Meeting Notice

Missouri Board of Pharmacy
Sterile Compounding Sub-Committee
Conference Call

May 3, 2016 5:30 p.m.
Division of Professional Registration
3605 Missouri Boulevard
Jefferson City, MO 65109

Three designated members of the Board will be meeting to review the sterile compounding rule. The full Board will not be meeting. In the interest of full compliance with Chapter 610, public notice of the meeting is being provided as detailed herein.

If any member of the public wishes to attend the meeting, s/he should be present at the Division of Professional Registration, Executive Conference Room, 3605 Missouri Boulevard, Jefferson City, Missouri, at approximately 5:30 p.m. on May 3, 2016.

Notification of special needs as addressed by the Americans with Disabilities Act should be forwarded to the Missouri Board of Pharmacy, P O Box 625, 3605 Missouri Blvd., Jefferson City, Missouri 65102, or by calling (573) 751-0091 to ensure available accommodations. The text telephone for the hearing impaired is (800) 735-2966.

Please see attached tentative agenda for this meeting.
TENTATIVE AGENDA
May 3, 2016 5:30 p.m.

Division of Professional Registration
3605 Missouri Boulevard
Jefferson City, MO 65109

1 Review of Sterile Compounding Rule/Draft Revisions to 20 CSR 2220-2.200
2 Review of Proposed USP Chapter 797
3 Future Meeting Dates/Times
PURPOSE: This rule establishes standards for the preparation, labeling, and distribution and dispensing of sterile pharmaceuticals compounded sterile preparations by licensed pharmacies, pursuant to a physician's order or prescription.

(1) Definitions.

(A) Aseptic processing: The technique involving procedures designed to preclude contamination of drugs, packaging, equipment, or supplies by microorganisms during processing.

(B) Batch: Compounding of multiple sterile product preparation units in a single discrete process, by the same individuals, carried out during one (1) limited time period.

(C) Beyond-Use date: A date after which a compounded preparation should not be used and is determined from the date the preparation is compounded. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates must be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

(D) Biological safety cabinet: Containment unit suitable for the preparation of low to moderate risk agents where there is a need for protection of the product preparation, personnel and environment, according to National Sanitation Foundation (NSF) International standards.

(E) Class 100 environment: An atmospheric environment which contains less than one hundred (100) particles 0.5 microns in diameter per cubic foot of air, according to federal standards.

(F) Class 10,000 environment: An atmospheric environment which contains less than ten thousand (10,000) particles 0.5 microns in diameter per cubic foot of air, according to federal standards.

(G) Clean room: A room—

1. In which the concentration of airborne particles is controlled;

2. That is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room; and
3. In which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

(H) Clean zone: Dedicated space—
1. In which the concentration of airborne particles is controlled;
2. That is constructed and used in a manner that minimizes the introduction, generation, and retention of particles inside the zone; and
3. In which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

This zone may be open or enclosed and may or may not be located within a clean room.

(E) Buffer Area: An ISO Class 7 or better area where the primary engineering control is physically located that is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room and in which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

(F) Compounding: For the purposes of this regulation, compounding is defined as in 20 CSR 2220-2.400(1). Compounded sterile medications may include, but are not limited to, injectables, parenteral nutrition solutions, irrigation solutions, inhalation solutions, intravenous solutions and ophthalmic preparations.

(G) Compounding Aseptic Containment Isolator (CACI): A RABS that is designed for compounding sterile hazardous drugs and designed to provide worker protection from exposure to undesirable levels of airborne drugs throughout the compounding and material transfer processes and to provide an aseptic environment for CSPs.

(H) Compounding Aseptic Isolator (CAI): A RABS specifically designed for compounding sterile non-hazardous pharmaceutical ingredients or CSPs and designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes.

(I) Controlled area: For purposes of these regulations, a controlled area is the area designated for preparing sterile preparations that is separated from other activities/operations by a line of demarcation that clearly separates the area from other operations. This is referred to as the buffer zone (i.e., the clean room in which the laminar airflow workbench is located) by the United States Pharmacopoeia (USP).
Critical area: Any area in the controlled area where products preparations or containers are exposed to the environment.

Critical site: An opening providing a direct pathway between a sterile product and the environment or any surface coming into contact with the product or environment. Any surface, pathway or opening (e.g., vial septa, injection ports, beakers, needle hubs) that provides a direct pathway between a compounded sterile preparation or other ingredient used to compound a sterile preparation and the air, environment or moisture or that poses a risk of touch contamination.

Critical surface: Any surface that comes into contact with previously sterilized products preparations or containers.

CSP: Compounded sterile preparation.

Cytotoxic drugs: A pharmaceutical product that has the capability of direct toxic action on living tissue that can result in severe leukopenia and thrombocytopenia, depression of the immune system and the alteration of a host’s inflammatory response system.

Emergency dispensing: Is a situation where a Risk Level 3 product preparation is necessary for immediate administration of the product preparation and no alternative product is available and the prescriber is informed that the product preparation is being dispensed prior to appropriate testing. Documentation of the dispensing of the product preparation, the prescriber’s approval for dispensing prior to the receipt of test results and the need for the emergency must appear within the prescription record. A separate authorization from the prescriber is required for each emergency dispensing.

High-Efficiency Particulate Air (HEPA) filter: A filter composed of pleats of filter medium separated by rigid sheets of corrugated paper or aluminum foil that direct the flow of air forced through the filter in a uniform parallel flow. HEPA filters remove ninety-nine point ninety-seven percent (99.97%) of all particles three-tenths (0.3) microns or larger. When HEPA filters are used as a component of a horizontal- or vertical-laminar-airflow workbench, an environment can be created consistent with standards for a Class 100 clean room an ISO 5 environment.

ISO Class 5: An area with less than 3,520 particles (0.5 μm and larger in size) per cubic meter.
(R) ISO Class 7: An area with less than 352,000 particles (0.5 µm and larger in size) per cubic meter.

(Q) Isolator (or barrier isolator): A closed system made up of four (4) solid walls, an air-handling system, and transfer and interaction devices. The walls are constructed so as to provide surfaces that are cleanable with coving between wall junctures. The air-handling system provides HEPA filtration of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports. Transfers are designed to minimize the entry of contamination. Manipulations can take place through either glove ports or half suits.

(S) Multiple-Dose Container: A multiple unit container for articles or compounded sterile preparations that contains more than one dose of medication.

(R)(T) Parenteral: A sterile preparation of drugs for injection through one (1) or more layers of skin.

(U) Primary Engineering Control (PEC): A system that provides an ISO 5 environment for the exposure of critical sites when compounding sterile preparations. PECs include, but may not be limited to, horizontal/vertical laminar airflow hoods, biological safety cabinets, RABS such as compounding aseptic isolators (CAIs) or compounding aseptic containment isolators (CACIs).

(V) Point of Care Assembled System: A closed system device that creates a physical barrier between diluents, fluids or other drug components and is designed to be activated by the end user by allowing the components to mix prior to administration.

(S)(W) Process validation or simulation: Microbiological simulation of an aseptic process with growth medium processed in a manner similar to the processing of the product preparation and with the same container or closure system.

(T)(X) Quality assurance: For purposes of these regulations, quality assurance is the set of activities used to ensure that the processes used in the preparation of sterile drug product preparations lead to product preparations that meet predetermined standards of quality.

(Y) Quality control: For the purposes of these regulations, quality control is the set of testing activities used to determine that the ingredients, components and final sterile product preparations prepared meet predetermined requirements with respect to identity, purity, nonpyrogenicity and sterility.

(Z) RABS: Restricted access barrier system (RABS): A primary engineering control that is comprised of a closed system made up of four (4) solid walls, an air-handling system, and
transfer and interaction devices. The walls are constructed so as to provide surfaces that are
cleanable with coving between wall junctures. The air-handling system provides HEPA filtration
of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports.
Transfers are designed to minimize the entry of contamination. Manipulations can take place
through either glove ports or half suits. Examples of a RABS may include, but is not limited to, a
CAI or CACI.

(AA) Repackaging: The subdivision or transfer of a compounded product preparation from
one container or device to a different container or device.

(BB) Single-Dose/Single-Unit Container/Vial: A container/vial of medication intended for
administration that is meant for use in a single patient for a single case, procedure or injection.

(CC) Sterile pharmaceutical: A dosage form free from living microorganisms.

(CC) Sterilization: A validated process used to render a preparation free of viable
organisms.

(DD) Temperatures:

1. Frozen means temperatures between twenty below zero and ten degrees Celsius (−20 and
10°C) (four below zero and fourteen degrees Fahrenheit (4 and 14°F)).

2. Refrigerated means temperatures between two and eight degrees Celsius (2 and 8°C)
(twenty-six and forty-six degrees Fahrenheit (36 and 46°F)).

3. Controlled Room temperatures means room temperatures between fifteen and thirty
degrees Celsius (15 and 30°C) (fifty-nine and eighty-six degrees Fahrenheit (59 and 86°F)), a
temperature maintained thermostatically that encompasses the usual and customary working
environment of 20°C to 25°C Celsius (68°F to 78°F) and that results in a mean kinetic temperature
calculated to be not more than 25°C Celsius. Excursions between 15°C and 30°C Celsius (59°F to 86°F)
as commonly experienced in pharmacies and other facilities shall be deemed
compliant. Provided the mean kinetic temperature remains in the allowed range, transient spikes
up to 40°C Celsius are permitted as long as they do not exceed 24 hours. Spikes above 40°C Celsius
are permitted if allowed by the manufacturer.

(EE) USP: The United States Pharmacopeia and the National Formulary (USP-NF) as
adopted and published by the United States Pharmacopeial Convention, effective May 2013.
Copies of the USP-NF are published by, and available from, USP, 12601 Twinbrook Parkway,
Rockville, MD 20852-1790 or online at http://www.usp.org/. The USP-NF is incorporated
herein by reference. This rule does not include any later amendments or additions to the USP-NF.

(Z)(FF) Validation: Documented evidence providing a high degree of assurance that specific processes will consistently produce a product preparation meeting predetermined specifications and quality attributes.

(AA)(GG) Definitions of sterile compounded product preparations by risk level:

1. Risk Level 1: Applies to compounded sterile product preparations that exhibit characteristics A., B., and/or C., stated below. All Risk Level 1 product preparations shall be prepared with sterile equipment, sterile ingredients and solutions and sterile contact surfaces for the final product preparation. Risk Level 1 includes the following:

   A. Product Preparations:
   
   (I) Stored at room temperature and completely administered within assigned a beyond-use date of forty-eight (48) hours after preparation or less; or
   
   (II) Stored under refrigeration for and assigned a beyond-use date of seven (7) days or less before complete administration to a patient over a period not to exceed forty-eight (48) hours; or
   
   (III) Stored frozen for and assigned a beyond-use date of thirty (30) days or less before complete administration to a patient over a period not to exceed forty-eight (48) hours.

