RULE ANALYSIS

Introduction: **THE AMENDMENTS ARE SUBMITTED TO THE BOARD FOR CONSIDERATION AS AN ADOPTED RULE**

Short Title: Pharmacies Compounding Sterile Preparations.

Rule Number: §291.133

Statutory Authority: Texas Pharmacy Act, Chapter 551-569, Occupations Code:

(1) Section 551.002 specifies that the purpose of the Act is to protect the public through the effective control and regulation of the practice of pharmacy; and
(2) Section 554.051 gives the Board the authority to adopt rules for the proper administration and enforcement of the Act.

Purpose: The amendments, if adopted, update the personnel, environment, compounding process, cleaning and disinfecting, beyond-use dating, cleansing and garbing, environmental testing, sterility testing, recall procedure, and recordkeeping requirements for pharmacies compounding sterile preparations.

The Board reviewed and voted to propose the amendments during the November 5, 2024, meeting. The proposed amendments were published in the December 27, 2024, issue of the *Texas Register* (49 TexReg 10463).

TITLE 22. EXAMINING BOARDS
PART 15. TEXAS STATE BOARD OF PHARMACY
CHAPTER 291. PHARMACIES
SUBCHAPTER G. SERVICES PROVIDED BY PHARMACIES

§291.133. Pharmacies Compounding Sterile Preparations.

The Texas State Board of Pharmacy proposes amendments to §291.133, concerning Pharmacies Compounding Sterile Preparations. The amendments, if adopted, update the personnel, environment, compounding process, cleaning and disinfecting, beyond-use dating, cleansing and garbing, environmental testing, sterility testing, recall procedure, and recordkeeping requirements for pharmacies compounding sterile preparations.

Daniel Carroll, Pharm.D., Executive Director/Secretary, has determined that, for the first five-year period the rules are in effect, there will be no fiscal implications for state or local government as a result of enforcing or administering the rule. Dr. Carroll has determined that, for each year of the first five-year period the rule will be in effect, the public benefit anticipated as a result of enforcing the amendments will be to ensure the safety and efficacy of compounded sterile preparations for patients, improve the health, safety, and welfare of patients by ensuring that Class A, Class B, Class C, and Class E pharmacies engaged in sterile compounding operate in a safe and sanitary environment, and provide clearer regulatory language that is appropriately informed by the recently updated guidance in the United States Pharmacopeia-National Formulary. For each year of the first five-year period the rule will be in effect, the probable economic cost to persons required to comply with the amendments is estimated to be $0-$1,970 per employee, $0-$300 in fixed costs, and $0-$1,109.69 per batch in variable costs based on number of batches and formulations. Additionally, dependent on a pharmacy's current operations and equipment, a pharmacy would potentially incur one-time expenses of $0-$5,000 for cleanroom modifications, $0-$6,000 for an autoclave, $0-$4,000 for a pharmaceutical oven, $0-$500 for temperature logs and monitors, and $0-6,330 per formulation for preliminary testing.

Economic Impact Statement

The Texas State Board of Pharmacy (Board) anticipates a possible adverse economic impact on some small or micro-businesses (pharmacies) or rural communities as a result of the proposed amendments to §291.133. The Board is unable to estimate the number of small or micro-businesses subject to the proposed amendments. As of November 21, 2024, there are 877 Class A, Class B, Class C, and Class E pharmacies that perform sterile compounding, as indicated by the pharmacies on Board licensing forms. The Board estimates that 77 rural communities in Texas have a Class A, Class B, Class C, or Class E pharmacy that performs sterile compounding.

The economic impact of the proposed amendments on a particular pharmacy would be dependent on that pharmacy's current environment and the policies and procedures the pharmacy previously had in place for compounding sterile preparations. The additional costs of training personnel who do not compound nor supervise compounding personnel on a pharmacy's SOPs are estimated to be $0 to $1,200 per employee. The additional costs of the updated media-fill testing procedures depend on the compounding risk-level in which a pharmacy is currently engaged. For a pharmacy that is currently engaged in only low-risk and medium-risk compounding, the additional costs are estimated to be $9.95 to $300 annually per

employee who engages in sterile compounding. For a pharmacy that is currently engaged in high-risk compounding, no additional costs are anticipated. The additional costs of the updated gloved fingertip sampling depend on the compounding risk-level in which a pharmacy is currently engaged. For a pharmacy that is currently engaged in only low-risk and medium-risk compounding, the additional costs are estimated to be $90 to $250 annually per employee who engages in sterile compounding. For a pharmacy that is currently engaged in high-risk compounding, no additional costs are anticipated. The additional costs of the updated garbing competency testing depend on the compounding risk-level in which a pharmacy is currently engaged. For a pharmacy that is currently engaged in only low-risk and medium-risk compounding, the additional costs are estimated to be $0 to $220 annually per employee who engages in sterile compounding. For a pharmacy that is currently engaged in high-risk compounding, no additional costs are anticipated. The additional costs of the updated surface sampling requirements are estimated to be $85 to $300 per sample taken. The additional costs of the updated sterilization and depyrogenation requirements, for a pharmacy that does not already possess a pharmaceutical oven or autoclave, are one-time costs of $1,000 to $6,000 for an autoclave, $1,000 to $4,000 for a pharmaceutical oven, and $500 for temperature logs and monitors, annual costs of $300 for calibration and $210 for endotoxin testing, and $40 to $50 per usage for washing and wrapping supplies. Preliminary testing is estimated to cost $510 to $1,800 per formulation for method suitability testing, $150 to $345 per formulation for sterility testing, $500 per formulation for endotoxin validation method, $110 to $210 per formulation for endotoxin testing, $250 to $1,200 per formulation for container closure integrity testing, $1,275 per formulation for antimicrobial effectiveness testing, and $1,000 per formulation for a method suitability test for antimicrobial effectiveness testing. The additional costs of the updated air exchange requirements are estimated to be a one-time cost of $0 to $5,000 based on the extent of the modifications, if any, needed for a pharmacy's cleanroom. The additional costs of expanded disinfecting with sterile 70% isopropyl alcohol in place of non-sterile 70% isopropyl alcohol are estimated to be a net increase of $4.69 per 32-ounce bottle. The additional costs of sterile low-lint garments and coverings are estimated to $0 to $45 per set. The additional costs of expanded sterility and bacterial endotoxin testing are estimated to be $300 to $500 per batch. The estimated cost of the new beyond-use date requirements is dependent on the pharmacy's current practices. A shortened beyond-use date may require the compound to be made more frequently or discarded more often. Additional testing costs may be incurred to prove that a specific compounded preparation can exceed a new beyond-use date standard.

The Board established a Compounding Rules Advisory Group, comprised of a Sterile Subcommittee and a Non-Sterile Subcommittee, to review the recently issued revisions to United States Pharmacopeia General Chapter <795> Pharmaceutical Compounding- Nonsterile Preparations and United States Pharmacopeia General Chapter <797> Pharmaceutical Compounding- Sterile Preparations, and the proposed amendments are based on the recommendations of the Sterile Subcommittee. The Subcommittee's recommendations were initially presented at the May 7, 2024, Board meeting and four Subcommittee members made oral public comments concerning the recommendations. The Board reviewed the recommendations and provided direction to Board staff on items for which the Subcommittee could not come to consensus. The Board voted to published the proposed amendments for public comment during its August 6, 2024, Board meeting. The amendments were published in the September 20, 2024, issue of the *Texas Register* (49 TexReg 7588). The Board received eight written public comments concerning the amendments. Additionally, the Board received six oral public comments at the November 5, 2024, Board meeting. After reviewing and considering the comments, the Board proposed amendments to the previously proposed amendments. Alternative methods of achieving the purpose of the proposed amendments were considered by the Sterile Subcommittee and the Board and the proposed amendments reflect

recommendations for the least restrictive methods of ensuring the safety and efficacy of compounded sterile preparations.

Regulatory Flexibility Analysis

The Texas State Board of Pharmacy (Board) anticipates a possible adverse economic impact on some small or micro-businesses (pharmacies) or rural communities as a result of the proposed amendments to §291.133. The Board established a Compounding Rules Advisory Group, comprised of a Sterile Subcommittee and a Non-Sterile Subcommittee, to review the recently issued revisions to United States Pharmacopeia General Chapter <795> Pharmaceutical Compounding- Nonsterile Preparations and United States Pharmacopeia General Chapter <797> Pharmaceutical Compounding- Sterile Preparations, and the proposed amendments are based on the recommendations of the Sterile Subcommittee. The Sterile Subcommittee reviewed the new provisions of USP <797>, discussed whether any of the provisions should be added to §291.133 to ensure patient safety in Texas, and considered various methods of achieving this purpose.

The Sterile Subcommittee discussed the changes to USP <797>during its meetings held on August 2, August 23, 2023, October 3, 2023, October 30, 2023, and January 23, 2024 meetings. The Sterile Committee considered different options and levels of personnel training, beyond-use dating, environmental requirements, compounding processes, environmental testing requirements, recall procedures, and recordkeeping requirements in determining recommendations for the least restrictive methods of ensuring the safety and efficacy of compounded sterile preparations. In reviewing the new provisions of USP <797>, the Sterile Subcommittee recommended limiting or not adopting several of the new provisions, including preparation per approved labeling, initial gowning competency, use of isolators, precision and accuracy of pressure differentials, compounding notification on label, packaging of compounded sterile preparations, and compounding allergenic extracts.

The Sterile Subcommittee's recommendations were initially presented at the May 7, 2024, Board meeting and four Subcommittee members made oral public comments concerning the recommendations. The Board reviewed the recommendations and provided direction to Board staff on items for which the Subcommittee could not come to consensus. The Board voted to published the proposed amendments for public comment during its August 6, 2024, Board meeting. The amendments were published in the September 20, 2024, issue of the *Texas Register* (49 TexReg 7588). The Board received eight written public comments concerning the amendments. Additionally, the Board received six oral public comments at the November 5, 2024, Board meeting. After reviewing and considering the comments, the Board proposed amendments to the previously proposed amendments. The Board finds that alternative regulatory methods would not be consistent with the health, safety, and environmental and economic welfare of the state.

For each year of the first five years the proposed amendments will be in effect, Dr. Carroll has determined the following:

(1) The proposed amendments do not create or eliminate a government program;

(2) Implementation of the proposed amendments does not require the creation of new employee positions or the elimination of existing employee positions;

(3) Implementation of the proposed amendments does not require an increase or decrease in the future legislative appropriations to the agency;

(4) The proposed amendments do not require an increase or decrease in fees paid to the agency;

(5) The proposed amendments do not create a new regulation;

(6) The proposed amendments both limit and expand an existing regulation by adding and amending operational standards for Class A, Class B, Class C, and Class E, pharmacies engaged in sterile compounding;

(7) The proposed amendments do not increase or decrease the number of individuals subject to the rule's applicability; and

(8) The proposed amendments would have a de minimis impact on this state's economy.

Written comments on the amendments may be submitted to Eamon D. Briggs, Deputy General Counsel, Texas State Board of Pharmacy, 1801 Congress Avenue, Suite 13.100, Austin, Texas, 78701-1319, FAX (512) 305-8061. Comments must be received by 5:00 p.m., January 25, 2025.

The amendments are proposed under §§551.002 and 554.051 of the Texas Pharmacy Act (Chapters 551 - 569, Texas Occupations Code). The Board interprets §551.002 as authorizing the agency to protect the public through the effective control and regulation of the practice of pharmacy. The Board interprets §554.051(a) as authorizing the agency to adopt rules for the proper administration and enforcement of the Act.

The statutes affected by these amendments: Texas Pharmacy Act, Chapters 551 - 569, Texas Occupations Code.

§291.133. Pharmacies Compounding Sterile Preparations.

(a) Purpose. Pharmacies compounding sterile preparations, prepackaging pharmaceutical products, and distributing those products shall comply with all requirements for their specific license classification and this section. The purpose of this section is to provide standards for the:

(1) compounding of sterile preparations pursuant to a prescription or medication order for a patient from a practitioner in Class A-S, Class B, Class C-S, and Class E-S pharmacies;

(2) compounding, dispensing, and delivery of a reasonable quantity of a compounded sterile preparation in Class A-S, Class B, Class C-S, and Class E-S pharmacies to a practitioner's office for office use by the practitioner;

(3) compounding and distribution of compounded sterile preparations by a Class A-S pharmacy for a Class C-S pharmacy; and

(4) compounding of sterile preparations by a Class C-S pharmacy and the distribution of the compounded preparations to other Class C or Class C-S pharmacies under common ownership.

(b) Definitions. In addition to the definitions for specific license classifications, the following words and terms, when used in this section, shall have the following meanings, unless the context clearly indicates otherwise.

(1) ACPE--Accreditation Council for Pharmacy Education.

(2) Airborne particulate cleanliness class--The level of cleanliness specified by the maximum allowable number of particles per cubic meter of air as specified in the International Organization of Standardization (ISO) Classification Air Cleanliness (ISO 14644-1). For example:

(A) ISO Class 5 (formerly Class 100) is an atmospheric environment that contains less than 3,520 particles 0.5 microns **and larger** in diameter per cubic meter of air (formerly stated as 100 particles 0.5 microns in diameter per cubic foot of air);

(B) ISO Class 7 (formerly Class 10,000) is an atmospheric environment that contains less than 352,000 particles 0.5 microns **and larger** in diameter per cubic meter of air (formerly stated as 10,000 particles 0.5 microns in diameter per cubic foot of air); and

(C) ISO Class 8 (formerly Class 100,000) is an atmospheric environment that contains less than 3,520,000 particles 0.5 microns **and larger** in diameter per cubic meter of air (formerly stated as 100,000 particles 0.5 microns in diameter per cubic foot of air).

(3) Ancillary supplies--Supplies necessary for the preparation and administration of compounded sterile preparations.

(4) **Anteroom**[~~Ante-area~~]--**An ISO Class 8 or cleaner room with fixed walls and doors where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels may be performed. The anteroom is the transition room between the unclassified area of the pharmacy and the buffer room.** [~~An ISO Class 8 or better area where personnel may perform hand hygiene and garbing procedures, staging of components, order entry, labeling, and other high-particulate generating activities. It is also a transition area that:~~]

[~~(A) provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas; and~~]

[~~(B) reduces the need for the heating, ventilating and air conditioning (HVAC) control system to respond to large disturbances.~~]

(5) Aseptic **processing**[~~Processing~~]--A mode of processing pharmaceutical and medical preparations that involves the separate sterilization of the preparation and of the package (containers-closures or packaging material for medical devices) and the transfer of the preparation into the container and its closure under at least ISO Class 5 conditions.

(6) Automated compounding device--An automated device that compounds, measures, and/or packages a specified quantity of individual components in a predetermined sequence for a designated sterile preparation.

(7) Batch--A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced during a single preparation cycle.

(8) Batch preparation compounding--Compounding of multiple sterile preparation units, in a single discrete process, by the same individual(s), carried out during one limited time period. Batch preparation/compounding does not include the preparation of multiple sterile preparation units pursuant to patient specific medication orders.

(9) Beyond-use date--**The date, or hour and the date, after which a compounded sterile preparation shall not be used, stored, or transported. The date is determined from the date and time the preparation is compounded.** [~~The date or time after which the compounded sterile preparation shall not be stored or transported or begin to be administered to a patient. The beyond-use date is determined from the date or time the preparation is compounded.~~]

(10) Biological **safety cabinet**[~~Safety Cabinet~~], Class II--A ventilated cabinet for personnel, product or preparation, and environmental protection having an open front with inward airflow for personnel protection, downward HEPA filtered laminar airflow for product protection, and HEPA filtered exhausted air for environmental protection.

(11) Buffer **room**[~~Area~~]--**An ISO Class 7 or cleaner or, if a Class B pharmacy, an ISO Class 8 or cleaner, room with fixed walls and doors where primary engineering controls that generate and maintain an ISO Class 5 environment are physically located. The buffer room may only be accessed through the anteroom or another buffer room.** [~~An ISO Class 7 or, if a Class B pharmacy, ISO Class 8 or better, area where the primary engineering control area is physically located. Activities that occur in this area include the preparation and staging of components and supplies used when compounding sterile preparations.~~]

(12) Clean room--A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class.

(13) Cleaning agent--An agent, usually containing a surfactant, used for the removal of substances (e.g., dirt, debris, microbes, residual drugs or chemicals) from surfaces.

(14) Cleanroom suite--A classified area that consists of both an anteroom and buffer room.

(15)[~~(13)~~] Component--Any ingredient **used in the compounding of a preparation, including any active ingredient, added substance, or conventionally manufactured product**[~~intended for use in the compounding of a drug preparation, including those that may not appear in such preparation~~].

(16)[~~(14)~~] Compounding--The preparation, mixing, assembling, packaging, or labeling of a drug or device:

(A) as the result of a practitioner's prescription drug or medication order based on the practitioner-patient-pharmacist relationship in the course of professional practice;

(B) for administration to a patient by a practitioner as the result of a practitioner's initiative based on the practitioner-patient-pharmacist relationship in the course of professional practice;

(C) in anticipation of prescription drug or medication orders based on routine, regularly observed prescribing patterns; or

(D) for or as an incident to research, teaching, or chemical analysis and not for sale or dispensing, except as allowed under §562.154 or Chapter 563 of the Occupations Code.

(17)[~~(15)~~] Compounding **aseptic isolator**[~~Aseptic Isolator~~]--A form of barrier isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment shall not occur unless it has first passed through a microbial retentive filter (HEPA minimum).

(18)[~~(16)~~] Compounding **aseptic containment isolator**[~~Aseptic Containment Isolator~~]--A compounding aseptic isolator designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where volatile hazardous drugs are prepared, the exhaust air from the isolator should be appropriately removed by properly designed building ventilation.

(19)[~~(17)~~] Compounding **personnel**[~~Personnel~~]--A pharmacist, pharmacy technician, or pharmacy technician trainee who performs the actual compounding; a pharmacist who supervises pharmacy technicians or pharmacy technician trainees compounding sterile preparations, and a pharmacist who performs an intermediate or final verification of a compounded sterile preparation.

(20)[~~(18)~~] Critical **area**[~~Area~~]--An ISO Class 5 environment.

(21)[~~(19)~~] Critical **sites**[~~Sites~~]--A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, beakers) or openings (e.g., opened ampules, needle hubs) exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination. Risk of microbial particulate contamination of the critical site increases with the size of the openings and exposure time.

(22) Designated person(s)--One or more individuals assigned to be responsible and accountable for the performance and operation of the pharmacy and personnel as related to the preparation of compounded sterile preparations.

(23)[~~(20)~~] Device--An instrument, apparatus, implement, machine, contrivance, implant, in-vitro reagent, or other similar or related article, including any component part or accessory, that is required under federal or state law to be ordered or prescribed by a practitioner.

(24)[~~(21)~~] Direct **compounding area**[~~Compounding Area~~]--A critical area within the ISO Class 5 primary engineering control where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.

(25)[~~(22)~~] Disinfectant--An agent that frees from infection, usually a chemical agent but sometimes a physical one, and that destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial and fungal spores. It refers to substances applied to inanimate objects.

(26)[~~(23)~~] First **air**[~~Air~~]--The air exiting the HEPA filter in a unidirectional air stream that is essentially particle free.

(27)[~~(24)~~] Hazardous **drugs**[~~Drugs~~]--Drugs that, studies in animals or humans indicate exposure to the drugs, have a potential for causing cancer, development or reproductive toxicity, or harm to organs. For the purposes of this chapter, radiopharmaceuticals are not considered hazardous drugs.

(28)[~~(25)~~] Hot water--The temperature of water from the pharmacy's sink maintained at a minimum of 105 degrees F (41 degrees C).

(29)[~~(26)~~] HVAC--Heating, ventilation, and air conditioning.

(30)[~~(27)~~] Immediate use--A sterile preparation that is not prepared according to USP 797 standards (i.e., outside the pharmacy and most likely not by pharmacy personnel) which shall be stored for no longer than **four hours following the start of preparing**[~~one hour after completion of~~] the preparation.

(31)[~~(28)~~] IPA--Isopropyl alcohol (2-propanol).

(32)[~~(29)~~] Labeling--All labels and other written, printed, or graphic matter on an immediate container of an article or preparation or on, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling on the immediate container.

(33) Master formulation record--A detailed record of procedures that describes how the compounded sterile preparation is to be prepared.

(34)[~~(30)~~] **Media-fill test**[~~Media-Fill Test~~]--A test used to qualify aseptic technique of compounding personnel or processes and to ensure that the processes used are able to produce sterile preparation without microbial contamination. During this test, a microbiological growth medium such as Soybean-Casein Digest Medium is substituted for the actual drug preparation to simulate admixture compounding. The issues to consider in the development of a media-fill test are the following: media-fill procedures, media selection, fill volume, incubation, time and temperature, inspection of filled units, documentation, interpretation of results, and possible corrective actions required.

(35)[~~(31)~~] **Multiple-dose container**[~~Multiple-Dose Container~~]--A multiple-unit container for articles or preparations intended for **parenteral**[~~potential~~] administration only and usually contains antimicrobial preservatives. The beyond-use date for an opened or entered (e.g.,

needle-punctured) multiple-dose container with antimicrobial preservatives is 28 days, unless otherwise specified by the manufacturer.

(36)[~~(32)~~] Negative **pressure room**[~~Pressure Room~~]--A room that is at a lower pressure compared to adjacent spaces and, therefore, the net flow of air is into the room.

(37)[~~(33)~~] Office use--The administration of a compounded drug to a patient by a practitioner in the practitioner's office or by the practitioner in a health care facility or treatment setting, including a hospital, ambulatory surgical center, or pharmacy in accordance with Chapter 562 of the Act, or for administration or provision by a veterinarian in accordance with §563.054 of the Act.

(38)[~~(34)~~] Pharmacy **bulk package**[~~Bulk Package~~]--A container of a sterile preparation for potential use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes. The closure shall be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set, which allows measured dispensing of the contents. The pharmacy bulk package is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area).

(39)[~~(35)~~] Prepackaging--The act of repackaging and relabeling quantities of drug products from a manufacturer's original container into unit dose packaging or a **multiple-dose**[~~multiple dose~~] container for distribution within a **pharmacy**[~~facility~~] licensed as a Class C pharmacy or to other pharmacies under common ownership for distribution within those **pharmacies**[~~facilities~~]. The term as defined does not prohibit the prepackaging of drug products for use within other pharmacy classes.

(40)[~~(36)~~] Preparation or **compounded sterile preparation**[~~Compounded Sterile Preparation~~]--A sterile admixture compounded in a licensed pharmacy or other healthcare-related facility pursuant to the order of a licensed prescriber. The components of the preparation may or may not be sterile products.

(41)[~~(37)~~] Primary **engineering control**[~~Engineering Control~~]--A device or room that provides an ISO Class 5 environment for the exposure of critical sites when compounding sterile preparations. Such devices include, but may not be limited to, laminar airflow workbenches, biological safety cabinets, compounding aseptic isolators, and compounding aseptic containment isolators.

(42)[~~(38)~~] Product--A commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the U.S. Food and Drug Administration (FDA). Products are accompanied by full prescribing information, which is commonly known as the FDA-approved manufacturer's labeling or product package insert.

(43)[~~(39)~~] Positive **control**[~~Control~~]--A quality assurance sample prepared to test positive for microbial growth.

(44)[~~(40)~~] Quality assurance--The set of activities used to ensure that the process used in the preparation of sterile drug preparations lead to preparations that meet predetermined standards of quality.

(45)[~~(41)~~] Quality control--The set of testing activities used to determine that the ingredients, components (e.g., containers), and final compounded sterile preparations prepared meet predetermined requirements with respect to identity, purity, non-pyrogenicity, and sterility.

(46)[~~(42)~~] Reasonable quantity--An amount of a compounded drug that:

(A) does not exceed the amount a practitioner anticipates may be used in the practitioner's office or facility before the **beyond-use**[~~beyond use~~] date of the drug;

(B) is reasonable considering the intended use of the compounded drug and the nature of the practitioner's practice; and

(C) for any practitioner and all practitioners as a whole, is not greater than an amount the pharmacy is capable of compounding in compliance with pharmaceutical standards for identity, strength, quality, and purity of the compounded drug that are consistent with United States Pharmacopoeia guidelines and accreditation practices.

(47) Restricted-access barrier system--An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air that allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations.

(48)[~~(43)~~] Segregated **compounding area**[~~Compounding Area~~]--**A designated space, area, or room that is not required to be classified and is defined with a visible perimeter. The segregated compounding area shall contain a PEC and is suitable for preparation of Category 1 compounded sterile preparations only.** [~~A designated space, either a demarcated area or room, that is restricted to preparing low-risk level compounded sterile preparations with 12-hour or less beyond-use date. Such area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of compounded sterile preparations and shall be void of activities and materials that are extraneous to sterile compounding.~~]

(49)[~~(44)~~] Single-dose container--A single-unit container for articles or preparations intended for parenteral administration only. It is intended for a single use. A single-dose container is labeled as such. Examples of single-dose containers include pre-filled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

(50)[~~(45)~~] SOPs--Standard operating procedures.

(51)[~~(46)~~] Sterilizing **grade membranes**[~~Grade Membranes~~]--Membranes that are documented to retain 100% of a culture of **10^7**[~~107~~] microorganisms of a strain of Brevundimonas (Pseudomonas) diminuta per square centimeter of membrane surface under a pressure of not less than 30 psi (2.0 bar). Such filter membranes are nominally at **0.22-micron or 0.2 micron**[~~0.22-micrometer or 0.2-micrometer~~] nominal pore size, depending on the manufacturer's practice.

(52)[~~(47)~~] Sterilization by **filtration**[~~Filtration~~]--Passage of a fluid or solution through a sterilizing grade membrane to produce a sterile **filtrate**[~~effluent~~].

(53)[~~(48)~~] Terminal **sterilization**[~~Sterilization~~]--The application of a lethal process, e.g., steam under pressure or autoclaving, to sealed final preparation containers for the purpose of achieving a predetermined sterility assurance level of usually less than **10^-6**[~~10-6~~] or a probability of less than one in one million of a non-sterile unit.

(54)[~~(49)~~] Unidirectional **airflow**[~~Flow~~]--An airflow moving in a single direction in a robust and uniform manner and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

(55)[~~(50)~~] USP/NF--The current edition of the United States Pharmacopeia/National Formulary.

(c) Personnel.

(1) Pharmacist-in-charge.

(A) General. The pharmacy shall have a pharmacist-in-charge in compliance with the specific license classification of the pharmacy.

(B) Responsibilities. In addition to the responsibilities for the specific class of pharmacy, the pharmacist-in-charge shall have the responsibility for, at a minimum, the following concerning the compounding of sterile preparations:

(i) developing a system to ensure that all pharmacy personnel responsible for compounding and/or supervising the compounding of sterile preparations within the pharmacy receive appropriate education and training and competency evaluation;

(ii) determining that all personnel involved in compounding sterile preparations obtain continuing education appropriate for the type of compounding done by the personnel;

(iii) supervising a system to ensure appropriate procurement of drugs and devices and storage of all pharmaceutical materials including pharmaceuticals, components used in the compounding of sterile preparations, and drug delivery devices;

(iv) ensuring that the equipment used in compounding is properly maintained;

(v) developing a system for the disposal and distribution of drugs from the pharmacy;

(vi) developing a system for bulk compounding or batch preparation of drugs;

(vii) developing a system for the compounding, sterility assurance, quality assurance, and quality control of sterile preparations; and

(viii) if applicable, ensuring that the pharmacy has a system to dispose of hazardous waste in a manner so as not to endanger the public health.

(2) Pharmacists.

(A) General.

(i) A pharmacist is responsible for ensuring that compounded sterile preparations are accurately identified, measured, diluted, and mixed and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed.

(ii) A pharmacist shall inspect and approve all components, drug preparation containers, closures, labeling, and any other materials involved in the compounding process.

(iii) A pharmacist shall review all compounding records for accuracy and conduct periodic in-process checks as defined in the pharmacy's policy and procedures.

(iv) A pharmacist shall review all compounding records for accuracy and conduct a final check.

(v) A pharmacist is responsible for ensuring the proper maintenance, cleanliness, and use of all equipment used in the compounding process.

(vi) A pharmacist shall be accessible at all times, 24 hours a day, to respond to patients' and other health professionals' questions and needs.

(B) Initial training and continuing education.

(i) All pharmacists who compound sterile preparations or supervise pharmacy technicians and pharmacy technician trainees compounding sterile preparations shall comply with the following:

(I) complete through a single course, a minimum of 20 hours of instruction and experience in the areas listed in paragraph (4)(D) of this subsection. Such training shall be obtained through completion of a recognized course in an accredited college of pharmacy or a course sponsored by an ACPE accredited provider;

(II) complete a structured on-the-job didactic and experiential training program at this pharmacy which provides sufficient hours of instruction and experience in the **pharmacy's**[~~facility's~~] sterile compounding processes and procedures. Such training may not be transferred to another pharmacy unless the pharmacies are under common ownership and control and use a common training program; and

(III) possess knowledge about:

(-a-) aseptic processing;

(-b-) quality control and quality assurance as related to environmental, component, and finished preparation release checks and tests;

(-c-) chemical, pharmaceutical, and clinical properties of drugs;

(-d-) container, equipment, and closure system selection; and

(-e-) sterilization techniques.

(ii) The required experiential portion of the training programs specified in this subparagraph **shall**[~~must~~] be supervised by an individual who is actively engaged in performing

sterile compounding and is qualified and has completed training as specified in this paragraph or paragraph (3) of this subsection.

(iii) In order to renew a license to practice pharmacy, during the previous licensure period, a pharmacist engaged in sterile compounding shall complete a minimum of:

(I) two hours of ACPE-accredited continuing education relating to one or more of the areas listed in paragraph (4)(D) of this subsection if the pharmacist is engaged in compounding **Category 1 or Category 2 compounded**[~~low and medium risk~~] sterile preparations; or

(II) four hours of ACPE-accredited continuing education relating to one or more of the areas listed in paragraph (4)(D) of this subsection if the pharmacist is engaged in compounding **Category 2 prepared from any non-sterile starting component or Category 3 compounded**[~~high risk~~] sterile preparations.

(3) Pharmacy technicians and pharmacy technician trainees.

(A) General. All pharmacy technicians and pharmacy technician trainees shall meet the training requirements specified in §297.6 of this title (relating to Pharmacy Technician and Pharmacy Technician Trainee Training).

(B) Initial training and continuing education.

(i) Pharmacy technicians and pharmacy technician trainees may compound sterile preparations provided the pharmacy technicians and/or pharmacy technician trainees are supervised by a pharmacist as specified in paragraph (2) of this subsection.

(ii) All pharmacy technicians and pharmacy technician trainees who compound sterile preparations for administration to patients shall:

(I) have initial training obtained either through completion of:

(-a-) a single course, a minimum of 40 hours of instruction and experience in the areas listed in paragraph (4)(D) of this subsection. Such training shall be obtained through completion of a course sponsored by an ACPE accredited provider which provides 40 hours of instruction and experience; or

(-b-) a training program which is accredited by the American Society of Health-System Pharmacists.

(II) and

(-a-) complete a structured on-the-job didactic and experiential training program at this pharmacy which provides sufficient hours of instruction and experience in the **pharmacy's**[~~facility's~~] sterile compounding processes and procedures. Such training may not be transferred to another pharmacy unless the pharmacies are under common ownership and control and use a common training program; and

(-b-) possess knowledge about:

(-1-) aseptic processing;

(-2-) quality control and quality assurance as related to environmental, component, and finished preparation release checks and tests;

(-3-) chemical, pharmaceutical, and clinical properties of drugs;

(-4-) container, equipment, and closure system selection; and

(-5-) sterilization techniques.

(iii) Individuals enrolled in training programs accredited by the American Society of Health-System Pharmacists may compound sterile preparations in a licensed pharmacy provided the:

(I) compounding occurs only during times the individual is assigned to a pharmacy as a part of the experiential component of the American Society of Health-System Pharmacists training program;

(II) individual is under the direct supervision of and responsible to a pharmacist who has completed training as specified in paragraph (2) of this subsection;

(III) supervising pharmacist conducts periodic in-process checks as defined in the pharmacy's policy and procedures; and

(IV) supervising pharmacist conducts a final check.

(iv) The required experiential portion of the training programs specified in this subparagraph **shall**[~~must~~] be supervised by an individual who is actively engaged in performing sterile compounding, is qualified and has completed training as specified in paragraph (2) of this subsection or this paragraph.

(v) In order to renew a registration as a pharmacy technician, during the previous registration period, a pharmacy technician engaged in sterile compounding shall complete a minimum of:

(I) two hours of ACPE accredited continuing education relating to one or more of the areas listed in paragraph (4)(D) of this subsection if the pharmacy technician is engaged in compounding **Category 1 or Category 2 compounded**[~~low and medium risk~~] sterile preparations; or

(II) four hours of ACPE accredited continuing education relating to one or more of the areas listed in paragraph (4)(D) of this subsection if the pharmacy technician is engaged in compounding **Category 2 prepared from any non-sterile starting component or Category 3 compounded**[~~high risk~~] sterile preparations.

(4) Evaluation and testing requirements.

(A) **All persons who perform or oversee compounding or support activities shall be trained in the pharmacy's SOPs.** All pharmacy personnel preparing sterile preparations shall be trained conscientiously and skillfully by expert personnel through multimedia instructional sources and professional publications in the theoretical principles and practical skills of aseptic manipulations, garbing procedures, aseptic work practices, achieving and maintaining ISO Class 5 environmental conditions, and cleaning and disinfection procedures before beginning to prepare compounded sterile preparations.

(B) All pharmacy personnel preparing sterile preparations shall perform didactic review and pass written [~~and media-fill~~] testing of aseptic manipulative skills initially **and every 12 months.**[~~followed by:~~]

[~~(i) every 12 months for low- and medium-risk level compounding; and~~]

[~~(ii) every six months for high-risk level compounding.~~]

(C) Pharmacy personnel who fail written tests or whose media-fill tests result in gross microbial colonization shall:

(i) be immediately re-instructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies; and

(ii) not be allowed to compound sterile preparations for patient use until passing results are achieved.

(D) The didactic and experiential training shall include instruction, experience, and demonstrated proficiency in the following areas:

(i) aseptic technique;

(ii) critical area contamination factors;

(iii) environmental monitoring;

(iv) structure and engineering controls related to facilities;

(v) equipment and supplies;

(vi) sterile preparation calculations and terminology;

(vii) sterile preparation compounding documentation;

(viii) quality assurance procedures;

(ix) aseptic preparation procedures including proper gowning and gloving technique;

(x) handling of hazardous drugs, if applicable;

(xi) cleaning procedures; and

(xii) general conduct in the clean room.

(E) The aseptic technique of **all compounding personnel and personnel who have direct oversight of compounding personnel but do not compound**[~~each person compounding or responsible for the direct supervision of personnel compounding sterile preparations~~] shall be observed and evaluated by expert personnel as satisfactory through written and practical tests, and **media-fill**[~~challenge~~] testing, and such evaluation documented. Compounding personnel shall not evaluate their own aseptic technique or results of their own media-fill[~~challenge~~] testing. **The pharmacy's SOPs shall define the aseptic technique evaluation for personnel who do not compound nor have direct oversight of compounding personnel such as personnel who restock or clean and disinfect the sterile compounding area, personnel who perform in-process checks or final verification of compounded sterile preparations, and others (e.g., maintenance personnel, certifiers, contractors, inspectors, surveyors).**

(F) Media-fill tests **shall**[~~must~~] be conducted at each pharmacy where an individual compounds **Category 1 or Category 2**[~~low or medium risk~~] sterile preparations. If pharmacies are under common ownership and control, the media-fill testing may be conducted at only one of the pharmacies provided each of the pharmacies are operated under equivalent policies and procedures and the testing is conducted under the most challenging or stressful conditions. In addition, each pharmacy **shall**[~~must~~] maintain documentation of the media-fill test. No preparation intended for patient use shall be compounded by an individual until the on-site media-fill tests indicate that the individual can competently perform aseptic procedures, except that a pharmacist may temporarily compound sterile preparations and supervise pharmacy technicians compounding sterile preparations without media-fill tests provided the pharmacist completes the on-site media-fill tests within seven days of commencing work at the pharmacy.

(G) Media-fill tests **shall**[~~must~~] be conducted at each pharmacy where an individual compounds **Category 2 prepared from any non-sterile starting component or Category 3**[~~high risk~~] sterile preparations. No preparation intended for patient use shall be compounded by an individual until the on-site media-fill tests indicate that the individual can competently perform aseptic procedures, except that a pharmacist may temporarily compound sterile preparations and supervise pharmacy technicians compounding sterile preparations without media-fill tests provided the pharmacist completes the on-site media-fill tests within seven days of commencing work at the pharmacy.

(H) For media-fill testing of compounds using only sterile starting components, the components shall be manipulated in a manner that simulates sterile-to-sterile compounding activities. The sterile soybean-casein digest media shall be transferred into the same types of container closure systems commonly used at the pharmacy.

[~~(H) Media-fill testing procedures for assessing the preparation of specific types of sterile preparations shall be representative of the most challenging or stressful conditions encountered by the pharmacy personnel being evaluated and, if applicable, for sterilizing high-risk level compounded sterile preparations.~~]

(I) For media-fill testing of compounds using any non-sterile starting components, a commercially available non-sterile soybean-casein digest powder shall be dissolved in non-bacteriostatic water to make a 3.0% non-sterile solution. The components shall be manipulated in a manner that simulates non-sterile-to-sterile compounding activities. At

least one container shall be prepared as the positive control to demonstrate growth promotion, as indicated by visible turbidity upon incubation.

[~~(I) Media-fill challenge tests simulating high-risk level compounding shall be used to verify the capability of the compounding environment and process to produce a sterile preparation.~~]

(J) Final containers shall be incubated in an incubator at 20 to 25 degrees Celsius and 30 to 35 degrees Celsius for a minimum of 7 days at each temperature band to detect a broad spectrum of microorganisms. The order of the incubation temperatures shall be described in the pharmacy's SOPs. Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container closure unit(s) on or before the end of the incubation period.

