Overview of USP Chapter <797>

"Pharmaceutical Compounding—Sterile Preparations": The Potential Impact for Compounding Pharmacies

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Effective January 1, 2004, new regulations from the United States Pharmacopeial Convention Chapter <797> "Pharmaceutical Compounding—Sterile Preparations" came into effect. The regulations, which evidently affect the compounding of sterile preparations, can be enforceable on both the state and federal levels.

The scope of USP Chapter <797> applies to healthcare institutions, pharmacies, physician practice facilities and other facilities in which compounded sterile preparations are prepared, stored and dispensed. Two major implications of the chapter are (1) the breadth of the definition for activities covered and (2) the activities defined as sterile compounding.

The chapter not only defines practices in pharmacies irrespective of location but also brings physician practice facilities under the regulations, which previously could not be regulated by state boards of pharmacy. Activities defined as compounding range from basic compounding, such as that involved in preparing sterile preparations according to the manufacturers' labeling, to preparations compounded by use of devices or ingredients that are not sterile, to preparations that must be sterilized prior to dispensing.

Preparations may be biologics, diagnostics, drugs, nutrients or radiopharmaceuticals, which include, but are not limited to, baths and soaks for live organs and tissues, implants, inhalations, injections, irrigations, metered sprays, and ophthalmic and otic preparations.

The regulations are described as being based on risk levels of microbial contamination, with major emphasis on responsibilities of compounding personnel, facilities and equipment (environmental quality and control), verification of compounding accuracy and sterilization, personnel training and evaluation in aseptic manipulation skills, maintenance of product quality and control after the compounded sterile preparation leaves the pharmacy and patient monitoring and adverse events reporting. Suggested standard operating procedures (SOPs) are also included in the document.

The acceptable environment for preparation of sterile products is an International Organization for Standardization (ISO) Class 8 cleanroom with an anteroom. The cleanroom must contain an ISO Class 5 environment in which the actual preparation of products takes place. A barrier isolator, which does not require the ISO Class 8 cleanroom, is also an acceptable ISO Class 5 environment.

Microbial Contamination Risk Levels

Low-Risk Conditions

Low-risk conditions include compounding with aseptic manipulations entirely with ISO Class 5 or better air quality, using only sterile ingredients, products, components and devices.

Examples of low-risk conditions include:

A. The use of sterile needles and syringes to transfer sterile drugs from the manufacturer's original packaging (vials, ampoules) and
B. The manual measuring and mixing of no more than three sterile products to compound drug admixtures and nutritional solutions.

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Medium-Risk Conditions

Medium-risk conditions include multiple individual or small doses of sterile products that are compounded or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions. Medium-risk conditions should be considered when:

- The compounding process includes complex aseptic manipulations other than the single-volume transfer;
- The compounding process requires an unusually long duration, such as that required to complete dissolution or homogeneous mixing;
- The compounded sterile products do not contain broad-spectrum bacteriostatic substances, and they are administered over several days.

For a medium-risk preparation that has not passed sterility testing, the storage period cannot exceed the following time periods: 30 hours at room temperature, 7 days at cold temperature, and 45 days in a solid frozen state at –20°C or colder.

Examples of medium-risk conditions include:

A. The compounding of total parenteral nutrition (TPN) fluids by using manual or automated devices that require multiple injections and detachments and attachments of the nutrient source products to the device or machine to deliver all nutritional components to the final sterile container;
B. The filling of reservoirs of injection and infusion devices with multiple sterile drug products and evacuations of air from these reservoirs before the filled device is dispensed;
C. The filling of reservoirs of injection and infusion devices with volumes of sterile drug solutions that will be administered over several days at ambient temperatures between 25 and 40°C and
D. The transfer of multiple ampoules or vials into a single, final sterile container or product.

High-Risk Conditions

High-risk conditions include:

- The compounding of nonsterile ingredients, including manufactured products for routes of administration other than those listed under *c* in the introduction of the official *Pharmacopeial Forum*[1] that are incorporated or a nonsterile device that is employed before terminal sterilization;
- The compounding of sterile ingredients, components, devices and mixtures exposed to air quality inferior to ISO Class 5; this includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives;
- The compounding of nonsterile products exposed to air quality inferior to ISO Class 5 for at least 6 hours before sterilization.

For high-risk preparations that have not passed sterility testing, the storage periods cannot exceed the following: 24 hours at controlled room conditions; 3 days at cold temperatures; and 45 days for solid frozen state at –20°C or colder.

Examples of high-risk conditions include:

A. The process of dissolving nonsterile bulk drug and nutrient powders to make a solution, which will be terminally sterilized;
B. The situation when sterile ingredients, components, devices and mixtures are exposed to air quality inferior to ISO Class 5; this includes storage in an environment inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives and
C. The process of measuring and mixing sterile ingredients in nonsterile devices before sterilization is performed.

