in alkalinity decreases bactericidal property; unpleasant taste and odor; tuberculocidal with extended contact	Follow spill procedure and dilution instructions; make fresh solutions before use; eye, skin, and respiratory irritant; corrosive; toxic	Bleach solutions (sodium hypochlorite), Clorox, Cyosan, Purex
Not stable in solution; has to be in alkaline solution; inactivated by organic material	Eye, skin, and respiratory irritant; sensitizer; toxic	Calgocide 14, Cidex, Vespore
May stain plastics or corrode metal; may stain skin or laundry; stains most materials; odor; some organic and inorganic substances neutralize effect; tuberculocidal with extended contact time; some sporicidal activity	Dilution critical; follow directions; use only EPA-registered hard surface iodophor disinfectants; do not confuse skin antiseptic iodophors for disinfectants; skin and eye irritant; corrosive; toxic	Bactergent, Hy Sine, Ioprep, Providone (iodine–betadine), Wescodyne
Unpleasant odor; some areas have disposal restrictions; effectiveness reduced by alkaline pH, natural soap, or organic material; no sporicidal activity	Skin and eye irritant; sensitizer; corrosive; toxic	Hil Phene, LpH, Metar, Vesphene
Does not eliminate spores, tuberculosis, bacteria, some viruses; effectiveness influenced by hard water; layer of soap interferes with activity	Select from EPA list of hospital disinfectants; skin and eye irritant; toxic	Coverage 258, End Bac, Hi Tor

representation of aseptic technique for ampul and vial transfer activities, many do not include aseptic manipulations performed in usual pharmacy operations. Other methods may be required to mimic various activities performed in pharmacies that compound parenteral solutions. Ideally, a media-fill procedure should incorporate all of the typical and multiple manipulations performed either by people or devices. This may include using syringes, ampuls, vials, transfer tubing, and empty bags for the administration of CSPs.

One MFU can be prepared using the following method, which simu-

lates a medium-risk batch compounding procedure:

1. Use a 20-gauge needle (not a filter needle) attached to a 5-mL syringe to withdraw 1 mL of sterile, preservative-free water from a glass ampul, and inject the water into each of two TSB bags.
2. Remove five additional and separate 1-mL samples from a vial of sterile, preservative-free water and inject the water into each TSB bag, five separate times.
3. Transfer the content of both TSB bags via a Y-type transfer set into an empty bag used for the administration of i.v. medications.

4. Clamp the tubing of the transfer set, crimp the tubing to seal it, cut the tubing, and incubate the bag for seven days at room temperature and then for seven days in an incubator at 30–35 °C.

The instructions of the manufacturers of media-fill test kits must be carefully followed. However, the MFU must be incubated according to the following guidelines from chapter 71: storage for 7 days at room temperature followed by 7 days at 30–35 °C or 14 days at 25–35 °C. Following the first incubation guidelines will allow heat-labile microorganisms to replicate, if present. If the TSB is placed directly into the incubator, these microorganisms could be destroyed. This incubation period is critical because microbial contamination is not visible when viewed with the naked eye until at least 10⁶ CFUs have formed. The incubation period has been designed to ensure that one viable microbial CFU would replicate to more than 10⁶ CFUs.

Ideally, MFUs should be read daily, but they must be read on days 7 (the last day of room temperature incubation) and 14 (the last day of incubator incubation). Cloudiness or turbidity indicates a media-positive (contaminated) sample. The result must be documented on a media-fill log (Appendix C) and retained in the employee-training file. Personnel should not be permitted to compound sterile preparations for use by patients until they can successfully prepare MFUs that exhibit no microbial growth. Growth media and media test kits can be obtained from various vendors. These kits must have a certificate of performance and meet the requirements of USP’s Growth Promotion Standard.

Processing. This section calls for a written employee-training and -evaluation program specific to preparation of CSPs in each health care setting to ensure that compounding personnel are knowledge-

Figure 1. Environmental sampling locations in a pharmacy cleanroom. BSC = biological-safety cabinet. LAFW = laminar-airflow workbench.