   B. Unpreserved sterile product preparations prepared for administration to one (1) patient or batch-prepared product preparations containing suitable preservatives prepared for administration to more than one (1) patient with an assigned beyond-use date that does not exceed the beyond-use date allowed for under section (1)(GG)1.A. of this rule.

   C. Product Preparations prepared by closed-system aseptic transfer of sterile, nonpyrogenic, finished pharmaceuticals (e.g., from vials or ampules) obtained from licensed manufacturers into sterile final containers obtained from licensed manufacturers with an assigned beyond-use date that does not exceed the beyond-use date allowed under section (1)(GG)1.A. of this rule.

2. Risk Level 2: Sterile product preparations exhibit characteristic A., B., or C., stated below. All Risk Level 2 product preparations shall be prepared with sterile equipment, sterile ingredients and solutions and sterile contact surfaces for the final product preparation and with closed-system transfer methods. Risk Level 2 includes the following:
A. Products stored beyond seven (7) days under refrigeration, stored beyond thirty (30) days frozen or administered beyond forty-eight (48) hours after preparation and storage at room temperature. Preparations stored under refrigeration and assigned a beyond-use date greater than seven (7) days or preparations stored frozen and assigned a beyond-use date greater than thirty (30) days or preparations stored at controlled room temperature and assigned a beyond-use date greater than forty-eight hours.

B. Batch-prepared product preparations without preservatives that are intended for use by more than one (1) patient.

C. Product preparations compounded by complex or numerous manipulations of sterile ingredients obtained from licensed manufacturers in a sterile container or reservoir obtained from a licensed manufacturer by using closed-system aseptic transfer (e.g., automated compounding).

3. Risk Level 3: Sterile product preparations exhibit either characteristic A. or B.:

A. Product preparations compounded from nonsterile ingredients or compounded with nonsterile components, containers or equipment before terminal sterilization.

B. Product preparations prepared by combining multiple ingredients (sterile or nonsterile) by using an open-system transfer or open reservoir before terminal sterilization.


(A) A manual, outlining policies and procedures encompassing all aspects of Risk Level 1, 2 and 3 products compounding, shall be available for inspection at the pharmacy. The manual shall be reviewed on an annual basis. The pharmacy shall have current reference materials related to sterile product preparations.

(3) Personnel Education, Training and Evaluation.

(A) Risk Level 1: All pharmacy personnel preparing sterile product preparations must receive suitable didactic and experiential training in aseptic technique and procedures and shall be skilled and trained to accurately and competently perform the duties assigned. Additional training must be provided if the level of sterile activity conducted by the individual changes or if there is a change in compounding methods. To ensure competency, individuals preparing sterile preparations must successfully pass an Aseptic Technique Skill Assessment that complies with section (10) of this rule.
(B) Risk Level 2: In addition to Risk Level 1 requirements, personnel training must include assessment of competency in all Risk Level 2 procedures via process simulation.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, operators have specific education, training and experience to prepare Risk Level 3 preparations. The pharmacist knows principles of good compounding practice for risk level preparations, including—

1. Aseptic processing;
2. Quality assurance of environmental, component, and end-product testing;
3. Sterilization; and
4. Selection and use of containers, equipment, and closures.

(4) Storage and Handling in the Pharmacy.

(A) Risk Level 1 and 2: Solutions, drugs, supplies and compounding equipment must be stored according to manufacturer or USP requirements and maintained in a manner that will maintain the chemical and microbiological stability of CSPs. Refrigeration and freezer and, if applicable, incubator temperatures shall be documented daily. Other storage areas shall be inspected regularly to ensure that temperature and lighting meet requirements. Drugs and supplies shall be shelved above the floor. Removal of products from boxes shall be done outside controlled areas. Removal of used supplies from the controlled area shall be done at least daily. Product recall procedures must comply with section (21) of this rule and must permit retrieving affected product from specific involved patients.

(B) Risk Level 3: In addition to Risk Level 1 and 2 requirements, the pharmacy must establish procedures for procurement, identification, storage, handling, testing, and recall of components and finished preparations. Finished but untested Risk Level 3 preparations awaiting test results must be quarantined under minimal risk for contamination.

(5) Facilities and Equipment.

(A) Risk Level 1: The controlled area shall be separated from other operations. The controlled area must be clean and well lit. A sink with hot and cold water must be near, but not in, the controlled area. The controlled area and inside equipment must be cleaned and disinfected regularly. Sterile products must be prepared in at least a Class 100 environment (the critical area). Computer entry, order processing, label generation, and record keeping shall be performed...
outside the critical area. The critical area must be disinfected prior to use. A workbench shall be
recertified every six (6) months and when it is moved; prefilters must be visually inspected on a
regularly scheduled basis and replaced according to manufacturer’s specifications. Pumps
utilized in the compounding process shall be recalibrated and documented according to
manufacturer procedures.

(B) Risk Level 2: In addition to all Risk Level 1 requirements, the controlled area must meet
Class 10,000 clean room standards; cleaning supplies should be selected to meet clean room
standards; critical area work surface must be cleaned between batches; floors should be
disinfectd daily; equipment surfaces weekly; and walls monthly, with applicable environmental
monitoring of air and surfaces. Automated compounding devices must be calibrated and verified
as to accuracy, according to manufacturer procedures. Clean rooms not utilized on a daily basis
must be cleaned prior to use as stated above.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, products must be prepared in
a Class 100 workbench in a Class 10,000 clean room, in a Class 100 clean room or within a
positive pressure barrier isolator. Access to the clean room must be limited to those preparing the
products and who are in appropriate garb. Equipment must be cleaned, prepared, sterilized,
calibrated, and documented according to manufacturer’s standards. Walls and ceilings must be
disinfecte weekly. All non-sterile equipment that is to come in contact with the sterilized final
product must be sterilized before introduction in the clean room. Appropriate cleaning and
disinection of the environment and equipment are required.

(5) Facilities and Equipment. The pharmacy shall establish and follow proper controls to
ensure environmental quality, prevent environmental contamination and maintain air quality in
all ISO classified areas.

(A) Risk Level 1: Risk Level 1 preparations must be prepared in a PEC located in a controlled
area that meets the requirements of this rule. A sink with hot and cold water must be near, but
not in, the controlled area. The controlled area and inside equipment must be cleaned and
disinfecte as provided in section (17) of this rule. Activities within the critical area shall be
kept to a minimum to maintain the ISO classified environment. Primary engineering controls
shall meet the requirements of section (6) of this rule; prefilters must be visually inspected on a
regularly scheduled basis and replaced according to manufacturer’s specifications. Pumps
utilized in the compounding process shall be recalibrated and documented according to manufacturer procedures.

(B) Risk Level 2: In addition to all Risk Level 1 requirements, Risk Level 2 preparations must be prepared in a PEC located in a buffer area or prepared in a RABS located within a controlled area. Applicable environmental monitoring of air and surfaces must be conducted. Risk Level 2 preparations shall at a minimum remain a Risk Level 2 for the life of the preparation.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, Risk Level 3 preparations must be prepared in a PEC located in a buffer area or prepared in a RABS located within a controlled area. All non-sterile equipment that is to come in contact with the sterilized final preparation must be sterilized before introduction in the buffer area. Once compounded, Risk Level 3 preparations shall at a minimum remain Risk Level 3 for the life of the preparation.

(D) Automated compounding devices shall be tested for content, volume and weight accuracy prior to both initial and daily use according to manufacturer procedures. Test results shall be reviewed by a pharmacist to ensure compliance. The identity of the reviewing pharmacist and the review date shall be documented in the pharmacy’s records.

(E) All PECs and ISO classified areas shall be certified to ensure compliance with requirements of this rule prior to beginning sterile compounding activities and every six (6) months thereafter. Certification shall be conducted by competent staff/vendors using recognized and appropriate certification and testing equipment. Certification results shall be reviewed by a pharmacist once received. Deficiencies or failures shall be investigated and corrected prior to further compounding.

1. The PEC and ISO classified areas must be recertified when: (1) any changes or major service occurs that may affect airflow or environmental conditions or (2) the PEC or room is relocated or the physical structure of the ISO classified area has been altered.

2. Corrections may include, but are not limited to, changes in the use of the affected PEC or ISO classified area or initiating a recall. The identity of the pharmacist conducting the required review and the review date shall be documented in the pharmacy’s records.

(F) Pressure Differential: If the controlled area is equipped with a device to monitor pressure differential, pressure differential results must be recorded and documented each day that the pharmacy is open for pharmacy activities. Alternatively, a continuous monitoring system may
be used to record pressure differential results if the system maintains ongoing documentation of
pressure recordings or maintains pressure alerts that are reviewed daily.

(6) Primary Engineering Controls (PECs):
(A) PECs must be properly used, operated and maintained and must be located out of traffic
patterns and away from conditions that could adversely affect their operation or disrupt intended
airflow patterns (e.g., ventilation systems or cross-drafts).
(B) PECs shall maintain ISO Class 5 or better conditions during dynamic operating conditions
and while compounding sterile preparations, including, when transferring ingredients into and
out of the PEC and during exposure of critical sites;
(C) PECs shall provide unidirectional (laminar flow) HEPA air at a velocity sufficient to
prevent airborne particles from contacting critical sites.
(D) Compounding Aseptic Isolators (CAI): Air exchange into the isolator from the
surrounding environment shall not occur unless the air has first passed through a microbial
retentive HEPA filter.
(E) Compounding Aseptic Containment Isolators (CACI): Air exchange with the surrounding
environment shall not occur unless the air is first passed through a microbial retentive HEPA
filter system capable of containing airborne concentrations of the physical size and state of the
drug being compounded.
(F) The recovery time to achieve ISO Class 5 air quality in any PEC shall be identified in the
pharmacy’s policies and procedures and internal procedures developed to ensure adequate
recovery time is allowed after material transfer and before or during compounding operations.

