| Title 20—DEPARTMENT OF INSURANCE, FINANCIAL |
| INSTITUTIONS AND PROFESSIONAL REGISTRATION |

**Division 2220—State Board of Pharmacy**

**Chapter 2—General Rules**

**20 CSR 2220-2.200250 Sterile Compounding**

**PURPOSE:** This rule establishes standards for the preparation, labeling, dispensing and distribution of compounded sterile preparations (CSPs).

(1) **General Applicability.** In lieu of 20 CSR 2220-2.400, the provisions of this rule shall be applicable to licensees, registrants or permit holders of the Board engaged in, or offering to engage in, compounding sterile preparations. The provisions of this rule are divided as follows:

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**In-line changes denoted in the text were suggested to the Board by the Missouri Hospital Advisory Commission.**
(2) **Definitions.**

(A) **Action Level:** A situation in which action must be taken in order to maintain compliance with this rule, USP Chapter 797 or both.

(B) **Adverse Event:** Any incident related to or resulting from the compounding process that did or may have resulted in an adverse patient outcome.

(C) **Ante-Area:** An area in which the concentration of airborne particles is controlled to meet ISO Class 8 or better air quality and that provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas.

(D) **Aseptic processing:** A mode of processing pharmaceutical and medical CSPs in an ISO Class 5 area that involves procedures designed to produce a CSP that meets a predetermined sterility assurance level and to preclude or prevent contamination by microorganisms during processing or preparation.

(E) **Batch:** Batch compounding includes: (1) compounding multiple CSP units in a single discrete process, by the same individual(s), carried out during one limited time period, (2) compounding in advance of receiving a prescription and (3) compounding a quantity in excess of the filling of an individual prescription or medication order.

(F) **Beyond-Use Date:** For purposes of this rule, the date or time after which a CSP should not be used.

(G) **Biological Safety Cabinet:** A ventilated cabinet for CSPs and for staff, preparation and environmental protection that has an open front with inward airflow for staff protection, downward high-efficiency particulate air (HEPA) filtered laminar airflow for CSP protection, and HEPA-filtered exhausted air for environmental protection.

(H) **Buffer Area:** An ISO 7 area where a primary engineering control is physically located.

(I) **CFU:** Colony forming units.

(J) **Compounding:** The preparation, incorporation, mixing, packaging or labeling of a drug or drug containing device: (1) as the result of a prescriber’s prescription or medication order based on the prescriber/patient/pharmacist relationship in the course of professional practice, or (2) in anticipation of a prescription or medication order as provided herein, or (3) for or incident to research, teaching or chemical analysis and not for sale or dispensing purposes.

(K) **Compounding Area:** The area designated for preparing CSPs and includes the ante-area and buffer area.

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Comment [A1]: The Hospital Advisory Committee (HAC) indicated the BUD definition is consistent with current industry practice/understanding.
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(L) Compounding Aseptic Containment Isolator (CACI): A compounding aseptic isolator (CAI) 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.

(M) Compounding Aseptic Isolator (CAI): A form of isolator specifically designed for compounding pharmaceutical ingredients or CSPs and to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes.

(N) Compounding Equipment: Equipment, instruments, apparatuses, and devices used to compound CSPs.

(O) Compounding Staff: Any person who engages or participates in any aspect of sterile compounding regardless of employment status.

(P) Compounded Sterile Preparation (CSP): Any low risk, medium risk or high risk CSP prepared by a pharmacy, including:

   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, irrigation solutions, ophthalmic preparations, parenteral nutrition solutions, and repackaged sterile preparations. Nasal sprays and irrigations intended for deposit in the nasal passages may be prepared as nonsterile compounds;
   
   b. An FDA approved manufactured sterile product that is either prepared according to the manufacturers’ approved labeling/recommendations or prepared differently than published in such labeling; and
   
   c. Assembling point-of-care activated systems.

(Q) Controlled Room Temperature: A controlled room temperature as defined by USP.

(R) Critical Area: An ISO Class 5 environment.

(S) Critical Site: Any surface, pathway or opening (e.g., vial septa, injection ports, beakers, needle hubs) that provides a direct pathway between a CSP or other ingredient used to compound a CSP and the air, environment or moisture or that poses a risk of touch contamination.
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(T) **Direct Compounding Area (DCA):** An area within an ISO Class 5 primary engineering control where critical sites are exposed to unidirectional HEPA-filtered air also known as first air.

(U) **Disinfectant:** An agent applied to inanimate objects that frees from infection and destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial and fungal spores.

(V) **Experiential Training:** Training based on experience and observation.

(W) **First Air:** The air exiting a HEPA filter in a unidirectional air stream that is essentially particle free.

(X) **Frozen:** The temperature range for a freezer as defined by USP.

(Y) **Hazardous Drugs:** A hazardous drug as indicated on the National Institute for Occupational Safety and Health’s (NIOSH) List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings.

(Z) **High-Efficiency Particulate Air (HEPA) filter:** A particulate filter that directs the flow of air forced through the filter in a uniform parallel flow and that is: (1) capable of retaining airborne particles and microorganisms while allowing gases to pass freely through and, (2) a minimum of 99.97% efficient when tested using 0.3-μm thermally generated particles and a photometer or rated at their most penetrating particle size using a particle counter.

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

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

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

(DD) **Line of Demarcation:** A visible line or barrier on the floor that separates a room into distinct and identifiable separate areas for the performance of sterile compounding from general pharmacy activities.