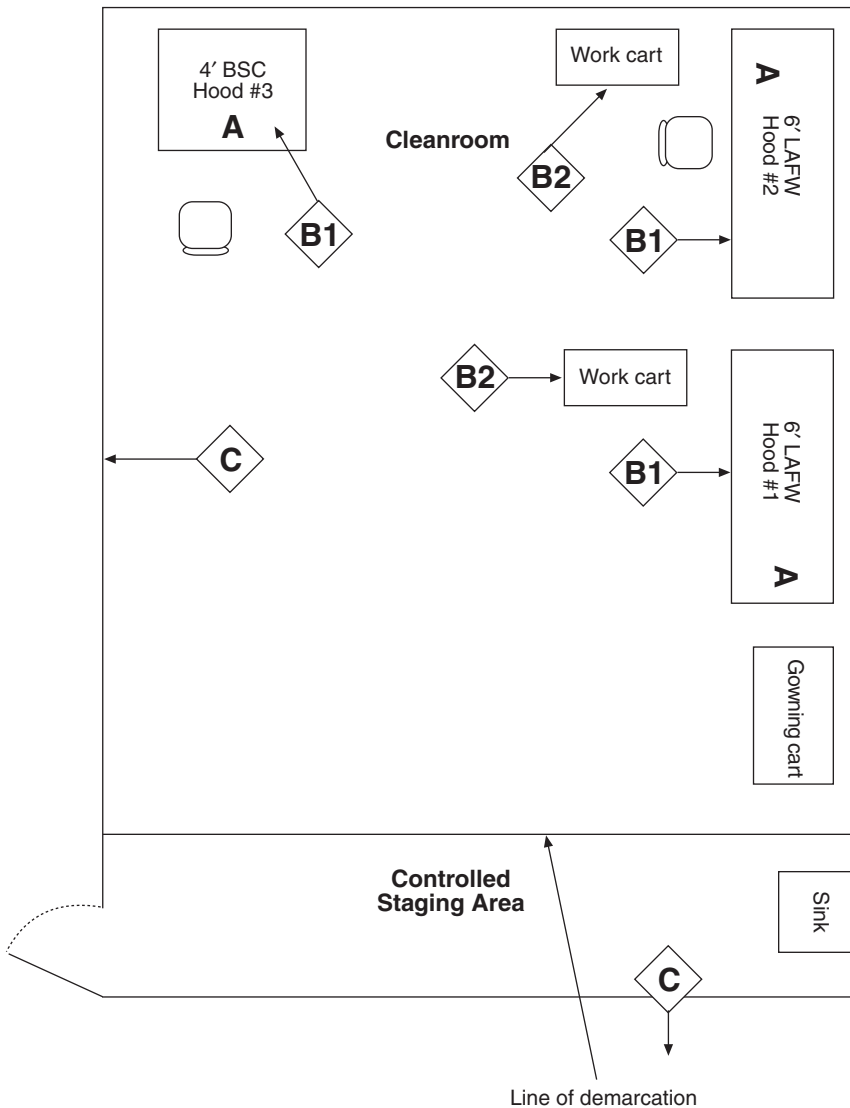


Table 6.
Baseline, Alert-Limit, and Action-Limit Values for Pharmacy Cleanroom Environmental Sampling^a

Room and Sample	Location ^b (Site)	Baseline (Ideal)	Alert Limit	Action Limit	
Cleanroom Air	A	0	0	3	
	B1	0	0	3	
	B2	≤5	>5	8	
Cleanroom Surface	A	0	>0	3	
	C	≤10	>10	15	
Gowning area and pass-through (if applicable)	Air	B2	≤10	>10	15
		Surface	C	≤20	>20

^aReprinted from reference 10, with permission.

^bA sites = surface samples, B sites = air samples, C sites = wall samples.

able and properly trained. As discussed previously, training is the cornerstone of ensuring the quality and safety of CSPs. A critical element of training is having policies and procedures that represent the actual compounding activities conducted on a daily basis. This quality domain and others detail the need for written policies and procedures and personnel job descriptions. Policy and procedures are important because they (1) are critical for properly training employees, (2) clearly define an organization's expectations, rules, and regulations, (3) ensure that everyone is performing a function in the same manner, and (4) can be used to document that a certain function or activity was performed.

Verification of automated compounding devices for parenteral nutrition compounding. Preparation of parenteral nutrition can be aided with automated compounding devices (ACDs). For these devices to accurately deliver the desired volume of ingredients, users must be adequately trained, and the ACDs must be properly calibrated, set up (correct solution containers hung on the correct solution inlet tubing), verified, and maintained. This section of chapter 797 details procedures to ensure the accuracy and precision of ACDs.