(7) Controlled Areas. The controlled area shall be designed, maintained and controlled to allow
effective cleaning and disinfection and to minimize the risk of contamination and the
introduction, generation and retention of particles inside the PEC.
(A) Controlled areas must be clean and well-lit and shall be free of infestation by insects,
rodents and other vermin. Trash shall be disposed of in a timely and sanitary manner and at least
daily. Tacky mats or similar articles shall be prohibited in the controlled area or any ISO
classified environment.
(B) Traffic flow in or around the controlled area shall be minimized and controlled. Food items, chewing gum, eating, drinking and smoking are prohibited in the area;

(C) Nonessential objects that shed particles shall not be brought into the controlled area, including, but not limited to, pencils, cardboard cartons, paper towels, and cotton items (e.g., gauze pads). Furniture, carts, supplies and equipment shall be removed from shipping cartons/containers and properly cleaned and disinfected with sterile alcohol before entering any ISO classified area. No shipping or other external cartons may be taken into the controlled area or an ISO classified area.

(D) Only supplies essential for compounding shall be stored in the controlled area. Supplies or other non-essential equipment shall not be stored in or on the PEC.

6. Apparel.
   (A) Risk Level 2: In the controlled area, personnel wear low particulate, clean clothing covers. Head and facial hair is covered. Gloves, gowns, and masks are required. During sterile preparation gloves shall be rinsed frequently with a suitable agent and changed when integrity is compromised.

(B) Risk Level 3: In addition to Risk Level 2 requirements, clean room apparel must be worn inside the controlled area at all times during the preparation of Risk Level 3 sterile products except when positive pressure barrier isolation is utilized. Attire shall consist of a low-shedding coverall, head cover, face mask, and shoe covers.

8. Garbing and Hand Hygiene. Individuals engaged in, or assisting with, CSPs shall be trained and demonstrate competence in proper personal garbing, gloving and hand hygiene. Competence must be documented and assessed through direct visual observation as part of the aseptic technique skill assessment required by this rule.

   (A) Risk Level 1: Low-particulate and non-shedding gowns, hair covers, gloves, face masks and beard covers must be worn during compounding and cleaning. All head and facial hair must be covered. During sterile preparation, gloves shall be disinfected before use and frequently thereafter with a suitable agent and changed when integrity is compromised. All personnel in the controlled area must be appropriately garbed as required by this section.

Comment [GK1]: The suggestion was strongly made that the rule require sterile gloves for all sterile compounding.
(B) Risk Level 2 and Risk Level 3: In addition to Risk Level 1 requirements, shoe covers and sterile gloves must be worn while compounding and cleaning, including, over RABS gloves. All personnel in the controlled or buffer area must garb as required by this section.

(7)(9) Aseptic Technique and Product Preparation. Appropriate quality control methods shall be maintained over compounding methods at all times to ensure proper aseptic technique.

(A) Risk Level 1: Sterile product preparations must be prepared in a Class 100 an ISO Class 5 environment. Personnel shall scrub their hands and forearms for an appropriate period at the beginning of each aseptic compounding process a minimum of thirty (30) seconds and remove debris from underneath fingernails under warm running water before donning the required gloves. Eating, drinking and smoking are prohibited in the controlled area. Talking shall be minimized to reduce airborne particles. Ingredients shall be determined to be stable, compatible, and appropriate for the product preparation to be prepared, according to manufacturer, USP, or scientific references. Ingredients and containers shall be inspected for defects, expiration and integrity before use. Only materials essential for aseptic compounding shall be placed in the workbenchPEC. Surfaces of ampules and vials shall be disinfected before placement in the workbench. Supplies, equipment and the surfaces of ampules and vials shall be disinfected before entering the PEC by wiping the outer surface with sterile alcohol or an equivalently effective non-residue generating disinfectant. Sterile components shall be arranged in the workbenchPEC to allow clear, uninterrupted laminar airflow path of HEPA-filtered air over critical surfaces of needles, vials, ampules, etc. Automated devices and equipment shall be cleaned, disinfected and placed in the workbenchPEC to enable laminar airflow. Aseptic technique shall be used to avoid touch contamination of critical sites of containers and ingredients. Particles shall be filtered from solutions. Needle cores shall be avoided. The pharmacist shall check before, during, and after preparation to verify the identity and amount of ingredients before release.

(B) Risk Level 2: In addition to Risk Level 1 requirements, a file containing the formula, components, procedures, sample label, and final evaluation shall be made for each product preparation batch. A separate work sheet and lot number for each batch shall be completed. When combining multiple sterile product preparations, a second verification of
calculations shall take place. The pharmacist shall verify data entered into any automatic
compounder before processing and check the end product preparation for accuracy.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, nonsterile components must
meet compendial standards if available, as or must be verified by a pharmacist and a certificate
of analysis. Batch preparation files shall also include comparisons of actual with anticipated
yields, sterilization methods, and quarantine specifications. Presterilized containers shall be used
when feasible. Final containers must be sterile and capable of maintaining product preparation
integrity throughout the shelf life. Sterilization methods must be based on properties of the
product preparation and must be conducted in a method recognized for the preparation by USP.

(D) Single-dose vials/containers and pharmacy bulk vial/containers exposed to ISO Class 5 or
cleaner air may be used in compounding until the assigned beyond-use date which shall not
exceed six (6) hours after initial needle puncture, unless otherwise specified by the manufacturer.
Opened single-dose ampules shall not be stored for any time period. The beyond-use date must
be placed on the vial/container.

(E) Unless otherwise specified by the manufacturer, multiple-dose vials/containers with an
antimicrobial preservative may be used in compounding until the assigned beyond-use date
which shall not exceed twenty-eight (28) days after initially entering or opening the
vial/container (e.g., needle-puncture). The beyond-use date must be placed on the vial/container.

(S) Process Validation.

(A) Risk Level 1: All pharmacy personnel who prepare sterile products shall pass a process
validation of aseptic technique before compounding sterile products. Pharmacy personnel
competency must be reevaluated by process validation at least annually, whenever the quality
assurance program yields an unacceptable result, or whenever unacceptable techniques are
observed. If microbial growth is detected, the entire sterile process must be evaluated, corrective
action taken, and the process simulation test performed again.

(B) Risk Level 2: In addition to Risk Level 1 requirements, process simulation procedures shall
cover all types of manipulations, products and batch sizes.

(C) Risk Level 3: In addition to all Risk Level 1 and 2 requirements, written policies shall be
maintained to validate all processes, procedures, components, equipment and techniques.
(10) **Aseptic Technique Skill Assessment.** Individuals engaged in sterile compounding must take and successfully pass an aseptic technique skill assessment to verify aseptic competency. The assessment must include a direct visual observation of the individual’s aseptic competency during a process simulation that represents the most challenging or stressful conditions encountered or performed by the person being evaluated. The assessment must include media fill testing for all risk levels.

   (A) The required visual observation shall assess:

   1. Proper aseptic technique, manipulations and work practices, including, but not limited to, avoiding touch contamination, proper use of first air and if applicable, sterilizing high risk CSPs;
   2. Cleaning and disinfection;
   3. Hand hygiene, gloving and garbing;
   4. Identifying, weighing, and measuring of ingredients;
   5. Maintaining and achieving sterility in ISO Class 5 areas and within primary engineering controls, and;

   (B) **Media-Fill Testing.** Pharmacies shall establish and follow policies and procedures for media-fill testing. Media-fill testing shall comply with USP Chapter 797’s recommended procedures and methods and must be conducted using the most challenging or stressful conditions/compounding actually encountered or performed by the person being evaluated using the same container or closure. A minimum of three media-fill tests must be completed during initial media-fill testing.

   (C) **Frequency:** The required Aseptic Technique Skill Assessment must be conducted prior to initial compounding and every twelve (12) months thereafter for Risk Levels 1 and 2 compounding and every (6) months thereafter for Risk Level 3 compounding. Additionally, an Aseptic Technique Skill Assessment must be conducted whenever the quality assurance program yields an unacceptable result or whenever unacceptable techniques are observed.
Individuals who fail written tests; visual observation of hand hygiene, garbing, and aseptic technique; or media-fill tests must undergo immediate requalification through additional training by competent compounding personnel. Individuals who fail visual observation of hand hygiene, garbing, and aseptic technique; or media-fill tests must pass three successive reevaluations in the deficient area before they can resume compounding of sterile preparations.

(9)(11) Record Keeping.

(A) Risk Level 1: The following must be documented:

1. Training and competency evaluation of pharmacy personnel involved in sterile product compounding, including, the dates and results of the required aseptic technique training, aseptic technique skill assessment and media-fill testing;
2. Refrigerator, and freezer and, if applicable, incubator temperature logs;
3. Certification of workbenches dates and results for any PEC or ISO classified area;
4. Copies of any manufacturer standard manuals that are relied upon to maintain compliance with this rule; and
5. Other facility quality control logs as appropriate including all maintenance, cleaning, and calibration records; and
6. If applicable, pressure recordings including documentation of the review of continuous monitoring system results as required by section (5)(F).

(B) Risk Level 2: In addition to Risk Level 1 requirements, records of any end-product preparation testing and batch preparation records must be maintained.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, record requirements for Risk Level 3 product preparations must include:

1. Preparation work sheet;
2. Sterilization records;
3. Quarantine records, if applicable;
4. End-product preparation evaluation and testing records as required in section (12)(14); and
5. Ingredient validation records as required in section (12)(14).

(D) All records and reports shall be maintained either electronically or physically for two (2) years and shall be readily retrievable, and subject to inspections by the board of pharmacy or its agents. At a minimum, records shall be physically or electronically produced immediately or within two (2) hours of a request from the Board or the Board’s authorized designee.
Labeling.

(A) Risk Level 1: Sterile preparations dispensed to patients shall be labeled in accordance with section 338.059, RSMo and with the following supplemental information affixed to a permanent label:

1. Beyond-use date;
2. Storage requirements if stored at other than controlled room temperature;
3. Any device specific instructions; and
4. Auxiliary labels, when applicable; and
5. If applicable, a designation indicating the preparation is hazardous.

(B) Risk Level 2: All requirements for Risk Level 1 must be met.

(C) Risk Level 3: All requirements for Risk Level 1 must be met.

Beyond-Use Dating.

(A) Risk Level 1 and Risk Level 2: All sterile preparations must bear a beyond-use date. Beyond-use dates must be assigned based on current drug and microbiological stability information and sterility considerations.

(B) Risk Level 2: All requirements for Risk Level 1 must be met.

(C) Risk Level 3: In addition to all Risk Level 1 requirements, there must be a reliable method for establishing all expiration beyond-use dates, including laboratory testing of product stability, pyrogenicity, particulate contamination and potency. Expiration dating not specifically referenced in the product’s approved labeling or not established by product specific instrumental analysis, shall be limited to thirty (30) days. Beyond-use dating not specifically referenced in the products approved labeling or not established by product specific instrumental analysis shall be limited to thirty (30) days. There must be a reliable method for establishing all beyond-use dating. Preparations assigned a beyond-use date of greater than thirty (30) days shall have lab testing of stability and potency.