Note: ISO standards for air quality have replaced Federal Standard 209. ISO class 8 is equivalent to class 100,000, and ISO class 5 is equivalent to class 100.

Responsibilities of Compounding Personnel

Compounding personnel are responsible for:

- Ensuring that compounded sterile preparations are accurately identified, measured, diluted and mixed;
- Ensuring that compounded preparations are correctly

purified, sterilized, packaged, sealed, labeled, stored, dispensed and distributed;
- Maintaining appropriate levels of cleanliness and
- Providing proper labeling and instructions for administration to patients.

Other responsibilities include ensuring that
- Preparations are within monograph limits or within 10%, if not specified, until the beyond-use date;
- All compounded sterile preparations are prepared in a manner that maintains sterility and minimizes the introduction of particulate matter;
- Written quality-assurance procedures are in place, including process checks that are critical points such as weighing, sterilization, purification and any step that could affect the efficacy of the final product. Beyond-use dates and packaging and storage requirements should be included;
- The dispenser shall, when appropriate and practical, obtain results for preparation and ingredient identity, strength, purity and sterility, and review before the preparation is dispensed;
- Professionals who supervise compounding personnel ensure that the activities achieve the following goals and objectives:
  A. Personnel are trained and possess the skills, education and knowledge to perform and document their compounding duties.
  B. Ingredients are correctly identified and have the proper quality and purity.
  C. Opened or partially used packages' ingredients for subsequent use are properly stored with consideration for environmental conditions. (These packages should be inspected and verified to be within quality and purity specifications before reuse.)
  D. The generation of bacterial endotoxins is minimized.
  E. Sterilization methods achieve sterility while maintaining the labeled strength of the ingredients and physical integrity of the package.
  F. Equipment used in preparation is clean, accurate and appropriate for its intended use.
  G. Potential harm for added substances and differences in rate and extent of bioavailability is reviewed and evaluated before dispensing and administration.
  H. Proper packaging is selected with consideration that the packaging is capable of maintaining sterility and strength beyond the beyond-use date.
  I. The compounding environment maintains the proper conditions in terms of air quality and sanitation.
  J. Labeling includes all ingredients, including names and concentrations.
  K. Before dispensing, the product is visually inspected, and documentation of the compounding is reviewed for accuracy and completeness.
  L. Beyond-use dating is established and indicated on the label. (Dating should be established based on testing or reliable literature sources.)

Facilities and Equipment (Environmental Quality and Control)

Sterility and the elimination of contamination are dependent on the components and processes used, personnel conformance to procedures, and environmental conditions under which operations are performed. Requirements for environmental conditions depend on the potential amount of exposure the preparation undergoes during processing. The degree of exposure of the preparation is affected by the length of time of the exposure, the size of the critical area exposed and the nature of the critical site.

An open pathway between the critical site and the environment, such as that created by filling an unstoppered vial or any surface that may come into direct contact with the critical site, increases with the amount of time of exposure. Exposure of the critical site should be minimized in processing.

Size of the critical site is also a factor in the potential for contamination, with an open-vial exposure being higher than a tip of a syringe needle.

Prevention or elimination of airborne particles must be given high priority. Two technologies are identified for controlling airborne particulates: cleanrooms and barrier isolators. Barrier isolators minimize the extent of personnel contact, which is the largest source of contamination. A well-designed barrier isolator supported by adequate procedures for maintenance, monitoring and control offers an acceptable alternative to a cleanroom. An important part of cleanroom technology is the pressurization of the controlled area to prevent migration of particulates. A well-designed cleanroom must have positive pressure to the surrounding environment.

Cleanrooms

Low and Medium Risk

Compounding low- and medium-risk preparations in a cleanroom requires adherence to the following requirements:
- The compounder must have an ante area, but it need not be separated with a physical wall.
- Air classification or quality for the cleanroom must meet ISO Class 8 standards (class 100,000).
- Adjacent areas must have positive pressure, per ISO 14644-4.
- The physical characteristics of construction of the cleanroom should meet the following requirements:
  A. Walls, floors, fixtures and ceilings should be smooth, impervious and free of cracks and crevices and should be nonshedding.
  B. Surfaces should be resistant to damage from sanitizing agents.
  C. Junctures of ceilings to walls should be coved and caulked.
  D. If ceilings consist of inlaid panels, the panels should

be impregnated with a polymer to render them impervious and hydrophobic. Panels are to be caulked around each perimeter to seal them to the support frame.

E. Walls may be panels locked together and sealed or epoxy-coated gypsum board.
F. Floors should be overlaid with wide-sheet vinyl flooring, with heat-sealed seams and coving at the sidewall.
G. The buffer or ante area should contain no sinks or floor drains.