ACD manufacturers validate the capability of their equipment to measure components from source containers and to produce an accurate (but not sterile) CSP. This requirement must also be verified routinely by the user using TSB in the environment where the device is used. In different class 5 environments, the direction of airflow in a horizontal LAFW is much different than it is in a biological-safety cabinet. This can affect the ability of the operator using the ACD to produce a sterile preparation.

The accuracy-verification procedure can be easily performed by hanging sterile water for injection on each of the ACD pumping stations

and, using an empty i.v. bag that has been tared, pumping 40 and 1000 mL of sterile water for injection from each source container. The weight of the bag should be documented after each volume of water is pumped into it. Since sterile water for injection has a specific gravity of 1.00, the weight of the bag should be directly related to the volume pumped.

In addition to performing an accuracy verification procedure, an aseptic-verification procedure for each type of equipment used to compound sterile products, according to written policy, is strongly recommended. After the initial aseptic-verification procedure equipment should be revalidated (1) at least annually as a part of an operator aseptic media verification procedure and (2) when it is moved or physically modified. If, for example, a syringe filler or an ACD is relocated to a different type or size of hood, revalidation is required. Environmental factors can adversely affect the aseptic operation of compounding equipment. Changes in the environment in which equipment for sterile compounding is used necessitate reverification.

The initial verification procedure for all pieces of equipment should be consistent. TSB should be used as the source solution during equipment validation, during which the entire compounding process must be mimicked. Ten MFUs should be prepared and incubated for a total of 14 days (7 days at room temperature followed by 7 days in the incubator). Evidence of no growth is usually sufficient to verify the aseptic ability of the equipment and the person compounding. After successful verification, an ACD can be used to prepare sterile preparations for patients. This process verifies only the capability of the ACD to prepare sterile preparations and does not replace the need for its daily calibration, which is necessary to ensure the sterility of CSPs.

The integration of technology into ACDs and the use of software are im-

proving the safety and accuracy of CSPs. The desirable functionality in ACDs includes the following:

- Repeatable fluid delivery accuracy (macronutrient and micronutrient volumes) within $\pm 5\%$,
- Multisource (macronutrient and micronutrient component) volume transfer capabilities using presterilized closed-tubing sets,
- Bar-code technology consistent with FDA's bar-coding rule that reduces medication errors by using bar-coded patient prescriptions, source containers, and final containers, which can also track ingredient lot numbers, expiration dates, and volume usage,
- A user-definable component database, and
- An integrated compounding pump and central processing unit configuration.

Ideally, an ACD should be capable of delivering the maximum of additives at the lowest volume possible in an effort to minimize or eliminate the need for manually added ingredients.

Emerging compounding and testing technology

Meeting the compounding demand for CSPs has been extremely difficult. With the requirements of USP chapter 797, many pharmacists are looking for advances in engineering controls and compounding technology to make compounding sterile preparations easier, quicker, and safer. Necessity is the mother of innovation, and companies are rising to the challenge in an effort to assist pharmacists.

Emerging compounding technology. A new syringe-based compounding system, IntelliFill i.v. (ForHealth Technology, Inc., Daytona Beach, FL), incorporates all of the technology currently used in the pharmaceutical manufacturing industry on a pharmacy scale that improves accuracy and the sterility of CSPs.

Through design, engineering, and integrated control systems, the IntelliFill i.v. compounding system addresses several important requirements established by chapter 797, including

- System software is integrated with existing hospital profiling and order-entry systems, which eliminates the introduction of human error from double-order entry.
- The software allows the user to customize the compounding formulary for the patient population served, such as neonates and pediatric patients.
- All compounding activities are recorded on a control log, providing traceability and quality assurance analysis, including images taken from the vision system that captures events as they occur.
- The compounding system has several redundant processes that prevent the wrong drug, wrong concentration, and wrong diluent from being delivered to the patient.
- Environmental conditions where the critical aseptic compounding procedures occur meet and exceed chapter 797's physical plant requirements of class 5 (class 100) environments. The engineering control of the compounding system meets class 4 (class 10) requirements for airflow and particle count.
- The system has been validated by preparing over 3000 MFUs using TSB without a positive control to achieve a sterility assurance level of 10^{-3} .¹⁹ Trissel et al.²⁰ demonstrated a contamination rate of 5.2% for MFUs manually prepared under medium-risk conditions.