End-Product Preparation Evaluation.

(A) Risk Level 1: The final preparation must be inspected for clarity, container leaks, integrity, and appropriate solution cloudiness or phase separation, particulates in solution, appropriate solution color, and solution volume. The pharmacist must verify that the preparation was compounded accurately as to the ingredients, quantities, containers, and
reservoirs. Background light or other means for the visual inspection of product preparations for any particulate and/or foreign matter must be used as part of the inspection process.

(B) Risk Level 2: All Risk Level 1 requirements must be met.

(C) Risk Level 3: In addition to all Risk Level 1 requirements, the process validation procedure shall be supplemented with a program of end-product preparation sterility testing according to a formal sampling plan. Samples shall be statistically valid to ensure that batches are sterile. A method for recalling batch product preparations shall be established if end-product preparation testing results are unacceptable. All sterile product preparations must be tested for sterility. All parenteral sterile product preparations must also be tested for pyrogenicity. Sterile products compounded from non-sterile components, Risk Level 3 preparations, must be quarantined and stored to maintain chemical and microbiological stability pending results of end-product preparation testing.

1. Sterility testing: Sampling for the sterility test shall occur promptly upon the completion of preparation. The sterility test, including the sampling scheme, shall be conducted according to one (1) of the recognized USP methods for the preparation.

2. Pyrogen/Endotoxin testing: Each sterile parenteral product preparation prepared from non-sterile drug components shall be tested for pyrogen or endotoxin according to recommended USP methods.

3. Potency: The pharmacy shall have a procedure for a pre-release check of the potency of the active ingredients in the compounded sterile product preparation prepared from non-sterile bulk active ingredients. The procedure shall include at least the following verifications by a pharmacist:

   A. The lot of the active ingredients used for compounding have the necessary labeling, potency, purity, certificate of analysis and other relevant qualities;
   B. All weighings, volumetric measurements, and additions of ingredients were carried out properly;
   C. The compounding or control records include documentation that the fill volumes of all units available for release were checked and were correct; and
   D. The final potency is confirmed by instrumental analysis for sterile product preparations that have been assigned a beyond-use date of more than thirty (30) days.
(D) Emergency Dispensing of a Risk Level 3 Sterile Product: When a compounded Risk Level 3 product must be released prior to the completion of testing, the sterile product may be dispensed pending test results. Emergency dispensing shall be defined as, and comply with, section (1)(O) of this rule.

(13) Handling Sterile Products Outside the Pharmacy: (15) Storage, Handling and Transport

(A) Risk Level 1: Sterile preparations shall be correctly packaged, stored, dispensed and distributed. The pharmacist-in-charge shall assure the environmental control of all sterile compounded products shipped. Sterile products shall be transported so as to be protected from excesses of temperatures and light within appropriate packaging or delivery containers that maintain necessary storage conditions to preserve the quality and integrity of sterile products. The pharmacy shall follow written procedures that specify packing techniques, configuration, and materials for groups of products with common storage characteristics and for specific products where unique storage conditions are required to retain adequate stability and product quality.

(B) Risk Level 2: All requirements for Risk Level 1 must be met.

(C) Risk Level 3: All requirements for Risk Level 1 must be met.

(16) Point-of-Care Assembled Systems: Assembly of point-of-care assembled systems shall be considered Risk Level 1 compounding. Point-of-care assembled systems shall be assigned a beyond-use date which may exceed the beyond-use-date authorized for Risk Level 1 preparations provided the date is assigned in accordance with the manufacturer’s recommendations or labeling.

(A) When dispensed, an assembled non-activated system shall be labeled with beyond-use dates for both activated and non-activated states. The compounding record must document both dates. The beyond-use date of an assembled non-activated system shall be limited to a maximum of fifteen (15) days unless the pharmacy has documentation from the system’s manufacturer that a longer date is acceptable.

(B) Point of care assembled systems shall be assembled and stored in accordance with the manufacturer’s labeling and recommendations.
(17) General Cleaning and Disinfection Requirements. Except as otherwise provided herein, cleaning and disinfection of controlled and buffer areas, supplies and equipment shall be performed and conducted in accordance with USP Chapter 797 timeframes and procedures. Controlled areas that do not meet ISO air classifications shall be cleaned and disinfected as required by USP Chapter 797 for segregated compounding areas. If compounding is done less frequently than the cleaning and disinfection timeframes specified in USP Chapter 797, cleaning and disinfection must occur before each compounding session begins.

(A) The pharmacy shall establish and follow written policies and procedures governing all aspects of cleaning and disinfection, including, authorized cleaning/disinfecting agents and materials, schedules of use and methods of application.

(B) Individuals shall be trained in proper cleaning and disinfection procedures prior to performing such activities. Training shall include direct visual observation of the individual’s cleaning and disinfecting process by qualified staff. The individual shall be annually reassessed for competency through direct visual observation. Documentation of the required training and training dates shall be maintained in the pharmacy’s records.

Individuals who fail to demonstrate competency shall be re instructed and successfully reevaluated prior to any further cleaning or disinfection.

(C) Cleaning and disinfection activities shall be performed using approved agents and procedures described in the pharmacy’s written policies and procedures. Manufacturers’ directions for minimum contact time shall be followed.

(D) All cleaning tools (e.g., wipes, sponges, and mop heads) must be low-lint and dedicated for use in the controlled area.

(E) Primary engineering controls shall be cleaned with a germicidal agent followed by sterile alcohol. Sterile water for irrigation shall be used to dilute germicidal agents used inside the PEC that require dilution.

(F) At a minimum, the critical area shall be cleaned and disinfected prior to compounding, between batches and whenever contamination is suspected using sterile alcohol which is allowed to dry immediately prior to compounding.

(18) Cytotoxic Drugs.

(A) The following additional requirements are necessary for those licensed pharmacies that prepare cytotoxic drugs to insure the protection of the personnel involved:
1. Cytotoxic drugs shall be compounded in a vertical flow, Class II biological safety cabinet or an isolator. If used for other non-sterile preparations, the cabinet must be thoroughly cleaned;

2. Protective apparel shall be worn by personnel compounding cytotoxic drugs which shall include disposable masks, gloves and gowns with tight cuffs;

3. Appropriate safety and containment techniques for compounding cytotoxic drugs shall be used in conjunction with the aseptic techniques required for preparing sterile preparations;

4. Appropriate disposal containers for used needles, syringes, and if applicable, cytotoxic waste from the preparation of chemotherapy agents and infectious waste from patients’ homes. Disposal of cytotoxic waste shall comply with all applicable local, state and federal requirements;

5. Written procedures for handling major and minor spills and generated waste of cytotoxic agents must be developed and must be included in the policy and procedure manual;

6. Prepared doses of cytotoxic drugs must be labeled with proper precautions inside and outside, and shipped in a manner to minimize the risk of accidental rupture of the primary container.

(15) Exemption: Pharmacists and pharmacies where sterile compounding is provided may be exempt from this rule when compounding is restricted to utilizing compounds or products that are contained only in a closed or sealed system and can be transferred or compounded within this self-contained system or topical products that require further transfer or combination in order to achieve a finished product without further modification of the product.

(16)(19) In addition to the requirements outlined in this rule, all standards and requirements as outlined in 20 CSR 2220-2.400 must be maintained. Pharmacies that are registered with the Food and Drug Administration (FDA) are exempt from the distribution restrictions in 20 CSR 2220-2.400(12) for compounded sterile pharmaceuticals distributed with FDA’s knowledge and enforcement discretion. This exemption applies only to a twenty-four (24)-hour course of therapy which is needed:

(A) To treat an emergency situation; or
(B) For an unanticipated procedure for which a time delay would negatively affect a patient outcome. In order to continue beyond twenty-four (24) hours, the pharmacy must obtain a prescription and comply with all record and labeling requirements as defined by law or regulation.

(20) Remedial Investigations: A remedial investigation shall be required if: (1) any sampling or testing required by this rule demonstrates a colony forming unit (CFU) count that exceeds USP Chapter 797 recommended action levels for the type of sampling/testing or (2) if a highly pathogenic microorganism is detected in any preparation or ISO classified area (e.g., Gram-negative rods, coagulase positive staphylococcus, molds, fungus or yeasts).

(A) CSPs and any ingredients used within the compounding process that are part of the remedial investigation shall be quarantined until the results of the investigation are known. All affected areas shall be resampled to ensure a suitable state of microbial control prior to further compounding. The pharmacy shall ensure that no misbranded, contaminated or adulterated CSP is administered or dispensed for patient use.

(B) The pharmacy shall notify the Board in writing within seven (7) days if any preparation or environmental monitoring/testing detects a highly pathogenic microorganism, regardless of CFU count.

(21) Recalls. A recall must be initiated when a CSP is deemed to be misbranded, adulterated or non-sterile or if end-preparation testing results are out of specification. The pharmacy shall notify the prescriber of the nature of the recall, the problem(s) identified and any recommended actions to ensure public health and safety. In cases where the CSP has the potential to harm the patient, the same notification shall be provided to all patients that received the recalled CSP(s). Any recall initiated by a pharmacy shall be reported, in writing, to the board within three (3) business days.

20 CSR 2220-2.200 Sterile Pharmaceuticals Compounding

PURPOSE: This rule establishes standards for the preparation, labeling, and distribution and dispensing of sterile pharmaceuticals compounded sterile preparations by licensed pharmacies, pursuant to a physician’s order or prescription.

(1) Definitions.

(A) Aseptic processing: The technique involving procedures designed to preclude contamination of drugs, packaging, equipment, or supplies by microorganisms during processing.

(B) Batch: Compounding of multiple sterile preparation units in a single discrete process, by the same individuals, carried out during one (1) limited time period.

(C) Beyond-Use date: A date after which a compounded preparation should not be used and is determined from the date the preparation is compounded. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates must be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

(D) Biological safety cabinet: Containment unit suitable for the preparation of low to moderate risk agents where there is a need for protection of the preparation, personnel and environment, according to National Sanitation Foundation (NSF) International standards.

(E) Class 100 environment: An atmospheric environment which contains less than one hundred (100) particles 0.5 microns in diameter per cubic foot of air, according to federal standards.

(F) Class 10,000 environment: An atmospheric environment which contains less than ten thousand (10,000) particles 0.5 microns in diameter per cubic foot of air, according to federal standards.