[~~(J) Commercially available sterile fluid culture media for low and medium risk level compounding or non-sterile fluid culture media for high risk level compounding shall be able to promote exponential colonization of bacteria that are most likely to be transmitted to compounding sterile preparations from the compounding personnel and environment. Media-filled vials are generally incubated at 20 to 25 degrees Celsius or at 30 to 35 degrees Celsius for a minimum of 14 days. If two temperatures are used for incubation of media-filled samples, then these filled containers should be incubated for at least 7 days at each temperature. Failure is indicated by visible turbidity in the medium on or before 14 days.~~]

(K) The pharmacist-in-charge shall ensure continuing competency of pharmacy personnel through in-service education, training, and media-fill tests to supplement initial training. Personnel competency shall be evaluated:

(i) during orientation and training prior to the regular performance of those tasks;

(ii) whenever the quality assurance program yields an unacceptable result;

(iii) whenever unacceptable techniques are observed; and

(iv) at least **every 12 months, with the exception of media-fill testing which shall be completed every six months for compounding personnel**[~~on an annual basis for low- and medium-risk level compounding, and every six months for high-risk level compounding~~].

(L) The pharmacist-in-charge shall ensure that proper hand hygiene and garbing practices of **all** compounding personnel **and personnel who have direct oversight of compounding personnel but do not compound** are evaluated prior to compounding, supervising, or verifying sterile preparations intended for patient use and whenever an aseptic **media-fill**[~~media fill~~] is performed.

(i) **Gloved fingertip sampling shall be performed for all**[~~Sampling of~~] compounding personnel **and personnel who have direct oversight of compounding personnel but do not compound**[~~glove fingertips shall be performed for all risk level compounding~~]. If pharmacies are under common ownership and control, the gloved fingertip **and thumb** sampling may be conducted at only one of the pharmacies provided each of the pharmacies are operated under equivalent policies and procedures and the testing is conducted under the most challenging or stressful conditions. In addition, each pharmacy **shall**[~~must~~] maintain documentation of the gloved fingertip **and thumb** sampling[~~of all compounding personnel~~].

(ii) All compounding personnel **and personnel who have direct oversight of compounding personnel but do not compound** shall demonstrate competency in proper hand hygiene and garbing procedures and in aseptic work practices (e.g., disinfection of component surfaces, routine disinfection of gloved hands).

(iii) Sterile **sampling media devices**[~~contact agar plates~~] shall be used to sample the gloved fingertips of compounding personnel **and personnel who have direct oversight of compounding personnel but do not compound** after garbing in order to assess garbing competency and after completing the media-fill preparation (without applying sterile 70% IPA).

(iv) The visual observation shall be documented and maintained to provide a permanent record and long-term assessment of personnel competency.

(v) All compounding personnel **and personnel who have direct oversight of compounding personnel but do not compound** shall successfully complete an initial competency evaluation and gloved **fingertip and thumb**[~~fingertip/thumb~~] sampling procedure no less than three times before initially being allowed to compound sterile preparations for patient use. Immediately after the [~~compounding~~] personnel completes the hand hygiene and garbing procedure (i.e., after donning of sterile gloves and before any disinfecting with sterile 70% IPA), the evaluator will collect a gloved fingertip and thumb sample from both hands of the compounding personnel onto contact plates or swabs by having the individual lightly touching each fingertip onto the testing medium. **Samples shall be incubated in an incubator. The media device shall be incubated at 30 to 35 degrees Celsius for no less than 48 hours and then at 20 to 25 degrees Celsius for no less than five additional days. Alternatively, to shorten the overall incubation period, two sampling media devices may be incubated concurrently in separate incubators with one media device incubated at 30 to 35 degrees Celsius for no less than 48 hours and the other media device incubated at 20 to 25 degrees Celsius for no less than five days. Media devices shall be handled and stored so as to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert containers)**[~~The contact plates or swabs will be incubated for the appropriate incubation period and at the appropriate temperature~~]. **Action levels for gloved fingertip and thumb sampling are based on the total cfu count from both hands.** Results of the initial gloved fingertip **and thumb sampling** evaluations **after garbing** shall indicate **not greater than** zero colony-forming units **(0 cfu)**[(~~0 CFU~~)] growth on the contact plates or swabs, or the test shall be considered a failure. **Results of the initial gloved fingertip evaluations after media-fill testing shall indicate not greater than three colony-forming units (3 cfus) growth on the contact plates or swabs, or the test shall be considered a failure.** In the event of a failed gloved fingertip **and thumb** test, the evaluation shall be repeated until the individual can successfully don sterile gloves and pass the gloved fingertip **and thumb sampling** evaluation, defined as zero **cfus**[~~CFUs~~] growth. **Surface sampling of the direct compounding area shall be performed.** No preparation intended for patient use shall be compounded by an individual until the results of the initial gloved fingertip **and thumb and surface sampling evaluations**[~~evaluation~~] indicate that the individual can competently perform aseptic procedures except that a pharmacist may temporarily physically supervise pharmacy technicians compounding sterile preparations before the results of the evaluation have been received for no more than three days from the date of the test.

(vi) Re-evaluation of all compounding personnel shall occur at least **every six months**[~~annually for compounding personnel who compound low and medium risk level preparations and every~~

~~six months for compounding personnel who compound high risk level preparations~~]. **Re-evaluation of personnel who have direct oversight of compounding personnel but do not compound shall occur at least every 12 months.** Results of gloved fingertip **and thumb** tests conducted immediately after compounding personnel complete a compounding procedure shall indicate no more than 3 **cfus**[~~CFUs~~] growth, or the test shall be considered a failure, in which case, the evaluation shall be repeated until an acceptable test can be achieved (i.e., the results indicated no more than 3 **cfus**[~~CFUs~~] growth).

(vii) Personnel who have direct oversight of compounding personnel but do not compound shall complete a garbing competency evaluation every 12 months. The pharmacy's SOPs shall define the garbing competency evaluation for personnel who do not compound nor have direct oversight of compounding personnel such as personnel who restock or clean and disinfect the sterile compounding area, personnel who perform in-process checks or final verification of compounded sterile preparations, and others (e.g., maintenance personnel, certifiers, contractors, inspectors, surveyors).

(M) The pharmacist-in-charge shall ensure surface sampling shall be conducted in all ISO classified areas on a periodic basis. Sampling shall be accomplished using contact plates or swabs at the conclusion of compounding. The sample area shall be gently touched with the agar surface by rolling the plate across the surface to be sampled.

(i) Each classified area, including each room and the interior of each ISO Class 5 primary engineering control (PEC) and pass-through chambers connecting to classified areas (e.g., equipment contained within the PEC, staging or work area(s) near the PEC, frequently touched areas), shall be sampled for microbial contamination using a risk-based approach.

(ii) For pharmacies compounding Category 1 or Category 2 compounded sterile preparations, surface sampling of all classified areas and pass-through chambers connecting to classified areas shall be conducted at least monthly. For pharmacies compounding any Category 3 compounded sterile preparations, surface sampling of all classified areas and pass-through chambers connecting to classified areas shall be completed prior to assigning a beyond-use-date longer than the limits established for Category 2 compounded sterile preparations and at least weekly on a regularly scheduled basis regardless of the frequency of compounding Category 3 compounded sterile preparations.

(iii) (iii) The following action levels for surface sampling apply:

(I) for ISO Class 5, greater than 3 cfus per media device;

(II) for ISO Class 7, greater than 5 cfus per media device; and

(III) for ISO Class 8, greater than 50 cfus per media device.

(iv) If levels measured during surface sampling exceed the levels in clause (iii) of this subparagraph for the ISO classification levels of the area sampled, the cause shall be investigated and corrective action shall be taken. Data collected in response to corrective actions shall be reviewed to confirm that the actions taken have been effective. The corrective action plan shall be dependent on the cfu count and the

microorganism recovered. The corrective action plan shall be documented. If levels measured during surface sampling exceed the levels in clause (iii) of this subparagraph, an attempt shall be made to identify any microorganism recovered to the genus level with the assistance of a competent microbiologist.

(N) Personnel who only perform restocking or cleaning and disinfecting duties outside of the primary engineering control shall complete ongoing training as required by the pharmacy's SOPs.

(5) Documentation of **training**[~~Training~~]. The pharmacy shall maintain a record of the training and continuing education on each person who compounds sterile preparations. The record shall contain, at a minimum, a written record of initial and in-service training, education, and the results of written and practical testing and media-fill testing of pharmacy personnel. The record shall be maintained and available for inspection by the board and contain the following information:

(A) name of the person receiving the training or completing the testing or media-fill tests;

(B) date(s) of the training, testing, or media-fill [~~challenge~~] testing;

(C) general description of the topics covered in the training or testing or of the process validated;

(D) name of the person supervising the training, testing, or media-fill [~~challenge~~] testing; and

(E) signature or initials of the person receiving the training or completing the testing or media-fill [~~challenge~~] testing and the pharmacist-in-charge or other pharmacist employed by the pharmacy and designated by the pharmacist-in-charge as responsible for training, testing, or media-fill [~~challenge~~] testing of personnel.

(d) Operational **standards**[~~Standards~~].

(1) General **requirements**[~~Requirements~~].

(A) Sterile preparations may be compounded:

(i) upon presentation of a practitioner's prescription drug or medication order based on a valid pharmacist/patient/prescriber relationship;

(ii) in anticipation of future prescription drug or medication orders based on routine, regularly observed prescribing patterns; or

(iii) in reasonable quantities for office use by a practitioner and for use by a veterinarian.

(B) Sterile compounding in anticipation of future prescription drug or medication orders **shall**[~~must~~] be based upon a history of receiving valid prescriptions issued within an established pharmacist/patient/prescriber relationship, provided that in the pharmacist's professional judgment the quantity prepared is stable for the anticipated shelf time. **The**

maximum batch size for all preparations requiring sterility testing shall be limited to 750 final yield units.

(i) The pharmacist's professional judgment shall be based on the criteria used to determine a beyond-use date outlined in paragraph **(8)(J)**[~~(6)(G)~~] of this subsection.

(ii) Documentation of the criteria used to determine the stability for the anticipated shelf time **shall**[~~must~~] be maintained and be available for inspection.

(iii) Any preparation compounded in anticipation of future prescription drug or medication orders shall be labeled. Such label shall contain:

(I) name and strength of the compounded preparation or list of the active ingredients and strengths;

(II) facility's lot number;

(III) beyond-use date as determined by the pharmacist using appropriate documented criteria as outlined in paragraph **(8)(J)**[~~(6)(G)~~] of this subsection;

(IV) quantity or amount in the container;

(V) appropriate ancillary instructions, such as storage instructions or cautionary statements, including hazardous drug warning labels where appropriate; and

(VI) device-specific instructions, where appropriate.

(C) Commercially available products may be compounded for dispensing to individual patients or for office use provided the following conditions are met:

(i) the commercial product is not reasonably available from normal distribution channels in a timely manner to meet individual patient's needs;

(ii) the pharmacy maintains documentation that the product is not reasonably available due to a drug shortage or unavailability from the manufacturer; and

(iii) the prescribing practitioner has requested that the drug be compounded as described in subparagraph (D) of this paragraph.

(D) A pharmacy may not compound preparations that are essentially copies of commercially available products (e.g., the preparation is dispensed in a strength that is only slightly different from a commercially available product) unless the prescribing practitioner specifically orders the strength or dosage form and specifies why the individual patient needs the particular strength or dosage form of the preparation or why the preparation for office use is needed in the particular strength or dosage form of the preparation. The prescribing practitioner shall provide documentation of a patient specific medical need and the preparation produces a clinically significant therapeutic response (e.g., the physician requests an alternate preparation due to hypersensitivity to excipients or preservative in the FDA-approved product, or the physician requests an effective alternate dosage form) or if the drug product is not commercially available.

The unavailability of such drug product **shall**[~~must~~] be documented prior to compounding. The methodology for documenting unavailability includes maintaining a copy of the wholesaler's notification showing back-ordered, discontinued, or out-of-stock items. This documentation **shall**[~~must~~] be available in hard-copy or electronic format for inspection by the board.

(E) A pharmacy may enter into an agreement to compound and dispense prescription drug or medication orders for another pharmacy provided the pharmacy complies with the provisions of §291.125 of this title (relating to Centralized Prescription Dispensing).

(F) Compounding pharmacies/pharmacists may advertise and promote the fact that they provide sterile prescription compounding services, which may include specific drug preparations and classes of drugs.

(G) A pharmacy may not compound veterinary preparations for use in food producing animals except in accordance with federal guidelines.

(H) Compounded sterile preparations, including hazardous drugs and radiopharmaceuticals, shall be prepared only under conditions that protect the pharmacy personnel in the preparation and storage areas.

(2) Compounded sterile preparation categories. Category 1, Category 2, and Category 3 are primarily based on the state of environmental control under which they are compounded, the probability for microbial growth during the time they will be stored, and the time period within which they must be used.

(A) A Category 1 compounded sterile preparation is a compounded sterile preparation that is assigned a beyond-use date in accordance with paragraph (8)(J)(ii)(I) of this subsection and all applicable requirements of this section for Category 1 compounded sterile preparations.

(B) A Category 2 compounded sterile preparation is a compounded sterile preparation that is assigned a beyond-use date in accordance with paragraph (8)(J)(ii)(II) of this subsection and all applicable requirements of this section for Category 2 compounded sterile preparations.

(C) A Category 3 compounded sterile preparation is a compounded sterile preparation that is assigned a beyond-use date in accordance with paragraph (8)(J)(ii)(III) of this subsection and all applicable requirements of this section for Category 3 compounded sterile preparations.

[~~(2) Microbial Contamination Risk Levels. Risk Levels for sterile compounded preparations shall be as outlined in Chapter 797, Pharmacy Compounding--Sterile Preparations of the USP/NF and as listed in this paragraph.~~]

[~~(A) Low-risk level compounded sterile preparations.~~]

[~~(i) Low-Risk conditions. Low-risk level compounded sterile preparations are those compounded under all of the following conditions:~~]

[~~(I) The compounded sterile preparations are compounded with aseptic manipulations entirely within ISO Class 5 or better air quality using only sterile ingredients, products, components, and devices;~~]

[~~(II) The compounding involves only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package (e.g., bag, vial) of sterile product or administration container/device to prepare the compounded sterile preparation;~~]

[~~(III) Manipulations are limited to aseptically opening ampules, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing;~~]

[~~(IV) For a low-risk level preparation, in the absence of passing a sterility test the storage periods cannot exceed the following time periods: before administration, the compounded sterile preparation is stored properly and are exposed for not more than 48 hours at controlled room temperature, for not more than 14 days if stored at a cold temperature, and for 45 days if stored in a frozen state between minus 25 degrees Celsius and minus 10 degrees Celsius. For delayed activation device systems, the storage period begins when the device is activated.~~]

[~~(ii) Examples of Low-Risk Level Compounding. Examples of low-risk level compounding include the following:~~]

[~~(I) Single volume transfers of sterile dosage forms from ampules, bottles, bags, and vials using sterile syringes with sterile needles, other administration devices, and other sterile containers. The solution content of ampules shall be passed through a sterile filter to remove any particles;~~]

[~~(II) Simple aseptic measuring and transferring with not more than three packages of manufactured sterile products, including an infusion or diluent solution to compound drug admixtures and nutritional solutions.~~]

[~~(B) Low-Risk Level compounded sterile preparations with 12-hour or less beyond-use date. Low-risk level compounded sterile preparations are those compounded pursuant to a physician's order for a specific patient under all of the following conditions:~~]

[~~(i) The compounded sterile preparations are compounded in compounding aseptic isolator or compounding aseptic containment isolator that does not meet the requirements described in paragraph (7)(C) or (D) of this subsection (relating to Primary Engineering Control Device) or the compounded sterile preparations are compounded in laminar airflow workbench or a biological safety cabinet that cannot be located within the buffer area;~~]

[~~(ii) The primary engineering control device shall be certified and maintain ISO Class 5 for exposure of critical sites and shall be located in a segregated compounding area restricted to sterile compounding activities that minimizes the risk of contamination of the compounded sterile preparation;~~]

[~~(iii) The segregated compounding area shall not be in a location that has unsealed windows or doors that connect to the outdoors or high traffic flow, or that is adjacent to construction sites, warehouses, or food preparation.~~]

[~~(iv) For a low-risk level preparation compounded as described in clauses (i) - (iii) of this subparagraph, administration of such compounded sterile preparations must commence within 12 hours of preparation or as recommended in the manufacturers' package insert, whichever is less. However, the administration of sterile radiopharmaceuticals, with documented testing of chemical stability, may be administered beyond 12 hours of preparation.~~]

[~~(C) Medium-risk level compounded sterile preparations.~~]

[~~(i) Medium-Risk Conditions. Medium-risk level compounded sterile preparations, are those compounded aseptically under low-risk conditions and one or more of the following conditions exists:~~]

[~~(I) Multiple individual or small doses of sterile products are combined or pooled to prepare a compounded sterile preparation that will be administered either to multiple patients or to one patient on multiple occasions;~~]

[~~(II) The compounding process includes complex aseptic manipulations other than the single-volume transfer;~~]

[~~(III) The compounding process requires unusually long duration, such as that required to complete the dissolution or homogenous mixing (e.g., reconstitution of intravenous immunoglobulin or other intravenous protein products);~~]

[~~(IV) The compounded sterile preparations do not contain broad spectrum bacteriostatic substances and they are administered over several days (e.g., an externally worn infusion device); or~~]

[~~(V) For a medium-risk level preparation, in the absence of passing a sterility test the storage periods cannot exceed the following time periods: before administration, the compounded sterile preparations are properly stored and are exposed for not more than 30 hours at controlled room temperature, for not more than 9 days at a cold temperature, and for 45 days in solid frozen state between minus 25 degrees Celsius and minus 10 degrees Celsius.~~]

[~~(ii) Examples of medium-risk compounding. Examples of medium-risk compounding include the following:~~]

[~~(I) Compounding of total parenteral nutrition fluids using a manual or automated device during which there are multiple injections, detachments, and attachments of nutrient source products to the device or machine to deliver all nutritional components to a final sterile container;~~]

[~~(II) Filling of reservoirs of injection and infusion devices with more than three sterile drug products and evacuations of air from those reservoirs before the filled device is dispensed;~~]

[~~(III) 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 degrees Celsius (77 and 104 degrees Fahrenheit); and~~]

[~~(IV) Transfer of volumes from multiple ampules or vials into a single, final sterile container or product.~~]

[~~(D) High-risk level compounded sterile preparations.~~]

[~~(i) High-risk Conditions. High-risk level compounded sterile preparations are those compounded under any of the following conditions:~~]

[~~(I) Non-sterile ingredients, including manufactured products not intended for sterile routes of administration (e.g., oral) are incorporated or a non-sterile device is employed before terminal sterilization.~~]

[~~(II) Any of the following are exposed to air quality worse than ISO Class 5 for more than 1 hour:~~]

[~~(a) sterile contents of commercially manufactured products;~~]

[~~(b) CSPs that lack effective antimicrobial preservatives; and~~]

[~~(c) sterile surfaces of devices and containers for the preparation, transfer, sterilization, and packaging of CSPs;~~]

[~~(III) Compounding personnel are improperly garbed and gloved;~~]

[~~(IV) Non-sterile water-containing preparations are exposed no more than 6 hours before being sterilized;~~]

[~~(V) It is assumed, and not verified by examination of labeling and documentation from suppliers or by direct determination, that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened packages of bulk ingredients;~~]

[~~(VI) For a sterilized high-risk level preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the compounded sterile preparations are properly stored and are exposed for not more than 24 hours at controlled room temperature, for not more than 3 days at a cold temperature, and for 45 days in solid frozen state between minus 25 degrees Celsius and minus 10 degrees Celsius; or~~]

[~~(VII) All non-sterile measuring, mixing, and purifying devices are rinsed thoroughly with pyrogen-free or depyrogenated sterile water, and then thoroughly drained or dried immediately before use for high-risk compounding. All high-risk compounded sterile solutions subjected to terminal sterilization are prefiltered by passing through a filter with a nominal pore size not larger than 1.2 micron preceding or during filling into their final containers to remove particulate matter. Sterilization of high-risk level compounded sterile preparations by filtration shall be performed with a sterile 0.2 micrometer or 0.22 micrometer nominal pore size filter entirely within an ISO Class 5 or superior air quality environment.~~]

[~~(ii) Examples of high-risk compounding. Examples of high-risk compounding include the following.~~]

[~~(I) Dissolving non-sterile bulk drug powders to make solutions, which will be terminally sterilized;~~]

(II) Exposing the sterile ingredients and components used to prepare and package compounded sterile preparations to room air quality worse than ISO Class 5 for more than one hour;

[~~(III) Measuring and mixing sterile ingredients in non-sterile devices before sterilization is performed; and~~]

[~~(IV) Assuming, without appropriate evidence or direct determination, that packages of bulk ingredients contain at least 95% by weight of their active chemical moiety and have not been contaminated or adulterated between uses.~~]

(3) Depyrogenation. Dry heat depyrogenation shall be used to render glassware, metal, and other thermostable containers and components pyrogen free. The duration of the exposure period shall include sufficient time for the items to reach the depyrogenation temperature. The items shall remain at the depyrogenation temperature for the duration of the depyrogenation period. The effectiveness of the dry heat depyrogenation cycle shall be established initially and verified annually using endotoxin challenge vials to demonstrate that the cycle is capable of achieving a greater than or equal to 3-log reduction in endotoxins. The effectiveness of the depyrogenation cycle shall be re-established if there are changes to the depyrogenation cycle described in the pharmacy's SOPs (e.g., changes in load conditions, duration, or temperature). This verification shall be documented.

(4)[~~(3)~~] Immediate **use compounded sterile preparations**[~~Use Compounded Sterile Preparations~~]. **When all of the following conditions are met, compounding of compounded sterile preparations for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 compounded sterile preparations:**[~~For the purpose of emergency or immediate patient care, such situations may include cardiopulmonary resuscitation, emergency room treatment, preparation of diagnostic agents, or critical therapy where the preparation of the compounded sterile preparation under low-risk level conditions would subject the patient to additional risk due to delays in therapy. Compounded sterile preparations are exempted from the requirements described in this paragraph for low-risk level compounded sterile preparations when all of the following criteria are met:~~]

(A) Only simple aseptic measuring and transfer manipulations are performed with not more than three **different** sterile [~~non-hazardous commercial drug and diagnostic radiopharmaceutical~~] drug products, including an infusion or diluent solution, from the manufacturers' original containers and not more than two entries into any one container or package of sterile infusion solution or administration container/device;

(B) Unless required for the preparation, the compounding procedure occurs continuously without delays or interruptions and does not exceed 1 hour;

(C) During preparation, aseptic technique is followed and, if not immediately administered, the finished compounded sterile preparation is under continuous supervision to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter of biological fluids, mix-ups with other compounded sterile preparations, and direct contact with outside surfaces;

(D) Administration begins not later than **four hours**[~~one hour~~] following the **start**[~~completion~~] of preparing the compounded sterile preparation;

(E) When the compounded sterile **preparation**[~~preparations~~] is not administered by the person who prepared it, or its administration is not witnessed by the person who prepared it, the compounded sterile preparation shall bear a label listing patient identification information such as name and identification number(s), the names and amounts of all ingredients, the name or initials of the person who prepared the compounded sterile preparation, and the exact **4-hour**[~~1-hour~~] beyond-use time and date;

(F) If administration has not begun within **four hours**[~~one hour~~] following the completion of preparing the compounded sterile preparation, the compounded sterile preparation is promptly and safely discarded. Immediate use compounded sterile preparations shall not be stored for later use; [~~and~~]

(G) Hazardous drugs shall not be prepared as immediate use compounded sterile preparations**; and**[~~.~~]

(H) Personnel are trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the pharmacy's SOPs.

(5)[~~(4)~~] Single-dose and **multiple-dose**[~~multiple dose~~] containers.

(A) Opened or needle punctured single-dose containers, such as bags bottles, syringes, and vials of sterile products shall be used within one hour if opened in worse than ISO Class 5 air quality. Any remaining contents **shall**[~~must~~] be discarded.

(B) **If a single-dose vial is entered or punctured only in ISO Class 5 or cleaner air, it may be used up to 12 hours after initial entry or puncture as long as the labeled storage requirements during that 12 hour period are maintained**[~~Single-dose containers, including single-dose large volume parenteral solutions and single-dose vials, exposed to ISO Class 5 or cleaner air may be used up to six hours after initial needle puncture~~].

(C) **Open single-dose ampules shall not be stored for any time period**[~~Opened single-dose fusion sealed containers shall not be stored for any time period~~].

(D) **Once initially entering or puncturing a multiple-dose container, the multiple-dose container shall not be used for more than 28 days unless otherwise specified by the manufacturer on the labeling**[~~Multiple-dose containers may be used up to 28 days after initial needle puncture unless otherwise specified by the manufacturer~~].

(E) Conventionally manufactured pharmacy bulk packages shall be restricted to the sterile preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile containers. The pharmacy bulk package shall be used according to the manufacturer's labeling and entered or punctured only in an ISO Class 5 primary engineering control.

(F) Multiple-dose compounded sterile preparations shall meet the criteria for antimicrobial effectiveness testing and the requirements of subparagraph (G) of this paragraph. Multiple-dose compounded sterile preparations shall be stored under

conditions upon which the beyond-use date is based (e.g., refrigerator or controlled room temperature). After a multiple-dose compounded sterile preparation is initially entered or punctured, the multiple-dose compounded sterile preparation shall not be used for longer than the assigned beyond-use date or 28 days, whichever is shorter.

(G) A multiple-dose compounded sterile preparation shall be prepared as a Category 2 or Category 3 compounded sterile preparation. An aqueous multiple-dose compounded sterile preparation shall additionally pass antimicrobial effectiveness testing. In the absence of supporting documentation or data, compounding personnel may rely on antimicrobial effectiveness testing conducted or contracted for once for each formulation in the particular container closure system in which it will be packaged.

(H) In the absence of container closure data, the container closure system used to package the multiple-dose compounded sterile preparation shall be evaluated for and conform to container closure integrity. The container closure integrity test shall be conducted only once on each formulation and on fill volume in the particular container closure system in which the multiple-dose compounded sterile preparation shall be packaged.

(I) Multiple-dose, nonpreserved, aqueous topical, and topical ophthalmic compounded sterile preparations. Antimicrobial effectiveness testing under subparagraph (G) of this paragraph is not required if the preparation is prepared as a Category 2 or Category 3 compounded sterile preparation, for use by a single patient, and labeled to indicate that once opened, it shall be discarded after 24 hours when stored at controlled room temperature, 72 hours when stored under refrigeration, or 90 days when frozen if based on documented published stability and effectiveness data.

(J) When a single-dose compounded sterile preparation or compounded sterile preparation stock solution is used as a component to compound additional compounded sterile preparations, the original single-dose compounded sterile preparation or compounded sterile preparation stock solution shall be entered or punctured in ISO Class 5 or cleaner air and stored under the conditions upon which its beyond-use date is based (e.g., refrigerator or controlled room temperature). The component compounded sterile preparation may be used for sterile compounding for up to 12 hours once accessed or its assigned beyond-use date, whichever is shorter, and any remainder shall be discarded.

(6) Proprietary bag and vial systems. Docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for immediate administration to an individual patient is not considered compounding and may be performed outside of an ISO Class 5 environment. Docking of the proprietary bag and vial system for future activation and administration is considered compounding and shall be performed in an ISO Class 5 environment. Beyond-use dates for proprietary bag and vial systems shall not be longer than those specified in the manufacturer's labeling.

(7)[~~(5)~~] Library. In addition to the library requirements of the pharmacy's specific license classification, a pharmacy shall maintain current or updated copies in hard-copy or electronic format of each of the following:

(A) a reference text on injectable drug preparations, such as Handbook on Injectable Drug Products;

(B) a specialty reference text appropriate for the scope of pharmacy services provided by the pharmacy, e.g., if the pharmacy prepares hazardous drugs, a reference text on the preparation of hazardous drugs;

(C) the United States Pharmacopeia/National Formulary containing USP Chapter 71, Sterility Tests, USP Chapter 85, Bacterial Endotoxins Test, Pharmaceutical Compounding--Nonsterile Preparations, USP Chapter 795, USP Chapter 797, Pharmaceutical Compounding--Sterile Preparations, and USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding; and

(D) any additional USP/NF chapters applicable to the practice of the pharmacy (e.g., USP Chapter 800, Hazardous Drugs--Handling in Healthcare Settings, USP Chapter 823, Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses).

(8)[~~(6)~~] Environment. Compounding facilities shall be physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites.

(A) Air exchange requirements. For cleanroom suites, adequate HEPA-filtered airflow to the buffer room(s) and anteroom(s) is required to maintain appropriate ISO classification during compounding activities. Airflow is measured in terms of the number of air changes per hour (ACPH).

(i) Unclassified sterile compounding area. No requirement for ACPH.

(ii) ISO Class 7 room(s). A minimum of 30 total HEPA-filtered ACPH shall be supplied to ISO Class 7 rooms. At least 15 ACPH of the total air change rate in a room shall come from the HVAC through HEPA filters located in the ceiling. The ACPH from HVAC, ACPH contributed from the PEC, and the total ACPH shall be documented on the certification report.

(iii) ISO Class 8 room(s). A minimum of 20 total HEPA-filtered ACPH shall be supplied to ISO Class 8 rooms. At least 15 ACPH of the total air change rate in a room shall come from the HVAC through HEPA filters located in the ceiling. The total ACPH shall be documented on the certification report.

(B) Cleanroom suite. Seals and sweeps should not be installed at doors between buffer rooms and anterooms. Access doors should be hands-free. Tacky mats shall not be placed within ISO-classified areas.

(C)[~~(A)~~] **Category 1 and Category 2 preparations**[~~Low and Medium Risk Preparations~~]. A pharmacy that prepares **Category 1 compounded sterile preparations outside of a segregated compounding area or Category 2 compounded sterile**[~~low- and medium-risk~~] preparations shall have a clean room for the compounding of sterile preparations that is constructed to minimize the opportunities for particulate and microbial contamination. The clean room shall:

(i) be clean, well lit, and of sufficient size to support sterile compounding activities;

(ii) be maintained at a temperature of 20 degrees Celsius or cooler and at a humidity **of 60% or** below [~~60%~~];

(iii) be used only for the compounding of sterile preparations;

(iv) be designed such that hand sanitizing and gowning occurs outside the buffer **room**[~~area~~] but allows hands-free access by compounding personnel to the buffer **room**[~~area~~];

(v) have non-porous and washable floors or floor covering to enable regular disinfection;

(vi) be ventilated in a manner to avoid disruption from the HVAC system and room cross-drafts;

(vii) have walls, ceilings, floors, fixtures, shelving, counters, and cabinets that are smooth, impervious, free from cracks and crevices (e.g., coved), non-shedding and resistant to damage by disinfectant agents;

(viii) have junctures of ceilings to walls coved or caulked to avoid cracks and crevices;

(ix) have drugs and supplies stored on shelving areas above the floor to permit adequate floor cleaning;

(x) contain only the appropriate compounding supplies and not be used for bulk storage for supplies and materials. Objects that shed particles shall not be brought into the clean room. A Class B pharmacy may use low-linting absorbent materials in the primary engineering control device;

(xi) contain an **anteroom**[~~ante-area~~] that contains a sink with hot and cold running water that enables hands-free use with a closed system of soap dispensing to minimize the risk of extrinsic contamination. A Class B pharmacy may have a sink with hot and cold running water that enables hands-free use with a closed system of soap dispensing immediately outside the **anteroom**[~~ante-area~~] if antiseptic hand cleansing is performed using a waterless alcohol-based surgical hand scrub with persistent activity following manufacturers' recommendations once inside the **anteroom**[~~ante-area~~]; and

(xii) contain a buffer **room**[~~area~~]. The following is applicable for the buffer **room**[~~area~~]:

(I) There shall be some demarcation designation that delineates the **anteroom**[~~ante-area~~] from the buffer **room**[~~area~~]. The demarcation shall be such that it does not create conditions that could adversely affect the cleanliness of the **room**[~~area~~];

(II) The buffer **room**[~~area~~] shall be segregated from surrounding, unclassified spaces to reduce the risk of contaminants being blown, dragged, or otherwise introduced into the filtered unidirectional airflow environment, and this segregation should be continuously monitored;

(III) A buffer **room**[~~area~~] that is not physically separated from the **anteroom**[~~ante-area~~] shall employ the principle of displacement airflow as defined in Chapter 797, Pharmaceutical Compounding--Sterile Preparations, of the USP/NF, with limited access to personnel; and

(IV) The buffer **room**[~~area~~] shall not contain sources of water (i.e., sinks) or floor drains other than distilled or sterile water introduced for facilitating the use of heat block wells for radiopharmaceuticals.

(D)[~~(B)~~] **Category 2 prepared from any non-sterile starting component and Category 3 preparations**[~~High-risk Preparations~~].

(i) In addition to the requirements in subparagraph **(C)**[~~(A)~~] of this paragraph, when **Category 2 prepared from any non-sterile starting component or Category 3 compounded sterile**[~~high-risk~~] preparations are compounded, the primary engineering control shall be located in a buffer **room**[~~area~~] that provides a physical separation, through the use of walls, doors and pass-throughs and has a minimum differential positive pressure of 0.02 [~~to 0.05~~] inches water column.

(ii) Presterilization procedures for **Category 2 prepared from any non-sterile starting component or Category 3**[~~high-risk level~~] compounded sterile preparations, such as weighing and mixing, shall be completed in no worse than an ISO Class 8 environment **using depyrogenated equipment**.

(E)[~~(C)~~] Automated compounding device.

(i) General. If automated compounding devices are used, the pharmacy shall have a method to calibrate and verify the accuracy of automated compounding devices used in aseptic processing and document the calibration and verification on a daily basis, based on the manufacturer's recommendations, and review the results at least weekly.

(ii) Loading bulk drugs into automated compounding devices.

(I) Automated compounding devices may be loaded with bulk drugs only by a pharmacist or by pharmacy technicians or pharmacy technician trainees under the direction and direct supervision of a pharmacist.

(II) The label of an automated compounding device container shall indicate the brand name and strength of the drug; or if no brand name, then the generic name, strength, and name of the manufacturer or distributor.

(III) Records of loading bulk drugs into an automated compounding device shall be maintained to show:

(-a-) name of the drug, strength, and dosage form;

(-b-) manufacturer or distributor;

(-c-) manufacturer's lot number;

(-d-) manufacturer's expiration date;

(-e-) quantity added to the automated compounding device;

(-f-) date of loading;

(-g-) name, initials, or electronic signature of the person loading the automated compounding device; and

(-h-) name, initials, or electronic signature of the responsible pharmacist.

(IV) The automated compounding device shall not be used until a pharmacist verifies that the system is properly loaded and affixes his or her signature or electronic signature to the record specified in subclause (III) of this clause.

(F)[~~(D)~~] Hazardous drugs. If the preparation is hazardous, the following is also applicable:

(i) Hazardous drugs shall be prepared only under conditions that protect personnel during preparation and storage;

(ii) Hazardous drugs shall be stored separately from other inventory in a manner to prevent contamination and personnel exposure;

(iii) All personnel involved in the compounding of hazardous drugs shall wear appropriate protective apparel, such as gowns, face masks, eye protection, hair covers, shoe covers or dedicated shoes, and appropriate gloving at all times when handling hazardous drugs, including receiving, distribution, stocking, inventorying, preparation, for administration and disposal;

(iv) Appropriate safety and containment techniques for compounding hazardous drugs shall be used in conjunction with aseptic techniques required for preparing sterile preparations;

(v) Disposal of hazardous waste shall comply with all applicable local, state, and federal requirements;

(vi) Prepared doses of hazardous drugs **shall**[~~must~~] be dispensed, labeled with proper precautions inside and outside, and distributed in a manner to minimize patient contact with hazardous agents.

(G)[~~(E)~~] Blood-labeling procedures. When compounding activities require the manipulation of a patient's blood-derived material (e.g., radiolabeling a patient's or donor's white blood cells), the manipulations shall be performed in **an**[~~a~~] ISO Class 5 biological safety cabinet located in a buffer **room**[~~area~~] and shall be clearly separated from routine material-handling procedures and equipment used in preparation activities to avoid any cross-contamination. The preparations shall not require sterilization.

(H)[~~(F)~~] Cleaning and disinfecting the sterile compounding areas. The following cleaning and disinfecting practices and frequencies apply to direct and contiguous compounding areas, which include ISO Class 5 compounding areas for exposure of critical sites as well as buffer **rooms**[~~areas~~], **anterooms**[~~ante-areas~~], and segregated compounding areas.

(i) The pharmacist-in-charge is responsible for developing written standard operating procedures (SOPs) for cleaning and disinfecting the direct and contiguous compounding areas and assuring the procedures are followed.

(ii) **In a PEC, sterile 70% IPA shall be applied after cleaning and disinfecting, or after the application of a one-step disinfectant cleaner or sporicidal disinfectant, to remove any residue. Sterile 70% IPA shall also be applied immediately before initiating compounding. During the compounding process sterile 70% IPA shall be applied to the horizontal work surface, including any removable work trays, of the PEC at least every 30 minutes if the compounding process takes 30 minutes or less. If the compounding process takes more than 30 minutes, compounding shall not be disrupted and the work surface of the PEC shall be disinfected immediately after compounding**[~~These procedures shall be conducted at the beginning of each work shift, before each batch preparation is started, when there are spills, and when surface contamination is known or suspected resulting from procedural breaches, and every 30 minutes during continuous compounding of individual compounded sterile preparations, unless a particular compounding procedure requires more than 30 minutes to complete, in which case, the direct compounding area is to be cleaned immediately after the compounding activity is completed~~].

(iii) **Surfaces shall be cleaned prior to being disinfected unless a one-step disinfectant cleaner is used to accomplish both the cleaning and disinfection in one step. The manufacturer's directions or published data for the minimum contact time shall be followed for each of the cleaning, disinfecting, and sporicidal disinfectants used. When sterile 70% IPA is used, it shall be allowed to dry.** [~~Before compounding is performed, all items shall be removed from the direct and contiguous compounding areas and all surfaces are cleaned by removing loose material and residue from spills, followed by an application of a residue-free disinfecting agent (e.g., IPA), which is allowed to dry before compounding begins~~]. In a Class B pharmacy, objects used in preparing sterile radiopharmaceuticals (e.g., dose calibrator) which cannot be reasonably removed from the compounding area shall be sterilized with an application of a residue-free disinfection agent.