Emerging testing technology. A new end-preparation testing system, ValiMed Regulatory Compliance Solution (CBEX, Rockville, MD), comprises three distinct components: the instrument, a proprietary library of chemical "fingerprints," and proprietary process automation software. It

was designed to reduce errors in medication selection and the preparation of sterile compounds of admixtures, deter inadvertent substitutions, and prevent mislabeling of the medication.

It is important that any emerging technology be thoroughly investigated to ensure that the technology has been proven or validated to meet the needs of the pharmacist.

Finished-preparation release testing

All finished CSPs must be checked by a pharmacist before they are dispensed to ensure that the preparation is sterile and accurate. This can be accomplished in several ways.

- Preparation integrity (e.g., absence of cores, other particulate matter, phase changes, and discoloration) should be examined by visual inspection.
- Compounding accuracy should be verified by someone other than the compounder to ensure proper measurement, reconstitution, and component use.
- High-risk CSPs in groups of more than 25 must be tested in accordance with *USP* chapters 71 for sterility and 85 for the presence of bacterial endotoxins.
- Low- and medium-risk CSPs that exceed *USP* guidelines for beyond-use dating must be tested in accordance with the guidelines in *USP* chapter 71.
- Data from quantitative and qualitative automated verification systems (refractometers, flame spectrophotometers, bar-code readers, machine-aided particulate matter inspection systems, weight verification methods, or other advanced technologies) must be verified.

Component inspection. To ensure that the ingredients used to prepare CSPs are the correct ones and in the prescribed quantities, (1) use *USP* and *National Formulary* grade ingredients, (2) review certificates of analysis that should accompany the

ingredients if they are bulk, nonsterile powders, (3) visually inspect ingredients upon receipt, and (4) calibrate scales and other measuring devices (ACDs) daily.

If we examine a CSP as the end product of a process that has both a beginning and an end, we can analyze each phase of the process to ensure that the CSP maintains its desired strength, purity, and potency at all times. Once the ingredients of a CSP are chosen and the CSP is prepared, it is labeled, inspected, transported, and stored until dispensed to a patient.

Visual inspection. Visual inspection provides some very basic information about the CSP. The primary concern is that the actual preparation contains the ingredients specified in the original prescription. All final CSPs should be evaluated for

- Container leaks, holes, and other container-closure breaches,
- Mobile, randomly sourced, extraneous substances other than gas bubbles.²¹ (A light-and-dark background observation device is an effective tool for performing a thorough visual inspection for particulates²²),
- Phase separation (oiling, creaming, or cracking),
- Discoloration and other signs of the wrong drug or an undesirable chemical reaction, and
- Clear, legible, and correct labeling, including proper ancillary and auxiliary labeling.

Weight verification. Weight verification is often used to evaluate preparations compounded from ingredients with different specific gravities, such as total parenteral nutrition and cardioplegia solutions. Gravimetric measurement allows the operator to evaluate the accuracy of the ACD.²³ Using the gravimetric method, the fluid volume delivered from the source container to the final container is determined by weighing the fluid transferred and dividing

the weight by the solution's known specific gravity, thereby converting weight to volume. Once the specific gravity of each solution and the desired volume are known, the final bag weight of the CSP can be calculated and used to verify that the final preparation was compounded correctly.

Microbial testing. The concept of beyond-use dating has historically been based on the chemical stability of the CSP, with little regard given to the sterility of the final preparation. Based on the rates of bacterial and fungal contamination of CSPs prepared by pharmacists and technicians, CSPs assigned beyond-use dates for periods exceeding chapter 797's guidelines must be tested. Beyond-use dating must also be consistent with the stability of the CSP during the labeled storage period. Confirmed sterility allows CSPs to be assigned beyond-use dates greater than *USP* guidelines and equivalent to its chemical stability.

There are two official methods of microbial testing: (1) direct transfer of a sample to sterile culture media and (2) membrane filtration.^{24,25} All personnel performing CSP sterility testing must be properly trained, be qualified to conduct the testing, and use proper aseptic technique when manipulating the equipment, supplies, and CSPs. Proper garbing techniques must be followed, and testing for microbial contamination must be conducted in class 5 (class 100) environments using aseptic technique to prevent unintended environmental and operator contamination.