(E) Buffer Area: An ISO Class 7 or better area where the primary engineering control is physically located that is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room and in which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

(G) Clean room: A room—

1. In which the concentration of airborne particles is controlled;
2. That is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room; and

3. In which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

(H) Clean zone: Dedicated space—
1. In which the concentration of airborne particles is controlled;
2. That is constructed and used in a manner that minimizes the introduction, generation, and retention of particles inside the zone; and
3. In which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

This zone may be open or enclosed and may or may not be located within a clean room.

(I)(F) Compounding: For the purposes of this regulation, compounding is defined as in 20 CSR 2220-2.400(1). Compounded sterile medications may include, but are not limited to, injectables, parenteral nutrition solutions, irrigation solutions, inhalation solutions, intravenous solutions and ophthalmic preparations.

(G) Compounding Aseptic Containment Isolator (CACI): A RABS that is designed for compounding sterile hazardous drugs and designed to provide worker protection from exposure to undesirable levels of airborne drugs throughout the compounding and material transfer processes and to provide an aseptic environment for CSPs.

(H) Compounding Aseptic Isolator (CAI): A RABS specifically designed for compounding sterile non-hazardous pharmaceutical ingredients or CSPs and designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes.

(I)(J) Controlled area: For purposes of these regulations, a controlled area is the area designated for preparing sterile preparations that is separated from other activities/operations by a line of demarcation that clearly separates the area from other operations. This is referred to as the buffer zone (i.e., the clean room in which the laminar airflow workbench is located) by the United States Pharmacopeia (USP).

(K)(J) Critical area: Any area in the controlled area where preparations or containers are exposed to the environment.

Comment [GK1]: The 2015 drafts included the language below in the definition of compounding. Should any of it be included in the amended rule?

a. Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that must or are required to be sterile when they are administered to patients, including, but not limited to the following dosage forms: bronchial and inhaled nasal preparations intended for deposition in the lung, baths and soaks for live organs and tissues, epidural and intrathecal solutions, bladder/wound solutions, injectables, implantable devices and dosage forms, inhalation solutions, intravenous solutions, ophthalmic preparations, parenteral nutrition solutions, and repackaged sterile preparations.

b. An FDA approved manufactured sterile product that is either prepared according to the manufacturer's approved labeling/recommendations or prepared differently than published in such labeling; and

c. Assembling point-of-care activated systems.
Critical site: An opening providing a direct pathway between a sterile product and the environment or any surface coming into contact with the product or environment. Any surface, pathway or opening (e.g., vial septa, injection ports, beakers, needle hubs) that provides a direct pathway between a compounded sterile preparation or other ingredient used to compound a sterile preparation and the air, environment or moisture or that poses a risk of touch contamination.

Critical surface: Any surface that comes into contact with previously sterilized product preparations or containers.

CSP: Compounded sterile preparation.

Cytotoxic drugs: A pharmaceutical product that has the capability of direct toxic action on living tissue that can result in severe leukopenia and thrombocytopenia, depression of the immune system and the alteration of a host’s inflammatory response system.

Emergency dispensing: Is a situation where a Risk Level 3 product preparation is necessary for immediate administration of the product preparation and no alternative product is available and the prescriber is informed that the product preparation is being dispensed prior to appropriate testing. Documentation of the dispensing of the product preparation, the prescriber’s approval for dispensing prior to the receipt of test results and the need for the emergency must appear within the prescription record. A separate authorization from the prescriber is required for each emergency dispensing.

High-Efficiency Particulate Air (HEPA) filter: A filter composed of pleats of filter medium separated by rigid sheets of corrugated paper or aluminum foil that direct the flow of air forced through the filter in a uniform parallel flow. HEPA filters remove ninety-nine point ninety-seven percent (99.97%) of all particles three-tenths (0.3) microns or larger. When HEPA filters are used as a component of a horizontal- or vertical-laminar-airflow workbench, an environment can be created consistent with standards for a Class 100 clean room.

ISO Class 5: An area with less than 3,520 particles (0.5 µm and larger in size) per cubic meter.

ISO Class 7: An area with less than 352,000 particles (0.5 µm and larger in size) per cubic meter.
(S) ISO Class 8: An area with less than 3,520,000 particles (0.5 µm and larger in size) per cubic meter.

(Q) Isolator (or barrier isolator): A closed system made up of four (4) solid walls, an air-handling system, and transfer and interaction devices. The walls are constructed so as to provide surfaces that are cleanable with coving between wall junctures. The air-handling system provides HEPA filtration of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports. Transfers are designed to minimize the entry of contamination. Manipulations can take place through either glove ports or half suits.

(T) Multiple-Dose Container: A multiple unit container for articles or compounded sterile preparations that contains more than one dose of medication.

(R)(U) Parenteral: A sterile preparation of drugs for injection through one (1) or more layers of skin.

(V) Primary Engineering Control (PEC): A system that provides an ISO 5 environment for the exposure of critical sites when compounding sterile preparations. PECs include, but may not be limited to, horizontal/vertical laminar airflow hoods, biological safety cabinets, RABS such as compounding aseptic isolators (CAIs) or compounding aseptic containment isolators (CACIs).

(W) Point of Care Assembled System: A closed system device that creates a physical barrier between diluents, fluids or other drug components and is designed to be activated by the end user by allowing the components to mix prior to administration.

(S)(X) Process validation or simulation: Microbiological simulation of an aseptic process with growth medium processed in a manner similar to the processing of the product preparation and with the same container or closure system.

(T)(Y) Quality assurance: For purposes of these regulations, quality assurance is the set of activities used to ensure that the processes used in the preparation of sterile drug product preparations lead to product preparations that meet predetermined standards of quality.

(U)(Z) Quality control: For the purposes of these regulations, quality control is the set of testing activities used to determine —that the ingredients, components and final sterile product preparations prepared meet predetermined requirements with respect to identity, purity, nonpyrogenicity and sterility.

(AA) RABS: Restricted access barrier system (RABS): A primary engineering control that is comprised of a closed system made up of four (4) solid walls, an air-handling system, and...
transfer and interaction devices. The walls are constructed so as to provide surfaces that are cleanable with coving between wall junctures. The air-handling system provides HEPA filtration of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports. Transfers are designed to minimize the entry of contamination. Manipulations can take place through either glove ports or half suits. Examples of a RABS may include, but is not limited to, a CAI or CACI.

**(V)** Repackaging: The subdivision or transfer of a compounded product from one container or device to a different container or device.


**(W)** Sterile pharmaceutical: A dosage form free from living microorganisms.

**(X)** Sterilization: A validated process used to render a product free of viable organisms.

**(EE)** Temperatures:

1. Frozen means temperatures between twenty below zero and ten degrees Celsius (two below zero and fourteen degrees Fahrenheit (20°C and 10°F)).
2. Refrigerated means temperatures between two and eight degrees Celsius (two and eight degrees Fahrenheit (2°C and 8°F)).
3. Controlled room temperatures means room temperatures between fifteen and thirty degrees Celsius (fifteen and thirty degrees Fahrenheit (59°F and 86°F)), a temperature maintained thermostatically that encompasses the usual and customary working environment of twenty to twenty-five degrees Celsius (sixty-eight to seventy-eight degrees Fahrenheit (68°F to 78°F)) and that results in a mean kinetic temperature calculated to be not more than twenty-five degrees Celsius. Excursions between fifteen and thirty degrees Celsius (fifty-nine and eighty-six degrees Fahrenheit (59°F to 86°F)) as commonly experienced in pharmacies and other facilities shall be deemed compliant. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to forty degrees Celsius are permitted as long as they do not exceed twenty-four hours. Spikes above forty degrees Celsius are permitted if allowed by the manufacturer.

**(FF)** USP: The United States Pharmacopeia and the National Formulary (USP-NF) as adopted and published by the United States Pharmacopeial Convention, effective May 2013. Copies of the USP-NF are published by, and available from, USP, 12601 Twinbrook Parkway, Rockville,
Validation: Documented evidence providing a high degree of assurance that specific processes will consistently produce a product preparation meeting predetermined specifications and quality attributes.

Definitions of sterile compounded product preparations by risk level:

1. Risk Level 1: Applies to compounded sterile product preparations that exhibit characteristics A., B., and/or C., stated below. All Risk Level 1 product preparations shall be prepared with sterile equipment, sterile ingredients and solutions and sterile contact surfaces for the final product preparation. Risk Level 1 includes the following:

   A. Product Preparations:
      (I) Stored at room temperature controlled room temperature and completely administered within assigned a beyond-use date of forty-eight (48) hours after preparation or less; or
      (II) Stored under refrigeration for and assigned a beyond-use date of seven (7) days or less before complete administration to a patient over a period not to exceed forty-eight (48) hours; or
      (III) Stored frozen for and assigned a beyond-use date of thirty (30) days or less before complete administration to a patient over a period not to exceed forty-eight (48) hours.

   B. Unpreserved sterile product preparations prepared for administration to one (1) patient or batch-prepared product preparations containing suitable preservatives prepared for administration to more than one (1) patient with an assigned beyond-use date that does not exceed the beyond-use date allowed for Risk Level 1 under section (1)(HH)1.A. of this rule.

   C. Product Preparations prepared by closed-system aseptic transfer of sterile, nonpyrogenic, finished pharmaceuticals (e.g., from vials or ampules) obtained from licensed manufacturers into sterile final containers obtained from licensed manufacturers with an assigned beyond-use date that does not exceed the beyond-use date allowed under section (1)(HH)1.A. of this rule.

2. Risk Level 2: Sterile product preparations exhibit characteristic A., B., or C., stated below. All Risk Level 2 product preparations shall be prepared with sterile equipment, sterile ingredients and solutions and sterile contact surfaces for the final product preparation and with closed-system transfer methods. Risk Level 2 includes the following:
A. Products stored beyond seven (7) days under refrigeration, stored beyond thirty (30) days frozen or administered beyond forty-eight (48) hours after preparation and storage at room temperature. Preparations stored under refrigeration and assigned a beyond-use date greater than seven (7) days or preparations stored frozen and assigned a beyond-use date greater than thirty (30) days or preparations stored at controlled room temperature and assigned a beyond-use date greater than forty-eight hours.

B. Batch-prepared product preparations without preservatives that are intended for use by more than one (1) patient.

C. Product preparations compounded by complex or numerous manipulations of sterile ingredients obtained from licensed manufacturers in a sterile container or reservoir obtained from a licensed manufacturer by using closed-system aseptic transfer (e.g., automated compounder).