Gowning Requirements

Before entering the ante or buffer area, personnel should remove outer lab coats, make-up and jewelry and thoroughly scrub hands and arms to the elbow. After drying their hands and arms, personnel should don clean, nonshedding uniforms consisting of:

- Hair covers,
- Shoe covers,
- Coveralls or knee-length coats (coats to fit snugly at the wrists and be zipped or snapped in the front),
- Appropriate gloves and
- Facemasks (should be put on after entering the cleanroom)

Leaving and Re-entry

Upon leaving the cleanroom, personnel should carefully remove coveralls and coats and hang them outside the entry in the buffer area. Coveralls and coats can be used for only one shift. All other coverings should be discarded and new ones donned prior to re-entry. Re-entry follows the original gowning procedure.

High-Risk

All low- to medium-risk procedures and facilities, except the ante area, must be a separate room.

Barrier Isolator

Physical Facility

It is not necessary to locate the barrier isolator in an ISO Class 8 area.

Gowning Requirements

The following are required:

- Hair covers,
- Shoe covers,
- Lab coats and
- Facemasks (for covering facial hair).

Verification of Compounding Accuracy and Sterilization

The procedures and sterilization methods for compounded sterile preparations should be correctly designed and verified with written documentation. Verification requires planned testing designed to demonstrate the effectiveness of all procedures critical to producing the correct preparation in terms of accuracy of dose and purity.

Sterilization Methods

Select the sterilization process based on experience or appropriate information sources. Verify the selected method whenever possible. Guidelines for selection of sterilization methods include the following:

A. The method has been shown to maintain the preparation's physical and chemical stability and efficacy during the process selected for sterilization.
B. Glass and metal devices may be covered tightly with aluminum foil, then exposed to dry heat in an oven at a mean temperature of 250°C for 2 hours to achieve sterility and depyrogenation. Items may be used immediately or stored in an environment suitable for compounding low- and medium-risk products.
C. If sterile microporous membrane filters are used to sterilize compounded sterile preparations, the filters must be both chemically and physically compatible with the product. Determine this from appropriate information sources before use.

Sterilization by Filtration

To sterilize pharmaceutical fluids, commercially available sterile filters must be approved for applications in human use. Filters that must be sterilized and commercially available disposable sterile and pyrogen-free filters must have a nominal porosity of 0.2 µm (includes 0.22-µm porosity) and should be certified by the manufacturer to retain at least 10^7 microorganisms (see *United States Pharmacopeia* for definition). The filters must be chemically and physically stable at the temperature and pressure conditions at which they are used. If the preparation is known to contain excessive particulate, a prefilter must be used or a larger-porosity filter may be used as a prefilter.

Filter integrity should be checked after use. Filter devices used on handheld syringes may be checked by feeling for a greater resistance on the plunger when filtering air after filtering aqueous fluid.

Steam Sterilization

Autoclaving is the preferred method of terminally sterilizing aqueous preparations that have been verified as maintaining their full chemical and physical stability under the conditions required for sterilization.

To achieve sterility, the preparation must be exposed to 121°C under a pressure required to achieve that temperature for a duration of time verified to achieve sterility. An allowance of time must be made for the preparation to achieve the 121°C. The amount and type of materials in the autoclave impact the length of time required for individual products.

Items not directly exposed to pressurized steam may allow for the survival of microbial organisms and spores. Before sterilization, tightly wrap plastic, glass and metal items in

low-particle–shedding paper or fabric, or seal in envelopes that prevent poststerilization microbial penetration. Immediately before filling vials that are to be steam sterilized, pass the solutions through a filter having a porosity not larger than 1.2 µm for removal of particulate matter. Sealed containers must be capable of generating steam internally; thus, stoppered or crimped empty vials must contain a small amount of moisture to generate steam.

The description of conditions for steam sterilization and duration for specific compounded sterile preparations must be in the form of a written document in the compounding facility. The effectiveness of steam sterilization must be verified using appropriate biological indicators or other confirmation methods.

Personnel Training and Evaluation in Aseptic Manipulation Skills

Before beginning to prepare compounded sterile preparations, personnel must be provided with appropriate training by expert personnel, audio-video instructional sources or professional sources.

Personnel shall perform didactic review, written testing and media-fill testing of aseptic manipulative skills initially and at least annually for low- and medium-risk level and semiannually for high-risk level compounding.

Use media-fill challenge testing to access the quality of aseptic skills. The skill of personnel to aseptically prepare compounded sterile preparations may be evaluated using sterile fluid bacterial culture for media-fill validation. Commercially available sterile culture media can be used to simulate actual aseptic manipulations. Media-fill vials are to be incubated at 25°C temperatures for a period of 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days.