Pyrogen and bacterial endotoxin testing. Pyrogens and bacterial endotoxins are metabolic products of living microorganisms or the dead microorganisms themselves. When present in parenteral drugs administered to patients, they can cause fever and chills. Contaminated preparations for intrathecal use may cause septic or aseptic meningitis or aseptic shock.²⁶⁻²⁹ CSPs made from nonster-

ile, bulk components are required to be tested for pyrogens and endotoxins when compounded in batches greater than 25 units. High-risk CSPs injected into vascular or central nervous systems that exceed chapter 797's storage conditions must be tested to ensure that they do not contain excessive bacterial endotoxins. The maximum allowable amount of endotoxin units (EUs) for most CSPs is 0.25–0.5 EU/hr/kg, depending on the *USP* monograph. *USP* chapter 85 should be reviewed for more information regarding this requirement. Sterility and pyrogenicity are two distinct and exclusive concepts.

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 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. Chemical stability and microbial sterility are described. Once CSP sterility has been determined, the preparation's beyond-use date can be designated using reference books, peer-reviewed literature, manufacturer's data, or other reliable means of determining chemical stability. It is also important to consider the potential effect of the container (e.g., glass, polyvinyl chloride, ethylvinyl acetate, polypropylene), temperature, and light exposure on the CSP's stability.

Quality assurance program

The intent of a quality assurance program is to ensure that adequate controls exist throughout the life cycle of the CSPs. Many of the elements of *USP* chapter 797 focus on controls through formalized policies, defined processes, and established best practices and procedures. A majority of the time required to achieve compliance with chapter 797 will involve

the planning and preparation phase of these activities. Once the elements of the quality assurance program have been established, the focus can shift to compliance and vigilance in documenting activities.

Good documentation. Documentation serves as proof that policies and procedures are being followed and that quality is being maintained by the pharmacy staff. It links personnel with operational responsibility. It is important that data be collected, documented, and reviewed for operational compliance, process excursions, and procedural deviations. The following is a list of documentation to consider including in a quality assurance system:

- Refrigerator temperature logs,
- Compounding room and storage room temperature logs,
- Cleaning logs for the LAFWs, the biological-safety cabinets, compounding room, anteroom, and compounding equipment,
- Equipment calibration logs,
- Aseptic-media-fill logs,
- Employee didactic and psychomotor skill assessment checklist,
- Environmental monitoring logs,
- Batch records or compounding documents,
- Engineering control certification reports (LAFW and cleanroom certificates),
- Patient incident, adverse-drug-reaction, and complaint logs, and
- Annual policy and procedure review statement.

Good documentation is another component of final preparation evaluation. It provides a means of tracing or recreating a set of events that can be investigated and acted upon. Many of the newer ACDs automatically generate documents that capture and record each of the critical elements when compounding a sterile preparation.

Preparation traceability. Preparation traceability is an essential

element of any sterile preparation compounding program. Proper documentation follows the final preparation back to the source providing the necessary assurance for the configuration, characteristics, and integrity of the preparation. Ideally, working from a master compounding document, known as the recipe, formulation or batch records can drive the quality and completeness of documentation.

Preparation recallability. Preparation traceability forward through distribution channels is an essential element for an effective and targeted preparation withdrawal and/or recall, if and when necessary.

Risk management tool. The expression "If it isn't documented, it didn't happen" is routinely used to stress the importance of proper documentation practices. Documentation becomes evidence and can be used to prove that the final preparation was prepared properly.

Proper documentation practices. Proper documentation practices are fostered only by active participation and review from management. People generally respect what others inspect. If documentation activities are just exercises with no monitoring and improvement efforts, they should not be done. Aside from direct observation, a quality-control system can only be supported by the documentation produced regarding compounding activities. Documentation is not helpful if it is not used proactively to identify problems and allow for their correction.

Pharmacist verification. A pharmacist should verify that the final preparation was compounded accurately according to the compounding batch record or worksheet. Specifically, the pharmacist should verify that

1. Proper components (vials, ampuls, and final solution container) were checked before compounding and use.
2. Proper compounding methods (constitution, solution-transfer quan-

tities) were used. (In some instances, the use of the syringe plunger pull-back method is acceptable.²)

3. Proper quantities of components were used by comparing desired batch yields to actual batch yields (e.g., 10 1-g antibiotic syringes were expected and 10 syringes were prepared using 1 10-g source vial of antibiotic with no residual solution in the source container).
4. The correct and proper number of labels (the right label for the right CSP for the right patient) were used to allow for unencumbered administration.