3. Risk Level 3: Sterile product preparations exhibit either characteristic A. or B.:

A. Product preparations compounded from nonsterile ingredients or compounded with nonsterile components, containers or equipment before terminal sterilization.

B. Product preparations prepared by combining multiple ingredients (sterile or nonsterile) by using an open-system transfer or open reservoir before terminal sterilization.


(A) A manual, outlining policies and procedures encompassing all aspects of Risk Level 1, 2 and 3 products compounding, shall be available for inspection at the pharmacy. The manual shall be reviewed on an annual basis. The pharmacy shall have current reference materials related to sterile product preparations.

(B) The required policy and procedure manual must include policies/procedures for:

1. Staff education, training and evaluation and monitoring competency;
2. Maintaining, verifying and testing the accuracy and functioning of compounding equipment, including, time frames for calibration, testing, equipment monitoring and both annual and routine maintenance;
3. Certifying primary engineering controls and ISO classified areas;
4. Staff garbing and hand hygiene;
5. Aseptic technique and preparation, including, compounding, labeling and dispensing CSPs;
6. Aseptic technique skill assessment, including glove-fingertip sampling;
7. Media-fill testing. Policies and procedures shall address/identify media-fill procedures, media selection, fill volume, incubation requirements, time and temperature requirements, testing documentation, analyzing results, and any corrective action guidelines or procedures;

8. Beyond-use dating;

9. End-preparation evaluation, including, approved methods of sterilization;

10. Storing, transporting and delivering CSPs;

11. Handling and reporting accidental exposures or spills of hazardous CSPs, including, reporting methods and timeframes;

12. Measures for preventing cross-contamination when compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., radiolabeling a patient's or donor's white blood cells);

13. Environmental sampling, including, specified time frames and locations;

14. Reporting and investigating environmental deficiencies;

15. Cleaning and disinfection. Policies and procedures shall identify authorized cleaning/disinfecting agents and materials, schedules of use and methods of application;

16. Reporting and investigating any real or suspected adverse event or any real or suspected contaminated, non-sterile or defective final CSP;

17. Conducting remedial investigations;

18. Recall procedures which must include procedures for identifying and notifying affected patients, prescribers and regulators when applicable; and

19. Educating patients and/or caregivers concerning the appropriate storage, use and control of CSPs, when applicable.

(3) Personnel Education, Training and Evaluation.

(A) Risk Level 1: All pharmacy personnel preparing sterile products must receive suitable didactic and experiential training in aseptic technique and procedures and shall be skilled and trained to accurately and competently perform the duties assigned. Additional training must be provided if the level of sterile activity conducted by the individual changes or if there is a change in compounding methods. To ensure competency, individuals preparing sterile preparations must successfully pass an Aseptic Technique Skill Assessment that complies with section (10) of this rule.

(B) Risk Level 2: In addition to Risk Level 1 requirements, personnel training must include assessment of competency in all Risk Level 2 procedures via process simulation.
(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, operators have specific education, training and experience to prepare Risk Level 3 product preparations. The pharmacist knows principles of good compounding practice for risk level product preparations, including—

1. Aseptic processing;
2. Quality assurance of environmental, component, and end-product preparation testing;
3. Sterilization; and
4. Selection and use of containers, equipment, and closures.

(4) Storage and Handling in the Pharmacy.

(A) Risk Level 1 and 2: Solutions, drugs, supplies and compounding equipment must be stored according to manufacturer or USP requirements and maintained in a manner that will maintain the chemical and microbiological stability of CSPs. Refrigeration and freezer temperatures shall be documented daily. Other storage areas shall be inspected regularly to ensure that temperature and lighting meet requirements. Drugs and supplies shall be shelved above the floor. Removal of drugs and supplies from boxes shall be done outside controlled areas. Removal of used supplies from the controlled area shall be done at least daily. Product preparation recall procedures must comply with section (22) of this rule and must permit retrieving affected product preparations from specific involved patients.

(B) Risk Level 3: In addition to Risk Level 1 and 2 requirements, the pharmacy must establish procedures for procurement, identification, storage, handling, testing, and recall of components and finished product preparations. Finished but untested—Risk Level 3 product preparations awaiting test results must be quarantined under minimal risk for contamination.

(5) Facilities and Equipment.

(A) Risk Level 1: The controlled area shall be separated from other operations. The controlled area must be clean and well-lit. A sink with hot and cold water must be near, but not in, the controlled area. The controlled area and inside equipment must be cleaned and disinfected regularly. Sterile products must be prepared in at least a Class 100 environment (the critical area). Computer entry, order processing, label generation, and record keeping shall be performed outside the critical area. The critical area must be disinfected prior to use. A workbench shall be recertified every six (6) months and when it is moved; prefilters must be visually inspected on a
Facilities and Equipment.

Risk Level 1: Risk Level 1 preparations must be prepared in a PEC located in a controlled area that meets the requirements of this rule. A sink with hot and cold water must be near, but not in, the controlled area. The controlled area and inside equipment must be cleaned and disinfected as provided in section (17) of this rule. Activities within the critical area shall be kept to a minimum to maintain the ISO classified environment. Primary engineering controls shall meet the requirements of section (6) of this rule; prefilters must be visually inspected on a regularly scheduled basis and replaced according to manufacturer’s specifications. Pumps utilized in the compounding process shall be recalibrated and documented according to manufacturer procedures.

Risk Level 2: In addition to all Risk Level 1 requirements, Risk Level 2 preparations must be prepared in a PEC located in a buffer area or prepared in a RABS located within a controlled positive pressure barrier isolator.
area. Risk Level 2 preparations shall at a minimum remain a Risk Level 2 for the life of the
preparation.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, Risk Level 3 preparations
must be prepared in a PEC located in a buffer area or prepared in a RABS located within a
controlled area. All non-sterile equipment that is to come in contact with the sterilized final
preparation must be sterilized and depyrogenated before introduction in the buffer area in
accordance with a USP method. Once compounded, Risk Level 3 preparations shall at a
minimum remain Risk Level 3 for the life of the preparation.

(D) Automated compounding devices shall be tested for content, volume and weight accuracy
prior to both initial and daily use according to manufacturer procedures. Test results shall be
reviewed by a pharmacist to ensure compliance. The identity of the reviewing pharmacist and
the review date shall be documented in the pharmacy’s records.

(E) All PECs and ISO classified areas shall be certified to ensure compliance with
requirements of this rule prior to beginning sterile compounding activities and every six (6)
months thereafter. Certification shall be conducted by competent staff/vendors using recognized
and appropriate certification and testing equipment. For PECs, the required certification shall
include nonviable airborne particle sampling, airflow velocity testing, airflow smoke study
testing and a HEPA filter leak test. For RABS, certification shall also include chamber pressure
testing and preparation ingress and egress testing. For buffer areas, the required certification
shall include nonviable airborne particle sampling, HEPA filter leak testing and pressure
differential testing. Certification results shall be reviewed by a pharmacist once received.
Deficiencies or failures shall be investigated and corrected prior to further compounding.

1. The PEC and ISO classified areas must be recertified when: (1) any changes or major
service occurs that may affect airflow or environmental conditions or (2) the PEC or room is
relocated or the physical structure of the ISO classified area has been altered.

2. Corrections may include, but are not limited to, changes in the use of the affected PEC
or ISO classified area or initiating a recall. The identity of the pharmacist conducting the
required review and the review date shall be documented in the pharmacy’s records.

(F) Pressure Differential: If the controlled area is equipped with a device to monitor pressure
differential, pressure differential results must be recorded and documented each day that the
pharmacy is open for pharmacy activities. Alternatively, a continuous monitoring system may
be used to record pressure differential results if the system maintains ongoing documentation of pressure recordings or maintains pressure alerts that are reviewed daily.

(6) Primary Engineering Controls (PECs):

(A) PECs must be properly used, operated and maintained and must be located out of traffic patterns and away from conditions that could adversely affect their operation or disrupt intended airflow patterns (e.g., ventilation systems or cross-drafts).

(B) PECs shall maintain ISO Class 5 or better conditions during dynamic operating conditions and while compounding sterile preparations, including, when transferring ingredients into and out of the PEC and during exposure of critical sites;

(C) PECs shall provide unidirectional (laminar flow) HEPA air at a velocity sufficient to prevent airborne particles from contacting critical sites.

(D) Compounding Aseptic Isolators (CAI): Air exchange into the isolator from the surrounding environment shall not occur unless the air has first passed through a microbial retentive HEPA filter.

(E) Compounding Aseptic Containment Isolators (CACI): Air exchange with the surrounding environment shall not occur unless the air is first passed through a microbial retentive HEPA filter system capable of containing airborne concentrations of the physical size and state of the drug being compounded.

(F) The recovery time to achieve ISO Class 5 air quality in any PEC shall be identified in the pharmacy’s policies and procedures and internal procedures developed to ensure adequate recovery time is allowed after material transfer and before or during compounding operations.

(7) Controlled Areas. The controlled area shall be designed, maintained and controlled to allow effective cleaning and disinfection and to minimize the risk of contamination and the introduction, generation and retention of particles inside the PEC.

(A) Controlled areas must be clean and well-lit and shall be free of infestation by insects, rodents and other vermin. Trash shall be disposed of in a timely and sanitary manner and at least daily. Tacky mats or similar articles shall be prohibited in the controlled area or any ISO classified environment.
(B) Traffic flow in or around the controlled area shall be minimized and controlled. Food items, chewing gum, eating, drinking and smoking are prohibited in the area.

(C) Nonessential objects that shed particles shall not be brought into the controlled area, including, but not limited to, pencils, cardboard cartons, paper towels, and cotton items (e.g., gauze pads). Furniture, carts, supplies and equipment shall be removed from shipping cartons/containers and properly cleaned and disinfected with sterile alcohol before entering any ISO classified area. No shipping or other external cartons may be taken into the controlled area or an ISO classified area.

(D) Only supplies essential for compounding shall be stored in the controlled area. Supplies or other non-essential equipment shall not be stored in or on the PEC.

6) Apparel.

(A) Risk Level 2: In the controlled area, personnel wear low particulate, clean clothing covers. Head and facial hair is covered. Gloves, gowns, and masks are required. During sterile preparation gloves shall be rinsed frequently with a suitable agent and changed when integrity is compromised.

(B) Risk Level 3: In addition to Risk Level 2 requirements, clean room apparel must be worn inside the controlled area at all times during the preparation of Risk Level 3 sterile products except when positive pressure barrier isolation is utilized. Attire shall consist of a low-shedding coverall, head cover, face mask, and shoe covers.