(iv) Surfaces in classified areas used to prepare Category 1, Category 2, and Category 3 compounded sterile preparations shall be cleaned, disinfected, and sporicidal disinfectants applied in accordance with the following:

(I) PEC(s) and equipment inside PEC(s).

(-a-) Equipment and all interior surfaces of the PEC shall be cleaned daily on days when compounding occurs and when surface contamination is known or suspected. Equipment and all interior surfaces of the PEC shall be disinfected on days when compounding occurs and when surface contamination is known or suspected. Sporicidal disinfectants shall be applied monthly for pharmacies compounding Category 1 or Category 2 compounded sterile preparations and weekly for pharmacies compounding Category 3 compounded sterile preparations.

(-b-) Cleaning and disinfecting agents, with the exception of sporicidal disinfectants, used within the PEC shall be sterile. When diluting concentrated cleaning and disinfecting agents for use in the PEC, sterile water shall be used.

(II) Removable work tray of the PEC, when applicable. Work surfaces of the tray shall be cleaned daily on days when compounding occurs and all surfaces and the area underneath the work tray shall be cleaned monthly. Work surfaces of the tray shall be disinfected on days when compounding occurs and all surfaces and the area underneath the work tray shall be disinfected monthly. Sporicidal disinfectants shall be applied

monthly on work surfaces of the tray, all surfaces, and the area underneath the work tray monthly.

(III) Pass-through chambers. Pass-through chambers shall be cleaned daily on days when compounding occurs and disinfected daily on days when compounding occurs. Sporicidal disinfectants shall be applied monthly for pharmacies compounding Category 1 or Category 2 compounded sterile preparations and weekly for pharmacies compounding Category 3 compounded sterile preparations.

(IV) Work surface(s) outside the PEC. Work surfaces outside the PEC shall be cleaned daily on days when compounding occurs and disinfected daily on days when compounding occurs. Sporicidal disinfectants shall be applied monthly for pharmacies compounding Category 1 or Category 2 compounded sterile preparations and weekly for pharmacies compounding Category 3 compounded sterile preparations.

(V) Floor(s). Floors shall be cleaned daily on days when compounding occurs and disinfected daily on days when compounding occurs. Sporicidal disinfectants shall be applied monthly for pharmacies compounding Category 1 or Category 2 compounded sterile preparations and weekly for pharmacies compounding Category 3 compounded sterile preparations.

(VI) Wall(s), door(s), door frame(s), storage shelving and bin(s), and equipment outside of the PEC(s). Walls, doors, door frames, storage shelving and bins, and equipment outside of the PECs shall be cleaned, disinfected, and sporicidal disinfectants applied on a monthly basis.

(VII) Ceiling(s). Ceilings of the classified areas shall be cleaned, disinfected, and sporicidal disinfectant applied on a monthly basis. Ceilings of the segregated compounding area shall be cleaned, disinfected, and sporicidal disinfectants applied when visibly soiled and when surface contamination is known or suspected.

[~~(iv) Work surfaces in the buffer areas and ante-areas, as well as segregated compounding areas, shall be cleaned and disinfected at least daily. Dust and debris shall be removed when necessary from storage sites for compounding ingredients and supplies using a method that does not degrade the ISO Class 7 or 8 air quality.~~]

[~~(v) Floors in the buffer area, ante-area, and segregated compounding area shall be cleaned by mopping with a cleaning and disinfecting agent at least once daily when no aseptic operations are in progress. Mopping shall be performed by trained personnel using approved agents and procedures described in the written SOPs. It is incumbent on compounding personnel to ensure that such cleaning is performed properly.~~]

[~~(vi) In the buffer area, ante-area, and segregated compounding area, walls, ceilings, and shelving shall be cleaned and disinfected monthly. Cleaning and disinfecting agents shall be used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues.~~]

(v)[~~(vii)~~] All cleaning materials, such as wipers, sponges, and mops, shall be non-shedding, and dedicated to use in the buffer **room**[~~area~~], **anteroom**[~~ante-area~~], and segregated compounding areas and shall not be removed from these areas except for disposal. Floor mops may be used

in both the buffer **room**[~~area~~] and **anteroom**[~~ante-area~~], but only in that order. If cleaning materials are reused, procedures shall be developed that ensure that the effectiveness of the cleaning device is maintained and that repeated use does not add to the bio-burden of the area being cleaned.

(vi)[~~(viii)~~] Supplies and equipment removed from shipping cartons **shall**[~~must~~] be wiped with a disinfecting agent, such as sterile IPA. After the disinfectant is sprayed or wiped on a surface to be disinfected, the disinfectant shall be allowed to dry, during which time the item shall not be used for compounding purposes. However, if sterile supplies are received in sealed pouches, the pouches may be removed as the supplies are introduced into the ISO Class 5 area without the need to disinfect the individual sterile supply items. No shipping or other external cartons may be taken into the buffer **room**[~~area~~] or segregated compounding area.

(vii) Before any item is introduced into the clean side of the anteroom(s), placed into pass-through chamber(s), or brought into the segregated compounding area, providing that packaging integrity will not be compromised, the item shall be wiped with a sporicidal disinfectant, EPA-registered disinfectant, or sterile 70% IPA using low-lint wipers by personnel wearing gloves. If an EPA-registered disinfectant or sporicidal disinfectant is used, the agent shall be allowed to dwell the minimum contact time specified by the manufacturer. If sterile 70% IPA is used, it shall be allowed to dry. The wiping procedure should not compromise the packaging integrity or render the product label unreadable.

(viii) Immediately before any item is introduced into the PEC, it shall be wiped with sterile 70% IPA using sterile low-lint wipers and allowed to dry before use. When sterile items are received in sealed containers designed to keep them sterile until opening, the sterile items may be removed from the covering as the supplies are introduced into the ISO Class 5 PEC without the need to wipe the individual sterile supply items with sterile 70% IPA. The wiping procedure shall not render the product label unreadable.

(ix) Critical sites (e.g., vial stoppers, ampule necks, and intravenous bag septums) shall be wiped with sterile 70% IPA in the PEC to provide both chemical and mechanical actions to remove contaminants. The sterile 70% IPA shall be allowed to dry before personnel enter or puncture stoppers and septums or break the necks of ampules.

[~~(ix) Storage shelving emptied of all supplies, walls, and ceilings shall be cleaned and disinfected at planned intervals, monthly, if not more frequently.~~]

(x) Cleaning **shall**[~~must~~] be done by personnel trained in appropriate cleaning techniques.

(xi) Proper documentation and frequency of cleaning **shall**[~~must~~] be maintained and shall contain the following:

(I) date [~~and time~~] of cleaning;

(II) type of cleaning performed; and

(III) name of individual who performed the cleaning.

(I)[~~(G)~~] Security requirements. The pharmacist-in-charge may authorize personnel to gain access to that area of the pharmacy containing dispensed sterile preparations, in the absence of the pharmacist, for the purpose of retrieving dispensed prescriptions to deliver to patients. If the pharmacy allows such after-hours access, the area containing the dispensed sterile preparations shall be an enclosed and lockable area separate from the area containing undispensed prescription drugs. A list of the authorized personnel having such access shall be in the pharmacy's policy and procedure manual.

(J)[~~(H)~~] Storage requirements and beyond-use dating.

(i) Storage requirements. All drugs shall be stored at the proper temperature and conditions, as defined in the USP/NF and in §291.15 of this title (relating to Storage of Drugs).

(ii) Beyond-use dating. **When assigning a beyond-use date, compounding personnel shall consult and apply drug-specific and general stability documentation and literature where available, and they should consider the nature of the drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions, and the intended duration of therapy. A shorter beyond-use date shall be assigned when the physical and chemical stability of the preparation is less than the beyond-use date limits provided in subclauses (I) - (III) of this clause.**

(I) Beyond-use date limits for Category 1 compounded sterile preparations. Category 1 compounded sterile preparations shall be prepared in a segregated compounding area or cleanroom suite and have a beyond-use date of not more than 12 hours when stored at controlled room temperature or 24 hours when stored in a refrigerator.

[~~(I) Beyond-use dates for compounded sterile preparations shall be assigned based on professional experience, which shall include careful interpretation of appropriate information sources for the same or similar formulations.~~]

(II) Beyond-use date limits for Category 2 compounded sterile preparations. Category 2 compounded sterile preparations shall be prepared in a cleanroom suite.

(-a-) Aseptically processed compounded sterile preparations without sterility testing performed and passed.

(-1-) If prepared from one or more non-sterile starting component(s), the preparation shall have a beyond-use date of not more than one day when stored at controlled room temperature, four days when stored in a refrigerator, or 45 days when stored in a freezer.

(-2-) If prepared from only sterile starting component(s), the preparation shall have a beyond-use date of not more than four days when stored at controlled room temperature, 10 days when stored in a refrigerator, or 45 days when stored in a freezer.

(-b-) Terminally sterilized compounded sterile preparations without sterility testing performed and passed shall have a beyond-use date of not more than 14 days when stored at controlled room temperature, 28 days when stored in a refrigerator, or 45 days when stored in a freezer.

(-c-) If sterility testing is performed and passed, aseptically processed or terminally sterilized compounded sterile preparations shall have a beyond-use date of not more than 45 days when stored at controlled room temperature, 60 days when stored in a refrigerator, or 90 days when stored in a freezer.

[~~(II) Beyond-use dates for compounded sterile preparations that are prepared strictly in accordance with manufacturers' product labeling must be those specified in that labeling, or from appropriate literature sources or direct testing.~~]

(III) Beyond-use date limits for Category 3 compounded sterile preparations. Category 3 compounded sterile preparations shall be prepared in a cleanroom suite.

(-a-) Aseptically processed compounded sterile preparations that are sterility tested and passed all applicable tests for Category 3 compounded sterile preparations shall have a beyond-use date of not more than 60 days when stored at controlled room temperature, 90 days when stored in a refrigerator, or 120 days when stored in a freezer.

(-b-) Terminally sterilized compounded sterile preparations that are sterility tested and passed all applicable tests for Category 3 compounded sterile preparations shall have a beyond-use date of not more than 90 days when stored at controlled room temperature, 120 days when stored in a refrigerator, or 180 days when stored in a freezer.

(-c-) A Category 3 compounded sterile preparation in a nonaqueous dosage form (i.e., water activity level less than 0.6) may have a beyond-use date of not more than 180 days if based on documented current literature supporting stability and sterility.

(-d-) Additional requirements to assign Category 3 beyond-use dates to compounded sterile preparations.

(-1-) Category 3 personnel competency requirements as specified in subsection (c)(4)(L) of this section apply to personnel who participate in or oversee the compounding of Category 3 compounded sterile preparations.

(-2-) Category 3 garbing requirements as specified in paragraph (15)(C)(iv)(II) of this subsection apply to all personnel entering the buffer room where Category 3 compounded sterile preparations are compounded and apply at all times regardless of whether Category 3 compounded sterile preparations are being compounded on a given day.

(-3-) Increased environmental monitoring requirements as specified in subsection (c)(4)(M) of this section and paragraph (16)(C)(vi) of this subsection apply to all classified areas where Category 3 compounded sterile preparations are compounded and apply at all times regardless of whether Category 3 compound sterile preparations are being compounded on a given day.

(-4-) The frequency of application of sporicidal disinfectants as specified in paragraph (8)(H)(iv) of this subsection applies to all classified areas where Category 3 compounded sterile preparations are compounded and applies at all times regardless of whether Category 3 compounded sterile preparations are being compounded on a given day.

[~~(III) When assigning a beyond-use date, compounding personnel shall consult and apply drug-specific and general stability documentation and literature where available, and they should consider the nature of the drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions, and the intended duration of therapy.~~]

[~~(IV) The sterility and storage and stability beyond-use date for attached and activated container pairs of drug products for intravascular administration shall be applied as indicated by the manufacturer.~~]

(9)[~~(7)~~] Primary engineering control device. The pharmacy shall prepare sterile preparations in a primary engineering control device (PEC), such as a laminar air flow hood, biological safety cabinet, compounding aseptic isolator (CAI), or compounding aseptic containment isolator (CACI) which is capable of maintaining at least ISO Class 5 conditions for 0.5 **micron and larger**[~~micrometer~~] particles while compounding sterile preparations.

(A) Laminar air flow hood. If the pharmacy is using a laminar air flow hood as its PEC, the laminar air flow hood shall:

(i) be located in the buffer **room**[~~area~~] and placed in the buffer **room**[~~area~~] in a manner as to avoid conditions that could adversely affect its operation such as strong air currents from opened doors, personnel traffic, or air streams from the heating, ventilating and air condition system;

(ii) be certified for operational efficiency using certification procedures, such as those outlined in the Certification Guide for Sterile Compounding Facilities **(CAG-003-2022)**[~~(CAG-003-2006)~~], which shall be performed by a qualified independent individual **initially and** no less than every six months and whenever the device or room is relocated or altered or major service to the **pharmacy**[~~facility~~] is performed;

(iii) have pre-filters inspected periodically and replaced as needed, in accordance with written policies and procedures and the manufacturer's specification, and the inspection and/or replacement date documented; and

(iv) be located in a buffer **room**[~~area~~] that has a minimum differential positive pressure of 0.02 [~~to 0.05~~] inches water column. A buffer **room**[~~area~~] that is not physically separated from the **anteroom**[~~ante-area~~] shall employ the principle of displacement airflow as defined in Chapter 797, Pharmaceutical Compounding--Sterile Preparations, of the USP/NF, with limited access to personnel.

(B) Biological safety cabinet.

(i) If the pharmacy is using a biological safety cabinet (BSC) as its PEC for the preparation of hazardous sterile compounded preparations, the biological safety cabinet shall be a Class II or III vertical flow biological safety cabinet located in an ISO Class 7 area that is physically separated from other preparation areas. The area for preparation of sterile chemotherapeutic preparations shall:

(I) have not less than 0.01 inches water column negative pressure to the adjacent positive pressure ISO Class 7 or better **anteroom**[~~ante-area~~]; and

(II) have a pressure indicator that can be readily monitored for correct room pressurization.

(ii) Pharmacies that prepare a low volume of hazardous drugs, are not required to comply with the provisions of clause (i) of this subparagraph if the pharmacy uses a device that provides two tiers of containment (e.g., closed-system vial transfer device within a BSC).

(iii) If the pharmacy is using a biological safety cabinet as its PEC for the preparation of non-hazardous sterile compounded preparations, the biological safety cabinet shall:

(I) be located in the buffer **room**[~~area~~] and placed in the buffer **room**[~~area~~] in a manner as to avoid conditions that could adversely affect its operation such as strong air currents from opened doors, personnel traffic, or air streams from the heating, ventilating and air condition system;

(II) be certified for operational efficiency using certification procedures, such as those outlined in the Certification Guide for Sterile Compounding Facilities **(CAG-003-2022)**[~~(CAG-003-2006)~~], which shall be performed by a qualified independent individual **initially and** no less than every six months and whenever the device or room is relocated or altered or major service to the **pharmacy**[~~facility~~] is performed;

(III) have pre-filters inspected periodically and replaced as needed, in accordance with written policies and procedures and the manufacturer's specification, and the inspection and/or replacement date documented; and

(IV) be located in a buffer **room**[~~area~~] that has a minimum differential positive pressure of 0.02 [~~to 0.05~~] inches water column.

(C) Compounding aseptic isolator.

(i) If the pharmacy is using a compounding aseptic isolator (CAI) as its PEC, the CAI shall provide unidirectional airflow within the main processing and antechambers, and be placed in an ISO Class 7 buffer **room**[~~area~~] unless the isolator meets all of the following conditions:

(I) The isolator **shall**[~~must~~] provide isolation from the room and maintain ISO Class 5 during dynamic operating conditions including transferring ingredients, components, and devices into and out of the isolator and during preparation of compounded sterile preparations;

(II) Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site **shall**[~~must~~] maintain ISO Class 5 levels during compounding operations;

(III) The CAI **shall**[~~must~~] be certified for operational efficiency using certification procedures, such as those outlined in the Certification Guide for Sterile Compounding Facilities **(CAG-003-2022)**[~~(CAG-003-2006)~~], which shall be performed by a qualified independent individual **initially and** no less than every six months and whenever the device or room is relocated or altered or major service to the **pharmacy**[~~facility~~] is performed; and

(IV) The pharmacy shall maintain documentation from the manufacturer that the isolator meets this standard when located in worse than ISO Class 7 environments.

(ii) If the isolator meets the requirements in clause (i) of this subparagraph, the CAI may be placed in a non-ISO classified area of the pharmacy; however, the area shall be segregated from other areas of the pharmacy and shall:

(I) be clean, well lit, and of sufficient size;

(II) be used only for the compounding of **Category 1 or Category 2**[~~low- and medium-risk,~~] non-hazardous sterile preparations;

(III) be located in an area of the pharmacy with non-porous and washable floors or floor covering to enable regular disinfection; and

(IV) be an area in which the CAI is placed in a manner as to avoid conditions that could adversely affect its operation.

(iii) In addition to the requirements specified in clauses (i) and (ii) of this subparagraph, if the CAI is used in the compounding of **Category 2 prepared from any non-sterile starting component or Category 3**[~~high-risk~~] non-hazardous preparations, the CAI shall be placed in an area or room with at least ISO **Class 7**[~~8~~] quality air so that high-risk powders weighed in at least **ISO Class 7**[~~ISO-8~~] air quality conditions, compounding utensils for measuring and other compounding equipment are not exposed to lesser air quality prior to the completion of compounding and packaging of the **Category 2 prepared from any non-sterile starting component or Category 3**[~~high-risk~~] preparation.

(D) Compounding aseptic containment isolator.

(i) If the pharmacy is using a compounding aseptic containment isolator (CACI) as its PEC for the preparation of **Category 1 or Category 2**[~~low- and medium-risk~~] hazardous drugs, the CACI shall be located in a separate room away from other areas of the pharmacy and shall:

(I) provide at least 0.01 inches water column negative pressure compared to the other areas of the pharmacy;

(II) provide unidirectional airflow within the main processing and antechambers, and be placed in an ISO Class 7 **room**[~~area~~], unless the CACI meets all of the following conditions;

(-a-) The isolator **shall**[~~must~~] provide isolation from the room and maintain ISO Class 5 during dynamic operating conditions including transferring ingredients, components, and devices into and out of the isolator and during preparation of compounded sterile preparations;

(-b-) Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site **shall**[~~must~~] maintain ISO Class 5 levels during compounding operations;

(-c-) The CACI **shall**[~~must~~] be certified for operational efficiency using certification procedures, such as those outlined in the Certification Guide for Sterile Compounding Facilities **(CAG-003-2022)**[~~(CAG-003-2006)~~], which shall be performed by a qualified independent individual **initially and** no less than every six months and whenever the device or room is relocated or altered or major service to the **pharmacy**[~~facility~~] is performed; and

(-d-) The pharmacy shall maintain documentation from the manufacturer that the isolator meets this standard when located in worse than ISO Class 7 environments.

(ii) If the CACI meets all conditions specified in clause (i) of this subparagraph, the CACI shall not be located in the same room as a CAI, but shall be located in a separate room in the pharmacy, that is not required to maintain ISO classified air. The room in which the CACI is located shall provide a minimum of 0.01 inches water column negative pressure compared with the other areas of the pharmacy and shall meet the following requirements:

(I) be clean, well lit, and of sufficient size;

(II) be maintained at a temperature of 20 degrees Celsius or cooler and a humidity **of 60% or** below [~~60%~~];

(III) be used only for the compounding of **Category 1 or Category 2** hazardous sterile preparations;

(IV) be located in an area of the pharmacy with walls, ceilings, floors, fixtures, shelving, counters, and cabinets that are smooth, impervious, free from cracks and crevices, non-shedding and resistant to damage by disinfectant agents; and

(V) have non-porous and washable floors or floor covering to enable regular disinfection.

(iii) If the CACI is used in the compounding of **Category 2 prepared from any non-sterile starting component or Category 3**[~~high-risk~~] hazardous preparations, the CACI shall be placed in an area or room with at least ISO **Class 7**[~~8~~] quality air so that high-risk powders, weighed in at least **ISO Class 7**[~~ISO 8~~] air quality conditions, are not exposed to lesser air quality prior to the completion of compounding and packaging of the **Category 2 prepared from any non-sterile starting component or Category 3**[~~high-risk~~] preparation.

(iv) Pharmacies that prepare a low volume of hazardous drugs, are not required to comply with the provisions of clauses (i) and (iii) of this subparagraph if the pharmacy uses a device that provides two tiers of containment (e.g., CACI that is located in a non-negative pressure room).

(10)[~~(8)~~] Additional Equipment and Supplies. Pharmacies compounding sterile preparations shall have the following equipment and supplies:

(A) a calibrated system or device (i.e., thermometer) to monitor the temperature to ensure that proper storage requirements are met, if sterile preparations are stored in the refrigerator;

(B) a calibrated system or device to monitor the temperature where bulk chemicals are stored;

(C) a temperature-sensing mechanism suitably placed in the controlled temperature storage space to reflect accurately the true temperature;

(D) if applicable, a Class A prescription balance, or analytical balance and weights. Such balance shall be properly maintained and subject to periodic inspection by the Texas State Board of Pharmacy;

(E) equipment and utensils necessary for the proper compounding of sterile preparations. Such equipment and utensils used in the compounding process shall be:

(i) of appropriate design, appropriate capacity, and be operated within designed operational limits;

(ii) of suitable composition so that surfaces that contact components, in-process material, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug preparation beyond the desired result;

(iii) cleaned and sanitized immediately prior to and after each use; and

(iv) routinely inspected, calibrated (if necessary), or checked to ensure proper performance;

(F) appropriate disposal containers for used needles, syringes, etc., and if applicable, hazardous waste from the preparation of hazardous drugs and/or biohazardous waste;

(G) appropriate packaging or delivery containers to maintain proper storage conditions for sterile preparations;

(H) infusion devices, if applicable; and

(I) all necessary supplies, including:

(i) disposable needles, syringes, and other supplies for aseptic mixing;

(ii) disinfectant cleaning solutions;

(iii) sterile 70% isopropyl alcohol;

(iv) sterile gloves, both for hazardous and non-hazardous drug compounding;

(v) sterile alcohol-based or water-less alcohol based surgical scrub;

(vi) hand washing agents with bactericidal action;

(vii) disposable, lint free towels or wipes;

(viii) appropriate filters and filtration equipment;

(ix) hazardous spill kits, if applicable; and

(x) masks, caps, coveralls or gowns with tight cuffs, shoe covers, and gloves, as applicable.

(11)[~~(9)~~] Labeling.

(A) Prescription drug or medication orders. In addition to the labeling requirements for the pharmacy's specific license classification, the label dispensed or distributed pursuant to a prescription drug or medication order shall contain the following:

(i) the generic name(s) or the official name(s) of the principal active ingredient(s) of the compounded sterile preparation;

(ii) for outpatient prescription orders other than sterile radiopharmaceuticals, a statement that the compounded sterile preparation has been compounded by the pharmacy. (An auxiliary label may be used on the container to meet this requirement); and

(iii) a beyond-use date. The beyond-use date shall be determined as outlined in Chapter 797, Pharmacy Compounding--Sterile Preparations of the USP/NF, and paragraph **(8)(J)**[~~(7)(G)~~] of this subsection;

(B) Batch. If the sterile preparation is compounded in a batch, the following shall also be included on the batch label:

(i) unique lot number assigned to the batch;

(ii) quantity;

(iii) appropriate ancillary instructions, such as storage instructions or cautionary statements, including hazardous drug warning labels where appropriate; and

(iv) device-specific instructions, where appropriate.

(C) Pharmacy bulk package. The label of a pharmacy bulk package shall:

(i) state prominently "Pharmacy Bulk Package--Not for Direct Infusion;"

(ii) contain or refer to information on proper techniques to help ensure safe use of the preparation; and

(iii) bear a statement limiting the time frame in which the container may be used once it has been entered, provided it is held under the labeled storage conditions.

(12)[~~(10)~~] Written drug information for prescription drug orders only. Written information about the compounded preparation or its major active ingredient(s) shall be given to the patient at the time of dispensing a prescription drug order. A statement which indicates that the preparation was compounded by the pharmacy **shall**[~~must~~] be included in this written information. If there is no written information available, the patient shall be advised that the drug has been compounded and how to contact a pharmacist, and if appropriate, the prescriber, concerning the drug. This paragraph does not apply to the preparation of radiopharmaceuticals.

(13)[~~(11)~~] Pharmaceutical **care services**[~~Care Services~~]. In addition to the pharmaceutical care requirements for the pharmacy's specific license classification, the following requirements for sterile preparations compounded pursuant to prescription drug orders **shall**[~~must~~] be met. This paragraph does not apply to the preparation of radiopharmaceuticals.

(A) Primary provider. There shall be a designated physician primarily responsible for the patient's medical care. There shall be a clear understanding between the physician, the patient,

and the pharmacy of the responsibilities of each in the areas of the delivery of care, and the monitoring of the patient. This shall be documented in the patient medication record (PMR).

(B) Patient training. The pharmacist-in-charge shall develop policies to ensure that the patient and/or patient's caregiver receives information regarding drugs and their safe and appropriate use, including instruction when applicable, regarding:

(i) appropriate disposition of hazardous solutions and ancillary supplies;

(ii) proper disposition of controlled substances in the home;

(iii) self-administration of drugs, where appropriate;

(iv) emergency procedures, including how to contact an appropriate individual in the event of problems or emergencies related to drug therapy; and

(v) if the patient or patient's caregiver prepares sterile preparations in the home, the following additional information shall be provided:

(I) safeguards against microbial contamination, including aseptic techniques for compounding intravenous admixtures and aseptic techniques for injecting additives to premixed intravenous solutions;

(II) appropriate storage methods, including storage durations for sterile pharmaceuticals and expirations of self-mixed solutions;

(III) handling and disposition of premixed and self-mixed intravenous admixtures; and

(IV) proper disposition of intravenous admixture compounding supplies such as syringes, vials, ampules, and intravenous solution containers.

(C) Pharmacist-patient relationship. It is imperative that a pharmacist-patient relationship be established and maintained throughout the patient's course of therapy. This shall be documented in the patient's medication record (PMR).

(D) Patient monitoring. The pharmacist-in-charge shall develop policies to ensure that:

(i) the patient's response to drug therapy is monitored and conveyed to the appropriate health care provider;

(ii) the first dose of any new drug therapy is administered in the presence of an individual qualified to monitor for and respond to adverse drug reactions; and

(iii) reports of adverse events with a compounded sterile preparation are reviewed promptly and thoroughly to correct and prevent future occurrences.

(14)[~~(12)~~] Drugs, components, and materials used in sterile compounding.

(A) Drugs used in sterile compounding shall be [~~a~~] USP/NF grade substances manufactured in an FDA-registered facility.

(B) If USP/NF grade substances are not available**, substances used in sterile compounding** shall be of a chemical grade in one of the following categories:

(i) Chemically Pure (CP);

(ii) Analytical Reagent (AR);

(iii) American Chemical Society (ACS); or

(iv) Food Chemical Codex.

(C) If a drug, component or material is not purchased from a FDA-registered facility, the pharmacist shall establish purity and stability by obtaining a Certificate of Analysis from the supplier and the pharmacist shall compare the monograph of drugs in a similar class to the Certificate of Analysis.

(D) All components shall:

(i) be manufactured in an FDA-registered facility; or

(ii) in the professional judgment of the pharmacist, be of high quality and obtained from acceptable and reliable alternative sources; and

(iii) be stored in properly labeled containers in a clean, dry **place**[~~area~~], under proper temperatures.

(E) Drug preparation containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the compounded drug preparation beyond the desired result.

(F) Components, drug preparation containers, and closures shall be rotated so that the oldest stock is used first.

(G) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the compounded drug preparation.

(H) A pharmacy may not compound a preparation that contains ingredients appearing on a federal Food and Drug Administration list of drug products withdrawn or removed from the market for safety reasons.

(15)[~~(13)~~] Compounding process.

(A) Standard operating procedures (SOPs). All significant procedures performed in the compounding area shall be covered by written SOPs designed to ensure accountability,

accuracy, quality, safety, and uniformity in the compounding process. At a minimum, SOPs shall be developed and implemented for:

(i) the **pharmacy**[~~facility~~];

(ii) equipment;

(iii) personnel;

(iv) preparation evaluation;

(v) quality assurance;

(vi) preparation recall;

(vii) packaging; and

(viii) storage of compounded sterile preparations.

(B) USP/NF. Any compounded formulation with an official monograph in the USP/NF shall be compounded, labeled, and packaged in conformity with the USP/NF monograph for the drug.

(C) Personnel **cleansing and garbing**[~~Cleansing and Garbing~~].

(i) Any person with an apparent illness or open lesion, including rashes, sunburn, weeping sores, conjunctivitis, and active respiratory infection, that may adversely affect the safety or quality of a drug preparation being compounded shall be excluded from working in ISO Class 5, ISO Class 7, and ISO Class 8 compounding areas until the condition is remedied.

(ii) Before entering the buffer **room**[~~area~~], compounding personnel **shall**[~~must remove the following~~]:

(I) **remove** personal outer garments (e.g., bandanas, coats, hats, jackets, scarves, sweaters, vests);

(II) **remove** all cosmetics**;**[~~, because they shed flakes and particles; and~~]

(III) **remove** all hand, wrist, and other body jewelry or piercings (e.g., earrings, lip or eyebrow piercings) that can interfere with the effectiveness of personal protective equipment (e.g., fit of gloves and cuffs of sleeves)**; and**[~~.~~]

(IV) wipe eyeglasses, if worn.

(iii) The wearing of artificial nails or extenders is prohibited while working in the sterile compounding environment. Natural nails shall be kept neat and trimmed.

(iv) Personnel shall [~~don personal protective equipment and~~] perform hand hygiene **and garbing** in an order **determined by the pharmacy depending on the placement of the sink. The order of garbing shall be documented in the pharmacy's SOPs. Garb shall be donned**

and doffed in an order that reduces the risk of contamination. Donning and doffing garb shall not occur in the same area at the same time.[~~that proceeds from the dirtiest to the cleanest activities as follows:~~]

(I) The minimum garbing requirements for preparing Category 1 or Category 2 compounded sterile preparations include the following:

(-a-) low-lint garment with sleeves that fit snugly around the wrists and an enclosed neck (e.g., gown or coverall);

(-b-) low-lint covers for shoes;

(-c-) low-lint cover for head that covers the hair and ears, and if appliable, cover for facial hair;

(-d-) low-lint face mask;

(-e-) sterile powder-free gloves; and

(-f-) if using a restricted-access barrier system (i.e., a compounding aseptic isolator or compounding aseptic containment isolator), disposable gloves should be worn inside the gloves attached to the restricted-access barrier system sleeves. Sterile gloves shall be worn over the gloves attached to the restricted-access barrier system sleeve.

[~~(I) Activities considered the dirtiest include donning of dedicated shoes or shoe covers, head and facial hair covers (e.g., beard covers in addition to face masks), and face mask/eye shield. Eye shields are optional unless working with irritants like germicidal disinfecting agents or when preparing hazardous drugs.~~]

(II) The following additional garbing requirements shall be followed in the buffer room where Category 3 compounded sterile preparations are prepared for all personnel regardless of whether Category 3 compounded sterile preparations are compounded on a given day:

(-a-) skin may not be exposed in the buffer room (i.e., face and neck shall be covered);

(-b-) all low-lint outer garb shall be sterile, including the use of sterile sleeves over gauntlet sleeves when a restricted-access barrier system is used;

(-c-) disposable garbing items shall not be reused and any laundered garb shall not be reused without being laundered and resterilized with a validated cycle; and

(-d-) the pharmacy's SOPs shall describe disinfection procedures for reusing goggles, respirators, and other reusable equipment. If compounding a hazardous drug, appropriate personal protective equipment shall be worn.

(III)[~~(II)~~] After donning dedicated shoes or shoe covers, head and facial hair covers, and face masks, personnel shall perform a hand hygiene procedure by removing debris from underneath fingernails using a nail cleaner under running warm water followed by vigorous hand washing.

Personnel shall begin washing arms at the hands and continue washing to elbows for at least 30 seconds with either a plain (non-antimicrobial) soap, or antimicrobial soap, and water while in the **anteroom**[~~ante-area~~]. **Disposable soap containers shall not be refilled or topped off. Brushes shall not be used for hand hygiene.** Hands and forearms to the elbows shall be completely dried using lint-free disposable towels, an electronic hands-free hand dryer, or a HEPA filtered hand dryer.

(IV)[~~(III)~~] After completion of hand washing, personnel shall don clean non-shedding gowns with sleeves that fit snugly around the wrists and enclosed at the neck.

(V)[~~(IV)~~] Once inside the buffer **room**[~~area~~] or segregated compounding area, and prior to donning sterile powder-free gloves, antiseptic hand cleansing shall be performed using **an alcohol-based hand rub**[~~a waterless alcohol-based surgical hand scrub with persistent activity following manufacturers' recommendations~~]. Hands shall be allowed to dry thoroughly before donning sterile gloves.

(VI)[~~(V)~~] Sterile gloves that form a continuous barrier with the gown shall be the last item donned before compounding begins. Sterile gloves shall be donned **in a classified area or segregated compounding area** using proper technique to ensure the sterility of the glove is not compromised while donning. The cuff of the sterile glove shall cover the cuff of the gown at the wrist. When preparing hazardous preparations, the compounder shall double glove or shall use single gloves ensuring that the gloves are sterile powder-free chemotherapy-rated gloves. Routine application of sterile 70% IPA shall occur throughout the compounding day and whenever non-sterile surfaces are touched.

(v) **Garb shall be replaced immediately if it becomes visibly soiled or if its integrity is compromised. Gowns and other garb shall be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing). If compounding Category 1 or Category 2 compounded sterile preparations, gowns may be reused within the same shift by the same person if the gown is maintained in a classified area or adjacent to, or within, the segregated compounding area in a manner that prevents contamination. When personnel exit the compounding area, garb, except for gowns, may not be reused and shall be discarded or laundered before use. The pharmacy's SOPs shall describe disinfection procedures for reusing goggle, respirators, and other reusable equipment.**[~~When compounding personnel shall temporarily exit the buffer area during a work shift, the exterior gown, if not visibly soiled, may be removed and retained in the ante-area, to be re-donned during that same work shift only. However, shoe covers, hair and facial hair covers, face mask/eye shield, and gloves shall be replaced with new ones before re-entering the buffer area along with performing proper hand hygiene.~~]

(vi) During [~~high-risk level~~] compounding activities that precede terminal sterilization, such as weighing and mixing of non-sterile ingredients, compounding personnel shall be garbed and gloved the same as when performing compounding in an ISO Class 5 environment. Properly garbed and gloved compounding personnel who are exposed to air quality that is either known or suspected to be worse than ISO Class 7 shall re-garb personal protective equipment along with washing their hands properly, performing antiseptic hand cleansing with a sterile 70% IPA-based or another suitable sterile alcohol-based surgical hand scrub, and donning sterile gloves upon re-entering the ISO Class 7 buffer **room**[~~area~~].

(vii) When compounding aseptic isolators or compounding aseptic containment isolators are the source of the ISO Class 5 environment, at the start of each new compounding procedure, a new pair of sterile gloves shall be donned within the CAI or CACI. In addition, the compounding personnel should follow the requirements as specified in this subparagraph, unless the isolator manufacturer can provide written documentation based on validated environmental testing that any components of personal protective equipment or cleansing are not required.

(16)[~~(14)~~] Quality **assurance**[~~Assurance~~].

(A) Initial **formula validation**[~~Formula Validation~~]. Prior to routine compounding of a sterile preparation, a pharmacy shall conduct an evaluation that shows that the pharmacy is capable of compounding a preparation that is sterile and that contains the stated amount of active ingredient(s).

[~~(i) Low risk level preparations.~~]

(i)[~~(I)~~] Quality assurance practices include, but are not limited to the following:

(I)[~~(-a-)~~] Routine disinfection and air quality testing of the direct compounding environment to minimize microbial surface contamination and maintain ISO Class 5 air quality;

(II)[~~(-b-)~~] Visual confirmation that compounding personnel are properly donning and wearing appropriate items and types of protective garments and goggles;

(III) Confirmation that media-fill tests indicate that compounding personnel and personnel who have direct oversight of compounding personnel but do not compound can competently perform aseptic procedures;

(IV)[~~(-c-)~~] Review of all orders and packages of ingredients to ensure that the correct identity and amounts of ingredients were compounded; and

(V)[~~(-d-)~~] Visual inspection of compounded sterile preparations, except for sterile radiopharmaceuticals, to ensure the absence of particulate matter in solutions, the absence of leakage from vials and bags, and the accuracy and thoroughness of labeling.

[~~(II) Example of a Media-Fill Test Procedure. This, or an equivalent test, is performed at least annually by each person authorized to compound in a low-risk level under conditions that closely simulate the most challenging or stressful conditions encountered during compounding of low-risk level sterile preparations. Once begun, this test is completed without interruption within an ISO Class 5 air quality environment. Three sets of four 5-milliliter aliquots of sterile fluid culture media are transferred with the same sterile 10-milliliter syringe and vented needle combination into separate sealed, empty, sterile 30-milliliter clear vials (i.e., four 5-milliliter aliquots into each of three 30-milliliter vials). Sterile adhesive seals are aseptically affixed to the rubber closures on the three filled vials. The vials are incubated within a range of 20 - 35 degrees Celsius for a minimum of 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days. The media-fill test must include a positive-control sample.~~]

[~~(ii) Medium risk level preparations.~~]

[(I) Quality assurance procedures for medium-risk level compounded sterile preparations include all those for low-risk level compounded sterile preparations, as well as a more challenging media-fill test passed annually, or more frequently.]

[(II) Example of a Media-Fill Test Procedure. This, or an equivalent test, is performed at least annually under conditions that closely simulate the most challenging or stressful conditions encountered during compounding. This test is completed without interruption within an ISO Class 5 air quality environment. Six 100-milliliter aliquots of sterile Soybean-Casein Digest Medium are aseptically transferred by gravity through separate tubing sets into separate evacuated sterile containers. The six containers are then arranged as three pairs, and a sterile 10-milliliter syringe and 18-gauge needle combination is used to exchange two 5-milliliter aliquots of medium from one container to the other container in the pair. For example, after a 5-milliliter aliquot from the first container is added to the second container in the pair, the second container is agitated for 10 seconds, then a 5-milliliter aliquot is removed and returned to the first container in the pair. The first container is then agitated for 10 seconds, and the next 5-milliliter aliquot is transferred from it back to the second container in the pair. Following the two 5-milliliter aliquot exchanges in each pair of containers, a 5-milliliter aliquot of medium from each container is aseptically injected into a sealed, empty, sterile 10-milliliter clear vial, using a sterile 10-milliliter syringe and vented needle. Sterile adhesive seals are aseptically affixed to the rubber closures on the three filled vials. The vials are incubated within a range of 20 - 35 degrees Celsius for a minimum of 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days. The media-fill test must include a positive-control sample.]