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, regardless of physical location within the health system (hospital, home, or ambulatory care center). In hospitals, two significant factors require a pharmacist's attention: (1) time delay and change in storage conditions for CSPs (e.g., prepared at room temperature and stored in refrigeration) and (2) the handling and disposition of the CSP when sent to the nursing unit and the potential exposure of the CSP to storage conditions that will decrease the CSP's chemical stability and change the beyond-use date.

In alternative-site compounding operations, pharmacists must ensure that appropriate packaging (coolers, wet ice blocks, dry ice) capable of maintaining proper temperature and storage conditions are used during shipment via a common carrier and that the storage conditions of the CSP in the patient's home or other location are appropriate.

Patient or caregiver training and adverse-event reporting. Since most pharmacy settings are accredited by a national organization, they must have policies, procedures, and systems to address patient or caregiver training needs and monitor patients' therapeutic and adverse responses to CSPs.

There must also be a mechanism for the patient or caregiver to report these responses to the pharmacist.

Conclusion

Although the task of compliance with the requirements of *USP* chapter 797 may appear overwhelming, complicated, expensive, and even unattainable, quality systems can be established via a methodical and organized approach. After the systems have been implemented, maintaining them requires vigilance and follow-up. Compliance with chapter 797 involves upfront and ongoing costs associated with establishing these systems, but the time, energy, and cost required to maintain them are far less than those of retrospective or manual systems of collecting, reviewing, and collating quality assurance data on a monthly basis.

References

1. Pharmaceutical considerations—sterile preparations (general information chapter 797). In: The United States pharmacopeia, 27th rev., and The national formulary, 22nd ed. Rockville, MD: The United States Pharmacopeial Convention; 2004:2350-70.
2. American Society of Health-System Pharmacists. ASHP discussion guide for compounding sterile preparations: summary and implementation of *USP* chapter 797. www.ashp.org/SterileCpd/797guide.pdf (accessed 2004 Dec).
3. Microbiological evaluation of clean rooms and other controlled environments (general information chapter 1116). In: The United States pharmacopeia, 24th rev., and The national formulary, 19th ed. Rockville, MD: United States Pharmacopeial Convention; 1999:2099-106.
4. Millipore. Technical brief TB039: filter integrity test methods. www.millipore.com/publications.nsf/docs/TB039 (accessed 2004 Aug 1).
5. Baseline pharmaceutical engineering guide for sterile manufacturing facilities. Vol. 3. Tampa: International Society for Pharmaceutical Engineering; 1999 Jan.
6. Rahe H. Hospital sterility: cause for concern. Hospital's aseptic practices don't even cover the basics. www.mic4.com/articles/hospital-sterility.php (accessed 2005 Mar 22).
7. Kastango ES, DeMarco S. Pharmacy cleanroom project management considerations: an experience-based perspective. *Int J Pharm Compd.* 2001; 5:221-5.
8. Controlled Environment Testing Associ-