8) Garbing and Hand Hygiene. Individuals engaged in, or assisting with, CSPs shall be trained and demonstrate competence in proper personal garbing, gloving and hand hygiene. Competence must be documented and assessed through direct visual observation as part of the aseptic technique skill assessment required by this rule.

(A) Risk Level 1: Low-particulate and non-shedding gowns, sterile gloves, hair covers, face masks and beard covers must be worn during compounding and cleaning. For a RABS, sterile gloves should be worn over RABS gloves. All head and facial hair must be covered. During sterile preparation, gloves shall be disinfected frequently with a suitable agent and changed when integrity is compromised. All personnel in the controlled area must be appropriately garbed as required by this section. When personnel exit the controlled area, all garb shall be removed. If the gown is not visibly soiled, it may be retained within the controlled area for re-use, to be re-

Comment [GK2]: Our notes said that sterile gloves would not be required in the emergency but would be OK in the amended. Is this correct?
donned during that same work shift only. All other garb must be discarded and cannot be re-
used.

(B) **Risk Level 2 and Risk Level 3:** In addition to Risk Level 1 requirements, shoe covers
must be worn while compounding.

(7)(9) **Aseptic Technique and Product Preparation.** Appropriate quality control methods shall be
maintained over compounding methods at all times to ensure proper aseptic technique.

(A) **Risk Level 1:** Sterile product preparations must be prepared in a Class 100 an ISO Class 5
environment. Personnel shall scrub their hands and forearms for an appropriate period at the
beginning of each aseptic compounding process a minimum of thirty (30) seconds and remove
debris from underneath fingernails under warm running water using a disposable nail cleaner
before donning the required gloves. Eating, drinking and smoking are prohibited in the
controlled area. Talking shall be minimized to reduce airborne particles. Ingredients shall be
determined to be stable, compatible, and appropriate for the product preparation to be prepared,
according to manufacturer, USP, or scientific references. Ingredients and containers shall be
inspected for defects, expiration and integrity before use. Only materials essential for aseptic
compounding shall be placed in the workbench PEC. Surfaces of ampules and vials shall be
disinfect ed before placement in the workbench. Supplies, equipment and the surfaces of ampules
and vials shall be disinfected before entering the PEC by wiping the outer surface with sterile
alcohol or an equivalently effective non-residue generating disinfectant. Sterile components
shall be arranged in the workbench PEC to allow clear, uninterrupted laminar airflow path of
HEPA-filtered air over critical surfaces of needles, vials, ampules, etc. Automated devices and
equipment shall be cleaned, disinfected and placed in the workbench PEC to enable laminar
airflow. Aseptic technique shall be used to avoid touch contamination of critical sites of
containers and ingredients. Particles shall be filtered from solutions. Needle cores shall be
avoided. The pharmacist shall check before, during, and after preparation to verify the identity
and amount of ingredients before release.

(B) **Risk Level 2:** In addition to Risk Level 1 requirements, a file containing the formula,
components, procedures, sample label, and final evaluation shall be made for each
product preparation batch. A separate work sheet and lot number for each batch shall be
completed. When combining multiple sterile product preparations, a second verification of
calculations shall take place. The pharmacist shall verify data entered into any automatic compounder before processing and check the end product for accuracy.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, nonsterile components must meet compendial standards if available, or must be verified by a pharmacist and a certificate of analysis. Batch preparation files shall also include comparisons of actual with anticipated yields, sterilization methods, and quarantine specifications. Presterilized containers shall be used when feasible. Final containers must be sterile and capable of maintaining product integrity throughout the shelf life. Sterilization methods must be based on properties of the product and must be conducted in a method recognized for the preparation by USP.

(D) Single-dose vials/containers and pharmacy bulk vial/containers exposed to ISO Class 5 or cleaner air may be used in compounding until the assigned beyond-use date which shall not exceed six (6) hours after initial needle puncture, unless otherwise specified by the manufacturer. Opened single-dose ampules shall not be stored for any time period. The beyond-use date must be placed on the vial/container.

(E) Unless otherwise specified by the manufacturer, multiple-dose vials/containers with an antimicrobial preservative may be used in compounding until the assigned beyond-use date which shall not exceed twenty-eight (28) days after initially entering or opening the vial/container (e.g., needle-puncture). The beyond-use date must be placed on the vial/container.

(S) Process Validation.

(A) Risk Level 1: All pharmacy personnel who prepare sterile products shall pass a process validation of aseptic technique before compounding sterile products. Pharmacy personnel competency must be reevaluated by process validation at least annually, whenever the quality assurance program yields an unacceptable result, or whenever unacceptable techniques are observed. If microbial growth is detected, the entire sterile process must be evaluated, corrective action taken, and the process simulation test performed again.

(B) Risk Level 2: In addition to Risk Level 1 requirements, process simulation procedures shall cover all types of manipulations, products, and batch sizes.

(C) Risk Level 3: In addition to all Risk Level 1 and 2 requirements, written policies shall be maintained to validate all processes, procedures, components, equipment and techniques.
(10) Aseptic Technique Skill Assessment. Individuals engaged in sterile compounding must take and successfully pass an aseptic technique skill assessment to verify aseptic competency. The assessment must include a direct visual observation of the individual’s aseptic competency during a process simulation that represents the most challenging or stressful conditions encountered or performed by the person being evaluated. The assessment must include media fill testing for all risk levels and glove fingertip sampling.

(A) The required visual observation shall assess:

1. Proper aseptic technique, manipulations and work practices, including, but not limited to, avoiding touch contamination, proper use of first air and if applicable, sterilizing high risk CSPs;
2. Cleaning and disinfection;
3. Hand hygiene, gloving and garbing;
4. Identifying, weighing, and measuring of ingredients;
5. Maintaining and achieving sterility in ISO Class 5 areas and within primary engineering controls, and;

(B) Media-Fill Testing. Pharmacies shall establish and follow policies and procedures for media-fill testing. Media-fill testing shall comply with USP Chapter 797’s recommended procedures and methods and must be conducted using the most challenging or stressful conditions/compounding actually encountered or performed by the person being evaluated using the same container or closure. A minimum of three media-fill tests must be completed during initial media-fill testing.

(C) Glove-Fingertip Sampling. Initial and ongoing fingertip sampling must be completed in accordance with USP Chapter 797 procedures and methods. Ongoing sampling must be conducted after each required media-fill test.

(D) Frequency: The required Aseptic Technique Skill Assessment must be conducted prior to initial compounding and every twelve (12) months thereafter for Risk Levels 1 and 2 compounding and every (6) months thereafter for Risk Level 3 compounding. Additionally, an Aseptic Technique Skill Assessment must be conducted whenever the quality assurance program yields an unacceptable result or whenever unacceptable techniques are observed.
(E) Individuals who fail written tests; visual observation of hand hygiene, garbing, and aseptic technique; gloved fingertip/thumb sampling; or media-fill tests must undergo immediate requalification through additional training by competent compounding personnel. Individuals who fail visual observation of hand hygiene, garbing, and aseptic technique; gloved fingertip/thumb sampling; or media-fill tests must pass three successive reevaluations in the deficient area before they can resume compounding of sterile preparations.

(9)(11) Record Keeping.

(A) Risk Level 1: The following must be documented:

1. Training and competency evaluation of pharmacy personnel involved in sterile product preparation compounding, including the dates and results of the required aseptic technique training, aseptic technique skill assessment, glove fingertip sampling and media-fill testing;
2. Refrigerator, and freezer and, if applicable, incubator temperature logs;
3. Certification of workbenches dates and results for any PEC or ISO classified area;
4. Copies of any manufacturer standards manuals that are relied upon to maintain compliance with this rule; and
5. Other facility quality control logs as appropriate including all maintenance, cleaning, and calibration records; and
6. If applicable, pressure recordings including documentation of the review of continuous monitoring system results as required by section (5)(F).

(B) Risk Level 2: In addition to Risk Level 1 requirements, records of any end-product preparation testing and batch preparation records must be maintained.

(C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, record requirements for Risk Level 3 preparations must include:

1. Preparation work sheet;
2. Sterilization records;
3. Quarantine records, if applicable;
4. End product preparation evaluation and testing records as required in section (12)(14); and
5. Ingredient validation records as required in section (12)(14).

(D) All records and reports shall be maintained either electronically or physically for two (2) years and shall be readily retrievable; and subject to inspections by the board of pharmacy or its...
agents. At a minimum, records shall be physically or electronically produced immediately or within two (2) hours of a request from the Board or the Board’s authorized designee.

(10)(12) Labeling.
(A) Risk Level 1: Sterile product preparations dispensed to patients shall be labeled in accordance with section 338.059, RSMo and with the following supplemental information affixed to a permanent label:
1. Beyond-use date;
2. Storage requirements if stored at other than controlled room temperature;
3. Any device specific instructions; and
4. Auxiliary labels, when applicable; and
5. If applicable, a designation indicating the preparation is hazardous.
(B) Risk Level 2: All requirements for Risk Level 1 must be met.
(C) Risk Level 3: All requirements for Risk Level 1 must be met.

(11)(13) Beyond-Use Dating.
(A) Risk Level 1 and Risk Level 2: All sterile product preparations must bear a beyond-use date that complies with section of this rule. Beyond-use dates must be assigned based on current drug and microbiological stability information and sterility considerations.
(B) Risk Level 2: All requirements for Risk Level 1 must be met.
(C) Risk Level 3: In addition to all Risk Level 1 requirements, there must be a reliable method for establishing all expiration beyond-use dates, including laboratory testing of product stability, pyrogenicity, particulate contamination and potency. Expiration dating not specifically referenced in the product’s approved labeling or not established by product specific instrumental analysis, shall be limited to thirty (30) days. Beyond-use dating not specifically referenced in the products approved labeling or not established by product specific instrumental analysis shall be limited to thirty (30) days to twenty-four (24) hours if stored at controlled room temperature, three (3) days if stored at cold temperature and forty-five (45) days if stored frozen. There must be a reliable method for establishing all beyond-use dating. Products maintaining beyond-use dating Preparations assigned a beyond-use date of greater than thirty (30) days shall have lab testing of product preparation stability and potency.

(A) Risk Level 1: The final product preparation must be inspected for clarity, container leaks, integrity, and appropriate solution cloudiness or phase separation, particulates in solution, appropriate solution color, and solution volume. The pharmacist must verify that the product preparation was compounded accurately as to the ingredients, quantities, containers, and reservoirs. Background light or other means for the visual inspection of product preparations for any particulate and/or foreign matter must be used as part of the inspection process.