Maintaining Product Quality and Control after the Compounded Sterile Preparation Leaves the Pharmacy

The pharmacy is responsible for maintaining quality and control after the compounded sterile preparation leaves the pharmacy and goes through its life cycle. In fulfilling this responsibility, the pharmacy must provide for proper packaging, handling and storage of the preparation. The proper education, training and supervision of personnel assigned to these functions assists in ensuring the quality and control of the compounded sterile preparation.

Packaging, Handling and Transportation

The critical requirements unique to compounded sterile preparations to ensure quality must be addressed in written procedures. Address specific issues that can impact package integrity, such as dislodging syringe tips during handling. Transportation and handling in inappropriate ways can impact the stability of preparations. Address issues such as exposure to light or heat on a preparation-specific basis. Hazardous drugs need to be protected during transport and handling not only for protecting the preparation but also for minimizing potential environmental exposure. Special requirements associated with packaging, handling and transport to prevent breakage and spills should be considered. Secondary containment such as sealed plastic bags should be used.

Use and Storage

The pharmacy is responsible for the preparation in patient-care settings until administration. Written procedures have to exist to ensure that the storage conditions in patient-care settings are suitable for the preparation. Compounding facilities that ship compounded sterile products to patients must ascertain or provide the following assurances:

A. Labels and accessory labeling for preparations include clearly readable beyond-use dating, storage instructions and disposal instructions of outdated preparations.
B. Each patient is able to store the preparation properly, including the use of refrigerator or freezer if labeling requires such storage.

Redispensed Compounded Sterile Products

The pharmacy must have the sole authority to determine whether a compounded sterile preparation not administered for original intended use is to be used for an alternate patient or under alternate conditions.

All preparations that involve redispensing must be returned to the pharmacy for appropriate disposal but only if adequate continuing quality can be fully assured. Assurance that the preparation was maintained under required conditions and shows no evidence of tampering or manipulation after leaving the pharmacy is a key element in determining whether the preparation can be dispensed. There must be enough time left on the beyond-use dating to ensure the use of the preparations.

Patient Monitoring and Adverse Events Reporting

Compounding facilities must clinically monitor patients treated with compounded sterile preparations according to the regulations and guidelines of their state healthcare practitioner licensure boards or acceptable standards of practice. Compounding facilities must provide patients with a way of addressing questions and report any concerns about preparations. The facility SOP manual must describe instructions for receiving, acknowledging and dating receipts.

Reports of adverse events must be reviewed promptly and thoroughly by compounding supervisors to correct and prevent any future occurrences.

Suggested SOPs

The pharmacy should have written, properly approved SOPs. These procedures should be designed to ensure the quality of the environment in which the compounded sterile preparation is prepared. The following procedures are recommended:

A. For cleanrooms, access to the buffer or ante area must be restricted to qualified personnel assigned to the area.
B. All supplies in cartons must be decontaminated by removing them from the cartons and wiping or spraying them with disinfecting agents.
C. Supplies that are frequently required must be stored on shelving in the anteroom area.
D. Cleanroom carts used to bring in supplies from the storeroom cannot be rolled beyond the demarcation line in the anteroom area, and carts used in the cleanroom cannot be rolled beyond the demarcation line without being cleaned and sanitized before being returned to the cleanroom.
E. Supplies required for shift operation must be prepared and brought into the buffer area on portable carts.
F. Objects (including pencils, cardboard cartons, paper towels and cotton items) that shed particles cannot be brought into the anteroom or cleanroom.
G. Traffic flow must be minimized in the compounding area.
H. Cleanroom personnel must follow proper personal preparation before gowning, including washing their hands and elbows and removing jewelry and make-up.
I. Proper gowning requirements must be followed.
J. Chewing of gum, candy or food items must not be allowed in the ante- or cleanroom.
K. At the beginning of each compounding activity or after spills, surfaces of the direct compounding environment must be cleaned and sanitized.
L. When laminar airflow devices or barrier isolators are used as the ISO class 5 air-quality environment, their blowers must be operated continuously during the compounding activity, including during interruptions of less than 8 hours.
M. All procedures must be performed in a manner to minimize the risk of touch contamination.
N. Gloves must be sanitized with an approved disinfectant prior to operations.
O. All rubber stoppers of vials must be sanitized prior to the introduction of a needle or spike.
P. After procedures are complete, used syringes, vials and other supplies must be removed with a minimum of exit and re-entry to minimize the introduction of contamination.

Reference

1. United States Pharmacopeial Convention, Inc. *Pharmacopeial Forum.* Rockville, MD:US Pharmacopeial Convention, Inc.; 2003;29:2003.

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