[(iii) High-risk level preparations.]

[(I) Procedures for high-risk level compounded sterile preparations include all those for low-risk level compounded sterile preparations. In addition, a media-fill test that represents high-risk level compounding is performed twice a year by each person authorized to compound high-risk level compounded sterile preparations.]

[(II) Example of a Media-Fill Test Procedure for Compounded Sterile Preparations Sterilized by Filtration. This test, or an equivalent test, is performed under conditions that closely simulate the most challenging or stressful conditions encountered when compounding high-risk level compounded sterile preparations. Note: Sterility tests for autoclaved compounded sterile preparations are not required unless they are prepared in batches of more than 25 units. This test is completed without interruption in the following sequence:]

[(-a-) Dissolve 3 grams of non-sterile commercially available fluid culture media in 100 milliliters of non-bacteriostatic water to make a 3% non-sterile solution.]

[(-b-) Draw 25 milliliters of the medium into each of three 30-milliliter sterile syringes. Transfer 5 milliliters from each syringe into separate sterile 10-milliliter vials. These vials are the positive controls to generate exponential microbial growth, which is indicated by visible turbidity upon incubation.]

[(-c-) Under aseptic conditions and using aseptic techniques, affix a sterile 0.2-micron porosity filter unit and a 20-gauge needle to each syringe. Inject the next 10 milliliters from each syringe into three separate 10-milliliter sterile vials. Repeat the process for three more vials. Label all vials, affix sterile adhesive seals to the closure of the nine vials, and incubate them at 20 to 35

~~degrees Celsius for a minimum of 14 days. Inspect for microbial growth over 14 days as described in Chapter 797 Pharmaceutical Compounding - Sterile Preparations, of the USP/NF.~~]

(ii)[~~(III)~~] Filter **integrity testing**[~~Integrity Testing~~]. Filters **shall**[~~need to~~] undergo testing to evaluate the integrity of filters used to sterilize **Category 2 prepared from any non-sterile starting component or Category 3 compounded sterile**[~~high-risk~~] preparations, such as **bubble point testing**[~~Bubble Point Testing~~] or comparable filter integrity testing. Such testing is not a replacement for sterility testing and shall not be interpreted as such. Such test shall be performed after a sterilization procedure on all filters used to sterilize each **Category 2 prepared from any non-sterile starting component or Category 3 compounded sterile**[~~high-risk~~] preparation or batch preparation and the results documented. The results should be compared with the filter manufacturer's specification for the specific filter used. If a filter fails the integrity test, the preparation or batch **shall**[~~must~~] be sterilized again using new unused filters.

(B) Finished preparation release checks and tests.

(i) **Each time a Category 3 compounded sterile preparation is prepared, it shall be tested for sterility and meet the requirements of Chapter 71, Sterility Tests of the USP/NF, or a validated alternative method that is noninferior to Chapter 71 testing. Each time a Category 2 injectable compounded sterile preparation compounded from one or more non-sterile components and assigned a beyond-use date that requires sterility testing is prepared, the preparation shall be tested to ensure that it does not contain excessive bacterial endotoxins. Each time a Category 3 injectable compounded sterile preparation compounded from one or more non-sterile components is prepared, the preparation shall be tested to ensure that it does not contain excessive bacterial endotoxins.**[~~All high-risk level compounded sterile preparations that are prepared in groups of more than 25 identical individual single-dose packages (such as ampules, bags, syringes, and vials), or in multiple dose vials for administration to multiple patients, or are exposed longer than 12 hours at 2 - 8 degrees Celsius and longer than six hours at warmer than 8 degrees Celsius before they are sterilized shall be tested to ensure they are sterile and do not contain excessive bacterial endotoxins as specified in Chapter 71, Sterility Tests of the USP/NF before being dispensed or administered.~~]

(ii) All compounded sterile preparations, except for sterile radiopharmaceuticals, that are intended to be solutions **shall**[~~must~~] be visually examined for the presence of particulate matter and not administered or dispensed when such matter is observed.

(iii) The prescription drug and medication orders, written compounding procedure, preparation records, and expended materials used to make compounded sterile preparations [~~at all contamination risk levels~~] shall be inspected for accuracy of correct identities and amounts of ingredients, aseptic mixing and sterilization, packaging, labeling, and expected physical appearance before they are dispensed or administered.

(iv) Written procedures for checking compounding accuracy shall be followed for every compounded sterile preparation during preparation, in accordance with pharmacy's policies and procedures, and immediately prior to release, including label accuracy and the accuracy of the addition of all drug products or ingredients used to prepare the finished preparation and their volumes or quantities. A pharmacist shall ensure that components used in compounding are

accurately weighed, measured, or subdivided as appropriate to conform to the formula being prepared.

(C) Environmental **testing**[~~Testing~~].

(i) Viable and nonviable environmental sampling testing. Environmental sampling shall occur, at a minimum, every six months as part of a comprehensive quality management program and under any of the following conditions:

(I) as part of the commissioning and certification of new facilities and equipment;

(II) following any servicing of facilities and equipment;

(III) as part of the re-certification of facilities and equipment;

(IV) in response to identified problems with end products or staff technique; or

(V) in response to issues with compounded sterile preparations, observed compounding personnel work practices, or patient-related infections (where the compounded sterile preparation is being considered as a potential source of the infection).

(ii) Total particle counts. Certification that each ISO classified area (e.g., ISO Class 5, 7, and 8), is within established guidelines shall be performed no less than every six months and whenever the equipment is relocated or the physical structure of the buffer **room**[~~area~~] or **anteroom**[~~ante-area~~] has been altered. All certification records shall be maintained and reviewed to ensure that the controlled environments comply with the proper air cleanliness, room pressures, and air changes per hour. These certification records **shall**[~~must~~] include acceptance criteria and be made available upon inspection by the Board. Testing shall be performed by qualified operators using current, state-of-the-art equipment, with results of the following:

(I) ISO Class 5 - not more than **3,520**[~~3520~~] particles 0.5 **microns**[~~micrometer~~] and larger **in diameter**[~~size~~] per cubic meter of air;

(II) ISO Class 7 - not more than 352,000 particles of 0.5 **microns**[~~micrometer~~] and larger **in diameter**[~~size~~] per cubic meter of air for any buffer **room**[~~area~~]; and

(III) ISO Class 8 - not more than 3,520,000 particles of 0.5 **microns**[~~micrometer~~] and larger **in diameter**[~~size~~] per cubic meter of air for any **anteroom**[~~ante-area~~].

(iii) Pressure differential monitoring. A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer **room**[~~area~~] and the **anteroom**[~~ante-area~~] and between the **anteroom**[~~ante-area~~] and the general environment outside the compounding area. The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device. The pressure between the ISO Class 7 or ISO Class 8 and the general pharmacy area shall not be less than 0.02 inch water column.

(iv) Sampling plan. An appropriate environmental sampling plan shall be developed for airborne viable particles based on a risk assessment of compounding activities performed. Selected

sampling sites shall include locations within each ISO Class 5 environment and in the ISO Class 7 and 8 areas and in the segregated compounding areas at greatest risk of contamination. The plan shall include sample location, method of collection, frequency of sampling, volume of air sampled, and time of day as related to activity in the compounding area and action levels.

(v) Viable air sampling. Evaluation of airborne microorganisms using volumetric collection methods in the controlled air environments shall be performed by properly trained individuals for all **compounded sterile preparations**[~~compounding risk levels~~]. **Volumetric active air sampling of all active classified areas using an impaction air sampler shall be conducted in each classified area (e.g., ISO Class 5 PEC and ISO Class 7 and 8 room(s)) during dynamic operating conditions. For entities compounding Category 1 or Category 2 compounded sterile preparations, this shall be completed at least every six months. For entities compounding any Category 3 compounded sterile preparations, this shall be completed within 30 days prior to the commencement of any Category 3 compounding and at least every three months thereafter regardless of the frequency of compounding Category 3 compounded sterile preparations. Air sampling sites shall be selected in all classified areas.**[~~For low-, medium-, and high-risk level compounding, air sampling shall be performed at locations that are prone to contamination during compounding activities and during other activities such as staging, labeling, gowning, and cleaning. Locations shall include zones of air backwash turbulence within the laminar airflow workbench and other areas where air backwash turbulence may enter the compounding area. For low-risk level compounded sterile preparations within 12-hour or less beyond-use-date prepared in a primary engineering control that maintains an ISO Class 5, air sampling shall be performed at locations inside the ISO Class 5 environment and other areas that are in close proximity to the ISO Class 5 environment during the certification of the primary engineering control.~~]

(vi) Air sampling [~~frequency and~~] process. [~~Air sampling shall be performed at least every 6 months as a part of the re-certification of facilities and equipment.~~]

(I) A sufficient volume of air shall be sampled [~~and the manufacturer's guidelines for use of the electronic air sampling equipment followed~~]. **Follow the manufacturer's instructions for operation of the impaction air sampler, including placement of media device(s). Using the impaction air sampler, test at least 1 cubic meter or 1,000 liters of air from each location sampled. At the end of each sampling period, retrieve the media device and cover it. Handle and store media devices to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert plates).** At the end of the designated sampling or exposure period for air sampling activities, the microbial growth media plates are recovered and their covers secured and they are inverted and incubated **pursuant to the procedures in subclause (II) of this clause**[~~at a temperature and for a time period conducive to multiplication of microorganisms~~]. Sampling data shall be collected and reviewed on a periodic basis as a means of evaluating the overall control of the compounding environment.

(II) Incubation procedures.

(-a-) Incubate the media device at 30 to 35 degrees Celsius for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.

(-b-) Then incubate the media at 20 to 25 degrees Celsius for no less than five additional days. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu per cubic meter of air on an environmental sampling form based on sample type (i.e., viable air), sample location, and sample date.

(-c-) Alternatively, to shorten the overall incubation period, two sampling media devices may be collected for each sample location and incubated concurrently.

(-1-) The media devices shall either both be trypticase soy agar or shall be one trypticase soy agar and the other fungal media (e.g., malt extract agar or Sabouraud dextrose agar).

(-2-) Incubate each media device in a separate incubator. Incubate one media device at 30 to 35 degrees Celsius for no less than 48 hours, and incubate the other media device at 20 to 25 degrees Celsius for no less than five days. If fungal media are used as one of the samples, incubate the fungal media sample at 20 to 25 degrees Celsius for no less than five days.

(-3-) Count the total number of discrete colonies of microorganisms on each media device, and record these results as cfu per cubic meter of air.

(-4-) Record the results of the sampling on an environmental sampling form based on sample type (i.e., viable air), and include the sample location and sample date.

(III) The following action levels for viable air sampling apply: a[~~If an activity consistently shows elevated levels of microbial growth, competent microbiology or infection control personnel shall be consulted. A~~] colony forming unit (cfu) count greater than 1 cfu per cubic meter of air for ISO Class 5, greater than 10 **cfus**[~~cfu~~] per cubic meter of air for ISO Class 7, and greater than 100 **cfus**[~~cfu~~] per cubic meter of air for ISO Class 8**. If levels measured during viable air sampling exceed the action levels in this subclause for the ISO classification levels of the area sampled, the cause shall be investigated and corrective action shall be taken. Data collected in response to corrective actions shall be reviewed to confirm that the actions taken have been effective. The corrective action plan shall be dependent on the cfu count and the microorganism recovered. The corrective action plan shall be documented. If levels measured during viable air sampling exceed the action levels in this subclause, an attempt shall be made to identify any microorganism recovered to the genus level with the assistance of a competent microbiologist.**[~~or worse should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location. An investigation into the source of the contamination shall be conducted. The source of the problem shall be eliminated, the affected area cleaned, and resampling performed. Counts of cfu are to be used as an approximate measure of the environmental microbial bioburden. Action levels are determined on the basis of cfu data gathered at each sampling location and trended over time. Regardless of the number of cfu identified in the pharmacy, further corrective actions will be dictated by the identification of microorganisms recovered by an appropriate credentialed laboratory of any microbial bioburden captured as a cfu using an impaction air sampler. Highly pathogenic microorganisms (e.g., gram-negative rods, coagulase positive staphylococcus, molds and yeasts) can be potentially fatal to patient receiving compounded sterile preparations and must be immediately remedied, regardless of colony forming unit count, with the assistance, if needed, of a competent microbiologist, infection control professional, or industrial hygienist.~~]

(vii) Compounding accuracy checks. Written procedures for checking compounding accuracy shall be followed for every compounded sterile preparation during preparation and immediately prior to release, including label accuracy and the accuracy of the addition of all drug products or ingredients used to prepare the finished preparation and their volumes or quantities. At each step of the compounding process, the pharmacist shall ensure that components used in compounding are accurately weighed, measured, or subdivided as appropriate to conform to the formula being prepared.

(17)[~~(15)~~] Quality control.

(A) Quality control procedures. The pharmacy shall follow established quality control procedures to monitor the compounding environment and quality of compounded drug preparations for conformity with the quality indicators established for the preparation. When developing these procedures, pharmacy personnel shall consider the provisions of USP Chapter 71, Sterility Tests, USP Chapter 85, Bacterial Endotoxins Test, Pharmaceutical Compounding-Non-sterile Preparations, USP Chapter 795, USP Chapter 797, Pharmaceutical Compounding--Sterile Preparations, USP Chapter 800, Hazardous Drugs--Handling in Healthcare Settings, USP Chapter 823, Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses, USP Chapter 1160, Pharmaceutical Calculations in Prescription Compounding, and USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding of the current USP/NF. Such procedures shall be documented and be available for inspection.

(B) Verification of compounding accuracy and sterility.

(i) The accuracy of identities, concentrations, amounts, and purities of ingredients in compounded sterile preparations shall be confirmed by reviewing labels on packages, observing and documenting correct measurements with approved and correctly standardized devices, and reviewing information in labeling and certificates of analysis provided by suppliers.

(ii) If the correct identity, purity, strength, and sterility of ingredients and components of compounded sterile preparations cannot be confirmed such ingredients and components shall be discarded immediately. Any compounded sterile preparation that fails sterility testing following sterilization by one method (e.g., filtration) is to be discarded and not subjected to a second method of sterilization.

(iii) If individual ingredients, such as bulk drug substances, are not labeled with expiration dates, when the drug substances are stable indefinitely in their commercial packages under labeled storage conditions, such ingredients may gain or lose moisture during storage and use and shall require testing to determine the correct amount to weigh for accurate content of active chemical moieties in compounded sterile preparations.

(C) Sterility testing. Sterility testing shall be performed on a number of units equal to 5% of the number of compounded sterile preparations prepared, rounded up to the next whole number. Sterility tests resulting in failure shall prompt an investigation into the possible causes of the failure and shall include identification of the microorganism and an evaluation of the sterility testing procedure, compounding facility, process, and personnel that may have contributed to the failure. The sources of the contamination, if identified, shall be corrected and the pharmacy shall determine whether the conditions causing the sterility failure affect other compounded sterile preparations. The investigation and resulting corrective actions shall be documented.

(e) Records. Any testing, cleaning, procedures, or other activities required in this subsection shall be documented and such documentation shall be maintained by the pharmacy.

(1) Maintenance of records. Every record required under this section **shall**[~~must~~] be:

(A) kept by the pharmacy and be available, for at least two years for inspecting and copying by the board or its representative and to other authorized local, state, or federal law enforcement agencies; and

(B) supplied by the pharmacy within 72 hours, if requested by an authorized agent of the Texas State Board of Pharmacy. If the pharmacy maintains the records in an electronic format, the requested records **shall**[~~must~~] be provided in an electronic format. Failure to provide the records set out in this section, either on site or within 72 hours, constitutes prima facie evidence of failure to keep and maintain records in violation of the Act.

(2) Compounding records.

(A) Compounding pursuant to patient specific prescription drug orders or medication orders **not prepared from non-sterile ingredient(s)**. Compounding records for all compounded preparations shall be maintained by the pharmacy and shall include **a complete formula, including methodology and necessary equipment which includes the brand name(s) of the raw materials, or if no brand name, the generic name(s) or official name and name(s) of the manufacturer(s) or distributor of the raw materials and the quantities of each; however, if the sterile preparation is compounded according to the manufacturer's labeling instructions, then documentation of the formula is not required.**[~~:~~]

[~~(i) the date and time of preparation;~~]

[~~(ii) a complete formula, including methodology and necessary equipment which includes the brand name(s) of the raw materials, or if no brand name, the generic name(s) or official name and name(s) of the manufacturer(s) or distributor of the raw materials and the quantities of each; however, if the sterile preparation is compounded according to the manufacturer's labeling instructions, then documentation of the formula is not required;~~]

[~~(iii) written or electronic signature or initials of the pharmacist or pharmacy technician or pharmacy technician trainee performing the compounding;~~]

[~~(iv) written or electronic signature or initials of the pharmacist responsible for supervising pharmacy technicians or pharmacy technician trainees and conducting finals checks of compounded pharmaceuticals if pharmacy technicians or pharmacy technician trainees perform the compounding function;~~]

[~~(v) the container used and the number of units of finished preparation prepared; and~~]

[~~(vi) a reference to the location of the following documentation which may be maintained with other records, such as quality control records:~~]

[~~(I) the criteria used to determine the beyond-use date; and~~]

[~~(II) documentation of performance of quality control procedures.~~]

(B) Compounding records **for compounded sterile preparations prepared from non-sterile ingredient(s) or prepared for more than one patient**[~~when batch compounding or compounding in anticipation of future prescription drug or medication orders.~~]

(i) [~~Master work sheet~~]. A **master formulation record**[~~master work sheet~~] shall be **created for compounded sterile preparations prepared from non-sterile ingredient(s) or prepared for more than one patient. Any changes or alterations to the master formulation record shall be approved and documented according to the pharmacy's SOPs. The master formulation record shall include at least the following information:**[~~developed and approved by a pharmacist for preparations prepared in batch. Once approved, a duplicate of the master work sheet shall be used as the preparation work sheet from which each batch is prepared and on which all documentation for that batch occurs. The master work sheet shall contain at a minimum:~~]

(I) **name, strength or activity, and dosage form of the compounded sterile preparation**[~~the formula~~];

(II) **identities and amounts of all ingredients and, if applicable, relevant characteristics or components (e.g., particle size, salt form, purity grade, solubility)**[~~the components~~];

(III) **type and size of container closure system(s)**[~~the compounding directions~~];

(IV) **complete instructions for preparing the compounded sterile preparation, including equipment, supplies, a description of the compounding steps, and any special precautions**[~~a sample label~~];

(V) **physical description of the final compounded sterile preparation**[~~evaluation and testing requirements~~];

(VI) **beyond-use date and storage requirements;**[~~specific equipment used during preparation; and~~]

(VII) **reference source to support the stability of the compounded sterile preparation;**[~~storage requirements.~~]

(VIII) quality control procedures (e.g., pH testing, filter integrity testing); and

(IX) other information as needed to describe the compounding process and ensure repeatability (e.g., adjusting pH and tonicity; sterilization method, such as steam, dry heat, irradiation, or filter).

(ii) A compounding record that documents the compounding process shall be created for all compounded sterile preparations. The compounding record shall include at least the following information:

(I) name, strength or activity, and dosage form of the compounded sterile preparation;

(II) date and time of preparation of the compounded sterile preparation;

(III) assigned internal identification number (e.g., prescription, order, or lot number);

(IV) written or electronic signature or initials of the pharmacist or pharmacy technician or pharmacy technician trainee performing the compounding;

(V) written or electronic signature or initials of the pharmacist responsible for supervising pharmacy technicians or pharmacy technician trainees and conducting final checks of compounded preparations if pharmacy technicians or pharmacy technician trainees perform the compounding function;

(VI) name of each component;

(VII) vendor, lot number, and expiration date for each component for compounded sterile preparations prepared for more than one patient or prepared from non-sterile ingredient(s);

(VIII) weight or volume of each component;

(IX) strength or activity of each component;

(X) total quantity compounded;

(XI) final yield (e.g., quantity, containers, number of units);

(XII) assigned beyond-use date and storage requirements;

(XIII) results of quality control procedures (e.g., visual inspection, filter integrity testing, pH testing);

(XIV) if applicable, master formulation record for the compounded sterile preparation; and

(XV) if applicable, calculations made to determine and verify quantities or concentrations of components.

~~[(ii) Preparation work sheet. The preparation work sheet for each batch of preparations shall document the following:]~~

~~[(I) identity of all solutions and ingredients and their corresponding amounts, concentrations, or volumes;]~~

~~[(II) lot number for each component;]~~

~~[(III) component manufacturer/distributor or suitable identifying number;]~~

~~[(IV) container specifications (e.g., syringe, pump cassette);]~~

[~~(V) unique lot or control number assigned to batch;~~]

[~~(VI) expiration date of batch-prepared preparations;~~]

[~~(VII) date of preparation;~~]

[~~(VIII) name, initials, or electronic signature of the person(s) involved in the preparation;~~]

[~~(IX) name, initials, or electronic signature of the responsible pharmacist;~~]

[~~(X) finished preparation evaluation and testing specifications, if applicable; and~~]

[(XI) comparison of actual yield to anticipated or theoretical yield, when appropriate.]

(f) Office **use compounding and distribution of sterile compounded preparations.**[~~Use Compounding and Distribution of Sterile Compounded Preparations~~]

(1) General.

(A) A pharmacy may compound, dispense, deliver, and distribute a compounded sterile preparation as specified in Subchapter D, Texas Pharmacy Act Chapter 562.

(B) A Class A-S pharmacy is not required to register or be licensed under Chapter 431, Health and Safety Code, to distribute sterile compounded preparations to a Class C or Class C-S pharmacy.

(C) A Class C-S pharmacy is not required to register or be licensed under Chapter 431, Health and Safety Code, to distribute sterile compounded preparations that the Class C-S pharmacy has compounded for other Class C or Class C-S pharmacies under common ownership.

(D) To compound and deliver a compounded preparation under this subsection, a pharmacy **shall**[~~must~~]:

(i) verify the source of the raw materials to be used in a compounded drug;

(ii) comply with applicable United States Pharmacopoeia guidelines, including the testing requirements, and the Health Insurance Portability and Accountability Act of 1996 (Pub. L. No. 104-191);

(iii) enter into a written agreement with a practitioner for the practitioner's office use of a compounded preparation;

(iv) comply with all applicable competency and accrediting standards as determined by the board; and

(v) comply with the provisions of this subsection.

(E) This subsection does not apply to Class B pharmacies compounding sterile radiopharmaceuticals that are furnished for departmental or physicians' use if such authorized users maintain a Texas radioactive materials license.

(2) Written Agreement. A pharmacy that provides sterile compounded preparations to practitioners for office use or to another pharmacy shall enter into a written agreement with the practitioner or pharmacy. The written agreement shall:

(A) address acceptable standards of practice for a compounding pharmacy and a practitioner and receiving pharmacy that enter into the agreement including a statement that the compounded drugs may only be administered to the patient and may not be dispensed to the patient or sold to any other person or entity except to a veterinarian as authorized by §563.054 of the Act;

(B) require the practitioner or receiving pharmacy to include on a patient's chart, medication order or medication administration record the lot number and beyond-use date of a compounded preparation administered to a patient; and

(C) describe the scope of services to be performed by the pharmacy and practitioner or receiving pharmacy, including a statement of the process for:

(i) a patient to report an adverse reaction or submit a complaint; and

(ii) the pharmacy to recall batches of compounded preparations.

(3) Recordkeeping.

(A) Maintenance of Records.

(i) Records of orders and distribution of sterile compounded preparations to a practitioner for office use or to an institutional pharmacy for administration to a patient shall:

(I) be kept by the pharmacy and be available, for at least two years from the date of the record, for inspecting and copying by the board or its representative and to other authorized local, state, or federal law enforcement agencies;

(II) be maintained separately from the records of preparations dispensed pursuant to a prescription or medication order; and

(III) be supplied by the pharmacy within 72 hours, if requested by an authorized agent of the Texas State Board of Pharmacy or its representative. If the pharmacy maintains the records in an electronic format, the requested records **shall**[~~must~~] be provided in an electronic format. Failure to provide the records set out in this subsection, either on site or within 72 hours for whatever reason, constitutes prima facie evidence of failure to keep and maintain records.

(ii) Records may be maintained in an alternative data retention system, such as a data processing system or direct imaging system provided the data processing system is capable of producing a hard copy of the record upon the request of the board, its representative, or other authorized local, state, or federal law enforcement or regulatory agencies.

(B) Orders. The pharmacy shall maintain a record of all sterile compounded preparations ordered by a practitioner for office use or by an institutional pharmacy for administration to a patient. The record shall include the following information:

(i) date of the order;

(ii) name, address, and phone number of the practitioner who ordered the preparation and if applicable, the name, address and phone number of the institutional pharmacy ordering the preparation; and

(iii) name, strength, and quantity of the preparation ordered.

(C) Distributions. The pharmacy shall maintain a record of all sterile compounded preparations distributed pursuant to an order to a practitioner for office use or by an institutional pharmacy for administration to a patient. The record shall include the following information:

(i) date the preparation was compounded;

(ii) date the preparation was distributed;

(iii) name, strength and quantity in each container of the preparation;

(iv) pharmacy's lot number;

(v) quantity of containers shipped; and

(vi) name, address, and phone number of the practitioner or institutional pharmacy to whom the preparation is distributed.

(D) Audit **trail**~~Trail~~.

(i) The pharmacy shall store the order and distribution records of preparations for all sterile compounded preparations ordered by and or distributed to a practitioner for office use or by a pharmacy licensed to compound sterile preparations for administration to a patient in such a manner as to be able to provide an audit trail for all orders and distributions of any of the following during a specified time period:

(I) any strength and dosage form of a preparation (by either brand or generic name or both);

(II) any ingredient;

(III) any lot number;

(IV) any practitioner;

(V) any facility; and

(VI) any pharmacy, if applicable.

(ii) The audit trail shall contain the following information:

(I) date of order and date of the distribution;

(II) practitioner's name, address, and name of the institutional pharmacy, if applicable;

(III) name, strength and quantity of the preparation in each container of the preparation;

(IV) name and quantity of each active ingredient;

(V) quantity of containers distributed; and

(VI) pharmacy's lot number.

(4) Labeling. The pharmacy shall affix a label to the preparation containing the following information:

(A) name, address, and phone number of the compounding pharmacy;

(B) the statement: "For Institutional or Office Use Only--Not for Resale"; or if the preparation is distributed to a veterinarian the statement: "Compounded Preparation";

(C) name and strength of the preparation or list of the active ingredients and strengths;

(D) pharmacy's lot number;

(E) beyond-use date as determined by the pharmacist using appropriate documented criteria;

(F) quantity or amount in the container;

(G) appropriate ancillary instructions, such as storage instructions or cautionary statements, including hazardous drug warning labels where appropriate; and

(H) device-specific instructions, where appropriate.

(g) Recall **procedures**[~~Procedures~~].

(1) The pharmacy shall have **SOPs**[~~written procedures~~] for the recall of any compounded sterile preparation provided to a patient, to a practitioner for office use, or a pharmacy for administration. The **SOPs**[~~Written procedures~~] shall include, but not be limited to the requirements as specified in paragraph (3) of this subsection.

(2) The pharmacy shall immediately initiate a recall of any sterile preparation compounded by the pharmacy upon identification of a potential or confirmed harm to a patient.

(3) In the event of a recall, the pharmacist-in-charge shall ensure that:

(A) the distribution of any affected compounded sterile preparation is determined, including the date and quantity of distribution;

(B)[~~(A)~~] each practitioner, facility, and/or pharmacy to which the preparation was distributed is notified, in writing, of the recall;

(C)[~~(B)~~] each patient to whom the preparation was dispensed is notified, in writing, of the recall;

(D)[~~(C)~~] the board is notified of the recall, in writing, not later than 24 hours after the recall is issued;

(E)[~~(D)~~] if the preparation is distributed for office use, the Texas Department of State Health Services, Drugs and Medical Devices Group, is notified of the recall, in writing;

(F)[~~(E)~~] **any unused dispensed compounded sterile preparations are recalled and any stock remaining in the pharmacy is quarantined**[~~the preparation is quarantined~~]; and

(G)[~~(F)~~] the pharmacy keeps a written record of the recall including all actions taken to notify all parties and steps taken to ensure corrective measures.

(4) Recall of out-of-specification dispensed compounded sterile preparations.

(A) If a compounded sterile preparation is dispensed or administered before the results of testing are known, the pharmacy shall have SOPs in place to:

(i) immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., sterility, strength, purity, bacterial endotoxin, or other quality attributes); and

(ii) investigate if other lots are affected and recall if necessary.

(B) SOPs for recall of out-of-specification dispensed compounded sterile preparations shall contain procedures to:

(i) determine the severity of the problem and the urgency for implementation and completion of the recall;

(ii) determine the disposal and documentation of the recalled compounded sterile preparation; and

(iii) investigate and document the reason for failure.

(5)[~~(4)~~] If a pharmacy fails to initiate a recall, the board may require a pharmacy to initiate a recall if there is potential for or confirmed harm to a patient.

(6)[~~(5)~~] A pharmacy that compounds sterile preparations shall notify the board immediately of any adverse effects reported to the pharmacy or that are known by the pharmacy to be potentially attributable to a sterile preparation compounded by the pharmacy.

Pharmacy Leaders. Transforming Patient Care.

Subject: Urging Adherence to USP Standards for Sterile Compounding in Texas

Dear Members of the Texas State Board of Pharmacy (TSBP),

The Texas Society of Health-System Pharmacy (TSHP) respectfully urges the Board to adopt the recommended revisions to §291.133 as presented by the TSBP <797> Sterile Compounding Task Force. It is important to adopt and enforce sterile compounding practices that align with the national standards outlined in the United States Pharmacopeia (USP) Chapter <797>.

USP standards on the compounding of sterile preparations ensure patient safety and minimize the risk of contamination. This includes standards for personnel training, environmental controls, aseptic technique, quality assurance, and risk assessment.

Specifically, TSHP appreciates the Board's careful consideration of the entire <797> Chapter including the rationale, BUDs, and Batch size requirements of Categories 1, 2, and 3. As outlined below, several organizations, including the FDA are supportive of this. Specifically, the FDA has concerns with compounders extending BUDs beyond what is provided in USP <797> "Based on FDA's experience, the proposed default BUDs in the remanded Chapters would meet the needs for most patient-specific compounded drug products."[1]

In the included document provided by USP, the intended scope of compounded CSPs under Chapter <797> standards are for patient specific prescriptions, therefore BUDs of CSPs are not intended to be stored for long periods of time. The USP also acknowledges batch size limits have taken into account that contamination risk is higher the larger the batch, particularly for manual processes. [4]

A pharmacy which operates under 503A of the Federal Food Drug and Cosmetic Act requires CSPs with patient specific prescriptions. TSHP is appreciative of the Board's careful oversight, through the rules, to ensure that BUD's and batch sizes are in alignment with this act and USP <797> standards to not avoid CGMP standards set forth in section 503B.

Supporting Organizations:

- **Texas Society of Health-System Pharmacy (TSHP) & American Society of Health-System Pharmacists (ASHP):** TSHP and ASHP strongly support the adoption and enforcement of USP standards by state boards of pharmacy. Their position statements emphasize the critical role of these standards in safeguarding patient health and maintaining the quality of compounded sterile preparations.
- **American Pharmacists Association (APhA):** APhA similarly advocates for the adoption of USP standards. Their position statements highlight the importance of these standards for ensuring patient safety and maintaining public trust in pharmacy practice.
- **National Association of Boards of Pharmacy (NABP):** NABP, through its Model Rules for the Practice of Pharmacy, encourages state boards of pharmacy to adopt USP standards. Furthermore, aligning with USP is crucial for participating in the NABP Multistate Inspection Program, which can streamline inspections and improve efficiency.

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- **Food and Drug Administration (FDA):** "FDA encourages USP to examine whether a need to extend BUDs exists from a patient need perspective. Concerning this point, it is unclear to FDA why a patient-specific prescription would require BUDs that are longer than the default BUDs proposed in remanded Chapters <795> and <797>. Extending BUDs for compounded drugs in the absence of CGMP requirements would unnecessarily lead to increased risks to patients…".[1]

Risks of Non-Alignment:

- **Patient Safety:** Deviation from USP standards can increase the risk of microbial contamination in compounded sterile preparations, potentially leading to serious adverse patient outcomes.[2, 3] The USP CMP EC determined batch sizes and BUD from the careful consideration and analysis of a plethora of information and data from multiple sources to determine these limits and the TSBP is encouraged to be as vigilant as the USP in querying multiple data sources and information to ensure patient safety and protecting the public from harm.[4]
- **Legal and Regulatory Challenges:** Non-compliance with USP may expose pharmacies, pharmacists, and TSBP to increased legal and regulatory risks, including potential litigation, sanctions, and disciplinary actions.
- **Reduced Efficiency:** Lack of alignment with USP can hinder participation in the NABP Multistate Inspection Program, leading to increased inspection burdens and potential delays in licensure and other regulatory processes.

We believe that formal adoption and enforcement of USP standards by the Texas State Board of Pharmacy are essential to protect the health and safety of Texas patients and maintain high standards of pharmacy practice in the state.

We respectfully request that the Board carefully consider this matter and take appropriate action to ensure the safe and effective compounding of sterile preparations in Texas. We are available to meet with the Board to further discuss this important issue and answer any questions you may have.

Sincerely,

Aaron D. Reich, Pharm.D.
President, TRINU Healthcare
President, Texas Society of Health-System Pharmacy

References:

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2. Proffer, Erica. "54,000% higher: Austin woman almost dies after pharmacy's dosage mistake." KVUE, May 7, 2019. https://www.kvue.com/article/news/investigations/defenders/austin-central-texas-compounding-pharmacies-compounded-drugs-dangers/269-8f03b797-5fcc-457b-9bb7-dbc517aafa4f.
3. ProfferE, EllisJ. "Are Patients in Danger? Investigation into Central Texas Compounding Pharmacies Raises Concerns." KVUE, February 6, 2020. https://www.kvue.com/article/news/investigations/defenders/54000-higher-austin-woman-almost-dies-after-pharmacys-dosage-mistake/269-d1bf71e7-025b-44d4-b8ec-8a45e108b8b8
4. USP. **BUD Scientific Rationale for the 2021 Proposed Revisions to <797>**, 5-9. September 1, 2021. https://go.usp.org/l/323321/2021-08-31/5kmcjf/323321/1630438802OI493yjz/BUD_Scientific_Rationale_for_the_2021_Proposed_Revisions_to__795_.docx

2501 STATE REGULATION OF COMPOUNDING

To advocate state laws and regulations that govern compounding by any health professional align to the applicable compendial standards of the United States Pharmacopoeia (USP); further,

To advocate for safe patient care through education of regulatory inspectors, effective compliance inspections, enhanced interagency communication, and continuous quality improvement.

Rationale

Sterile compounding best practices and standards of practice have evolved with the advancement of pharmaceutical manufacturing and individualized medications. However, cases of contamination, adulteration, and misbranding have persisted, culminating in numerous avoidable cases of death and patient harm, highlighting the need for both federal and state oversight of compounding. TSHP advocates state oversight of entities that compound and engage in state commerce to address the wider public health threat when these preparations can potentially be distributed nationwide. TSHP calls for state regulation of compounding by health professionals (including pharmacists, physicians, and nurses) that would require meeting the applicable USP standards. TSHP believes that state-registered facilities engaged in "traditional compounding" (i.e., compounding for specific patient prescriptions or in anticipation of specific patient prescriptions or medication orders) be required to meet applicable USP standards. TSHP also advocates for inspection by the relevant regulatory body, training of inspectors, and enhanced communication among state regulatory authorities.

Background

The compounding of medications, particularly sterile preparations, is a critical area of pharmacy practice directly impacting patient safety and healthcare outcomes. Recent incidents involving contamination in compounded medications have underscored the urgent need for standardized regulatory frameworks to mitigate risks. Despite the existence of national standards, such as those established by the United States Pharmacopeia (USP), variations in state laws and enforcement practices have created inconsistencies jeopardizing patient safety and pharmacy efficiency.

USP Chapter <797> sets comprehensive guidelines for sterile compounding, encompassing personnel training, aseptic techniques, environmental controls, and quality assurance protocols. Adherence to these standards minimizes microbial contamination risks, reduces medication errors, and ensures the preparation of high-quality compounds. However, in states like Texas, inconsistent adoption and enforcement of these standards can lead to significant vulnerabilities in patient care and operational efficiency. Deviations from USP standards increase the risk of contamination, potentially resulting in severe adverse events or even fatalities. Additionally, non-alignment with USP can hinder pharmacies' participation in programs such as the National Association of Boards of Pharmacy (NABP) Multistate Inspection Program, which streamlines compliance inspections and promotes efficiency. Legal and regulatory challenges also mount when compounding practices fail to meet established benchmarks, exposing pharmacists and institutions to sanctions and reputational damage.

This policy advocates state laws to align with USP standards to ensure safe, high-quality compounding practices. By enhancing regulatory inspector training, fostering effective interagency communication, and encouraging continuous quality improvement, this policy aims to protect patients, uphold pharmacy excellence, and support compliance with evolving regulatory requirements.

<797> FAQs

Updated: December 11, 2023

General

1. Where can I find FAQs and other information on USP Compounding Standards?

For FAQs on USP Compounding Standards, please see below:

- General Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations
- General Chapter <797> Pharmaceutical Compounding—Sterile Preparations
- General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings
- General Chapter <825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging
- Compounded Preparation Monographs (CPMs)

2. Where can I find information about how to interpret and apply General Chapters?

The *General Notices and Requirements* describe the basic assumptions, definitions, and default conditions for the interpretation and application of *USP–NF* content. For example, Section 2.30. *Legal Recognition* describes the legal recognition of USP and NF. Section *3.10.30 Applicability of Standards to the Practice of Compounding* describes when USP compounding practice standards are or are not applicable.