- ation. Frequently asked questions relating to controlled environment facility and equipment requirements of *USP* 797. www.cetainternational.org/reference/usp797faq.pdf (accessed 2004 Sep 18).
9. Matthew RA. Playing by the rules. *Cleanrooms.* 1999; 13:42.
10. Kastango ES, Douglass K. Quality assurance for sterile products. *Int J Pharm Compd.* 2001; 5:246-53.
11. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. *Clin Microbiol Rev.* 1999; 12:147-79.
12. American Society of Health-System Pharmacists. ASHP guidelines on quality assurance of pharmacy-prepared sterile products. *Am J Health-Syst Pharm.* 2000; 57:1150-69.
13. Compounding sterile preparations video training program. Bethesda, MD: American Society of Health-System Pharmacists; 2004. DVD and video.
14. Buchanan EC, Schneider PJ, eds. Compounding sterile preparations, 2nd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2004.
15. Sterile product preparation: a multimedia learning tool. Bethesda, MD: American Society of Health-System Pharmacists; 2004. CD-ROM.
16. Valiteq aseptic technique validation system. Des Plaines, IL: Lab Safety Corporation; 2004. Video.
17. Halls NA. Practicalities of setting acceptance criteria for media fill trials. *PDA J Pharm Sci Technol.* 2000; 54:247-52.
18. Parenteral Drug Association. Process simulation testing for aseptically filled products. *PDA J Pharm Sci Technol.* 1996; 50(suppl 1):S1-16.
19. Kawamura K, Abe H. Consideration of media fill tests for evaluation and control of aseptic processes: a statistical approach to quality criteria. *PDA J Pharm Sci Technol.* 2002; 56:235-41.
20. Trissel LA, Gentempo JA, Anderson RW et al. Using a medium-fill simulation to evaluate the microbial contamination rate for *USP* medium-risk-level compounding. *Am J Health-Syst Pharm.* 2005; 62:285-8.
21. Particulate matter in injections (general information chapter 788). In: The United States pharmacopeia, 27th rev., and The national formulary, 22nd ed. Rockville, MD: United States Pharmacopeial Convention; 2004:2338-44.
22. Standard operating procedure for particulate testing for sterile products. *Int J Pharm Compd.* 1998; 2:78.
23. American Society of Health-System Pharmacists. ASHP guidelines on the safe use of automated compounding devices for the preparation of parenteral nutrition admixtures. *Am J Health-Syst Pharm.* 2000; 57:1343-8.
24. Sterility test (general information chapter 71). In: The United States pharmacopeia, 27th rev., and The national formulary, 22nd ed. Rockville, MD: United States Pharmacopeial Convention; 2004:2157-62.

- 25. Sterilization and sterility assurance of compendial articles (general information chapter 1211). In: The United States pharmacopeia, 27th rev., and The national formulary, 22nd ed. Rockville, MD: United States Pharmacopeial Convention; 2004:2616-21.
- 26. Cooper JF, Harbert JC. Endotoxin as a cause of aseptic meningitis after radionuclide cisternography. *J Nucl Med.* 1975; 16:809-13.
- 27. Alderson PO, Siegel BA. Adverse reactions following 3In-DTPA cisternography. *J Nucl Med.* 1973; 14:609-11.
- 28. Food and Drug Administration. Inspector's technical guide no. 40. Bacterial endotoxins/pyrogens. www.fda.gov/ora/inspect_ref/itg/itg40.html (accessed 2005 Mar 22).
- 29. Jones TD, Feler CA, Simmons BP et al. Neurologic complications including paralysis after a medication error involving implanted intrathecal catheters. *Am J Med.* 2002; 112:31-6.

Appendix A—Air sampling results log^a

Week/Month of: _____
(Start of week ALWAYS on Sunday)

Samples Pulled By: _____ Date Samples Pulled: _____

TSA: Micro Diagnostics Lot Number: _____ Expiration Date: _____

Time Placed in Incubator: _____ A.M./P.M. (Incubation time is minimum of 48 hours and not to exceed 72 hours)

Agar Plate Information	Date Out	Time Out	Colony Count	CFU Threshold Limit ^b	CFU Action Limit ^c	Results		Comments	Inspected By
						Pass	Fail		
Cleanroom Environment			Colonies/plate	Colonies/plate	(X)	(X)			
HA	H1R			>0	>2				
	H1L			>0	>2				
	H24			>0	>2				
	H2L			>0	>2				
	H3R			>0	>2				
	H3L			>0	>2				
	H4R			>0	>2				
	H4L			>0	>2				
	H5R			>0	>2				
	H5L			>0	>2				
	H6R			>0	>2				
	H6L			>0	>2				
	H7R			>0	>2				
	H7L			>0	>2				
	H8R			>0	>2				
H8L			>0	>2					
RA	Hd #: _____			>4	>24				
	Hd #: _____			>4	>24				
	Hd #: _____			>4	>24				
	Cart by: _____			>4	>24				
	Cart by: _____			>4	>24				
	Cart by: _____			>4	>24				

*Review of entire form after completion: _____ Date: _____
(Person other than that in Inspected By) **Note:** Fill in any unused sections with NA prior to filing form

^aTSA = tryptic soy agar, CFU = colony-forming unit, HA = laminar airflow workbench or biological-safety cabinet, RA = room air, H1R = hood #1 right side of high-efficiency particulate air (HEPA) filter, H1L = hood #1 left side of HEPA filter, and so on, Hd = hood.
^bIf count greater than threshold level, retest failed area immediately and notify pharmacy manager.
^cIf count greater than action-limit level, retest failed area immediately, perform one-time cleaning to failed area, retest, and notify pharmacy manager.