(B) Risk Level 2: All Risk Level 1 requirements must be met.

(C) Risk Level 3: In addition to all Risk Level 1 requirements, the process validation procedure shall be supplemented with a program of end-product preparation sterility testing according to a formal sampling plan. Samples shall be statistically valid to ensure that batches are sterile. A method for recalling batch product preparations shall be established if end-product preparation testing results are unacceptable. All sterile product preparations must be tested for sterility. All parenteral sterile product preparations must also be tested for pyrogenicity. Sterile products compounded from nonsterile components Risk Level 3 preparations must be quarantined and stored to maintain chemical and microbiological stability pending results of end-product preparation testing.

1. Sterility testing: Sampling for the sterility test shall occur promptly upon the completion of preparation. The sterility test, including the sampling scheme, shall be conducted according to one (1) of the recognized USP methods for the preparation.

2. Pyrogen/Endotoxin testing: Each sterile parenteral product preparation prepared from non-sterile drug components shall be tested for pyrogen or endotoxin according to recommended USP methods.

3. Potency: The pharmacy shall have a procedure for a pre-release check of the potency of the active ingredients in the compounded sterile product preparation prepared from non-sterile bulk active ingredients. The procedure shall include at least the following verifications by a pharmacist:

   A. The lot of the active ingredients used for compounding have the necessary labeling, potency, purity, certificate of analysis and other relevant qualities;

   B. All weighings, volumetric measurements, and additions of ingredients were carried out properly;
C. The compounding or control records include documentation that the fill volumes of all units available for release were checked and were correct; and

D. The final potency is confirmed by instrumental analysis for sterile product preparations that have been assigned a beyond-use date of more than thirty (30) days.

4. Filters used for sterilization shall be tested for integrity (e.g., bubble point testing) after use. Testing shall comply with manufacturer recommendations. Testing dates and results must be documented in the pharmacy’s records and reviewed by a pharmacist prior to releasing the CSP.

(D) Emergency Dispensing of a Risk Level 3 Sterile Product Preparation: When a compounded Risk Level 3 product preparation must be released prior to the completion of testing, the sterile product preparation may be dispensed pending test results. Emergency dispensing shall be defined as and comply with section (1)(O) of this rule.

13) Handling Sterile Products Outside the Pharmacy. (15) Storage, Handling and Transport
1. Risk Level 1: Sterile preparations shall be correctly packaged, stored, dispensed and distributed. The pharmacist-in-charge shall assure the environmental control of all sterile compounded product preparations shipped. Sterile product preparations shall be transported so as to be protected from excesses of temperatures and light within appropriate packaging or delivery containers that maintain necessary storage conditions to preserve the quality and integrity of sterile product preparations. The pharmacy shall follow written procedures that specify packing techniques, configuration, and materials for groups of product preparations with common storage characteristics and for specific product preparations where unique storage conditions are required to retain adequate stability and product preparation quality.
2. Risk Level 2: All requirements for Risk Level 1 must be met.
3. Risk Level 3: All requirements for Risk Level 1 must be met.

16) Point-of-Care Assembled Systems. Assembly of point-of-care assembled systems shall be considered Risk Level 1 compounding. Point-of-care assembled systems shall be assigned a beyond-use date which may exceed the beyond-use-date authorized for Risk Level 1 preparations provided the date is assigned in accordance with the manufacturer’s recommendations or labeling.
(A) When dispensed, an assembled non-activated system shall be labeled with beyond-use dates for both activated and non-activated states. The compounding record must document both dates. The beyond-use date of an assembled non-activated system shall be limited to a maximum of fifteen (15) days unless the pharmacy has documentation from the system’s manufacturer that a longer date is acceptable.

(B) Point of care assembled systems shall be assembled and stored in accordance with the manufacturer’s labeling and recommendations.

(17) General Cleaning and Disinfection Requirements. Except as otherwise provided herein, cleaning and disinfection of controlled and buffer areas, supplies and equipment shall be performed and conducted in accordance with USP Chapter 797 timeframes and procedures.

Controlled areas that do not meet ISO air classifications shall be cleaned and disinfected as required by USP Chapter 797 for segregated compounding areas. If compounding is done less frequently than the cleaning and disinfection timeframes specified in USP Chapter 797, cleaning and disinfection must occur before each compounding session begins.

(A) The pharmacy shall establish and follow written policies and procedures governing all aspects of cleaning and disinfection, including, authorized cleaning/disinfecting agents and materials, schedules of use and methods of application.

(B) Individuals shall be trained in proper cleaning and disinfection procedures prior to performing such activities. Training shall include direct visual observation of the individual’s cleaning and disinfecting process by qualified staff. The individual shall be annually reassessed for competency through direct visual observation. Documentation of the required training and training dates shall be maintained in the pharmacy’s records. Individuals who fail to demonstrate competency shall be re instructed and successfully reevaluated prior to any further cleaning or disinfection.

(C) Cleaning and disinfection activities shall be performed using approved agents and procedures described in the pharmacy’s written policies and procedures. Manufacturers’ directions for minimum contact time shall be followed.

(D) All cleaning tools (e.g., wipes, sponges, and mop heads) must be low-lint and dedicated for use in the controlled area.
(E) Primary engineering controls shall be cleaned with a germicidal agent followed by sterile alcohol. Sterile water for irrigation shall be used to dilute germicidal agents used inside the PEC that require dilution.

(F) At a minimum, the critical area shall be cleaned and disinfected prior to compounding, between batches and whenever contamination is suspected using sterile alcohol which is allowed to dry immediately prior to compounding.

18 Environmental Sampling/Testing. The pharmacy shall establish and follow proper controls to ensure environmental quality, prevent environmental contamination and maintain air quality in all ISO classified areas. Sampling/testing shall be conducted during dynamic operating conditions in accordance with USP Chapter 797. Samples must be tested for bacteria and fungus and shall comply with the following:

(A) Surface Sampling: Surface sampling shall be conducted in the PEC and in all ISO classified areas in accordance with USP Chapter 797 using media for the identification of bacteria and fungus. Surface sampling must be performed every six (6) months for Risk Level 1 and Risk Level 2 compounding and every thirty (30) days for Risk Level 3 compounding.

(B) Viable Airborne Particle Testing: Volumetric viable air sampling by impaction shall be conducted in all ISO classified environments. Each viable air sample shall sample 1,000 liters for all ISO areas. Sampling shall be conducted in accordance with USP Chapter 797 using media for the identification of bacteria and fungus. Use of settling plates alone shall not be sufficient. Viable Airborne Particle Testing must be conducted prior to initial compounding and every six (6) months thereafter. Testing shall also occur:

1. As part of the initial certification and recertification of new facilities and equipment;

2. Whenever the physical structure of the ISO classified has been altered;

3. In response to identified problems with CSPs or end-preparation testing failure; and

4. Whenever maintenance, repairs or changes to the PEC or ISO classified area may affect the airflow pattern. The date and type of maintenance, repair or change shall be documented in the pharmacy’s records.

19 Cytotoxic Drugs.

(A) The following additional requirements are necessary for those licensed pharmacies that prepare cytotoxic drugs to insure the protection of the personnel involved:
1. Cytotoxic drugs shall be compounded in a vertical flow, Class II biological safety cabinet or an isolator CACI. If used for other product preparations, the cabinet must be thoroughly cleaned;

2. Protective apparel shall be worn by personnel compounding cytotoxic drugs which shall include disposable masks, gloves and gowns with tight cuffs;

3. Appropriate safety and containment techniques for compounding cytotoxic drugs shall be used in conjunction with the aseptic techniques required for preparing sterile product preparations;

4. Appropriate disposal containers for used needles, syringes, and if applicable, cytotoxic waste from the preparation of chemotherapy agents and infectious waste from patients’ homes. Disposal of cytotoxic waste shall comply with all applicable local, state and federal requirements;

5. Written procedures for handling major and minor spills and generated waste of cytotoxic agents must be developed and must be included in the policy and procedure manual;

6. Prepared doses of cytotoxic drugs must be labeled with proper precautions inside and outside, and shipped in a manner to minimize the risk of accidental rupture of the primary container.

(15) Exemption: Pharmacists and pharmacies where sterile compounding is provided may be exempt from this rule when compounding is restricted to utilizing compounds or products that are contained only in a closed or sealed system and can be transferred or compounded within this self-contained system or topical products that require further transfer or combination in order to achieve a finished product without further modification of the product.

(16) In addition to the requirements outlined in this rule, all standards and requirements as outlined in 20 CSR 2220-2.400 must be maintained. Pharmacies that are registered with the Food and Drug Administration (FDA) are exempt from the distribution restrictions in 20 CSR 2220-2.400(12) for compounded sterile pharmaceuticals distributed with FDA’s knowledge and enforcement discretion. This exemption applies only to a twenty-four (24) hour course of therapy which is needed.

(A) To treat an emergency situation; or
(B) For an unanticipated procedure for which a time delay would negatively affect a patient outcome. In order to continue beyond twenty-four (24) hours, the pharmacy must obtain a prescription and comply with all record and labeling requirements as defined by law or regulation.

(20) Remedial Investigations: A remedial investigation shall be required if: (1) any sampling or testing required by this rule demonstrates a colony forming unit (CFU) count that exceeds USP Chapter 797 recommended action levels for the type of sampling/testing or (2) if a highly pathogenic microorganism is detected in any preparation or ISO classified area (e.g., Gram-negative rods, coagulase positive staphylococcus, molds, fungus or yeasts).

(A) CSPs and any ingredients used within the compounding process that are part of the remedial investigation shall be quarantined until the results of the investigation are known. All affected areas shall be resampled to ensure a suitable state of microbial control prior to further compounding. The pharmacy shall ensure that no misbranded, contaminated or adulterated CSP is administered or dispensed for patient use.

(B) The pharmacy shall notify the Board in writing within seven (7) days if any preparation or environmental monitoring/testing detects a highly pathogenic microorganism, regardless of CFU count.

(21) Recalls. A recall must be initiated when a CSP is deemed to be misbranded, adulterated or non-sterile or if end-preparation testing results are out of specification. The pharmacy shall notify the prescriber of the nature of the recall, the problem(s) identified and any recommended actions to ensure public health and safety. In cases where the CSP has the potential to harm the patient, the same notification shall be provided to all patients that received the recalled CSP(s).

Any recall initiated by a pharmacy shall be reported, in writing, to the board within three (3) business days.