Introduction and Scope

3. What is the definition of sterile compounding?

For purposes of General Chapter <797>, sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile medication. However, administration and preparation per the manufacturer's approved labeling are out of the scope of the chapter as described in *1.2 Administration* and *1.4 Preparation Per Approved Labeling,* respectively.

4. To whom do the standards in General Chapter <797> apply?

This chapter applies to all persons who prepare compounded sterile preparations (CSPs) and all places where CSPs are prepared for human and animal patients. This includes, but is not limited to, pharmacists, technicians, nurses, physicians, veterinarians, dentists, naturopaths, and chiropractors in all places including, but not limited to, hospitals and other healthcare institutions, medical and surgical patient treatment sites, infusion facilities, pharmacies, and physicians' or veterinarian practice sites. Any person entering a sterile compounding area, whether preparing a CSP or not, must meet the requirements in *3. Personal Hygiene and Garbing*.

Please note, compounding of sterile hazardous drugs (HDs) must additionally comply with General Chapter <800> *Hazardous Drugs—Handling in Healthcare Settings*.

5. What is considered a compounding facility? Are there requirements that have to be met in order to be considered a compounding facility?

The requirements of the chapter apply to all places where CSPs are prepared for human and animal patients. Additionally, there may be local or federal requirements that must be met.

6. How do I know what are requirements versus recommendations in the chapter?

Generally, requirements in a General Chapter are conveyed by use of the term "must". Recommendations are conveyed by use of the terms "should" and "may".

7. What does "official date" mean?

The USP "official date" indicates the date by which affected users are expected to meet the requirements of a particular standard. Ensuring compliance with the requirements of these standards is the responsibility of the applicable regulatory jurisdiction. USP has no role in enforcement. All text in the United States Pharmacopeia (USP) or National Formulary (NF) that has reached its official date is "official text." Although all text of the *USP–NF* that has reached its official date is "official text," not all official text states requirements with which compendial users must comply. Some official text is intended to assist or guide compendial users or to serve informational purposes.

8. When do the revisions to General Chapter <797> become official?

The revision of <797> published on November 1, 2022, became "official" on November 1, 2023. The "official date" indicates the date by which affected users are expected to meet the requirements of a particular standard. However, ensuring compliance with the requirements of these standards is the responsibility of the applicable regulatory jurisdiction. Regulatory bodies such as state boards of pharmacy may have a different official date. USP has no role in enforcement.

a) Why is there a version of <797> in the *USP-NF* that shows up as "To be Official on 01-May-2024"?

The revision of <797> published on November 1, 2022, became official on November 1, 2023. Section *14.4.3 Stability Requirements for Category 3 CSPs* in <797> includes a reference to *USP* <789>. The USP General Chapters – Dosage Forms Expert Committee revised the title of <789> from <789> *Particulate Matter in Ophthalmic Solutions* to <789> *Subvisible Particulate Matter in Intraocular Solutions*, with this change scheduled to become official on May 1, 2024. Due to this title revision, the reference to <789> in <797> *14.4.3* will be revised to reflect the new title when the <789> revision becomes official. This is the only change in the <797> version that shows as "To be Official on 01-May-2024" in the *USP-NF* and the *Compounding Compendium*. An alert has been added to the <797> version to be official on May 1, 2024, for clarification. To view the version of <797> that became official on November 1, 2023, please visit: https://online.uspnf.com/uspnf/document/1_GUID-A4CAAA8B-6F02-4AB8-8628-09E102CBD703_7_en-US.

9. Are the temperatures in the chapter expressed in degrees Fahrenheit or Celsius?

Unless otherwise specified, all temperatures in the *USP–NF* are expressed in degrees centigrade (Celsius) (see also *General Notices 8.180 Temperatures*).

10. Who can be the designated person(s)?

The designated person is one or more individuals assigned by the facility to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of compounded sterile preparations (CSPs). Facilities must determine whether they have one or more designated person(s), select the designated person(s), and determine how to allocate responsibility if there is more than one designated person. The designated person(s) can delegate activities to an assigned trainer provided that is described in the organization's policies.

11. Why were the categories of low-risk, medium-risk, and high-risk CSPs renamed?

In the 2015 proposed revision of *USP* <797>, it was first introduced to change the compounded sterile preparation (CSP) categories from a three-termed format of low-risk, medium-risk, and high-risk to a two-termed format of Category 1 and Category 2. This change was to avoid inaccurately conferring a level of risk to a particular CSP without consideration for all factors that influence the quality of that CSP. Renaming the CSP categories as Category 1 and Category 2, distinguished primarily by the conditions under which they are made and the time within which they are used, is intended to be a neutral designation. The 2021 proposed revision of *USP* <797> added Category 3 which allows compounders who are willing to add additional quality assurance requirements, the ability to assign BUDs longer than Category 2 BUDs.

12. What are Category 3 CSPs?

Category 3 describes CSPs made in a compounding facility that meets additional quality assurance requirements. Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14,* if compounded in accordance with all applicable requirements for Category 3 CSPs in <797>. Category 3 CSPs undergo sterility testing, supplemented by endotoxin testing when applicable, and have more requirements than Category 2 CSPs for personnel qualification, use of sterile garb, use of sporicidal disinfectants, frequencies for environmental monitoring, and determining stability.

13. Does docking and activation of a proprietary bag and vial system for immediate administration in accordance with the manufacturer's labeling instructions have to occur under ISO 5 conditions?

No. Docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for *immediate* administration to an individual patient is not considered compounding and may be performed outside of an ISO Class 5 environment.

14. When does the chapter apply for docking a proprietary bag and vial system?

Docking of the proprietary bag and vial systems for *future activation* and administration is considered compounding and must be performed in an ISO Class 5 environment in accordance with <797>, with the exception of *14. Establishing Beyond-Use Dates*. BUDs for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

15. Am I required to keep proprietary bags and vials which have been docked for future activation in a classified cleanroom?

The chapter does not address storage of the docked proprietary bag and vial system, nor does the chapter require it to be stored in a cleanroom suite. The chapter states that docking of the proprietary bag and vial systems for future activation and administration is considered compounding and must be performed in accordance with this chapter, with the exception of *14. Establishing Beyond-Use Dates*. Users should refer to the manufacturer's labeling for storage recommendations.

16. Does the chapter apply for repackaging of a conventionally manufactured sterile product?

Yes, repackaging of a sterile product or preparation from its original container into another container must be performed in accordance with the requirements in this chapter.

17. Is administration out of the scope of the chapter?

Yes. The intent of the chapter is to establish minimum standards for practitioners when compounding sterile products in order to minimize harm, including death, to human and animal patients. The scope of the chapter is intended to ensure a CSP maintains its integrity up until the time when administration begins. Standard precautions such as the Centers for Disease Control and Prevention's (CDC's) safe injection practices apply to administration (see *1.2 Administration*).

18. Does a conventionally manufactured sterile product prepared for administration to a single patient in accordance with manufacturer's approved labeling outside of ISO Class 5 conditions have to be administered within 4 hours of reconstitution or mixing if it meets all the conditions in *1.4 Preparation Per Approved Labeling*?

No. When all of the conditions in *1.4 Preparation Per Approved Labeling* are met, the storage information in the manufacturer's approved labeling may be followed.

19. What is the appropriate BUD to assign when preparing a conventionally manufactured sterile product for administration?

Preparation of a single dose of a conventionally manufactured sterile product in accordance with the approved labeling that includes information about the diluent to be used, the resultant strength, storage time, and container closure system is not considered compounding and these preparations are not subject to the BUD limits in the chapter. The BUD provided in the approved labeling may be assigned to these preparations when the labeling contains the required information mentioned above. (See *1.4 Preparation per Approved Labeling*).

20. Is withdrawing a dose from a container of a conventionally manufactured sterile product or spiking an IV bag, without any further manipulation, for immediate administration to a patient considered compounding?

No, withdrawing a dose from a container or spiking an IV bag of a conventionally manufactured sterile product without any further manipulation is considered administration rather than compounding and is out of the scope of <797>. If the dose is further mixed with another product, it would be considered compounding and subject to the requirements of <797>.

21. Is spiking IV fluids (taking IV spikes and putting them into a bag; putting a set into an IV bag) considered compounding?

No, a facility's policies and procedures regarding spiking IV fluids is outside the scope of the chapter.

22. When compounding immediate-use CSPs, may more than three individual containers of a sterile products be used?

The immediate-use CSPs provision states that the preparation must not involve more than 3 different sterile products. Two or more of the same sterile components (product) may be used as long as there are not more than three different sterile components (products). For example, two vials of the same component (drug product) are reconstituted using two vials of *Sterile Water for Injection* (component products) and added to a single component product intravenous diluent bag such as NS or D5W. As another example, when the CSP requires combining 4 vials of the same component (drug product) into a single component product intravenous bag of diluent, only 2 different sterile components (products) are used to prepare the CSP. Both examples may be considered immediate-use as long as the criteria listed in *1.3 Immediate-Use* CSPs are met.

23. Are COVID-19 vaccines limited by the 4-hour immediate-use BUD or can the BUD from the manufacturer be used?

As long as the approved labeling or supplemental materials provided by the product's manufacturer includes information for the diluent, the resultant strength, the container closure system, and storage time, then this would be considered *1.4 Preparation Per Approved Labeling* and is not considered compounding.

24. Can a single-dose container be used to prepare doses for more than one patient when compounding an immediate-use CSP?

No. One of the conditions of the immediate-use CSP provision specifies that any unused starting components from a single-dose container must be discarded after preparation for the individual patient is complete. Single-dose containers must not be used for more than 1 patient when used for preparing immediate-use CSPs.

25. Why does the immediate-use CSP provision allow for administration to begin within 4 hours following the start of the preparation?

The immediate-use CSP provision was revised to allow up to 4 hours for beginning administration to balance the need for ensuring CSP quality with timely access to medication in a variety of healthcare settings. The allowance of up to 4 hours was based on the 4-to-6-hour lag phase of microbial growth, during which potential bacterial cells are adjusting to their environment and change very little, and they do not immediately start reproducing.[1] In the event bacterial cells were inadvertently introduced into a CSP during compounding, replication is unlikely and therefore there is a window of time in which a CSP can be held prior to administration.

[1] References:

- Daquigan N et al. Early recovery of *Salmonella* from food using a 6-hour non-selective pre-enrichment and reformulation of tetrathionate broth. *Front Microbiol*. 2016;7:2103.
- Jarvis, Basil. *Statistical Aspects of the Microbiological Examination of Foods, Third Edition*. Academic Press, 2016.
- Ryan, Kenneth et al. *Sherris Medical Microbiology, Sixth Edition*. McGraw-Hill Education, 2014.
- Wang J et al. A novel approach to predict the growth of *Staphylococcus aureus* on rice cake. *Front Microbiol*. 2017;8:1140.

26. Is it considered compounding if the steps used to prepare a single dose of a conventionally manufactured product are different from the directions contained in the manufacturer's approved labeling?

Yes. Any compounding (e.g., mixing, reconstituting) that is not performed according to the manufacturer's approved labeling is considered sterile compounding and is subject to the requirements in the chapter.

27. What information is needed to meet the requirements of Section *1.4 Preparation Per Approved Labeling?*

The approved labeling or supplemental materials provided by the product's manufacturer, including information for the diluent, the resultant strength, the container closure system, and storage time.

28. Does the chapter address compounded radiopharmaceutical dosage forms?

No. Compounding of radiopharmaceuticals is not required to meet the standards of this chapter as they are subject to the requirements in General Chapter <825> *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging*.

29. Do pharmaceutical manufacturers have to comply with <797>?

No. Manufacturers must comply with FDA's current good manufacturing practices (CGMP) and/or laws and regulations of the applicable regulatory jurisdiction.

30. What is the difference between compounding and what is described in *1.4 Preparation Per Approved Labeling?*

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer if the product is prepared as a single dose for an individual patient and the approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

31. Where may Category 1 CSPs be prepared?

Category 1 CSPs must be prepared in a primary engineering control (PEC) that may be placed in an unclassified segregated compounding area (SCA) or a cleanroom suite.

32. What qualifications must a designated person have?

This must be determined by the facility's SOPs. Some states and accreditation organizations have more specific guidance.

33. Is the use of technology other than what is listed in the chapter allowed?

The introduction and scope section outlines the use of technologies, techniques, materials, and procedures not specifically covered by the chapter, as it would be impossible for this chapter to address all of the current technology on the market and potential for new technology coming to market in upcoming years after release of the finalized chapter. It is important that the technology that is being used as indicated in the manufacturer's approval documentation or if it is being used for a different intended purpose that it is validated for that purpose. This ensures that any use of technology does not bypass any safety requirements within the chapter itself and meets or exceeds those requirements. *USP* chapters <1223> and <1225> can assist compounders in this validation process.

34. What is USP's position on drug vial optimization (DVO)?

USP <797> does not address drug vial optimization (DVO). The organization would need to determine if the process used is noninferior to the requirements of the chapter.

35. Will there be any future USP guidance on the use of technology in compounding?

The Compounding Expert Committee will consider the development of future resources or a standard related to the use of technology in compounding. The introduction and scope section of <797> outlines the use of technologies, techniques, materials, and procedures not specifically covered by the chapter, as it would be impossible for this chapter to address all of the current technology on the market and potential for new technology coming to market in upcoming years after release of the finalized chapter. It is important that the technology that is being used as indicated in the manufacturers approval documentation or if it is being used for a different intended purpose that it is validated for that purpose. This ensures that any use of technology does not bypass any safety requirements within the chapter itself and meets or exceeds those requirements. *USP* chapters <1223> and <1225> can assist compounders in this validation process.

36. If a device (e.g., a repeater pump) has undergone validation by the FDA, is the compounder required to verify the volumetric accuracy each day of use?

Yes. Before using automated compounding devices or other similar equipment, compounding personnel must conduct an accuracy assessment before the first use and again each day the equipment is used to compound CSPs.

37. Are albumin, IVIG, etc., included as part of "blood-derived and other biological materials" in Section *1.1.2*?

No. These commercial products have been processed by the manufacturer to be sterile. Blood or biological materials derived directly from a patient are not sterile.

38. Do facilities have to change their standard operating procedures (SOPs) and practices for immediate-use from 1 h to 4 h?

No, facilities may choose to maintain the 1-hour limit for administration of immediate-use CSPs, however increasing the time to 4 hours would be considered acceptable.

39. Can immediate-use CSPs be made in a batch for more than one patient?

Compounders can prepare multiple doses of immediate-use CSPs intended for use in one or more patients in a single batch as long as the conditions in Section *1.3* are met.

40. What does "directly administered" mean in *1.3 Immediate-Use CSPs*?

"Directly administered" refers to the dose being prepared and then immediately administered by the person who prepared it, or administration is witnessed by the person who prepared it. In a situation where a CSP may be prepared for direct and immediate administration there is risk involved if a CSP is unlabeled and the person who compounded it is not administering or present for the administration.

41. What are the training and competency assessment requirements for personnel who only prepare immediate-use CSPs?

Training and competency assessment requirements are determined by the specific tasks performed and the facility's SOPs, and must include aseptic processes to minimize the potential for contact with nonsterile surface surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products or CSPs.

42. How often does the training and competency of personnel who perform immediate-use products need to be performed?

Section *1.3 Immediate-Use CSPs* requires that personnel are trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs. No specific frequency is identified for training and competency of personnel who perform compounding of immediate-use CSPs.

43. Is the use of dispensing pins allowed per <797>?

The chapter does not address the use of specific disposable supply items other than to say supplies in direct contact with the CSP must be sterile and depyrogenated. It is the responsibility of the facility to determine the appropriateness of specific items, including dispensing pins.

Personnel Training and Evaluation

44. Section *2.1 Demonstrating Knowledge and Competency of Core Skills* states that personnel must complete training and be able to demonstrate knowledge of principles initially and at least every 12 months. Does this mean that each person needs written or electronic testing on each of the listed topics in addition to competency testing?

The written training program must describe the required training and the process for evaluating the performance of personnel, but personnel must both demonstrate knowledge of principles and competency of skill for performing sterile manipulations and achieving and maintaining appropriate environmental conditions as applicable to their assigned job functions.

45. Must cleaning staff or personnel who restock the cleanroom undergo the same training as compounders?

Personnel who only perform restocking or cleaning and disinfecting duties outside of the primary engineering control (PEC) must be initially trained and demonstrate competency in maintaining the quality of the environment in which they are performing their assigned task. At a minimum, these personnel must meet the requirements for personal hygiene and garbing that are described in *3. Personal Hygiene and Garbing*. Facility SOPs must outline what initial and ongoing training is required.

46. Must vendors and certifiers be trained before entering the cleanroom?

Section *1.1.3* specifies that any person entering a sterile compounding area, whether preparing a CSP or not, must meet the requirements in *3. Personal Hygiene and Garbing*. Facility SOPs must outline specific requirements.

47. Do supervising pharmacists that do not compound have to undergo training and evaluation?

Yes. The following must be included:

1. **Core skills:** <797> requires that personnel who do not compound, but supervise compounding personnel, have to be trained and demonstrate competency initially and at least every 12 months as outlined in Section *2.1 Demonstrating Knowledge and Competency of Core Skills*.
2. **Garbing Competency:** Initially and at least every 12 months.
3. **Aseptic Manipulation Competency:** Personnel who have direct oversight of compounding must complete an aseptic manipulation competency evaluation at least every 12 months. The evaluation should correspond to the type of activities of the personnel they oversee but does not require the same quantities.

48. If a compounder floats between pharmacies under the same healthcare system, do media fills have to be repeated at each location?

This must be determined by the designated person(s) and specified in the facility's SOPs. Sites might differ in facilities and engineering controls, so media fills must capture the most difficult and challenging conditions and simulate the conditions and procedures encountered by the compounder and meet the requirements of Section *2.3*.

The designated person(s) must develop a written training program that describes the required training, the frequency of training, and the process for evaluating the performance of individuals who compound, have direct oversight of compounding personnel, perform in-process checks, final verification, and dispensing of CSPs.

49. Compounding independently is mentioned multiple times. Does that mean someone can compound for patients before passing testing as long as they are observed? Is this left entirely to SOPs?

Before beginning any compounding (independently or with supervision), personnel must successfully complete the initial garbing competency. Additionally, all personnel entering a compounding area must abide by *3. Personal Hygiene and Garbing*. The process of developing competency requires practice. Each compounding facility must develop a written training program that outlines what is permitted.

50. How many gloved fingertip and thumb sampling tests and media-fill tests must be done initially and subsequently?

In the revised chapter gloved fingertip and thumb samplings are taken during both the aseptic manipulation competency (i.e., immediately after media-fills) and the garbing competency evaluation (i.e., after garbing and gloving). The complete garbing competency evaluation, including gloved fingertip and thumb sampling, must be successfully completed no fewer than 3 separate times initially, and only 1 time on subsequent evaluations. All aseptic manipulation competency evaluations, including media-fill and gloved fingertip and thumb sampling after media-fill, must be successfully completed 1 time for the initial and 1 time for all subsequent evaluations.

51. What is the purpose of the increased frequency of the garbing competency?

Personal hygiene and garbing are essential to maintain microbial control of the environment. Most microorganisms detected in cleanrooms are transferred from individuals. Preparation of compounded sterile preparations by personnel who lack proper training and competency may result in increased contamination risk and potentially poor outcomes for patients. Preventing contamination by ensuring personnel are trained and competent is more impactful than detecting contamination through sampling methods.

52. Is documentation of gloved fingertip and thumb sampling and media-fill testing only required when results exceed action levels?

No. All results of the evaluations must be documented and maintained to provide a record and long-term assessment of personnel competency. Documentation must at a minimum include the name of the person evaluated, evaluation date/time, media and components used including the manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

53. If compounding personnel fail media-fill testing or gloved fingertip and thumb sampling, are they required to stop compounding until corrective action and reevaluation have been completed?

General Chapter <797> chapter does not require compounding personnel to cease compounding, however, the facility must evaluate the cause of failure and determine appropriate corrective actions. The results of the evaluation and corrective action must be documented, and the documentation must be maintained to provide a record and long-term assessment of personnel competency. General Chapter <797> describes gloved fingertip and thumb sampling and media-fill testing in Sections *2.2 Demonstrating Competency in Garbing and Hand Hygiene* and *2.3 Competency Testing in Aseptic Manipulation,* and required documentation in *20. Documentation*.

54. Why are incubation conditions different for media-fill testing, gloved fingertip and thumb sampling, and environmental air and surface sampling?

Environmental air and surface samples and gloved fingertip and thumb samples are incubated at a high temperature 30°–35° for no less than 48 h and then a low temperature 20°–25° for no less than 5 additional days. Incubation at a lower temperature first may compromise recovery of Gram-positive cocci which are often associated with humans. The incubation conditions are consistent with General Chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*. Media-fill test samples are incubated for a longer period, 7 days each at two temperatures, 20°–25° and 30°–35° to detect a broad spectrum of microorganisms. The order of the incubation temperatures must be described in the facility's SOPs.

55. Why must a higher incubation temperature be used first for gloved fingertip and thumb sampling, and environmental air and surface sampling?

Incubating gloved fingertip and thumb samples, and environmental air and surface samples at a higher incubation temperature first helps recover bacteria first. Incubation at a lower temperature first may compromise recovery of Gram-positive cocci which are often associated with humans.

56. If the controlled room temperature is 20-25°, can the samples be incubated without an incubator?

No. Samples must be incubated in an incubator.

57. Do the three initial gloved fingertip tests need to be done on the same day?

Not necessarily. The organization can determine the interval for the three initial gloved fingertip tests. In any case, these need to be three separate instances of hand hygiene, garbing, and the gloved fingertip test. Garbing once and completing three sets of gloved fingertip tests does not meet the requirement for the initial testing. The 3 successful completions must be in succession—failure of any of the 3 initial garbing competency evaluations requires repeat testing until personnel successfully complete 3 evaluations in a row.

58. Are personnel who only prepare immediate-use CSPs required to perform media-fill testing?

No, but the facility's SOPs must determine how their competency will be evaluated. When specific conditions in <797> are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 CSPs. Personnel must be trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs. The competency should include appropriate preparation (e.g., hand washing, cleaning the area that will be used) and technique that is evaluated and approved by a qualified individual.

59. Can gloved fingertip testing be done more frequently than what is in the chapter?

The chapter provides minimum compounding standards. Compounders can implement more frequent sampling if they deem it appropriate for their facility.

60. The media used for the media-fill test doesn't filter easily and personnel may need to use additional filters for the media-fill test than used for the actual batch. Is this acceptable?

Yes. Additional filters may be used as necessary for the media-fill test. Using a pre-filter may help maximize the volume of the sterilizing filter. A filter integrity test (e.g., bubble point test) must be performed on all sterilizing filters used during media-fill testing.

61. Does the ongoing garbing competency include gloved fingertip and thumb sampling (GFT) after the visual observation of garbing?

Yes. Performing GFT after the visual observation of garbing ensures personnel can don sterile gloves without contaminating them.

62. Are the staff that are currently competent according to the <797> 2008 chapter required to repeat the initial GFT (three times) with the new incubation temperatures on November 1, 2023?

No. The initial requirement applies to personnel who are beginning to compound, not those who are currently competent according to the <797> 2008 chapter.

63. Describe how to appropriately handle and store samples for media-fill testing, including the right temperature.

All samples must be incubated for 7 days each at two temperatures, 20°–25° and 30°–35°, to detect a broad spectrum of microorganisms. The order of the incubation temperatures must be described in the facility's SOPs. If sending samples to the laboratory for incubation, samples must be sent as soon as possible (e.g., within 24 h) for the most accurate results. Samples must be protected from damage as well as temperature and humidity extremes during transit. Refer to <1117> *Microbiological Best Laboratory Practices* for additional information.

64. Does the media-fill need to include multiple dosage forms that are compounded?

No. When performing a media-fill test, simulate the most difficult and challenging aseptic compounding procedures encountered by the person replacing all the components used in the CSPs with soybean–casein digest media. Only one dosage form needs to be represented, but it must meet the requirements of Section *2.3* that require the elements that affect the sterility of the CSP be captured, including the complexity of manipulations that may be associated with dosage forms.

65. How many personnel are allowed in the buffer room or SCA during media-fill testing?

Media-fill testing must simulate the most difficult and challenging aseptic compounding procedures encountered by the person, and it must capture all elements that could potentially affect the sterility of the CSP. The chapter does not specify the exact number of personnel in the buffer room or SCA, but it must simulate the conditions encountered by the compounder.

Personal Hygiene and Garbing

66. What is the order and location of garbing?

General Chapter <797> does not specify the order and location of garbing. The order and location of donning and doffing each article of required garb would depend on the type of garb used (e.g., sterile gowns) and the placement of the sink (e.g., if the sink is located inside or outside of the anteroom). The garbing order, location, and donning/doffing each article of required garb must be determined by the facility and documented in the facility's SOP. For example, if a sink is located outside of the anteroom, a facility's garbing policies and procedures may indicate that certain garb would be donned outside of the anteroom to more easily transition into hand hygiene procedures. Garb must be donned and doffed in an order that reduces the risk of contamination. Please note, sterile gloves must be donned in a classified room or SCA. Skin must not be exposed inside the ISO Class 5 PEC (e.g., gloves must not be donned or doffed inside the ISO Class 5 PEC exposing bare hands).

67. Can donning and doffing activities by different personnel occur in the same room at the same time?

The chapter recommends (but does not require) that donning and doffing not occur in the anteroom or the segregated compounding area (SCA) at the same time. Personnel must be aware of activity in the room to ensure that the integrity of garb is not compromised. For example, if one person is performing hand hygiene while another is donning a gown, personnel must consider the risk of contaminating the gown (e.g., from potential splashing).

68. What are examples of methods to cover jewelry that cannot be removed?

Examples of jewelry that cannot be removed are dermal piercings (also known as a microdermal piercing), which is a piercing that is held in place with a dermal anchor that is installed underneath the skin. Facilities must determine the appropriate method for covering dermal piercings to minimize the risk of contaminating the CSP and the environment. For example, depending on the location of the piercing, an adhesive bandage or head cover may be used to cover the jewelry.

69. Are wedding rings permitted to be worn under sterile gloves?

The chapter requires removing all hand jewelry that could interfere with the effectiveness of garbing or otherwise increase the risk of contamination of the CSP. Wedding rings may potentially compromise the integrity of the glove (e.g., tearing) and prevent adequate hand hygiene.

70. Are eyelash extensions allowed in the cleanroom?

No. Cosmetics are not permitted.

71. What accommodations can the designated person allow with regards to garbing in the cleanroom?

The designated person(s) may permit accommodations to personnel preparation as long as the quality of the CSP and environment will not be affected. Accommodations must be documented.

72. Must the accommodation to personnel preparation be documented each time or just once?

The accommodation must be documented per the facility's SOPs and *20. Documentation*.

73. Are 3 pairs of gloves required for using a compounding aseptic isolator (CAI) or compounding aseptic containment isolator (CACI)?

No, if using a CAI or CACI, the chapter recommends disposable gloves to be worn inside gloves attached to the restricted-access barrier system (RABS) sleeves. However, the chapter requires sterile gloves to be worn over the gloves attached to the RABS sleeves. The use of disposable gloves inside of gloves attached to the RABS sleeve is intended to maintain the cleanliness of the gloves attached to the RABS sleeve which may collect sweat or other touch contaminants. Sterile gloves outside of the gauntlet gloves help minimize the risk of contamination to the environment and the CSP.

74. If I am compounding Category 1 CSPs in an SCA, do I have to wear the same garb as when compounding Category 2 CSPs in a cleanroom suite?

Yes. Minimum garbing requirements are not stratified based on facility design. The chapter lists the minimum garbing requirements to protect the CSP and the environment. Sterile gloves are required for preparing CSPs inside an ISO Class 5 PEC.

75. Can gowns be re-used?

Yes. If compounding Category 1 and Category 2 CSPs, gowns used for nonhazardous compounding may be reused within the same shift by the same person if the gown is maintained in a classified area or adjacent to, or within, the SCA in a manner that prevents contamination. Garb must be replaced immediately if it becomes visibly soiled or if its integrity is compromised. Additionally, gowns and other garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing).

76. Regarding Section *3.1*, gum-chewing and mints are considered food. Why can't compounders have anything in their mouths or put anything in their mouths while in the cleanroom suite?

It is too easy to want to blow bubbles or move gum and candy around in the mouth that could spew additional wet into the mask and contaminate it. The candy or gum can also fall out of the mouth, out of the mask and onto a hood counter or floor and contaminate the area.

77. Why is the use of brushes not allowed for hand hygiene?

The practice of using a brush to scrub hands in hand-antisepsis can damage skin of personnel and result in an increase of bacteria shed from the hands. The CDC recommended discontinuing the use of the brushes and the brush side of scrub/sponge brushes in 2002. See the CDC Guideline for Hand Hygiene in Health-Care Settings, Morbidity and Mortality Weekly Report, October 25, 2002, 51(RR16); 1-44.

78. Where should I garb when preparing Category 1 CSPs in an SCA?

Sections *3.2* and *3.3* outline the requirements for hand hygiene and garbing for Category 1. The order of hand washing and garbing depends on the placement of the sink, is determined by the facility, and is documented in the facility's SOPs.

An example garbing procedure in a facility that has a sink in the SCA is as follows:

1. The compounder enters the SCA and dons head, face, and shoe covers in an order determined by the facility and documented in the facility's SOPs.
2. The compounder washes their hands then dons a gown.
3. The compounder applies alcohol-based hand rub to all surfaces of hands and fingers and allows hands to dry thoroughly then dons sterile gloves.

79. When sterile garb is required, does the equipment, such as goggles or PAPRs, need to be sterile as well?

No. Sterile garb is limited to powder-free gloves when compounding Category 1, 2, and 3 CSPs, and low-lint garb when compounding Category 3 CSPs. Facilities must have an SOP describing the disinfection procedures for reusable equipment.

80. For which categories must the facility's SOPs describe disinfection procedures for reusing goggles, respirators, and other reusable equipment?

For Category 1, 2, and 3 CSPs, the facility's SOPs must describe disinfection procedures for reusing goggles, respirators, and other reusable equipment.

81. When must laundering be performed with a validated cycle?

For facilities that compound Category 3 CSPs, laundered sterile garb must not be reused without being laundered and resterilized with a validated cycle. The facility's SOPs must describe this process.

82. When should I apply sterile 70% IPA to gloves?

Application of sterile 70% IPA to gloves must occur immediately before compounding (e.g., before entering the ISO Class 5 PEC) and regularly throughout the compounding process.

83. Do conditions such as dandruff, eczema, or psoriasis exclude someone from compounding CSPs?

These are all conditions that could cause someone to be at higher risk for contaminating a CSP or the environment so they must be reported to the designated person(s). The designated person(s) is responsible for evaluating the situation and making a decision on whether the affected person must be excluded from working in compounding areas until the condition is resolved.

Facilities and Engineering Controls

84. Why must the HEPA filter be located in the ceiling of the buffer and anterooms?

Placement of HEPA filters in the ceiling eliminates the potential for post-filtration contamination of the air stream. Air distribution systems with duct-mounted HEPA filters are susceptible to introduction of unfiltered air into the airstream after the air is filtered. HEPA filter placement in the ventilation duct is difficult to leak test and susceptible to contamination, especially in the event of water leakage or other breaches. Ceiling mounted filters help facilitate testing and servicing.

85. Why are CAIs and CACIs required to be placed in an ISO Class 7 buffer room with an ISO Class 8 anteroom for preparing Category 2 CSPs?

The PEC must be located in a controlled environment for preparing Category 2 CSPs to minimize the risk of contamination. Movement of materials in and out of the RABS (e.g., CAI or CACI) in unclassified air carries a higher risk of contamination. Placement of the RABS in a classified area mitigates the risk of inadvertent contamination of CSPs with the longer BUDs that are permitted for Category 2 CSPs.

86. Does the integrated vertical laminar flow zone (IVLFZ) require 100% HEPA filter coverage in the ceiling? Can returns be under the worktable?

In the IVLFZ, unidirectional airflow is created by placing HEPA filters over the entire surface of the worktables and by effective placement of air returns. Strategic location of air returns in addition to full coverage of HEPA filters above the work surface is required. Specific location of the air returns is not specified. Both static and dynamic smoke studies verifying a continuous flow of HEPA-filtered air void of turbulence, dead air zones, and refluxing from the HEPA filters to and across the entire work area and to the air returns must be documented (e.g., with video). [Note—Dynamic airflow smoke pattern tests have shown that it is difficult to achieve this type of design and also achieve and maintain unidirectional airflow under dynamic operating conditions.]

87. Can a containment ventilated enclosure (CVE) be used for presterilization procedures (e.g., weighing, mixing nonsterile components)?

Presterilization procedures must be performed in a single-use containment glove bag, CVI, BSC, or CACI to minimize the risk of airborne contamination.

88. When pass-through chambers are used, do the doors have to be interlocking?

The chapter recommends that pass-through doors be interlocking. However, if a pass-through is used, both doors must never be opened at the same time.

89. How often are visual smoke studies performed (e.g., in rooms where air returns are not located low on the wall)?

Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow. This smoke study along with environmental monitoring must be repeated whenever a change is made to the placement of equipment within the room or any other alteration is performed within the cleanroom suite that affects the quality of the air (e.g., HVAC alterations, change of HEPA filter units). A visual smoke study uses a visible source of smoke, which is neutrally buoyant, to verify an absence of stagnant airflow where particulates can accumulate in ISO Class 7 and ISO Class 8 rooms that do not have unidirectional airflow.

90. What is the difference between a pharmaceutical isolator and a RABS (i.e., a CAI or CACI)?

Unlike RABS, pharmaceutical isolators are different in that they contain 4 major elements: controlled workspace, transfer device, access device, and a decontamination system. A pharmaceutical isolator is equipped with a generator that distributes a sporicidal disinfectant throughout the chamber. If the isolator is used to prepare Category 2 CSPs, it must be placed in an ISO Class 8 or better positive-pressure room. In contrast, if a CAI or CACI is used to prepare Category 2 CSPs, the CAI or CACI must be placed in a cleanroom suite with an ISO Class 7 or better positive-pressure buffer room with an ISO Class 8 or better positive-pressure anteroom.

91. Can analog pressure gauges be used for monitoring pressure differentials?

Yes, analog pressure gauges may be used to monitor pressure. The quantitative results from the pressure monitoring device must be reviewed and documented at least daily on the days when compounding is occurring. Some analog pressure gauges do not warn or alert personnel to events where there is a loss of pressure whereas there are other pressure monitoring systems that may have audible or visible alarms.

92. Why are sinks allowed to be placed outside of the anteroom? Does the sink placement in <797> contradict the sink placement requirements in <800>?

In facilities with cleanroom suites, the sink used for hand hygiene may be placed either inside or outside of the anteroom. If the sink is located outside of the anteroom, it must be located in a clean space to minimize the risk of bringing in contaminants into the anteroom. Sinks are permitted outside of the anteroom to offer more flexibility to the cleanroom design and help minimize the risk of contamination from water sources to the classified areas. In facilities preparing hazardous drugs (HDs) in a cleanroom suite, General Chapter <800> requires the sink to be placed in the anteroom at least 1 meter away from the entrance of the HD buffer room to avoid contamination migration into the negative-pressure HD buffer room. There are no conflicts for the sink placement in <797> and <800>. Facilities compounding sterile HDs must meet the requirements in both <797> and <800>.

93. Is an SCA required to be in an enclosed room (i.e., walls and doors)?

No. An SCA is defined as a designated, unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of only Category 1 CSPs.

94. Why do I need a line of demarcation in the anteroom?

The line of demarcation serves to create visible separation between the clean and dirty sides of the anteroom. Distinguishing the "dirty" side of the anteroom from the "clean" side ensures all personnel abide by the garbing and material transfer procedures defined by the sterile compounding organization's SOPs. The line of demarcation signifies the locations where specific contamination control principles are implemented to aid in decreasing the number of particles introduced into the buffer room. The facility may choose where the line of demarcation is located. Please note, the anteroom is entered through the dirty side, and the clean side is the area closest to the buffer room (see Section *4.2 Facility Design and Environmental Controls*). Facilities may also utilize a design with two physically separate anterooms, one clean and one dirty.

95. Can presterilization procedures (e.g., weighing) be performed in an unclassified environment?

Yes. Presterilization procedures can be performed in unclassified environments for Category 1 CSPs. For Category 2 and Category 3 CSPs, presterilization procedures must be completed in an ISO Class 8 or better environment (e.g., anteroom or buffer room) wherein the compounder uses a containment device (e.g., single-use containment glove bags, containment ventilated enclosure (CVE), BSC, or CACI) to minimize the risk of airborne contamination.

96. In an SCA, can the sink be in the same area or room?

The sink needs to be accessible to the compounding area. It can be inside the area defined as the SCA but cannot be closer than 1 meter to the PEC. That distance is intended to ensure that splashes do not reach the PEC.

97. How can the garbing location be in a classified area with a sink outside the anteroom?

The order of garbing must be determined by the facility and documented in the facility's SOPs. If hand hygiene is completed outside of a classified area, alcohol-based hand rub must be used prior to donning garb. Hands must also be sanitized with alcohol-based hand rub before donning sterile gloves.

An example garbing procedure in a facility that has a sink outside the anteroom is as follows:

1. The compounder washes their hands in the sink located outside of the anteroom.
2. The compounder enters the anteroom and applies alcohol-based hand rub to all surfaces of hands and fingers and allows hands to dry thoroughly.
3. The compounder dons garb in an order determined by the facility and documented in the facility's SOPs.
4. Before donning sterile gloves, hands are re-sanitized with alcohol-based hand rub and allowed to dry thoroughly.

98. What types of biological safety cabinets (BSCs) are appropriate for compounding?

A BSC is a ventilated cabinet that is typically used for compounding hazardous sterile and nonsterile preparations but may be used to compound nonhazardous sterile and nonsterile preparations as well. BSCs are divided into three general classes (Class I, Class II, and Class III). Class II and Class III BSCs provide an ISO Class 5 environment so are suitable for sterile compounding. Class II BSCs are further divided into types (Type A1, Type A2, Type B1, Type B2, and Type C1). Class I BSCs are suitable for nonsterile compounding only. A BSC used for hazardous drugs must exhaust to the outdoors.