Appendix B—Sample personnel assessment checklist

Employee Name: _____ Job: _____
 Date of Evaluation: _____ Name of Evaluator: _____ Title: _____
 Type of Evaluation: _____ Initial Assessment
 _____ Quarterly Recertification
 _____ Other (specify): _____

Observations must be made by qualified pharmacy staff. Please indicate performance in the appropriate box. Any skill marked “unmet” requires instruction and practice until standard is met. Document remedial activities in comments section.

Skill	Met	Unmet	Comments
Proper gowning procedure			
All jewelry is removed (earrings, watches, rings, etc.).			
All makeup is removed.			
Donned proper garments (booties, head cover, gown, mask, gloves).			
Scrubbed nails, hands, and arms to midforearm with disinfecting agent for at least 30 seconds.			
Protected outer surfaces of garment items as appropriate or applicable.			
Entry into controlled area performed with minimal contamination of gloved hands and outer garments, as required.			
Preparation of aseptic work area			
Remove any supply items not needed from hood or isolator. No extraneous articles (pens, labels, and scissors) are placed in hood or isolator.			
Clean all hood work surfaces and bar at the start of each workday. Side-to-side, back-to-front motion, with low-lint wipe and isopropyl alcohol/bleach or peroxide. Document ISO class 5 cleaning.			
Collected and introduced ingredients and compounding supplies into aseptic work area in proper manner.			
Collected all components and supplies needed for prescription. Items are inspected for expiration date and defects, documenting lot numbers and expiration dates on compounding batch records.			
All items in compounding area wiped with isopropyl alcohol/bleach/peroxide prior to being introduced.			
Removed outer wrap, where appropriate, at edge of aseptic work area.			
Arranged items more than 6 inches within aseptic work area and 3 inches from each side in a manner not to disrupt clean airflow.			
Arranged items for efficient operation.			

(Continued)

Appendix B (Continued)

Skill	Met	Unmet	Comments
Aseptic operations			
Meticulously conducted aseptic processes so that exposed critical sites were always directed into the HEPA air stream.			
Manipulated syringes so as to not touch the tip or plunger.			
Sanitized all rubber stoppers and ampul necks with isopropyl alcohol/bleach/peroxide before puncturing or breaking open.			
Injected proper amount of air into vials before withdrawing solution (when appropriate).			
Checked graduations on syringes, bags, and bottles carefully; relative to amount of medication ordered.			
Opened ampuls with a firm snapping motion and pointed toward the side of the hood.			
Filtered solutions taken from ampuls and any other solutions with visible particles.			
Made all syringe and tubing connections aseptically, expertly, and securely.			
Performed all aseptic manipulations in a manner showing obvious effort to prevent touch contamination.			
If contamination was suspected from the procedure or otherwise, the preparation was discarded.			
Inspected preparation for visible particulate matter, evidence of incompatibility, or other defects.			
Removed waste or unused supplies with minimal in-and-out motion. Partially used, multidose vials are dated and initialed.			
Cleaned and sanitized aseptic work area between each batch.			
All technician work is checked by a pharmacist.			
Aseptic technique process-simulation testing			
All compounded media-fill units are clear and do not exhibit any growth (negative).			

■ **REPORTS** *USP* chapter 797

Appendix C—Sample of a media-fill results log

Media fill for purposes of (check one): ___ Initial operator validation or ___ Operator revalidation or ___ Equipment evaluation or ___ Daily media

Operator Name:

Media Fill Date:

Bag No.	Operator Name	Hood	Days of Inspection														Results		Initials of Reader	Date
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	Pass	Fail		
Lot no. of media:			Incubate at room temperature Days 1–7							Incubate at 30–35 °C Days 8–14							Lot no. of water vials:		Lot no. of water ampuls:	
Expiration date:																	Expiration date:		Expiration date:	
If bag is clear, initial box on day of inspection. BUT if bag is cloudy, mark an X in the box, line out the remaining days, indicate "FAIL" in space provided, and notify pharmacy manager.																				

Signature of pharmacy manager after document review

Date