Nonsterile Non-HD	Nonsterile HD	Sterile Non-HD	Sterile HD
Class I, II, or III	Class I, II, III Must exhaust to outdoors	Class II, III	Class II, III Must exhaust to outdoors

99. What are the requirements for temperature and humidity for an SCA?

There are no specific requirements for temperature or humidity in an SCA, but it is reasonable to use the requirements for a cleanroom suite as guidance. However, if drugs or supplies are stored in the SCA, there may be other USP, FDA, or manufacturer/supplier requirements. See *USP* <659> for additional information on storage requirements for drugs.

100. May personnel reach across the perimeter of the SCA to access supplies without actually stepping over the perimeter?

The chapter requires that when personnel exit the compounding area, garb, except for gowns, cannot be reused. At minimum, this would require changing the affected garb (e.g., gloves).

101. May an anteroom be shared between a Category 2 and Category 3 buffer room?

Yes.

102. May an anteroom be shared between an HD and non-HD buffer room?

Yes.

Certification and Recertification

103. Is certification of the compounding area required to be performed using the current Controlled Environment Testing Association (CETA) *Certification Guide for Sterile Compounding Facilities?*

Before a compounding area is used to compound either Category 1, Category 2, or Category 3 CSPs, it must be independently certified using the requirements in this chapter and when applicable, manufacturer specifications. Facilities must determine the appropriate certification guide to use for certifying their compounding area.

104. What is ASHRAE?

The American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) is a professional organization that provides certification (including healthcare facility design) and professional development for engineers in this field.

105. What is CETA?

The Controlled Environment Testing Association is a professional organization for controlled environment certification personnel that provides certification (including Registered Certification Professional – Sterile Compounding Facilities), education, and resources for certification personnel.

106. A facility may have several cleanrooms under the same corporate structure (e.g., within a healthcare system) but state law requirements may require separate licenses for each compounding area. Are personnel that float between the different cleanrooms required to complete training and competency at each location if they are working in the same type of primary and secondary engineering controls?

This is in the purview of the state board of pharmacy and outside the scope of <797>. The chapter requires that each compounding facility develop a written training program that describes the required training, the frequency of training, and the process for evaluating performance. This program must equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks. The facility's SOPs should specify the training required for such tasks, and training and evaluation of personnel must be documented.

107. Regarding 'dynamic operating conditions', what does "the largest number of personnel and highest complexity" mean as it relates to certification of ISO-classified areas?

This refers to testing in a particular ISO-classified area (e.g., ISO Class 5 PEC, ISO Class 7 buffer room). The highest number of personnel that would be expected to work in a PEC and/or SEC should be present and performing the highest complexity of compounding expected including use of compounding equipment and performance of particle-generating activities (e.g., pre-sterilization activities such as weighing and mixing powders). Testing under dynamic operating conditions is required for particle testing of ISO-classified areas, air changes per hour (ACPH) of ISO-classified rooms, and some types of smoke studies.

Microbiological Air and Surface Monitoring

108. Why has the frequency of surface sampling changed?

Surface sampling was previously required "periodically", which was interpreted differently by users (e.g., monthly, quarterly, or biannually). The change requiring minimum frequencies based on the category of CSP the facility compounds is intended to provide an additional measure of control and monitoring in between viable air monitoring and certification requirements. Regular surface sampling provides additional data for trending and allows for monitoring of contamination risks.

109. How many microbiological air and surface samples are required based on the size of classified areas?

Microbiological air and surface testing must be conducted in all classified areas to confirm that the required environment quality is maintained. The microbiological air and surface sampling must be facility-specific and must be described in the facility's SOPs. The chapter does not specify a minimum number of air or surface samples based on the size of the room, however, the International Organization for Standards (ISO) 14644-1:2015(E) Table A.1 – 'Sampling locations related to cleanroom area' states the area of a cleanroom (m^2) and the minimum number of sampling locations to be tested (N_L) that are necessary for certification. Facilities must determine the appropriate number of locations and select the locations of sampling based on their relationship to the activities performed in the area.

110. What is the appropriate method for cleaning the hood after surface sampling?

After sampling, the sampled area must be thoroughly cleaned and disinfected using a cleaning agent followed by a disinfecting agent or by using a one-step disinfectant cleaner. Additionally, in a PEC, sterile 70% IPA must be applied after cleaning and disinfecting.

111. Do microorganisms need to be identified to the genus level regardless of action level?

No. An attempt must be made to identify any microorganisms recovered to the genus level if the levels measured during sampling exceed the action levels in the chapter.

112. What is the rationale for only requiring an attempt to identify any microorganisms recovered to the genus level if the levels measured during sampling exceed the action levels in the chapter?

In some instances, microorganisms cannot be identified to the genus level because the microorganism is no longer viable, or if a mold, it may not be producing the reproductive structures necessary for identification. In these instances, the genus may not be identified, but the chapter does require that an attempt be made to identify the microorganism to the genus level.

113. Is changing HEPA filters considered "servicing facilities or equipment" for the purposes of requiring microbiological air and surface monitoring?

Yes, changing HEPA filters in the ceiling would require microbiological air and surface sampling because there is potential for unclassified air to enter the cleanroom. Changing HEPA filters in the ISO Class 5 PEC would also require microbiological air and surface sampling to ensure the PEC is operating as expected. Changing prefilters for the ISO-classified rooms and PECs usually would not require additional sampling because the downstream HEPA filter remains intact.

114. If two media samples are collected at a single location, how are the colony-forming units (CFU) counted?

If a facility were to choose to utilize two different media devices for sampling, they would sample each location according to their sampling map using both devices (e.g., TSA and MEA). If each device at one location demonstrates growth, the CFU are counted separately. For example, if a TSA plate grows 5 CFU and the MEA plate at the same location grows 3 CFU, the CFU would be recorded separately as 5 CFU and 3 CFU for the respective plates. The count would NOT be recorded as 8 CFU.

115. Is a self-enclosed robotic device different than a "closed RABS" as used in <1211>? When should surface sampling occur in a self-enclosed robotic device?

This verbiage "self-enclosed robotic device" was specifically used in <797> as there are robotic enclosures on the market that do not meet the definition of a closed-RABS, whereas some would meet this definition. For self-enclosed robotic devices that meet the definition of closed-RABS, it would be detrimental to the air quality inside the device to surface sample at the completion of each batch. Therefore, the requirement for these specific devices is to be conducted at least once daily at the end of compounding operations. This is generally when the device is opened for cleaning and disinfecting.

116. May settle plates be used in place of an impaction air sampler for viable air sampling?

No. An impaction air sampler must be used to collect 1 cubic meter or 1000 L of air from each classified area.

117. When should samples be submitted by certifiers to the laboratory after collection?

If the certifier is sending samples to the laboratory for incubation and identification, samples must be sent as soon as possible (e.g., within 24 h) for the most accurate results. Samples must be protected from damage as well as temperature and humidity extremes during transit. Refer to <1117> *Microbiological Best Laboratory Practices* for additional information.

118. Describe the process and action levels associated with testing of pass-through chambers.

For entities compounding Category 1 and Category 2 CSPs, each pass-through chamber must have surface sampling performed monthly (see <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*). For entities compounding Category 3 CSPs, each pass-through chamber must have surface sampling completed prior to assigning a BUD longer than the limits established in *Table 13*, and at least weekly (see <1116>) on a regularly scheduled basis regardless of the frequency of compounding of Category 3 CSPs.

Neither General Chapter <797> nor <1116> states which ISO classification to correlate with. The facility's SOPs should describe how growth bacteria will be defined. For example, if a pass-through chamber goes between an ISO 7 and an ISO 8 area, the surface sampling growth criteria could be based on either the ISO 7 or ISO 8 limits.

Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA

119. What is the difference between cleaning and disinfecting?

Cleaning is the process of removing substances (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products. Disinfecting is the process of destroying fungi, viruses, and bacteria on inanimate surfaces and objects.

Sporicidal disinfectants are also indicated in the chapter. A sporicidal disinfectant destroys bacterial and fungal spores and is expected to kill all vegetative microorganisms.

120. What is a one-step disinfectant cleaner?

A one-step disinfectant cleaner is a product with an EPA-registered (or equivalent) claim that it can clean and disinfect a nonporous surface in the presence of light to moderate organic soiling without a separate cleaning step.

It is important to note that sterile isopropyl alcohol (IPA) is not a one-step disinfectant cleaner. Sterile IPA is a sanitizing agent which, when used on inanimate surfaces and objects, reduces the number of all forms of microbial life including fungi, viruses, and bacteria.

121. Where can I find examples or sources of EPA-registered one-step disinfectant cleaners?

USP cannot endorse particular products. Users may research one-step disinfectant cleaners or contact cleaning/disinfecting agent manufacturers to get more information on available products.

122. Does *Table 10. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporicidal Disinfectants in Classified Areas and in the SCA* apply to all surfaces in the SCA?

The minimum frequencies in *Table 10* apply to all surfaces within the perimeter of the SCA except the ceiling. Ceilings of the SCA are required to be cleaned, disinfected, and applied with sporicidal disinfectant only when visibly soiled and when surface contamination is known or suspected.

123. Does the equipment inside a PEC need to be cleaned?

Yes, the chapter requires equipment inside of the PEC to be cleaned, disinfected, and a sporicidal disinfectant applied (see *Table 10*).

124. Are cleaning supplies required to be sterile?

Cleaning and disinfecting supplies used in the PEC must be sterile with the exception of tool handles and holders, which must be cleaned and disinfected prior to use in a PEC. The chapter states that all cleaning supplies (e.g., wipers, sponges, and mop heads) with the exception of tool handles and holders must be low lint.

Further, the chapter recommends that wipers, sponges, and mop heads be disposable.

125. Are cleaning agents required to be sterile?

Cleaning, disinfecting, and sporicidal disinfectants used within the PEC must be sterile. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used.

126. Where can I find information about the minimum contact time for the cleaning, disinfecting, and sporicidal disinfectants used?

Refer to the manufacturer's directions or published data for the minimum contact time for the agent used. The minimum contact time may differ depending on the agent used and on the intended purpose. For example, an agent may have a 1-minute contact time to be bactericidal and a 3-minute contact time to be sporicidal.

127. Does the chapter require a separate cleaning and disinfecting step in addition to applying a sporicidal disinfectant?

The chapter requires cleaning and disinfecting of the compounding areas. These steps can be combined if an EPA-registered one-step disinfectant is used. One-step disinfectants have been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step. Sporicidal disinfectants must be used at least monthly. Some EPA-registered disinfectant cleaners may also have sporicidal properties. If the sporicidal disinfectant is an EPA-registered (or equivalent) one-step disinfectant sporicidal cleaner, separate cleaning and disinfecting steps are not required.

128. Is an EPA-registered disinfectant required if the compounding process is over 30 minutes? <797> states "During the compounding process sterile 70% IPA must be applied to the horizontal work surface, including any removable work trays, of the PEC at least every 30 min if the compounding process takes 30 min or less. If the compounding process takes more than 30 min, compounding must not be disrupted, and the work surface of the PEC must be *disinfected* immediately after compounding."

No. As with compounding that takes 30 minutes or less, sterile 70% IPA must be used when the compounding process is over 30 minutes, and must be applied immediately after compounding.

129. Is a biological safety cabinet the only PEC that has a removable work surface tray?

No. CAIs, CACIs, and some laminar airflow workbenches (LAFWs) have removable work trays.

130. Do cleaners and disinfectants have to be EPA-registered?

In the U.S., yes. Disinfectants are registered with the EPA in the USA, and depending on the international location, registered with entities with an equivalent jurisdiction in that nation.

131. Can containers of sterile supplies (such as bottles of sterile alcohol and containers of sterile saturated wipers) be used for more than one compounding session?

Yes, as long as they remain in the intended area once opened. This needs to be defined by the organization's policies, based on information provided by the manufacturer/supplier. Sterile solutions and supplies are used to avoid introducing spores or other contamination into the cleanroom. For example, a packet of saturated sterile alcohol wipers opened in the ISO 5 PEC can remain in the PEC until depleted, unless the packet is contaminated. A bottle of sterile alcohol can remain open and used in the ISO 7 cleanroom until depleted, unless contaminated.

132. Once opened, how long may a cleaning and disinfecting agent or package of sterile wipers be used?

Once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.

133. Are personnel that only clean and disinfect ISO 7 and ISO 8 areas, but not ISO 5 areas, required to wear sterile gloves?

Any person entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared must be properly garbed including sterile gloves.

134. If an IV bag has tubing attached in one hood and compounding is done in a second hood, does the IV bag need to be wiped with sterile 70% IPA before bringing into the second hood?

Yes. Just before any item is introduced into the PEC, it must be wiped with sterile 70% IPA using sterile low-lint wipers and allowed to dry before use.

135. Do personnel have to wipe gloves with sterile 70% IPA every time their hands enter the ISO Class 5 PEC even if not touching contaminated surfaces (e.g., throwing out trash without touching trash can or grabbing a supply that was disinfected for them prior to touching)?

Application of sterile 70% IPA to gloves must occur immediately before compounding and regularly throughout the compounding process. The facility SOPs should describe this process. For example, gloves might be wiped with sterile 70% alcohol before beginning to stage items into the hood then re-wiped before beginning compounding, after handling trash, when retrieving items outside the hood, etc. Handling trash or retrieving a supply item outside the hood could contaminate gloves so they should be re-wiped with sterile 70% alcohol after performing these tasks.

Equipment, Supplies, and Components

136. Why are active pharmaceutical ingredients (APIs) required to be obtained from an FDA-registered facility and components other than APIs only recommended to be obtained from an FDA-registered facility?

The Federal Food, Drug, and Cosmetic Act requires compounded preparations to be prepared from bulk drug substances that are obtained from FDA-registered facilities. The Expert Committee recognizes that there may be some components other than APIs that cannot be obtained from an FDA-registered facility, thus, it is a recommendation that these components be obtained from an FDA-registered facility.

137. How often do I need to calibrate my temperature monitoring equipment or verify its accuracy?

Section *9.3.4 Component handling and storage* states that all monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer. For example, if the manufacturer specifies to calibrate every 2 years, then that would be the correct interval. If a manufacturer does not specify the calibration interval, then it must occur at least every 12 months.

138. Does API refer to conventionally manufactured drug products?

The term "API" refers to any substance or mixture of substances intended to be used in the compounding of a preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body. Also referred to as *Bulk drug substance*. A conventionally manufactured drug product is not an API but is typically manufactured from an API(s).

139. If a CSP is stored outside of the pharmacy, do we need to monitor and document temperature readings for nursing unit floor refrigerators or remote-access Pyxis refrigerators?

Once a CSP is dispensed, you should handle this as you would any other medication (manufactured or compounded). Temperature storage conditions in healthcare facilities such as hospitals have requirements from other regulators and accreditors concerning maintaining and documenting temperatures of medication storage areas. Generally, this requires at least daily monitoring and documentation.

140. "All monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer." Does this statement apply to humidity sensors, pressure monitors, and thermostats?

Yes. Those are examples of monitoring equipment.

141. Do we need a certificate of quality for each lot of sterile empty bags we use? <797> states "Each lot of commercially available sterile, depyrogenated containers and container closure systems must be accompanied by a COA or other documentation showing conformance with established specifications (i.e., sterility and depyrogenation requirements)."

Sterile empty bags obtained from suppliers are described as such in the product labeling. The lot number is traceable back to the manufacturer/supplier if any concerns would be identified.

Sterilization and Depyrogenation

142. What is the difference between aseptic processing and terminal sterilization?

USP General Chapter <1229> *Sterilization of Compendial Articles* summarizes the common requirements for sterilization process: design, development, validation, and process control. *USP* <1229.4> *Sterilizing Filtration of Liquids* states, "Sterilization processes are divided broadly into two categories: destruction of microorganisms, and their physical removal from the material to be sterilized. Terminal sterilization (e.g., autoclaving) is an example of the former, and sterilizing filtration is an example of the latter."

Aseptic processing includes either 1) compounding with only sterile starting ingredient(s), or 2) compounding with nonsterile ingredient(s) followed by sterilization by filtration. Filtration sterilization is not terminal sterilization because it is not a lethal process of microbial destruction.

Terminal sterilization includes compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization with a lethal process intended to achieve a probability of a nonsterile unit (PNSU) of 10^{-6} (e.g., steam, dry heat, irradiation).

143. Can stoppered and crimped empty vials be sterilized using steam heat?

Sealed containers must be able to generate steam internally to be sterilized by steam heat. Stoppered and crimped empty vials must contain a small amount of sterile water to generate steam (see also *<1229> Sterilization of Compendial Articles*).

144. Does a sterile filter with a pore size of 0.2 µm meet the requirement of the chapter ("0.22 µm or smaller")?

Yes. For the purposes of <797> and *USP–NF* compounded preparation monographs, 0.2 µm and 0.22 µm filters are interchangeable, as they pass the same performance criteria.

145. Why is a prefiltration step with a filter of a pore size of 1.2 µm required before sterilization procedures?

A prefiltration step with a filter of a pore size of 1.2 µm removes particulate matter in the solution before sterilization. This is only required if CSPs are known to contain excessive particulate matter, which may also be an indication that the formulation may be problematic and therefore the formulation and the process should be assessed and modified if necessary.

146. What is the PNSU for CSPs sterilized by filtration?

A PNSU value cannot be applied to CSPs that are sterilized by filtration because sterilization by filtration is not terminal sterilization.

147. Is a biological indicator required for each sterilization cycle using steam or dry heat?

Yes, the effectiveness of the steam and dry heat sterilization method must be verified and documented with each run or load using an appropriate biological indicator.

148. Why does the chapter continue to exclude terminal filtration container systems from its definition of terminal sterilization?

Filtration-based methods of sterilization are not considered to be a method of terminal sterilization because they are not a lethal process of microbial destruction.

Each method of sterilization must take into consideration the container closure system that holds the compounded preparation. Since there are many container closure systems and methods of terminal sterilization, it becomes a complex matrix that is specific to the container closure system and the method of sterilization. The permutations are too numerous to include in the chapter.

149. What is depyrogenation?

Pyrogens are organic compounds that are soluble in water and not removed by filtration or steam sterilization. They are endotoxins; lipo-polysaccharides produced by Gram-negative bacteria. Depyrogenation is the destruction or elimination of endotoxins (i.e., pyrogens). There are several methods that can be used to accomplish depyrogenation.

Master Formulation and Compounding Records

150. Do I need a master formulation record (MFR) for repackaged conventionally manufactured components?

Repackaging conventionally manufactured components is within the scope of the chapter. General Chapter <797> requires a master formulation record for CSPs created for more than 1 patient and for CSPs prepared from nonsterile ingredients. If the CSP is created for more than 1 patient, such as repackaging several units, a master formulation record is required.

151. Are master formulation records required for patient-specific CSPs?

A master formulation record must be created for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s). If the CSP is only for a single patient and does not contain nonsterile ingredients, a master formulation record is not required.

152. When is a compounding record needed for immediate-use CSPs?

If the immediate-use CSPs are prepared in a batch and are intended for use in more than one patient, then a compounding record as described in Section *11.2 Creating Compounding Records* is required.

153. Does a change in any of the information listed as MFR requirements in *Box 9* when compounding the same drug require an entirely new MFR, or can an MFR be created to contain the differences?

Any change to the process, ingredients, or packaging specified in an MFR are to be noted on a compounding record. The MFR is not changed.

If a preparation is made repeatedly that has differences in process, ingredients, or packaging, consideration should be given to creating a new MFR for that version of the preparation. Otherwise, all changes are to be noted on a compounding record.

154. Where does the documentation of compounding occur (in process, in the buffer room, outside of classified areas)?

The master formulation record would be established prior to compounding a CSP, usually outside of the cleanroom suite. The compounding record should be initiated before the components of the CSP are assembled. When documented on paper, this is usually performed outside of the cleanroom suite. Depending on your work practices, final sign-off on the CR would be done in the most appropriate area. While labels need to be available for placement on the completed CSP in the buffer room, exposure of paper records should be minimized in the buffer room. Those organizations with workflow technology that supports completion of the CR in the buffer room will likely have a different process than those with only manual records.

Release Inspections and Testing

155. What is required to be documented for the visual inspection of the CSP and the container closure system?

All CSPs must be visually inspected to determine whether the physical appearance of the CSP is as expected. The master formulation record must list specific requirements for a particular CSP. Examples of visible quality characteristics might include discoloration, visible particulates, or cloudiness. Examples of visual inspection of the container closure system might include checking for leakage, cracks in the container, or improper seals.

156. Why should CSPs administered epidurally have the same endotoxin limit as that of intrathecally administered CSPs?

CSPs delivered by implanted pumps may be administered over a long period of time and may be compounded from nonsterile components. Bacterial endotoxin testing helps ensure that CSPs do not contain excessive bacterial endotoxins. Although <797> refers to General Chapter <85> *Bacterial Endotoxins Test* for calculating endotoxin limits for the appropriate route of administration, <85> does not address products administered epidurally or administered directly into the central nervous system. Compounders should be aware that endotoxin testing is also important for CSPs administered epidurally due to the close proximity of the epidural and intrathecal spaces.

157. Do all Category 2 CSPs need to undergo bacterial endotoxins testing?

No. General Chapter <797> Section *12.3 Bacterial Endotoxins Testing* requires Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing per *Table 13* to undergo bacterial endotoxins testing. For example, ophthalmic compounded preparations are not required to undergo bacterial endotoxins testing because they are not Category 2 injectable CSPs. Category 2 injectable CSPs made from one or more nonsterile component(s) and assigned a BUD that does not require sterility testing are recommended to be tested for bacterial endotoxins.

158. How is the endotoxin limit of CSPs for non-human species determined?

Endotoxin limits for non-human species are calculated as described in *USP* <85> based on the largest recommended dose and weight (or average weight for more than a single animal) of the target animal species unless a different limit is scientifically supported. The formula to calculate endotoxin limit is: K/M where K = the threshold pyrogenic limit for the dosage form (expressed as EU or endotoxin units), and where M = the largest dose/patient or per species average weight in kg per hour. K has been defined by route of administration as follows: injections = 5 EU/kg, radiopharmaceutical injections = 175 EU/dose, intrathecal injections = 0.2 EU/kg, and radiopharmaceutical intrathecal injections = 14 EU/dose. To calculate the endotoxin limit for compounded morphine sulfate 50 mg/ml injection in a 5 kg cat, the following calculations are performed. The maximum dose of morphine sulfate in cats is 0.25 mg/kg. K = 5 EU/kg/hr (as defined for injections) M = 0.25 mg x 5 kg x 1hr = 1.25 mg/kg/hr K/M = 5 EU/kg/hr / 1.25 mg/kg/hr = 4 EU/mg.

The average representative weights for non-human species can be found here: https://www.fda.gov/media/102469/download.

159. Why is there a maximum batch size of 250 units for CSPs requiring sterility testing?

Sterile compounding within 503A facilities is largely a manual process. The chapter sets a minimum standard for quality assurance that encompasses a wide variety of practice sites. These quality assurance parameters are not intended for outsourcing facilities or pharmaceutical manufacturers, as they were created to accommodate the equipment and processes normally performed by 503A facilities. The risk of contaminating a CSP is likely to increase as the batch size increases, especially for a manual process. For example, equipment limitations (such as the size of a PEC) may only permit a portion of a large batch to be packaged in one continuous process. If 25 units are packaged in one continuous process, a batch of 250 units would require repeating this process 10 times. A batch of 1000 units would require repeating this process 40 times.

Smaller batches reduce the potential for operator error due to fatigue. To help ensure sterility assurance, batch size is limited to 250 final dosage units for CSPs that require sterility testing. Sterility testing does not guarantee that an entire batch is sterile, only the units tested. The possibility of detecting a contaminated preparation is about 10% for batch sizes between 10 and 100 but drops to about 4% for a batch size of 250 and only 2% for a batch size of 500.

160. Why is there not a batch size limit in <71> *Sterility Tests*?

USP General Chapter <71> *Sterility Tests* falls under the Microbiology Expert Committee and was created for facilities that follow current good manufacturing practices (CGMP). Following CGMP requires a level of quality assurance significantly higher than what is required by 503A facilities who follow <797>. Modifications have been made in <797> to require a fewer number of test samples with batch sizes 1 to 39 units and to limit batch size to 250 final dosage units. Other aspects of <71>, including method suitability, number of units to be tested (for batch sizes 40 to 250), and quantity per unit tested, are required.

161. How many additional units of CSPs must be compounded to perform sterility testing if there are less than 40 units, and does this apply to ophthalmics, large volume parenteral (LVP) solutions, etc.?

If 1–39 CSPs are compounded in a single batch, the sterility testing must be performed on a number of units equal to 10% of the number of CSPs prepared, rounded up to the next whole number. This applies when the number of CSPs to be compounded in a single batch is less than the number of CSPs needed for testing as specified in <71>, *Table 3*. *Table 3* requires testing 5% or a minimum of 2 ophthalmic preparations, whichever is greater, so this would apply to ophthalmic preparation batch sizes of 1 or 2 units. If compounding more than 2 units of ophthalmic preparation, use the numbers in <71>, *Table 3*.

162. Do I have to wait for the results of the sterility tests before releasing the CSP?

Sterility testing is not required for Category 1 CSPs. Category 2 and Category 3 CSPs that require sterility testing may be administered or dispensed prior to receiving the results of release testing (including sterility testing).

In order to do this, the facility must have procedures in place to:

- Immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., sterility, strength, purity, bacterial endotoxin, or other quality attributes)
- Recall any unused dispensed CSPs and quarantine any stock remaining in the pharmacy
- Investigate if other lots are affected and recall if necessary

An SOP for recall of out-of-specification dispensed CSPs must contain:

- Procedures to determine the severity of the problem and the urgency for implementation and completion of the recall
- Procedures to determine the distribution of any affected CSP, including the date and quantity of distribution
- Procedures to identify patients who have received the CSP
- Procedures for disposal and documentation of the recalled CSP
- Procedures to investigate and document the reason for failure

163. <797> states, "When a CSP will not be released or dispensed on the day of preparation, a visual inspection must be conducted immediately before it is released or dispensed to make sure that the CSP does not exhibit any defects such as precipitation, cloudiness, or leakage, which could develop during storage." Would this prohibit stocking CSPs on the floors in automated dispensing cabinets (i.e., Pyxis) to no more than a 24-hour supply?

No, releasing a CSP to the floor is similar to dispensing to a patient so a second check is not required by a pharmacist. Nurses should be educated to check all types of sterile preparations – manufactured, from a registered outsourcer, prepared by pharmacy, or those that they activate or mix – prior to administration to a patient.

164. After a CSP has been verified by a pharmacist and placed in an area to be picked up for a specific patient in a specified timeframe, does the CSP need to be re-checked by a pharmacist before going out to a patient?

<797> requires that "at the completion of compounding, before release and dispensing, the CSP must be visually inspected to determine whether the physical appearance of the CSP is as expected". If the pharmacist has performed the release check and dispensed the CSP, and it is only awaiting pick-up or delivery, a re-check is not required.

165. Why is bacterial endotoxin testing required for Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing and Category 3 injectable CSPs compounded from one or more nonsterile component(s)?

The purpose of the bacterial endotoxins test is to ensure the source material does not contain excessive endotoxins and ensure any mitigation steps that were performed are adequate. Bacterial endotoxins entering patients' bloodstreams in sufficient concentrations can cause harmful effects such as fever and septic shock and can be fatal in the most severe cases.

Establishing Beyond-Use Dates

166. What is the difference between the beyond-use date (BUD) and "hang time" (e.g., administration time, infusion time)?

The BUD is the date, or the hour and date, after which the CSP must not be used. BUDs apply to CSPs and are not intended to limit the time during which a CSP is administered (e.g., infused). "Hang time" is often used to refer to the amount of time during which a CSP or conventionally manufactured product (e.g., pre-mix, large volume parenteral solution) may be infused before which either the tubing or the medication must be changed. General Chapter <797> does not address administration time (e.g., hang time).

167. Can a CSP be administered beyond the assigned BUD?

Administration cannot begin past the assigned BUD; however, it is not intended to limit administration that began before the BUD lapsed (see *14.1 Terminology*). For example:

- An intravenous preparation begins 1 hour before the BUD lapses; however, it is scheduled to continue infusing for a total of 2 hours. The BUD is not intended to limit the dose from being completed.
- An ophthalmic preparation is scheduled to be given once daily for 14 days; however, the BUD will lapse in 10 days. The medication can continue to be administered up until the assigned BUD in 10 days, beyond which the preparation must not be used and must be discarded.

168. After the CSP has begun to infuse, does it need to be taken down and discarded after the BUD is met?

No. Administration must begin before the BUD. The administration process is outside the scope of <797>. Standard precautions such as the Centers for Disease Control and Prevention (CDC) safe injection practices apply to administration. See <800> for additional recommendations for the administration of hazardous drugs.

169. How does the storage condition affect the BUD of a CSP? What is the relationship between storage temperature and BUDs?

Generally, longer BUDs are permitted for CSPs stored in colder conditions than for CSPs stored at controlled room temperature as colder temperatures have been shown to slow the growth of most microorganisms.

Temperature affects chemical reaction rates; thus, storage at higher temperatures will accelerate degradation and reduce a BUD. The accepted rule of thumb is reaction rates increase two-fold for every 10 degree increase in temperature. This means that 1 year storage at 30 °C is equivalent to approximately 6 months at 40 °C and approximately 3 months at 50 °C. Correlating this concept to a refrigerated product (stored at 5 °C) estimates the BUD to be one-fourth at room temperature (25 °C). The exact mechanism of degradation and rate of reaction will determine the actual difference, which can only be determined through a stability evaluation over time.

170. Are BUDs cumulative?

No, BUDs must not be additive. The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage condition.

For example, a CSP that is assigned a BUD based on storage at room temperature cannot subsequently be refrigerated or frozen in order to extend the original BUD assigned. Likewise, the BUD of a frozen CSP must not be extended based on storage at room temperature when it is thawed.

171. Can the BUDs of Category 2 CSPs be extended beyond those in *Table 13. BUD Limits for Category 2 CSPs*?

The chapter states that BUDs for Category 2 CSPs must be established in accordance with *Table 13*. However, if there is a compounded preparation monograph for a particular CSP formulation, that BUD may be assigned if the CSP is prepared according to the monograph and all monograph requirements are met (e.g., Specific Tests). *General Notices 3.10* states that where the requirements of a monograph differ from the requirements in an applicable general chapter, the monograph requirements apply and supersede the general chapter.

Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14*, if compounded in accordance with all applicable requirements for Category 3 CSPs.

BUDs must be assigned conservatively and must take into account factors such as validated stability-indicating analytical methods and testing for sterility, endotoxins, container closure integrity, and particulate matter.

172. Why is the BUD for aseptically prepared Category 2 CSPs using only sterile ingredients 4 days when stored at controlled room temperature?

The previous version of <797> specified a storage time of 48 hours and 30 hours at controlled room temperature for low- and medium-risk level CSPs, respectively. The longer BUD in the revised chapter is based on a risk-based approach to balance the need for quality CSPs and to facilitate patient access. Further, the revised chapter contains additional requirements (e.g., facility and engineering controls and surface sampling) to help mitigate risks of inadvertent contamination.

173. Is mixing MVI vial 1 and vial 2 compounding? What is the BUD?

No. Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer. Refer to the approved labeling for use of MVI once mixed.

174. If the compounding facility meets the requirements for compounding Category 3 CSPs, can a CSP still be given a Category 2 BUD to avoid sterility testing that particular CSP?

Yes. The chapter does not prohibit a compounder from assigning a shorter BUD than is specified in the BUD Limits tables (*Table 14* for Category 3 CSPs). As these are BUD limits, they are the date and time after which a CSP must not be used, stored, or transported, and a BUD shorter than the limit may be assigned to a CSP.

175. What is an example of a CSP requiring a shorter BUD based on stability and sterility?

Shorter BUDs must be assigned when the CSP's stability and/or sterility is less than the hours or days established in BUD limits for each CSP Category. For example, per guidelines, parenteral nutrition compounded as a total nutrient admixture (TNA) at a final concentration of amino acid > 4%, monohydrated dextrose > 10%, and lipid injectable emulsion > 2% are more likely to remain stable for up to 30 hours at room temperature or for 9 days refrigerated followed by 24 hours at room temperature.

176. Are there special considerations for CSPs that contain lipid emulsions?

Manufacturer recommendations regarding administration times and filtering must be followed for CSPs containing lipid emulsions. Some lipid-containing products should not exceed an administration hang time exceeding 12 hours and many require the use of a 1.2-micron filter.

177. Do Category 3 CSP BUDs have to be based on published stability studies?

The USP Compounding Expert Committee has compiled the Formulation and Stability Reference Document for Pharmaceutical Compounding posted here to help compounders understand when a stability study is suitable for assigning Category 3 BUDs to CSPs. While every CSP must meet release testing requirements for each batch to ensure sterility, evidence to prove the physicochemical stability of a CSP may be obtained from any stability-indicating assay method study, either published or unpublished, and does not have to be repeated for each batch as long as the formula, procedures, and container closure systems in the study are exactly the same for the CSP being prepared.

178. Describe when <51> testing is necessary.

An aqueous multiple-dose CSP must pass antimicrobial effectiveness testing in accordance with <51> *Antimicrobial Effectiveness Testing*.

179. Is <51> testing required for stock solutions?

No. When a CSP stock solution is used as a component to compound additional CSPs, the original CSP stock solution must be entered or punctured in ISO Class 5 or cleaner air and must be stored under the conditions upon which its BUD is based (e.g., refrigerator or controlled room temperature). The CSP stock solution may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded.

180. Must antimicrobial effectiveness testing results be provided by an FDA-registered facility?

The compounder may rely on antimicrobial effectiveness testing 1) conducted (or contracted for) once for each formulation in the particular container closure system in which it will be packaged or 2) results from an FDA-registered facility or published in peer-reviewed literature sources, provided that the CSP formulation (including any preservative) and container closure system are exactly the same as those tested, unless a bracketing study is performed. Outside of the United States, facilities must comply with the laws and regulations of the applicable regulatory jurisdiction.

181. The conversion from high, medium, and low-risk compounding to Category 1 and Category 2 CSPs means that CSPs previously categorized as low-risk (48 hours at room temperature; 14 days refrigerated), now categorized as Category 2 (4 days room temperature; 10 days refrigerated) would increase the BUD at room temperature but decrease the BUD if refrigerated. Why is that?

The Compounding Expert Committee replaced risk levels with categories based on criteria other than just starting ingredients and number of manipulations. In addition to starting ingredients, BUDs are also based on environmental quality, personnel hygiene and garbing, physicochemical stability, and requirements for release testing.

182. If I only compound Category 3 CSPs occasionally, do I still have to follow the Category 3 requirements at all times?

Yes, if a compounder desires to assign a BUD longer than those allowed in *Tables 12* and *13*, then the requirements outlined in Section *14.4 Additional Requirements for Category 3 CSPs* must be met at all times.

183. What BUD should we use if there is no stability data available for the exact concentration of a CSP?

In this case, the maximum allowable BUD limits in <797> must not be exceeded.

184. May a plastic luer lock vial be stored after access?

No. The container closure system must remain intact in order to store a single-dose container after opening. Opened plastic luer lock vials are treated like ampules and must not be stored for any time period.

185. May a vial that has the septum or metal septum ring removed be stored after access?

No. The container closure system must remain intact in order to store a single-dose container after opening. Vials that have the septum or metal septum ring removed are treated like ampules and must not be stored for any time period.

Use of Conventionally Manufactured Products as Components

186. Is a conventionally manufactured single-dose container required to be stored in an ISO Class 5 PEC in order for it to be allowed to be used for up to 12 hours?

No, opened or punctured conventionally manufactured single-dose containers may be stored outside of an ISO Class 5 PEC. However, the chapter does require that the conventionally manufactured single-dose container be entered or punctured inside of an ISO Class 5 PEC. These containers may be used up to 12 hours after initial entry or puncture provided that the storage requirements (e.g., controlled room temperature, cold temperature) are maintained. Opened single-dose ampules must not be stored for any period of time.

187. When determining the BUD for a single-dose vial after puncture, how long can the single-dose vial be stored if the package insert states "use immediately"?

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer. When preparing a product per approved labeling, the labeling must be followed.

When compounding a CSP, if a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12-h period are maintained and based on sterility assurance.

Package inserts are often based on stability assurance and lack sterility data, so if this is the case and the package insert states "use immediately", the same microbiological principles of a 4-hour immediate-use time may apply. Contact the manufacturer for stability information.

188. Are conventionally manufactured sterile topical ophthalmic products considered multiple-dose containers?

No, <659> *Packaging and Storage Requirements* defines multiple-dose containers as a container closure system that holds a sterile medication for parenteral administration (injection or infusion) that has met antimicrobial effectiveness testing requirements, or is excluded from such testing requirements by FDA regulation. Therefore, the requirement that multiple-dose containers not be used for more than 28 days unless otherwise specified on the labeling does not apply to conventionally manufactured sterile topical products.

189. If the approved labeling of a pharmacy bulk package describes a long storage time (e.g., 14 days), can the pharmacy bulk package be stored and used for that period of time?

Users should carefully review the manufacturer's approved labeling for pharmacy bulk packages. Some approved labeling may provide a storage time based on stability (e.g., 14 days) as well as a shorter time (e.g., 4 hours) based on the risk of microbial contamination. Users must use the shorter storage time specified in the manufacturer's approved labeling. The pharmacy bulk package must be used according to the manufacturer's approved labeling.

Use of CSPs as Components

190. How is the BUD of a CSP affected by pH-modifiers or other stock solutions that are used as components?

For CSPs prepared from one or more compounded components, the BUD should generally not exceed the shortest BUD of any of the individual compounded components. However, there may be acceptable instances when the BUD of the final CSP exceeds the BUD assigned to compounded components (e.g., pH-altering solutions). If the assigned BUD of the final CSP exceeds the BUD of the compounded components, the physical, chemical, and microbiological quality of the final CSP must not be negatively impacted.

191. What is an example of assigning a BUD to compounded stock solutions and their subsequent CSPs?

A compounder wants to reconstitute a conventionally manufactured sterile product and further dilute it to prepare a subsequent CSP *(see 16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions)*.

- Day 1: a 2-gram single-dose conventionally manufactured container of powder for solution is reconstituted with 8 mL of a conventionally manufactured diluent, yielding 10 mL of 200 mg/mL of drug (CSP-A, original CSP). CSP-A is assigned a BUD of 10 days because it is aseptically processed, has not passed sterility testing, was prepared from only sterile starting components, and will be stored in a refrigerator (see *Table 13*).
- Day 3: CSP-A is entered or punctured in an ISO Class 5 PEC, where 10 mL of CSP-A solution is further diluted with 40 mL of diluent, yielding 50 mL solution of 40 mg/mL of drug (CSP-B, a finished CSP). CSP-B is aseptically processed, has not passed sterility testing, was prepared from only sterile starting components, and will be stored in a refrigerator. The BUD of a CSP prepared from one or more compounded components may not exceed the shortest BUD of any of the individual starting components. Therefore, the assigned BUD for CSP-B will be 7 days (10 days minus the 3 lapsed days of CSP-A), because that is the shortest BUD of all of its individual components.
- Additionally, CSP-A must be used within 12 hours of initial entry/puncture or its originally assigned BUD, whichever is shorter, and the remainder must be discarded.

192. What BUD must be assigned to Category 2 or Category 3 CSPs made using a CSP stock solution?

The BUD assigned to a CSP, whether compounded from conventionally manufactured components or from compounded stock solutions, follows the same standards in Section *14. Establishing Beyond-Use Dates*. The one difference found in Section *14.3 Establishing a BUD for a CSP,* is that the BUD of CSPs made from compounded components may, at times, exceed the BUD of compounded components. For example, if a compounded pH-altering solution with a short BUD is used to compound a CSP, the resulting CSP would likely have greater stability, and thus a longer BUD than the pH-altering solution. Another example would be a Category 2 CSP that was not sterility tested and used to make a Category 3 CSP that will be sterilized and sterility tested. If the physical, chemical, and microbiological stability is not negatively impacted, the BUD of the resulting CSP may exceed that of the component. This exception does not exist for commercially available components. It is important to note that the BUD of the final CSP should not be further restricted by the time limits for entering or puncturing components found in Sections *15* and *16*.

193. Once punctured, can a CSP or conventionally manufactured product still be used for the length of its BUD?

Compounders may utilize both conventionally manufactured and compounded components. The chapter specifies the time in which each of these components can be stored and used after first entered. This is often called in-use time, although this term is not used in the chapter. The BUD is not the same as in-use time. A multiple-dose vial may have a BUD of 60 days but must still be discarded no later 28 days after first puncture.

194. The chapter states, "After a multiple-dose CSP is initially entered or punctured, the multiple-dose CSP must not be used for longer than the assigned BUD or 28 days, whichever is shorter. This time limit for entering or puncturing is not intended to restrict the BUD of the final CSP." Can you clarify what the last sentence means?

Each component, whether conventionally manufactured or compounded, must have a time limit for entering or puncturing after first use. For example, a conventionally manufactured multiple-dose vial may not be used after 28 days of first puncture. This 28-day time limit for use is not the same as the BUD of the component and is not intended to restrict the BUD of the resulting CSP. If a CSP is prepared from a multiple-dose vial either 1 day or 10 days after first puncture, the BUD of the resulting CSP would remain the same. For example, let's assume a conventionally manufactured multiple-dose vial with a one-year expiration date is used to compound a CSP with a 60-day BUD. The multiple-dose vial component may be punctured on day 1 to make the CSP and a BUD of 60 days would be given. Now, 27 days later the same multiple-dose vial component is punctured to make the CSP, and still, a 60-day BUD is assigned. In this instance, the time limit for entering or puncturing the MDV component does not further restrict the CSP being compounded.

195. Please explain the requirements as to the appropriate BUD for a reconstituted single-dose vial. For example, a reconstituted vial of daptomycin is stable for 2 days in the refrigerator. Can this vial be saved and reused for multiple preparations if kept in the refrigerator?

See Section *15* of <797>, which describes the different types of components that could be part of a CSP. When using a single-dose vial, <797> says: "If a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12-h period are maintained."

The vial of daptomycin mentioned in this example may be used for multiple preparations up to 12 hours after initial entry or puncture provided that the storage requirements (e.g., controlled room temperature, cold temperature) are maintained. If reconstituted in advance *as a single dose for a single patient*, then the daptomycin reconstituted solution may be stored per the approved labeling.

Quality Assurance and Quality Control

196. What does "the overall QA and QC program" entail?

A quality assurance program is guided by written procedures that define responsibilities and practices that ensure compounded preparations are produced with quality attributes appropriate to meet the needs of patients and healthcare professionals. The authority and responsibility for the quality assurance program should be clearly defined and implemented and should include at least the following nine separate but integrated components: (1) training; (2) standard operating procedures (SOPs); (3) documentation; (4) verification; (5) testing; (6) cleaning, disinfecting, and safety; (7) containers, packaging, repackaging, labeling, and storage; (8) outsourcing, if used; and (9) responsible personnel.

CSP Handling, Storage, Packaging, Shipping, and Transport

197. <797> states that the temperature in the storage area must be monitored each day, either manually or by a continuous recording device. ("The results of the temperature readings must be documented in a temperature log per facility SOPs or stored in the continuous temperature recording device and must be retrievable.") Does this mean that it would be acceptable to record temperatures on Monday if closed on weekends?

Yes.

198. Do all personnel who "touch" a CSP need to have training?

Yes, but not all personnel require the same training. <797> is specific about training for compounding, but leaves requirements for other personnel up to the organization. Personnel who receive sterile products and preparations, enter orders but do not compound or check CSP preparation, clean compounding areas, transport CSPs, or other activities must have documented competence as defined by the organization.

See related question in Personnel Training and Evaluation.

Compounding Allergenic Extracts

199. What are allergenic extracts?

Allergenic extracts are biological substances used for the diagnosis and/or treatment of allergic diseases such as allergic rhinitis, allergic sinusitis, allergic conjunctivitis, bee venom allergy, and food allergy. Allergenic extract prescription sets are combinations of licensed allergenic extracts which would be mixed and diluted to provide subcutaneous immunotherapy to an individual patient, even though these allergenic extract combinations are not specified in the approved biological license application (BLA) for the licensed biological products.

200. Does *21. Compounding Allergenic Extracts* apply to physician and pharmacy settings?

Yes, the provisions in *21. Compounding Allergenic Extracts* apply regardless of where the allergenic extract is compounded when:

1. The compounding process involves transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances, and
2. Manipulations are limited to penetrating stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile vials.

201. Why are the BUDs for compounded allergenic extracts longer than those required for Category 1 and Category 2 CSPs?

Because of certain characteristics of allergenic extracts and allergy practice (e.g., preservative systems and risk of anaphylaxis), preparation of allergenic extract for individual patient prescription sets is not subject to the requirements in this chapter that are applicable to other sterile CSPs. Further, FDA provides additional information for preparation of allergenic extracts in the FDA Guidance for Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application.

202. Does gloved fingertip and thumb sampling need to occur after media-fill testing for personnel who compound allergenic extracts?

No. Unlike personnel training for other CSPs, the goal of gloved fingertip and thumb sampling for personnel who compound allergenic extracts is to evaluate hand hygiene and garbing but not aseptic technique, due to the nature of the CSPs they compound. Therefore, personnel perform gloved fingertip and thumb sampling three times initially before compounding; thereafter gloved fingertip and thumb sampling is performed immediately after donning gloves at least once every 12 months. The action level for these samples is anything greater than 0 CFU per each hand.

203. Can allergenic extracts be prepared for immediate-use?

Yes.

204. Can this section apply for vials that are made for multiple patients?

No. Compounding allergenic extracts is per individual patient prescription set only.

BUD Scientific Rationale for the 2021 Proposed Revisions to <797>

Published September 1, 2021

Background

This informational document is intended to supplement the proposed *USP* General Chapter <797>. The proposed chapter and additional supplementary materials are posted online here. Proposed <797> is available for public comment until March 17, 2022. This supplemental document is not part of the proposed chapter, is not a comprehensive overview of the proposed chapter, and is not intended to be used in place of the proposed chapter. Rather, it provides history of the chapter and explains the rationale of some of the proposed revisions to the chapter.

This does not reflect the Compounding Expert Committee's (CMP EC) opinions on further revisions to the chapter. This document is not intended to be subject to public comment. Stakeholders are encouraged to submit comments on the proposed chapter for the CMP EC to continue to evaluate revisions to the chapter. The CMP EC will consider all comments received on the chapter.

Please note that neither the proposed chapter nor this document are official *United States Pharmacopeia – National Formulary* (*USP-NF*) text and they are not intended to be enforceable by regulatory authorities. Users must refer to the *USP-NF* for official text.

Questions may be sent to CompoundingSL@USP.org.

Introduction

USP has a long history of developing standards for sterile compounding. In 1985, prompted by injuries and deaths around the United States related to poorly compounded preparations, USP began developing a general informational chapter for the preparation of home parenteral products.[1,2] In 1992, General Chapter <1074> *Dispensing Practices for Sterile Drug Products Intended for Home Use* was proposed for public comment in USP's *Pharmacopeial Forum* (*PF*).[1,3] Around the same time, the American Society for Health System Pharmacists (ASHP) also published a draft guideline and a technical assistance bulletin on sterile compounding.[1, 4] Following review of public comments to <1074>, the chapter was later renumbered and republished into *PF* in 1993 as revised <1206> *Sterile Drug Products for Home Use*.[1,5] <1206> became official in 1995.

In 1997, the U.S. Congress passed the Food and Drug Administration Modernization Act (FDAMA), which amended the Federal Food, Drug, and Cosmetic Act to include, among other things, a compounding provision, section 503A, which exempts compounded human drug products from certain requirements if, among other things, a drug product is compounded using bulk drug substances and ingredients that comply with the standards of an applicable *USP–NF* monograph, if a monograph exists, and the USP chapter on pharmacy compounding.[6,7] Based on FDAMA, USP revised and renumbered <1206> to <797> *Pharmaceutical Compounding – Sterile Preparations*.[2] <797> was first published in 2004 and last revised in 2008. The 2008 revision of <797> remains the currently official chapter used into 2021.

Since 2010, the CMP EC has been working on revisions to <797> and has published two drafts in *PF* for public comment, first in 2015 and again in 2018. Both versions received a combined total of more than 10,000 comments. Following review of all comments, USP published a final revision of <797> in the *USP-NF* in June 2019, with an effective date of December 2019.

USP received appeals from various stakeholders regarding certain provisions in the revised 2019 standard. In accordance with USP's Bylaws, the CMP EC thoroughly considered the information raised in the appeals and issued decisions denying

the appeals. As part of the formal USP appeals process, some appellants requested further review by an appointed Appeals Panel. The Appeals Panel granted the appeals in March of 2020, remanding <797> to the CMP EC for further engagement on the issues raised by stakeholders, particularly concerning beyond-use date (BUD) provisions. Though the Appeals Panel did not determine the chapters to require revision, they noted that the issues raised in the appeals warranted additional dialogue and consideration. It was left to the purview of the CMP EC to determine the appropriateness of future revisions to the chapter.

Since May 2020, USP facilitated various stakeholder engagements to obtain additional input on the chapters, as the CMP EC considered next steps and revisions to the chapters. Details of the findings from these engagements are available on the compounding pages of the USP website. From stakeholder engagement activities, some common topics arose regarding BUDs, which were evaluated and considered by the CMP EC. Please see Appendices 1 and 2 to review examples of letters from stakeholders presenting views on assigning BUDs which the CMP EC considered in their deliberations.

Key concerns that stakeholders raised related to the 2019 revision of <797> included:

- Inability of compounders to assign BUDs longer than those established in the BUD limit tables when additional stability data is available
- Adequacy of the two categories of CSPs or if there is a need for a more layered approach
- Clarity of the testing requirements for all CSPs
- Practical applicability of the standards to compounders for various settings in which compounding occurs
- Need for additional guidance on CSPs in multiple-dose containers, particularly for preservative-free ophthalmic preparations.

The CMP EC kept these topics in consideration during the review process. In addition to stakeholder feedback, the CMP EC considered the following:

- Describing a scientifically robust and risk-based approach to assigning BUDs; including physical and chemical stability considerations along with requirements for sterility assurance for the various categories of CSPs
- Balancing the need for patient access to cost-effective CSPs with rigorous quality standards
- The cost implications of implementing the standards in a variety of practice settings; including evaluation of any operational implications of additional requirements when assigning longer BUDs
- Implications on regulatory oversight and enforcement for the requirements in the standard.

This paper highlights these considerations and discusses the rationale of the CMP EC in writing the recently revised <797> proposed in *PF* 47(6), November 2021.

Categories of CSPs

In the 2015 proposed revision of <797>, it was first introduced to change the CSP categories from a three termed format of low-risk, medium-risk, and high-risk to a two termed format of Category 1 and Category 2. This change was proposed to avoid inaccurately conferring a level of risk to a particular CSP without consideration for all factors that influence the quality of that CSP. Renaming the CSP categories as Category 1 and Category 2, distinguished primarily by the conditions under which they are made and the time within which they are used, is intended to be a neutral designation. Following review of input received from stakeholders in 2020, the CMP EC proposes to maintain this category naming based on the reasonings behind the original change. In addition, following extensive discussions and input received from stakeholders, the CMP EC added a Category 3 for CSPs assigned longer BUDs than those assigned for Category 1 or Category 2 CSPs.

Category 1 and Category 2 CSPs

In the predecessor chapter to <797>, <1206>, the only specific storage limit provided was 7 days under refrigeration. When <1206> was revised and renumbered to <797> in 2004, more comprehensive storage limits were included in consideration of those in the ASHP Guidelines.[2,8] When developing these BUD limits for sterile compounding, the minimum time periods necessary to perform required tests were considered (e.g., at least 14 days for <71> *Sterility Tests*, and at least 28 days for <51> *Antimicrobial Effectiveness Testing*). Requirements of other applicable general chapters were also considered, including chapters <7> *Labeling*, <85> *Bacterial Endotoxins Test*, and <659> *Packaging and Storage Requirements*. Parameters for establishing BUDs considered throughout the original development and the revisions have also included chemical and physical stability, the potential for microbial proliferation, the exponential growth rate of microorganisms with increasing temperatures, compatibilities with container closure, patient access and cost implications, frequency of personnel and environmental monitoring, and the potential for inadvertent contamination.

Table 1 summarizes the maximum BUD limits for CSPs in the absence of passing sterility testing in the currently official *USP* <797>, last revised in 2008. For comparison, Table 2 summarizes the maximum BUD limits for Category 1 and Category 2 CSPs in the subsequent proposed revisions to <797>, including those published in *PF* for public comment in 2015 and 2018, and the version published in the *USP-NF* in 2019, which was later remanded. The 2015 proposed revisions included distinctions for assigning BUDs based on whether or not the CSP contained a preservative. However, there were concerns about this parameter in establishing BUDs, including that it could be misleading and could give a false sense of security when compounding CSPs with preservatives. Additionally, public comments noted that the presence of preservatives may not always be clinically appropriate and may impact the stability of the formulation. Further, concerns were raised that inappropriate preservatives may be added to circumvent testing requirements or to inappropriately assign longer BUDs. The presence of preservatives in the parameters for establishing a BUD was removed in further revisions to the chapter.

Table 1. Maximum BUD limits for CSPs in the absence of passing a sterility test in the currently official *USP* <797>, last revised in 2008.

	2008 Published Chapter
Low-risk in segregated compounding area	12 hours at Controlled Room Temperature (CRT)
Low-risk	48 hours at CRT 14 days in a refrigerator 45 days in a freezer
Medium-risk	30 hours at CRT 9 days in a refrigerator 45 days in a freezer
High-risk	24 hours at CRT 3 days in a refrigerator 45 days in a freezer

Table 2. BUD Limits for Category 1 and Category 2 CSPs in the revisions to *USP* <797> published in 2015, 2018, 2019, and 2021.[a]

	2015 Revision Proposed in *PF*	2018 Revision Proposed in *PF*	2019 Revision Published in *USP-NF* (subsequently remanded)	2021 Revision Proposed in *PF* (currently available for public comment until March 17, 2022)
Category 1				
Prepared in an SCA	≤ 12 hours at CRT ≤ 24 hours in a refrigerator	≤ 12 hours at CRT ≤ 24 hours in a refrigerator	≤ 12 hours at CRT ≤ 24 hours in a refrigerator	≤ 12 hours at CRT ≤ 24 hours in a refrigerator
Category 2				
Aseptically processed No sterility testing Only sterile starting components	**No preservative added** ▸ 6 days at CRT ▸ 9 days in a refrigerator ▸ 45 days in a freezer	4 days at CRT 9 days in a refrigerator 45 days in a freezer	4 days at CRT 10 days in a refrigerator 45 days in a freezer	4 days at CRT 10 days in a refrigerator 45 days in a freezer
Aseptically processed No sterility testing One or more nonsterile starting component(s)	**No preservative added** ▸ 4 days at CRT ▸ 7 days in a refrigerator ▸ 45 days in a freezer	1 day at CRT 4 days in a refrigerator 45 days in a freezer	1 day at CRT 4 days in a refrigerator 45 days in a freezer	1 day at CRT 4 days in a refrigerator 45 days in a freezer
Aseptically processed No sterility testing	**Preservative added** ▸ 28 days at CRT ▸ 42 days in a refrigerator ▸ 45 days in a freezer	--	--	--
Aseptically processed Passed sterility testing	**No preservative added** ▸ 28 days at CRT ▸ 42 days in a refrigerator ▸ 45 days in a freezer **Preservative added** ▸ 42 days at CRT ▸ 42 days in a refrigerator ▸ 45 days in a freezer	30 days at CRT 45 days in a refrigerator 60 days in a freezer	30 days at CRT 45 days in a refrigerator 60 days in a freezer	30 days at CRT 45 days in a refrigerator 60 days in a freezer
Terminally sterilized No sterility testing	**No preservative added** ▸ 14 days at CRT ▸ 28 days in a refrigerator ▸ 45 days in a freezer **Preservative added** ▸ 28 days at CRT ▸ 42 days in a refrigerator ▸ 45 days in a freezer	14 days at CRT 28 days in a refrigerator 45 days in a freezer	14 days at CRT 28 days in a refrigerator 45 days in a freezer	14 days at CRT 28 days in a refrigerator 45 days in a freezer
Terminally sterilized Passed sterility testing	**No preservative added** ▸ 28 days at CRT ▸ 42 days in a refrigerator ▸ 45 days in a freezer **Preservative added** ▸ 42 days at CRT ▸ 42 days in a refrigerator ▸ 45 days in a freezer	45 days at CRT 60 days in a refrigerator 90 days in a freezer	45 days at CRT 60 days in a refrigerator 90 days in a freezer	45 days at CRT 60 days in a refrigerator 90 days in a freezer

[a] None of these revisions are official *USP-NF* text.

Category 3 CSPs

The currently official <797>, last revised in 2008, allows longer storage times if sterility testing is performed, and the BUD can be assigned based on professional experience and careful interpretation and application of stability and sterility consideration. Subsequent revisions to the chapter limited BUDs based on concerns expressed by various stakeholders related to sterility, stability, environmental monitoring, and personnel monitoring. This revision prompted concerns from several stakeholder that led to the appeals on the 2019 revision of the chapter. After further engagement with stakeholders and upon further deliberation, the CMP EC revised the chapter and proposed a new Category 3 for CSPs which allow compounders to assign longer BUDs than those established for Category 1 and Category 2 CSPs if additional requirements are met. However, the CMP EC maintained that BUDs should not be open-ended as they are in the chapter published in 2008. Category 3 CSPs have additional requirements that a compounding facility must follow at all times when assigning longer BUDs than the limits proposed for Category 2 CSPs. Table 3 summarizes the recommendations for assigning longer BUDs than those in <797> in the chapter revisions.

Table 3. Recommendations for assigning longer BUDs than those in the chapter in the revisions to *USP* <797> published in 2008, 2015, 2018, 2019, and 2021.

	2008 Published Chapter	**2015 Revision Proposed in *PF***	**2018 Revision Proposed in *PF***	**2019 Revision Published in *USP-NF*** (subsequently remanded)	**2021 Revision Proposed in *PF*** (currently available for public comment until March 17, 2022)
Assigning longer BUDs than those established in the chapter[a]	BUDs could be assigned up to the duration indicated by appropriate information sources for the same or similar formulations and by personal experience	The ability to assign longer BUDs was not described	BUDs could be assigned up to a maximum of 90 days if supported by stability data	BUDs could only be assigned up to the limits described in the chapter	Category 3 describes the requirements a compounding site must ensure at all times for assigning longer BUDs than those established for Category 2 CSPs, up to a maximum of 180 days

[a] If there is a compounded preparation monograph for a particular CSP formulation, the BUD in the monograph can be assigned if the CSP is prepared according to the monograph and all monograph requirements are met, including sterility testing.

The Need for Assigning Longer BUDs

The CMP EC considered the need for compounders to provide timely access to CSPs in various settings. In the United States, section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act) describes the conditions under which compounded drug products are exempt from certain provisions of the FD&C Act; including Current Good Manufacturing Practices (CGMP) requirements, FDA approval before marketing, and labeling of drugs with adequate directions for use.[9, 10] One of the conditions is that the drug products must be compounded based on the receipt of valid patient-specific prescriptions.[9] In 2013, the Drug Quality and Security Act added section 503B to the FD&C Act, which established compounding for outsourcing facilities that are subject to CGMP and other requirements.[10]

The CMP EC recognized the need to provide additional flexibility for 503A compounders as 503B outsourcing facilities may not be as willing or able to supply small quantities of patient-specific compounded drug products. Allowing the compounder to assign longer BUDs, up to a limit, helps in ensuring timely patient access to CSPs. The need for longer BUDs must also be weighed against potentially elevated risks to patients. Longer storage time increases risks for chemical degradation, physical incompatibilities, compromising of the container closure system, and microbial proliferation. To mitigate these risks, the 2021 proposed revision introduces additional requirements with the intention of elevating sterility assurance to a level that supports the assignment of longer BUDs. These additional conditions include maintaining a higher state of facility control through the use of sterile garb, more frequent application of sporicidal disinfectants, and more frequent personnel and environmental monitoring. Additionally, the chemical and physical stability, and compatibility of the preparation in the final container closure system must be verified using specific study designs and methodologies.

In response to stakeholder questions and concerns, the CMP EC has developed a supplementary Stability Study Reference Document as a resource for understanding and performing stability-indicating analytical methods, which may be found posted here. This document also describes some scenarios for compounders to consider regarding when assigning longer BUDs may be necessary. Additionally, detailed discussions of these scenarios are available on the compounding pages of the USP website.

Stability Testing

Ensuring the stability and integrity of a CSP that is assigned a longer BUD has been a major consideration for the CMP EC in developing the new Category 3 CSP criteria. Due to the variability in existing data currently used to assign BUDs, the CMP EC determined more guidance is needed for compounders assigning BUDs beyond the limits for Category 2. The 2021 proposed revision requires that the compounder supports the longer BUDs allowed with Category 3 with a stability-indicating analytical method. This helps ensure that the compounder is basing stability on the presence of active ingredient(s), separate from its degradants and impurities through forced degradation. Compounders must also validate the method based on <1225> *Validation of Compendial Procedures*. The stability study itself must include storing the preparation in temperature-controlled environments, testing the preparation at predetermined time points, and then determining the stability. The study must be conducted for the exact CSP active pharmaceutical ingredient (API) and formulation, and in the specific container closure system used.

While potency tests are designed to determine how much of the active drug is in a sample, stability testing is used to determine a beyond-use date for a CSP. Though stability-indicating methods can also determine potency, not all potency tests can conversely determine stability. Potency tests are not proven to differentiate between the compound of interest and its degradants or excipients, and thus do not meet <797>'s definition of stability: *"The extent to which a product or preparation retains physical and chemical properties and characteristics within specified limits throughout its expiration or BUD"*. The EC is aware of published data that indicates a marked difference between potency tests and stability-indicating analytical methods.

A medication with a narrow therapeutic index may produce a magnified or greatly reduced effect if its concentration is altered even slightly. Ultraviolet (UV) profiles of APIs and degradants can sometimes be so similar that one cannot discern the difference. Additionally, there are times when degradants may have a stronger UV signal, thus giving the false impression of stability. For these reasons, the proposed revision to <797> specifies that stability be determined using a stability-indicating method.

The aforementioned Stability Study Reference Document is also available as a resource in helping to understand and perform stability-indicating analytical methods, and may be found posted here.

Additional Requirements for Category 3

In addition to verifying physicochemical stability of the formulation, there are other requirements that must be followed at

all times in order to compound Category 3 CSPs. The CMP EC reviewed multiple studies and consulted with microbiology experts to develop these additional requirements to increase the level of sterility assurance through increased personnel and environmental monitoring.

The overarching rationale behind these requirements is that preventative strategies are more effective than detection methods at increasing levels of sterility assurance. Solely relying on environmental monitoring is insufficient as it is a measure of potential breaches that may have occurred in operational controls. Other concerns about relying only on environmental monitoring methods alone are that shedding from personnel and personal protective equipment (PPE) during normal operations may be undetectable by current monitoring methods, and environmental monitoring sampling levels at the frequencies required in the chapter do not provide sufficient data to detect statistically significant trends. With these considerations, aseptic process controls and personnel competency is more effective in controlling contamination than relying primarily on environmental monitoring, which is conducted periodically as opposed to continuously in CGMP settings.[11]

An area of focus for additional requirements for Category 3 CSPs is personnel competency. The increased requirements for personnel competency evaluation apply to all personnel who participate in or oversee the compounding of Category 3 CSPs. Didactic training for personnel must be completed at least every 12 months and must be representative of the complexity of the compounding activities being performed. This strategy is a cost-effective and high-impact method at minimizing the risk of contamination. The personnel competency evaluations include the garbing competency evaluation (visual observation and gloved fingertip and thumb sampling of both hands) and aseptic manipulation competency (media-fill testing, gloved fingertip and thumb sampling, and surface sampling of the direct compounding area). In the currently official chapter published in 2008, gloved fingertip sampling is a qualification measure for the individual compounder, not a real-time assessment of CSP batch quality. Conducting gloved fingertip sampling with every CSP batch as generally done in a CGMP environment was determined to be difficult for 503A compounders due to the need for additional personnel to complete the process. Instead, the CMP EC recommends increasing the frequency of the garbing competency evaluation and the aseptic manipulation competency evaluation to every 3 months for Category 3, compared to every 6 months required for Categories 1 and 2. When evaluating aseptic manipulation competency, the goal is to demonstrate that compounders can perform routine aseptic processes using sterile media without introducing contamination. The most critical attribute of a media-fill test is that it simulates the type and complexity of the procedures and manipulations compounders perform to capture any element that could potentially affect the sterility assurance of the preparation. Increasing the frequency of this aseptic manipulation competency evaluation to every 3 months for Category 3 compounding helps to ensure CSP sterility as the process is highly dependent on the competency of the compounder.

There are additional requirements for garbing for all personnel entering the classified areas where Category 3 CSPs are compounded. Whereas nonsterile garb may be used when compounding Category 1 and 2 CSPs, sterile, low-lint garb must be used at all times within the cleanroom suite for Category 3 CSPs. This is necessary to lower the overall bioburden in the cleanroom and reduce the potential for contamination during the compounding process. Most microorganisms in cleanroom air currents are the result of direct particle shedding from personnel. Properly donned and well-functioning garb acts as a barrier against human shedding. The garb itself must be low-linting to avoid being a significant particulate-contributor.

In addition to the preventative requirements, there are also increased environmental monitoring requirements that apply to all classified areas where Category 3 CSPs are compounded. Viable air sampling facilitates monitoring for trended variations in results over time that may indicate a problem exists with primary or secondary engineering controls or personnel compliance. Surface sampling is a cost-effective, high-impact detection method which, if performed during or shortly after compounding, provides a record of the conditions at the time when compounding is taking place. Monitoring surface sampling trends can provide information about the overall state of control.

An increased frequency of sporicidal disinfectant application is also required to compound Category 3 CSPs and applies to all classified areas where Category 3 CSPs are compounded. This increased frequency of sporicidal disinfection is a risk-based approach to destroy bacterial and fungal spores more frequently, thus reducing the potential for contamination in CSPs with longer BUDs.

Following Category 3 Requirements at All Times

Establishing and maintaining a state of control in the cleanroom suite is achieved by consistently performing personnel competency assessments and environmental control activities over time. To maintain this higher state of control, these activities must be performed at all times, and not just on days when Category 3 CSPs are compounded. While the complete eradication of microbes is unattainable, the goal of the additional requirements for Category 3 CSPs is to further minimize the risk of microbial growth in the cleanroom suite and subsequent risk of contamination of CSPs that will be assigned longer BUDs.

Limiting Category 3 BUDs to a Maximum of 180 Days

Table 4. BUD limits for Category 3 CSPs in the 2021 proposed revisions to <797>.

Preparation Characteristics	Storage Conditions		
Compounding Method	**Controlled Room Temperature (20°–25°)**	**Refrigerator (2°–8°)**	**Freezer (–25° to –10°)**
Aseptically processed, sterility tested, and passing all applicable tests for Category 3 CSPs	60 days	90 days	120 days
Terminally sterilized, sterility tested, and passing all applicable tests for Category 3 CSPs	90 days	120 days	180 days

The proposed BUD limits for Category 1 and Category 2 CSPs are stratified based on risk elements including compounding process (e.g., aseptic processing or terminal sterilization), the environment in which compounding occurs, and the starting ingredients used for compounding (e.g., nonsterile or sterile). Category 3 establishes BUD limits that are up to double those assigned for Category 2, thus maintaining the same risk stratification (see Table 4). The CMP EC determined that there should be a limit to allowing longer assigned BUDs for CSPs, as opposed to allowing BUDs to be assigned up to as long as those based on a stability study. The reasons for this are as follows.

The scope of compounding of CSPs as described in <797> is for patient-specific prescriptions that are not intended to be stored for long periods of time, in contrast to drugs compounded by outsourcing facilities and manufactured drug products. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) stability study guidelines and the FDA guidance document on stability studies highlight the differences between stability studies for CSPs and studies for manufactured products.[12, 13]

Below are some examples of the differences between stability studies for manufactured products and CSPs. In addition to the development and validation of a stability-indicating analytical method, manufacturers have ongoing stability study requirements to demonstrate repeatability and an overall state of control and are responsible for the following:.[12, 13, 14]

- Three initial production lots are tested for stability, with the product in its final packaging
- Studies are conducted under accelerated, intermediate, and long-term stability conditions
- Degradation products and impurities are identified and quantified
- Functional attributes, such as dissolution testing, are tested as part of the stability study

- At least 1 production batch is studied for stability annually and every batch must pass release testing before being placed into the marketplace
- A 5% change from initial results is considered significant and may halt a study or require more analysis
- Any process change necessitates a repeat of the stability study and process validations

In addition to manufactured drug product stability requirements, the CMP EC discussed the diversity of practice settings, environments, processes, and analytical approaches. All of this, coupled with there being not many cases in practice where patients require greater than a 6-month supply of a CSP, resulted in the CMP EC's proposal to maintain a BUD limit of 180 days for Category 3 CSPs.

Batch Size Limit

The maximum batch size for all CSPs requiring sterility testing is 250 final yield units. This batch size limitation applies to both Category 2 CSPs and to Category 3 CSPs that undergo sterility testing in order to assign a longer BUD. Contamination risk increases with larger batch sizes, particularly for manual processes. The process of sterility testing leads to destruction of the CSP used in testing, as the container closure system has to be breached. For this reason, not all units within a batch can be tested for sterility. Rather, samples from the batch need to be selected according to the sampling protocols described in <71> *Sterility* Tests.

The limit of 250 final yield units is based on *USP* <71>'s *Table 3*, which provides the minimum number of items to be tested in relation to the number of items in the batch. This table specifies that 10 containers are to be tested for quantities greater than 100 to up to 500 containers, leading the CMP EC to propose specifying 250 as the maximum batch size for CSPs requiring sterility testing. Also, contamination within a batch may not be uniformly distributed across all units. Therefore, the probability of detecting contamination during sterility testing decreases as batch size increases, and risk for unidentified contamination increases. The intent is to reduce the risk of patient harm from undetected contamination of CSPs by introducing a batch size limit.

Multiple-Dose CSPs

Stakeholder engagement also included discussions on BUD assignment for multiple-dose CSPs specifically for nonpreserved aqueous ophthalmic CSPs. The CMP EC proposes that a multiple-dose CSP must be prepared as a Category 2 or Category 3 to reduce the potential for contamination. Aqueous multiple-dose CSPs that contain a preservative must also pass antimicrobial effectiveness testing in accordance with <51> *Antimicrobial Effectiveness Testing*. Suitable preservatives are added to inhibit the growth of microorganisms that may be introduced from repeatedly withdrawing individual doses. <51> testing procedures demonstrate the effectiveness of these added antimicrobial preservatives. Testing the effectiveness of preservatives is necessary, as variations in the formulation and container closure system can affect the preservative's and the CSP's solubility, pH, and stability, potentially rendering the CSP active ingredients, or the preservative, ineffective.

The BUD limits for multiple-dose CSPs are assigned from the time compounding begins based on whether the CSP is prepared as a Category 2 or a Category 3. Additionally, upon initially entering or puncturing the CSP, the CSP must be used within 28 days, as long as these 28 days are within the original BUD limit assigned and if supported by <51> testing. If <51> testing shows that a shorter timeframe is required, then that shorter limit must then be assigned. The proposal to limit the use to within 28 days of puncture is from the limits established in <51>.

For some multiple-dose ophthalmic CSPs, including preservatives may not be appropriate due to irritation and potential harm to the eye. However, these formulations are at high risk of microbial proliferation if contaminated during use. Because these ophthalmic formulations do not include a preservative, the requirement to pass <51> testing does not apply as there is no preservative present to test. The BUD limits for these multiple-dose ophthalmic CSPs which do not contain a preservative system are still assigned based on their preparation as a Category 2 or a Category 3 CSP. However, an additional provision does apply regarding the time within which the CSP must be used. Upon first opening these containers, they must be discarded

within 24 hours if stored at room temperature, or within 72 hours if stored in a refrigerator. This requirement is consistent with what is required for similar ophthalmic products manufactured under CGMP.[11]

Conclusions

Through deliberation and proposed revisions, USP continues to focus on creating quality compounding standards based on robust scientific evidence and the expertise of its committees. The CMP EC expresses its appreciation to stakeholders for reviewing this rationale behind the proposed 2021 revisions to *USP* <797>. The CMP EC has significantly benefited from the additional engagement with stakeholders throughout the revision process and hopes that the proposed 2021 revisions to *USP* <797> provides additional clarity for compounders to help ensure the safety of patients.

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Appendix 1 – Letter from the Alliance for Pharmacy Compounding (APC).

100 Daingerfield Road, Suite 401
Alexandria, VA 22314
www.a4pc.org

Alliance for Pharmacy Compounding

May 6, 2021

Connie Sullivan
Chairman, USP Compounding Expert Committee <797> Subcommittee
U.S. Pharmacopeia
126 Twinbrook Parkway
Rockville, Maryland 20852

RE: USP <797> Beyond-Use Date Recommendations

Dear Chairman Sullivan:

On behalf of the Alliance for Pharmacy Compounding, and as chair of APC's Beyond-Use Date Task Force, I wish to offer input that we believe can assist your subcommittee's work to determine proper beyond-use date standards for sterile compounded preparations.

As you may know, the Alliance for Pharmacy Compounding (formerly the International Academy of Compounding Pharmacists) is the voice for pharmacy compounding, representing thousands of pharmacists, technicians, students, researchers and suppliers. Compounding exists for patients and animals who are not served by traditional pharmaceutical manufacturers. We create custom medications that patients simply cannot get anywhere else. Every day, our members play a critical, often life-or-death role in patients' lives. Pharmacy compounders are a valued part of the health care team, creating essential treatments unavailable elsewhere for a range of issues, including autism, oncology, dermatology, ophthalmology, pediatrics, women's health, and many others.

APC and its members have a great interest, of course, in the updated USP <797> chapter that was published in June of 2019. Along with other stakeholders, we appealed the new <795> and <797> chapters developed by USP based on our grave concerns about the restrictions on beyond-use dates in those chapters, and we understand that the current work of your subcommittee is the result of the granting of our appeal in March of last year.

On behalf of APC's Beyond-Use Date Task Force, I wish to share our recommendations regarding default BUDs for sterile products in Chapter <797>.

As a baseline matter, APC firmly believes that default BUDs for sterile compounded preparations need to be based on scientific evidence. We understand the need for default dates that apply to the greatest number of compounds in order to establish a consistent regulatory enforcement regime. However, as highly trained scientists, pharmacists should be able to avail themselves of many different resources to apply appropriate BUDs to compounded sterile products (CSPs). Preventing us from extending BUDs with testing will result in greatly reduced access to CSPs by our patients, increased cost to those patients, and will induce pharmacies to create smaller, more frequent batches of CSPs that are not tested for sterility at all.

The main source of confusion for us regarding the default BUDs published in the 2019 USP Chapter <797> is this: Were these default BUDs based on the achievement and maintenance of sterility for CSPs (sterility assurance) or were they based on the chemical and physical stability of CSPs (stability)? We assume both sterility assurance and stability were factors in establishing these default BUDs for CSPs, and our recommendations below are based on that assumption. However, it remains unclear to

us what specific sterility assurance practice standards published in the 2019 USP Chapter <797> were of greatest concern to USP and contributed to the establishment of the short default BUDs. For example, currently there are 22 compounded sterile preparation monographs that USP has published with BUDs of up to 180 days. But these monographs contain no additional sterility assurance requirements beyond those specified in <797>. This leads us to believe that USP's main concerns regarding extended BUDs for CSPS are based more on a compounder's ability to demonstrate chemical and physical stability of a CSP over time, including container-closure integrity and antimicrobial effectiveness, and less on whether a compounder can achieve sterility during the compounding process by following the standards already established in Chapter <797>.

We propose that USP create a Category 3 that would allow pharmacies compounding batches with extended BUDs (Category 3) to perform stability indicating studies and/or have greater QA/QC requirements than pharmacies that use the default BUDs. In the following pages, we provide suggestions as to what could be added to the requirements in USP <797> to allow pharmacies to extend BUDs, including proposed cleaning requirements and greater frequency of environmental and personnel monitoring. The increased requirements would be more rigorous than <797> procedures, but less rigorous than cGMP requirements.

Recommendations

Category Definitions

We recommend no changes to the proposed Categories 1 and 2, but we urge the creation of a new Category 3 that provides for extending the BUD of a CSP to at least 180 days and up to one year, under the storage conditions studied. Beyond the proposed <797> guidelines, this would require:

- Limited stability-indicating BUD studies be performed to establish true chemical/physical/ microbiological stability for a specific compound
- A QA/QC program that meets at least minimum standards, as proposed below, to ensure higher quality aseptic processes to warrant longer BUD dates
- That USP-compliant sterility and endotoxin testing be performed on each lot produced if extended BUDs beyond USP <797> defaults are to be assigned.

Limited Stability-Indicating BUD Study Requirements

One of the challenges to pharmacies wishing to perform stability indicating studies is understanding exactly what is required. We suggest that USP develop guidance along these lines, providing pharmacies with a clear definition of such studies. A good start might be a USP chapter on stability studies for 503a pharmacies that is numbered above <1000> for informational guidance, but not necessarily referenced in USP <797> as an enforceable chapter. This would provide best-practice industry guidance while allowing the flexibility of testing needed for a very wide array of CSPs.

Some suggestions for the content of such a chapter include:

- A requirement that stability-indicating studies must develop a stability-indicating assay that attempts forced degradation to differentiate between peaks related to the analyte versus peaks related to excipients, degradation products, impurities, or other matrix components. Additionally, having USP clearly define how to attempt forced degradation would be very helpful to industry and would improve the quality of these drug products for patients. Some information to clarify might include, for example, relevant stress conditions used in forced degradation (such as heat, humidity, light, oxidation, acid, and/or base). Additional clarification on processes to follow for formulations that are unable to undergo forced degradation would also be beneficial.
- Appropriate laboratory tests to be performed at various time points after a stability-indicating assay is developed. For example, at which time points in a BUD study should we minimally test potency, pH, sterility per USP <71>, endotoxin per UPS <85>, container closure, particulate matter, and antimicrobial effectiveness per USP <51>?

- Definitions and descriptions of appropriate bracketing, matrixing, and accelerated BUD studies. This would provide clarity to 503A pharmacies and various regulators on best practices, and of course give critical guidance to pharmacies.
- If a USP monograph, or a published or unpublished stability study for a CSP exists, the compounding pharmacist should be able to use the BUD established by that study if:
    - the additional QA/QC procedures proposed below are followed.
    - the formula is followed exactly.
    - a container closure study is performed.
    - sterility and endotoxin testing is performed on every batch.

Other Recommendation Notes

In order to extend BUDs, we recommend several additional QA/QC procedures in addition to those in the proposed chapter <797> revision, most notably increased frequency of environmental monitoring. The ability to ensure the suitability of a sterile compounding environment is arguably one of the most important factors in the ability to produce a sterile final product.

Cleaning/Personnel Competency/Process Verification

We recommend using only sterile disinfectants/sporicides and sterile IPA in the primary engineering control and other ISO 5 areas. We also recommend increasing the frequency of gloved fingertip sampling of compounding personnel to at least every two weeks.

Environmental Monitoring

We also propose increasing surface sampling to at least every two weeks in all ISO 5 areas, and monthly in other controlled air environments. We recommend increasing the frequency of viable air sampling to at least monthly. Identification of organisms recovered would be required if growth exceeds action limits, as is proposed in the current proposed <797> revision. We propose no changes to the nonviable air sampling regimen found in the current proposed <797> revision.

That concludes our recommendations.

We truly appreciate USP's and your subcommittee's openness to receiving input from all stakeholders regarding the updates to the chapters, specifically related to the proposed default BUDs. Thank you for this opportunity to share our recommendations.

Sincerely,

Tenille Davis, PharmD
Chairman, APC Beyond-Use Date Task Force
Pharmacist-in-Charge, Civic Center Pharmacy, Scottsdale, Arizona

C: APC Board of Directors
APC Beyond-Use Date Task Force

Appendix 2 – Letter from the Food and Drug Administration (FDA).

August 5, 2021

Ms. Jennifer Devine
Senior Vice President, Documentary Standards and Compendial Policy
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

Dear Ms. Devine:

We are writing to express the Agency's concerns regarding assignment of beyond-use-dates (BUDs) to compounded nonsterile drug products (CNSPs) and compounded sterile drug products (CSPs) in USP General Chapters <795> and <797>.[1,2] We understand that the remanded USP General Chapters <795> and <797> are being considered for possible revision because the appeals decision directed USP to evaluate whether and under what conditions compounders could be allowed to extend BUDs for compounded drug products.

In a 2018 letter to USP,[3] the Agency identified concerns regarding extension of BUDs in USP General Chapters <795> and <797>. The concerns that we expressed at that time remain unchanged.

When developing BUDs for CNSPs and CSPs, consideration must be given to both the stability and microbiological quality of the products. There are many factors that can affect the stability and microbiological quality of a drug product. A seemingly simple change in a compounding process or a component change can adversely affect the compounded drug product. Consequently, FDA is concerned that the risk of flawed stability studies and inadequate sterility assurance practices in compounding facilities can pose significant public health concerns and outweigh any potential public benefit obtained by extending the BUDs under Chapters <795> and <797>.

Extending BUDs for drugs compounded by pharmacies, federal facilities, and physicians without following current good manufacturing practice (CGMP) requirements, including stability studies, may result in compounded drug products that are unsafe, ineffective, or of poor quality. Stability studies conducted pursuant to CGMP requirements demonstrate whether a drug remains physically and chemically stable through its shelf life.

In addition, FDA would like to encourage USP in its efforts when revising Chapters <795> and <797> to consider the merits of the appeals by evaluating whether a need to extend BUDs exists from a patient need perspective.

Stability Studies

As noted above, stability studies demonstrate whether a drug remains physically and chemically stable through its shelf life. Most state-licensed pharmacies, federal facilities, physicians, and veterinarians do not have experience designing stability studies or determining what constitutes a high-quality stability study if contracting with an outside lab for these studies.

[1] We have limited our comments to the BUD topic that was associated with the appeals decision. However, after General Chapters <795> and <797> have been published in Pharmacopeial Forum (PF), FDA may have additional comments related to these chapters.

[2] We understand that per *USP <795>* and *<797>*, USP uses the term compounded drug preparation instead of compounded drug products.

[3] See FDA letter dated April 16, 2018 to Ms. Shawn Becker.

Stability studies need to ensure that the analytical methods used have been demonstrated to be stability indicating. However, there are no standards for defining, evaluating, or validating acceptable drug stability studies in USP General Chapters <795> and <797>. Without adequate standards for robust stability studies, compounders will have difficulty designing a meaningful stability study to ensure drug product quality during the BUD period. In addition, state regulators may have difficulty determining if the studies are suitable and therefore struggle in supporting an enforcement action or providing meaningful feedback to the compounding facility to minimize public health risk.

The purpose of stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a shelf life for the drug product and recommended storage conditions. An adequate stability program mitigates risks to the drug product such as degradation of assay, loss of sterility, formation of precipitates, presence of leachable and extractables, among others.

Importantly, a stability study conducted by one entity may provide minimal insight on whether the drug product will remain stable when produced by a different entity. For example, the materials (e.g., purity of the bulk drug substances, container), environment, staff training, and processes at one pharmacy may differ from those of the entity that performed the study.

FDA is concerned that compounders would consult the proposed chapter to extend BUDs based on flawed stability studies which could have significant public health implications.

Furthermore, stability studies do not model the risk of microbial contamination during production. A CSP that demonstrates physical and chemical stability at a longer date is not any less prone to microbial contamination. To conduct meaningful studies that demonstrate a drug product is stable and sterile through its BUD, a facility must conduct several tests that, in FDA's experience, state-licensed pharmacies, federal facilities, physicians, and veterinarians typically are not equipped or trained to perform.

Microbiological Quality

Merely passing a sterility test does not indicate that a CSP batch is, in fact, sterile.[4] Microbiological quality can only be assured through both proper microbiological controls of the drug production (e.g., cleaning/disinfecting, personnel qualification, and media fill frequencies) and microbiological testing procedures (e.g., sterility and bacterial endotoxins). Adequate sterility assurance for a CSP is a result of all activities that take place in a facility, including environmental and personnel monitoring. We note under USP <797> compounders are not required to validate sterilization processes, wear all sterile garb, or conduct daily monitoring of environmental conditions during production.

CNSPs require assurance that microbiological contamination is minimal to provide a safe product to consumers. Water activity and moisture content are important aspects to consider when reviewing product stability and minimizing microbial growth potentials. Additional environment factors need to be assessed during BUD dating, including temperature, light, humidity, and air.

Need for Extended BUDs; Role of Outsourcing Facilities

Finally, FDA encourages USP to examine whether a need to extend BUDs exists from a patient need perspective. Concerning this point, it is unclear to FDA why a patient-specific prescription would require BUDs that are longer than the default BUDs proposed in remanded Chapters <795> and <797>. For example, Chapter <797> proposed a default BUD of 45 days for aseptically processed CSPs that have passed sterility testing and are stored in the refrigerator. Terminally sterilized CSPs that have passed sterility testing would be assigned a default BUD of 60 days if stored in the refrigerator, or 90 days if frozen. Based on FDA's experience, the proposed default BUDs in the remanded Chapters would meet the needs for most patient-specific compounded drug products. If a compounder wants to produce drug products with extended BUDs, FDA encourages them to consider registering as an outsourcing facility under section 503B of FD&C Act.

[4] From USP <71> Sterility Tests – "These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures."

Congress passed the Drug Quality and Security Act (DQSA) in response to the 2012 fungal meningitis outbreak, as well as numerous other serious adverse events, including deaths, linked to poor quality compounded drugs. The DQSA clarified FDA's authority to regulate human compounding by state- licensed pharmacies, federal facilities, and licensed physicians under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and added a new section 503B to the FD&C Act, creating the category of compounders called outsourcing facilities.

Section 503A of the FD&C Act describes the conditions under which compounded human drug products are exempt from the FD&C Act sections on FDA approval prior to marketing, CGMP requirements, and labeling with adequate directions for use. One of these conditions is that the drugs must be compounded based on the receipt of valid patient-specific prescriptions.

Compounded drugs are not FDA approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality. In addition, FDA does not interact with the vast majority of licensed pharmacists and licensed physicians who compound drug products and seek to qualify for the exemptions under section 503A of the FD&C Act for the drug products they compound because these compounders are not licensed by FDA and generally do not register their compounding facilities with FDA. Therefore, FDA is often not aware of potential problems with their compounded drug products or compounding practices unless it receives a complaint such as a report of a serious adverse event or visible contamination. Such pharmacies are primarily subject to state oversight. FDA does not maintain a list of these pharmacies, and they are not subject to routine FDA inspection.

Unlike compounders operating under section 503A, outsourcing facilities under section 503B are subject to CGMP requirements, and they may distribute compounded drugs either pursuant to a patient-specific prescription or in response to an order from a health care provider, such as a hospital, that is not for an identified individual patient (e.g., for office stock). Outsourcing facilities must also register with FDA, are inspected by FDA according to a risk-based schedule, and must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound. This helps to mitigate the risk that their drug products will be contaminated or otherwise made under substandard conditions.

The revised draft guidance for industry entitled, "Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act" ("CGMP guidance"),5 describes, among other things, FDA's proposed policies regarding the conditions under which outsourcing facilities should conduct batch-release tests, including strength and antimicrobial content for sterile and non-sterile drug products, as well as for endotoxin, sterility, and visible and subvisible particulates, as applicable for drug products intended to be sterile. In addition, the draft CGMP guidance states that outsourcing facilities are expected, with limited exceptions, to conduct stability testing to ensure a drug product will retain its quality and remain sterile, if applicable, through the labeled expiration date.

The CGMP guidance includes a proposed enforcement discretion policy that provides a default BUD for products with a small aggregate batch size under the risk-based conditions described in the CGMP guidance. The proposed enforcement discretion policy would also apply to BUDs that are extended beyond the default BUD, as well as to the production of larger aggregate batch sizes, if limited stability studies as described under the conditions in the guidance are completed.

Pharmacies, federal facilities, and physicians that extend BUDs while not following CGMP requirements may produce compounded drug products that are unsafe, ineffective, or poor quality, which could result in the unintended consequence of undermining Congress' establishment of the outsourcing facility industry under section 503B of the FD&C Act. Furthermore, most state boards of pharmacy have limited resources and may not be able to appropriately evaluate or enforce standards pertaining to extension of BUDs, e.g., ones regarding stability studies.

Conclusion

FDA's concerns with compounders extending BUDs while not following CGMP requirements are based on our experience responding to infectious disease outbreaks associated with compounded drugs, as well as significant product quality issues that have the potential to cause patient harm. Pharmacies, federal facilities, and physicians that compound drug products look to USP standards to understand the practices and conditions that must be met to produce high quality drug products. Many states similarly look to USP standards to support regulatory inspections and enforcement. Extending BUDs for compounded drugs in the absence of CGMP requirements would unnecessarily lead to increased risks to patients compared to drugs compounded by outsourcing facilities in accordance with CGMP requirements.

FDA appreciates your attention to this important matter and looks forward to continuing to work with USP by providing scientific input on the development of standards pertaining to drug compounding.

Sincerely yours,

Gall Bormel
Director, Office of Compounding Quality and Compliance
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Cc: Mr. Mario Sindaco
Executive Secretariat
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
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[5] See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice- guidance-human-drug-compounding-outsourcing-facilities-under.

Texas Hospital Association

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January 25, 2025

Via fax at (512) 305.8061

PUBLIC COMMENT LETTER

Mr. Daniel Carroll, Executive Director
Texas State Board of Pharmacy
333 Guadalupe St. #3
Austin, TX 78701

Re: Proposed Rules - 25 TAC §291.133 Pharmacies Compounding Sterile Preparations

Dear Mr. Carroll,

On behalf of our more than 460 member hospitals, including rural, urban, children's, teaching, and specialty hospitals, the Texas Hospital Association (THA) appreciates the opportunity to provide comments on the proposed rule changes to 22 TAC §291.133 regarding Pharmacies Compounding Sterile Preparations. These proposed updates introduce revised requirements for sterile compounding, aligning Texas regulations with the United States Pharmacopeia (USP) standards.

Under Texas law, Freestanding Emergency Medical Centers (FEMCs) fall into two licensing categories issued by the Texas Health and Human Services Commission (HHSC). Chapter 254 of the Texas Health and Safety Code (HSC) governs independently owned FEMCs, while FEMCs owned and operated by acute care hospitals are licensed under the hospital's Chapter 241 HSC licensure. Despite these distinctions, most pharmacies located within FEMCs, regardless of licensing category, operate as Class-F pharmacies licensed by the Texas State Board of Pharmacy. However, the proposed rule changes do not address Class-F pharmacies.

Many Class-F pharmacies do not compound sterile medications on-site, instead relying on sterile compounded products from other licensed facilities, such as Class-C pharmacies. While the proposed amendments appropriately emphasize safety and compliance with updated compounding standards, they omit critical guidance regarding the transfer of sterile compounded medications from an acute care hospital's Class-C pharmacy to its associated FEMC's Class-F pharmacy. This oversight is significant, as the rules govern how compounded drugs may be "distributed" or transferred between facilities.

To support patient care and ensure regulatory clarity, we respectfully urge the Board to revise the proposed rules to address the absence of guidance for Class-F pharmacies. Specifically, we request the inclusion of clear standards and provisions for the transfer of sterile compounded medications from Class-C pharmacies to Class-F pharmacies under common ownership.

Thank you for your consideration of these comments. We look forward to collaborating with you to address these important issues. Should you have any questions, please do not hesitate to contact me at nlusardi@tha.org or (713) 458.0864.

Respectfully submitted,

Nicole Lusardi
Associate General Counsel
Texas Hospital Association

Facsimile

Note:

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Alliance for Pharmacy Compounding

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January 23, 2025

Eamon D. Briggs
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eamon.briggs@pharmacy.texas.gov

Dear Mr. Briggs,

On behalf of the Alliance for Pharmacy Compounding, we appreciate the opportunity to comment on the proposed sterile compounding rule changes outlined in Texas Pharmacy Rule §291.133.

We commend the Texas State Board of Pharmacy for its commitment to high standards for patient safety and quality in sterile compounding. The Board's efforts to align many of these rules with the latest U.S. Pharmacopeia (USP) standards while considering the practical implications of those changes on compounding pharmacies and patients is appreciated.

Comments on Proposed Definitions

- Anteroom: The definition states that "The anteroom is the transition room between the unclassified area of the pharmacy and the buffer room." However, that definition may inadvertently include classified gowning rooms that some pharmacies use as transition spaces. Facilities may have more than two rooms, with one designated as the anteroom and another as the buffer room. In a facility with a three-room setup, the second room may serve as the anteroom without directly transitioning between the unclassified area of the pharmacy and the buffer room. Instead, it may act as an intermediary space, such as a classified gowning room. We recommend refining the definition to account for classified gowning rooms serving this purpose.
- Aseptic Processing: For clarity and consistency, the definition should align with USP's phrasing: *"A method by which separate, sterile components (e.g., drugs, containers, or closures) are brought together under conditions that maintain their sterility. The components can either be purchased as sterile or, when starting with nonsterile components, can be separately sterilized prior to combining (e.g., by membrane filtration*

or by autoclave).” The current proposed definition references the sterilization of both the packaging and the preparation. However, in aseptic processing, the compounder may not be responsible for the sterilization of any component. While the wording in the proposed Texas definition may aim to address the sterilization of container-closure systems and drug products by manufacturers, it leaves room for misinterpretation.

- Biological Safety Cabinet: The proposed definition should match USP’s: *“A ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust. A BSC used to prepare a CSP must be capable of providing an ISO Class 5 or better environment for preparation of the CSPs.”*
- Clean Room: We question the need for definitions of both a buffer room and a clean room. It appears that a “clean room” as described is similar to what USP defines as a classified area: an area that maintains an air quality classification based on the ISO standards required in this chapter (see also the definition for *ISO class*.) We recommend removing “clean room” from the definition section, as this term is commonly used as a synonym for “buffer room.” We also recommend utilizing the term “classified area,” to align with USP’s definition.
- Compounding Aseptic Containment Isolator: This definition includes microbial retentive filtration but omits particulate filtration. The USP defines HEPA filtration as being, using, or containing a filter designed to remove 99.97% of airborne particles measuring 0.3-micron or greater in diameter passing through it.
- Critical Sites: Adding “and” to the phrase “microbial and particulate contamination” would enhance clarity and accuracy.
- Multiple-Dose Container: The definition should explicitly include sterile ophthalmic eye dropper containers. Additionally, the text should be amended to indicate that the beyond-use date may not exceed the original expiration date of a commercially available product.

Media-Fill and Gloved Fingertip Testing

We are concerned about the removal of the requirement for media-fill testing under the most challenging or stressful conditions for Category 3 compounding, while retaining this requirement for Category 1 and 2 compounding. Media-fill testing is a cornerstone of ensuring quality and sterility in compounding, and its omission for Category 3 compounds may compromise patient safety.

We support the proposed rule requiring gloved fingertip testing and gowning observations every 12 months for supervisory personnel who do not actively compound. This distinction acknowledges their roles and appropriately tailors the requirements.

Beyond-Use Dates and Batch Sizes

The allowance of up to a 180-day beyond-use-date for nonaqueous Category 3 sterile compounds demonstrates a forward-thinking perspective that recognizes stability science and

practical patient care needs. This 180-day BUD would be allowed based on documented "current literature supporting stability and sterility." However, sterility can only be supported by the testing of each particular batch and formulation specific container closure integrity testing.

The proposed increase in batch size to 750 units is an improvement over the 250 maximum batch size in USP <797>, and we appreciate the Board's recognition of the need for scalability in sterile compounding. However, we continue to encourage the Board and other regulators to allow pharmacies to determine batch sizes and assign beyond-use dates based on data, rather than imposing an arbitrary limit. This would align with scientific principles, potential for advancing technology, and ensure flexibility for pharmacies to meet diverse patient needs.

Additional Comments on Sterile Compounding Practices

- Sterility testing: The proposed flat 5 percent batch testing requirement deviates from USP <71> and <797>, which use batch-size-specific testing. We recommend adopting USP's approach for batches up to 250 units and applying the 5 percent rule only for larger batches.
- Component Sourcing: We support the flexibility to source components from non-FDA-registered facilities provided a Certificate of Analysis is available and the pharmacist deems the ingredient appropriate.
- Filter Integrity Testing: This requirement for Category 2 and 3 compounding is an important safeguard and we are pleased to see its inclusion.
- Hazardous Drug Compounding: The provisions for protecting employee safety without fully adopting USP <800> strike a reasonable balance between safety and feasibility.
- Copies of FDA-Approved Drug Products: We support the provision in the proposed rules that would allow pharmacists to compound copies of commercially available drug products that are not reasonably available, even if those products are not on the FDA's drug shortage list. This flexibility is important for addressing patient needs in real-time.
- Component Selection: Some active pharmaceutical ingredients (APIs), such as ketotifen EP, do not have USP/NF, CP, AR, ACS, or FCC grades. Current regulations must account for APIs that are allowed under federal law and FDA guidance. Without this flexibility, Texas licensed pharmacies will not be able to compound all medications that should be available to patients. We recommend aligning with section 503A of the Food, Drug, and Cosmetic Act with regard to component selection.

Some other comments

- The proposed rules reference a buffer room that is not physically separated from the anteroom, relying on the principle of displacement airflow as defined in the previous version of USP <797>. However, the current version of USP <797> no longer includes this concept. We recommend removing this outdated reference. The clean room required for compounding Category 1 and Category 2 preparations indicates there must be some demarcation designation that delineates the anteroom from the buffer room. This could

be read that a line of demarcation would be sufficient to comply, but we would expect a full physical separation (wall with a door) would be required.
- We recommend requiring sterile one-step disinfectants and sporicidal cleaners, as they are required for use in an ISO 5 environment by USP and FDA.
- In the section on handwashing, it appears that the personnel going into the buffer room is doing so before donning gloves, which should be performed while still in the anteroom.
- Filter integrity testing should be performed on each filter if multiple filters are required to be used for sterilization. This is not discussed in the proposed regulations.

In conclusion, we thank the Board for its thoughtful approach to these complex issues and for the opportunity to provide input. We urge the Board to align its regulations with national standards, ensure flexibility in compounding practices, and balance safety with practical implementation. APC stands ready to assist the Board in further refining these rules to ensure patient access to high-quality compounded medications.

Sincerely,

Tenille Davis, PharmD, RPh, BCSCP, FAPC
Chief Advocacy Officer
Alliance for Pharmacy Compounding
tenille@a4pc.org

The Alliance for Pharmacy Compounding is the voice for pharmacy compounding, representing more than 600 compounding small businesses – including compounding pharmacists and technicians in both 503A and 503B settings – as well as prescribers, educators, researchers, and suppliers.

John Daniel, PharmD, MHA, RPh, BCNP, BCSCP
Compounding Designated Person
CHRISTUS Mother Frances Hospital
800 East Dawson Street
Tyler, TX 75701

January 30, 2025

Eamon D. Briggs
Deputy General Counsel, Texas State Board of Pharmacy
1801 Congress Avenue, Suite 13.100
Austin, Texas 78701

Dear Mr. Briggs:

I am writing to you regarding the proposed updates to TAC 291.133 Pharmacies Compounding Sterile Preparations. I apologize that this correspondence comes after the January 25, 2025, deadline for submission, but I believe there are important changes to the proposal that need to be addressed, and it is my hope that my late submission will be considered.

- (b)(22)--Consider removing the definition of designated person. Inclusion here may lead to confusion because it is not referenced elsewhere.
- (c)(4)(E)--The proposal contains the phrase, "aseptic technique for personnel who do not compound nor have direct oversight of compounding personnel such as personnel who restock or clean and disinfect the sterile compounding area." Although this subset of personnel may require evaluation of hand hygiene, garbing, and gloving, aseptic manipulation and therefore testing is outside the scope of their practice and their inclusion here should be removed.
- (c)(4)(L)(iii)--The proposal requires the use of "sterile sampling media devices." Consider changing to "sterile or aseptically prepared media devices."
- (d)(1)(B)--The maximum batch size for all preparations requiring sterility testing is limited to 750 final yield units in the proposal. Consider decreasing the maximum batch size to 250 units consistent with USP <797>. The USP said the following regarding batch size, "contamination within a batch may not be uniformly distributed across all units. Therefore, the probability of detecting contamination during sterility testing decreases as batch size increases, and risk for unidentified contamination increases. The intent is to reduce the risk of patient harm from undetected contamination of CSPs by introducing a batch size limit."
- (d)(8)(C)(x)--The proposal states, "Objects that shed particles shall not be brought into the clean room." Consider changing the wording here considering that all objects shed particles, and the requirement is therefore impossible.
- (d)(8)(C)(xii)(III)--The description of a buffer room and anteroom is not consistent with the definitions of those rooms in (b)(4) and (b)(11), nor is it consistent with the The principle of

displacement airflow is an abandoned practice and is not described in the current revision of USP <797>, so the reference is outdated. The buffer room and anteroom requirements should be brought into alignment with the current revision of USP <797> in the interest of patient safety.

- (d)(8)(H)((iii)--The proposal states, "In a Class B pharmacy, objects used in preparing sterile radiopharmaceuticals (e.g., dose calibrator) which cannot be reasonably removed from the compounding area shall be sterilized with an application of a residue-free disinfection agent." Consider changing the word sterilized to disinfected.
- (d)(9)(A)(iv)--The phrase, ". A buffer room [area] that is not physically separated from the anteroom [ante-area] shall employ the principle of displacement airflow as defined in Chapter 797, Pharmaceutical Compounding--Sterile Preparations, of the USP/NF, with limited access to personnel," is inconsistent with the definitions of anteroom and buffer room in (b)(4) and (b)(11), furthermore the reference to USP <797> is inaccurate, therefore the phrase should be removed.
- (d)(9)(B)(I)--The proposal states, "The area for preparation of sterile chemotherapeutic preparations shall." Consider changing "chemotherapeutic" to "hazardous drugs."
- (d)(9)(B)(i)(I)--The pressure requirement here is incompatible with the pressure requirement in USP <800> and must be changed. USP <800> requires a pressure of –0.01 to –0.03 inches water column, with –0.03 being the minimum and –0.01 being the maximum.
- (d)(9)(D)(I)(I)--The requirement here to provide "at least 0.01 inches water column negative pressure" may be unclear. Suggest changing to the range indicated in USP <800> of –0.01" to –0.03".
- (d)(16)(C)(iii)--Suggest removing the requirement for an airflow velocity meter, since the airflow displacement design should not be used for reasons mentioned previously. If the decision is made to keep the airflow velocity meter, the minimum airflow velocity must be defined at least 40 fpm.

It is my hope that the board will remand this proposed revision back to committee for further revision and review.

Thank you for your time and consideration.

Kind regards,

John Daniel

EMPOWER

June 12, 2025

Eamon D. Briggs, J.D.
Deputy General Counsel
Texas State Board of Pharmacy
George H. W. Bush State Office Building
1801 Congress Avenue
Suite 13.100
Austin, TX 78701

Dear Mr. Briggs:

Empower Pharmacy respectfully requests that §291.133 be amended to allow batch size to be determined by validated sterility-testing plans rather than a fixed numerical limit.

Though the proposed increase in batch size to 750 units is an improvement over the 250 maximum batch size in USP <797>, and we appreciate the Board's recognition of the need for scalability in sterile compounding, we continue to encourage the Board and other regulators to allow pharmacies to determine batch sizes based on data, rather than imposing an arbitrary limit. This would align with scientific principles, availability of advanced automated technology, and ensure flexibility for pharmacies to meet diverse patient needs. Restricting batch sizes will include higher costs which will negatively affect medication adherence, health outcomes, and access for patients, among other concerns.

Based on the explanation provided in the BUD Scientific Rationale for the 2021 Proposed Revisions to <797>, USP originally created a batch size limit primarily based on the number of containers required for sterility testing per USP <71>. The requirements of USP <71> are that 10 units from a CSP batch be tested for sterility for batch sizes ranging from 100 units to 500 units. However, there is no data or evidence as to why limiting the batch size, rather than increasing the number of required samples, is the only allowable way to increase the probability of detecting contamination within a CSP batch. USP <71> itself gives a minimum number of units to be tested for batch sizes greater than 500 units (2% or 20 units).

A secondary rationale given by USP in the BUD Scientific Rationale for the 2021 Proposed Revisions to <797> for limiting batch sizes to a maximum of 250 units is the belief that "contamination risk increases with larger batch sizes, particularly for manual processes." In the *<797> FAQs*, the USP states that "Sterile compounding within 503A facilities is a largely manual process," and that "smaller batches reduce the potential for operator fatigue."

However, the practical impact of this batch-size limitation is that it will cause people, the most common source of contamination in any ISO classified area, to spend more time in ISO

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classified areas to produce the same number of units. By limiting batch sizes, the board will be forcing compounders to increase the frequency with which they will make entries and exits to and from ISO classified aseptic processing rooms in order to meet current patient needs. This is in direct conflict with practices outlined in FDA's Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing –Current Good Manufacturing Practice which states:

"Both personnel and material flow should be optimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, container-closures, or the surrounding environment…The number of personnel in an aseptic processing room should be minimized. The flow of personnel should be designed to limit the frequency with which entries and exits are made to and from an aseptic processing room and, most significant, its critical area. Regarding the latter, the number of transfers into the critical area of a traditional cleanroom, or an isolator, should be minimized. To prevent changes in air currents that introduce lower quality air, movement adjacent to the critical area should be appropriately restricted."

Furthermore, many larger pharmacies now utilize semi-automated or fully automated filling equipment, which significantly reduces the human element in aseptic processing. By minimizing manual intervention, automated systems lower the potential for microbial contamination and eliminate concerns related to operator fatigue.

Given these advancements, it is essential that automation technology be recognized and accounted for in the regulatory amendments. If semi-automated or automated equipment is used, batch size should be limited to the quantity that can be successfully validated through a media fill qualification.

Suggested Alternative Rule Language for §291.133(c)(3):

"Batch size shall be limited to the quantity that can be appropriately validated for sterility assurance using media fill simulation studies and sterility testing conducted in accordance with USP <71> or an equivalent compendial method as approved by the Board."

Thank you for your time and thoughtful consideration.

Sincerely,

Jordan Cuccia

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January 24, 2025

Eamon D. Briggs
Deputy General Counsel
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Austin, TX 78701

Dear Mr. Briggs,

I am submitting this comment for consideration regarding the proposed amendments to §291.133 Pharmacies Compounding Sterile Preparations, with a particular focus on the proposed limits for maximum batch sizes.

In the *<797> FAQs*, the United States Pharmacopeia addresses the rationale behind having a maximum batch size, stating: "Sterile compounding within 503A facilities is a largely manual process," and that "the risk of contaminating a CSP is likely to increase as the batch size increases, especially for a manual process." Additionally, it highlights that "smaller batches reduce the potential for operator fatigue."

The 750-unit limitation on batch size is understandable when considering manual filling operations and the associated risk of operator fatigue. However, many larger pharmacies now utilize semi-automated or fully automated filling equipment, which significantly reduces the human element in aseptic processing. By minimizing manual intervention, automated systems lower the potential for microbial contamination and eliminate concerns related to operator fatigue.

Given these advancements, it is essential that automation technology be recognized and accounted for in the regulatory amendments. I would suggest considering a provision stating that if semi-automated or automated equipment is used, batch size should be limited to the quantity that can be successfully validated through a media fill qualification.

Thank you for your time and thoughtful consideration.

Sincerely,

Jordan Cuccia

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GOVERNOR GREG ABBOTT

To: Julie Spier, Chair
Daniel Carroll, Executive Director
Megan Holloway, General Counsel
Texas State Board of Pharmacy

From: Caleb Gunnels, Assistant General Counsel
Office of the Governor

Date: May 2, 2025

Subject: Proposed Title 22 Texas Administrative Code Section 291.133 (RCD Rule Review #2025-002)

I. Syllabus

The Texas State Board of Pharmacy ("board") proposed amended 22 TAC §291.133, to update the personnel, environment, compounding process, cleaning and disinfecting, beyond-use dating, cleansing and garbing, environmental testing, sterility testing, recall procedure, and recordkeeping requirements for pharmacies compounding sterile preparations, and submitted the rule to the Regulatory Compliance Division ("division") for review, as published in the December 27, 2024, issue of the *Texas Register*.[1] Proposed amended §291.133 is primarily intended to ensure the safety and efficacy of compounded sterile preparations, that sterile compounding is conducted in a safe and sanitary environment, improve the health, safety, and welfare of patients, and provide clearer regulatory language informed by and in line with recently updated guidance in the United States Pharmacopeia-National Formulary.[2] The board submitted the proposed rule to the division for review on February 4, 2025.[3] The division invited public comments on the proposed rule for a 30-day period ending on March 12, 2025, and the division received no comments.

Based on the following analysis, the division has determined that the proposed rule is consistent with state policy, and thus, proposed amended 22 TAC §291.133 is approved by the division and may be finally adopted and implemented.

[1] 49 Tex. Reg. 10463 (2024) (to be codified at 22 TAC §291.133) (proposed Dec. 27, 2024) (Tex. State Bd. Pharmacy); Rule Submission Memorandum from the Texas State Board of Pharmacy (Feb. 4, 2025), at 1 (on file with the Regulatory Compliance Division of the Office of the Governor).
[2] Rule Submission Memorandum from the Texas State Board of Pharmacy (Feb. 4, 2025), at 1.
[3] *Id.*

II. Analysis

In 2022, the United States Pharmacopeia-National Formulary was updated to revise General Chapter 797 regarding Pharmaceutical Compounding and Sterile Preparations, and those revisions became effective on November 1, 2023.[4] During that time, the board voted to create a Compounding Rules Advisory Group Sterile Subcommittee ("subcommittee") to review the proposed revisions to Chapter 797 and any effects on current board rules.[5] The subcommittee met on five separate occasions in 2023, and subsequently proposed its recommendations to the board in two public meetings held in 2024.[6] On August 6, 2024, the board convened and heard oral comments from the subcommittee and voted to propose amendments to 22 TAC §291.133.[7] On November 5, 2024, the board convened once again and considered written and oral comments from the public before voting to propose additional changes to the previously proposed amendments.[8]

The purpose of the proposed amendments is to align board standards regarding compounded sterile preparations with the updated guidelines in the United States Pharmacopeia-National Formulary, which reflect advances in science and pharmacy practices that have created new techniques to reduce the risk of contamination, infection, or incorrect dosing when compounding drugs.[9] Specifically, the amended rule generally updates proper garbing requirements to ensure sterile work environments, specifies sampling and testing procedures to identify and reduce contamination both in the work space and in compounded preparations, details proper sterilization techniques and air exchange requirements to reduce contamination of tools and air quality, and updates beyond-use dates to identify the date and time by which a preparation must be used before the preparation becomes a risk to patient safety.[10]

In reviewing the updated guidelines in General Chapter 797, the subcommittee considered various methods of compliance to reduce burdensome impacts on industry participants while ensuring the health, safety, and welfare of the public.[11] The subcommittee ultimately recommended limiting or not adopting several provisions from the updated United States Pharmacopeia-National Formulary, and the board asserts that many of the proposed amendments to §291.133 are less restrictive than the guidelines in current General Chapter 797.[12] However, given that updated practice requirements could potentially result in higher prices or reduced

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[4] U.S. Pharmacopeia, *<797> FAQs*, GENERAL CHAPTER <797> (Dec. 11, 2023), https://go.usp.org/USP_GC_797_FAQs?_gl=1*17d5q2u*_gcl_au*MjkxMzYzODQ1LjE3MzU1OTIyNDk.*_ga*MTEzNDcyNDE1NC4xNzM1NTkyMjQ5*_ga_DTGQ04CR27*MTczNjYzNjEzNC40LjEuMTczNjYzNjkxOC4wLjAuMA.
[5] Rule Submission Memorandum from the Texas State Board of Pharmacy (Feb. 4, 2025), at 1-2.
[6] *Id*. at 2.
[7] *Id*.
[8] *Id*.
[9] *Id*. at 3.
[10] *Id*. at 3-4.
[11] *Id*. at 4.
[12] *Id*.

competition for a product or service provided by or to a license holder in the state, proposed amended §291.133 may affect competition pursuant to Section 57.105(d)(2), Texas Occupations Code.

Section 551.002, Texas Occupations Code, directs the board to liberally construe the Texas Pharmacy Act ("Act"), including to protect public health, safety, and welfare, and identifies effectively regulating the practice of pharmacy and licensing pharmacies as the primary means through which the board accomplishes the purpose of the Act. Section 554.051, Texas Occupations Code, provides the board with broad rulemaking authority to regulate the practice of pharmacy and to administer and enforce the Act. The practice of pharmacy as defined by Section 551.003(33), includes the compounding of drugs, which Section 551.003(9), in part, defines as the preparation, mixing, assembling, packaging, or labeling of a drug or device. And, Section 560.052(g), Texas Occupations Code, generally prohibits the board from issuing a license to a pharmacy that compounds sterile preparations unless the pharmacy has been inspected by the board to ensure the pharmacy meets any safety standards imposed by state law or board rules.

The board's regulatory authority to prescribe pharmacy requirements for recordkeeping and compounding, labeling, dispensing, storing, and packaging of drugs by pharmacies is broad. However, proposed amended 22 TAC §291.133 is the result of an effort that began in May 2023, when the board created an advisory subcommittee to specifically review newly enacted national standards related to sterile compounding, and the board requested nominations for licensees to serve as subcommittee members.[13] As discussed, the board and the subcommittee met on a number of occasions to develop the least restrictive methods of ensuring the safety and efficacy of compounded sterile preparations, and ultimately proposed rule amendments that were less restrictive than those published in the United States Pharmacopeia-National Formulary.[14] After the board first proposed amendments to the rule in September 2024, the board considered public comments and once again, in December, proposed new amendments in response to those comments.[15]

Ultimately, proposed amended 22 TAC §291.133, informed by national guidance, is a reasonable exercise of the board's regulatory authority to protect public health, safety, and welfare by ensuring that pharmacies engaged in sterile compounding operate in a safe and sanitary environment. Thus, proposed amended 22 TAC §291.133 is consistent with state policy.

III. Determination

Based on the above analysis, the proposed amended rule is approved by the division and may proceed to final adoption and implementation.

[13] *Id*. at 2 and 4.
[14] *Id*.
[15] *Id*.