(EE) **Media-Fill Test:** A test using a growth medium to verify aseptic compounding techniques or processes that are able to produce a CSP without microbial contamination.

(FF) **Multiple-Dose Container:** A multiple-unit container for articles or CSPs that contains more than one dose of medication and an antimicrobial preservative.

(GG) **Parenteral:** A CSP intended for injection through one (1) or more layers of skin.

(HH) **Peer-Reviewed Literature:** Literature that has been evaluated by other qualified scientific, academic or qualified professionals for quality or accuracy and has been
nationnally published in a pharmaceutical, scientific, compendial or other medical publication.

(II) Pharmacy Bulk Package: A manufactured sterile product that contains many single doses intended for use in pharmacy compounding.

(JJ) Point of Care Activated 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.

(KK) Primary Engineering Control (PEC): A device that provides an ISO Class 5 environment for the exposure of critical sites when compounding sterile preparations. PECs include, but may not be limited to, laminar airflow workbenches, biological safety cabinets, compounding aseptic isolators (CAIs) and compounding aseptic containment isolators (CACIs).

(LL) Product: A commercially manufactured drug or nutrient that has been evaluated for safety and efficacy by the United States Food and Drug Administration (FDA).

(MM) Refrigerated. A cold place in which the temperature is maintained thermostatically between 2° and 8° (36°F and 46°F).

(NN) Segregated Compounding Area: A designated area or room within the pharmacy that is restricted to preparing Low Risk or Medium Risk CSPs as allowed by section 8 of this rule.

(OO) 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.

(PP) Sterile Alcohol: Alcohol that contains 70% by volume USP grade Isopropanol (isopropyl alcohol) and 30% USP purified water and is free of viable organisms.

QQ) Sterilization: A validated USP recognized process used to render a CSP free of viable organisms.

RR) Terminal Sterilization: The application of a lethal process for the purpose of achieving a predetermined sterility assurance level of less than $10^6$, or a probability of less than one nonsterile unit in one million units.

SS) 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

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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.

Unidirectional Flow: An airflow moving in a single direction in a robust and uniform manner and at a sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

(3) **Risk Levels.** The following contamination risk levels shall be established for CSPs:

A. **Low Risk:** CSPs compounded under the following conditions:

1. CSPs compounded with aseptic manipulations entirely within an ISO Class 5 or better air quality using only sterile ingredients, products, components and devices;
2. Compounding involving the transfer, measuring, mixing or manipulation of no more than three commercially manufactured packages of sterile products and no more than two entries into any one sterile container or package (e.g., bag, vial) of sterile product or administration container/device;
3. Compounding manipulations are limited to aseptically opening ampules, penetrating disinfected stoppers on vials with sterile needles/syringes, and transferring sterile liquids in sterile syringes to sterile administration devices or package containers of other sterile products/containers for storage and dispensing;
4. CSPs prepared by closed-system aseptic transfer of sterile, non-pyrogenic finished pharmaceuticals obtained from licensed manufacturers into sterile final containers obtained from licensed manufacturers, or;
5. Assembly of point-of-care activated systems.

B. **Medium Risk:** CSPs compounded under any of the following conditions:

1. Compounding involving the transfer, measuring, or mixing manipulations of more than three commercially manufactured packages/vials of sterile products or involving more than two entries into any one sterile container or package (e.g., bag, vial) of sterile product or administration container/device;
2. Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple occasions;
3. CSPs compounded with a medium risk CSP, or
4. The compounding process includes complex aseptic manipulations other than single-volume transfer and the CSP does not otherwise meet the definition of a high risk sterile CSP.

5. Medium Risk CSPs shall remain medium risk for the life of the CSP.

C. High Risk: CSPs compounded under any of the following conditions:

1. CSPs compounded from nonsterile ingredients including, but not limited to, manufactured products not intended for sterile routes of administration (e.g., oral);

2. Compounding using nonsterile components, containers, devices or equipment before terminal sterilization. If any nonsterile components are used to make a CSP, the CSP shall be deemed high risk;

3. Confirmed or suspected exposure of any of the following to worse than ISO Class 5 air quality for more than one (1) hour: (1) sterile contents of commercially manufactured products, (2) CSPs that lack effective antimicrobial preservatives or (3) any sterile surface of a device or container used for the preparation, transfer, sterilization or packaging of CSPs;

4. CSPs prepared by using an open-system transfer or open reservoir before terminal sterilization;

5. CSPs compounded with a high risk CSP, or;

6. Nonsterile water-containing CSPs that are stored for more than 6 hours before being sterilized.

7. High Risk CSPs shall remain high risk for the life of the CSP.

4) Low-Risk or Medium Risk CSP with a 12-Hour or Less Beyond-use Date: A Low Risk or Medium Risk CSP may be compounded in a segregated compounding area if:

(A) The CSP is compounded in a PEC that complies with section (11) of this rule;

(B) The CSP is assigned the lesser of a 12-hour beyond-use date or the beyond-use date recommended in the manufacturers’ package insert. The CSP may not be dispensed or distributed after the assigned beyond-use date;

(C) Individuals engaged in, or assisting with, sterile compounding follow proper hand hygiene, garbing and aseptic technique in the segregated compounding area as required by this rule; and

(D) The PEC shall be cleaned and disinfected as required by this rule.

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(5) **General Compounding Requirements.** CSPs shall be correctly packaged, handled, transported, stored, dispensed and distributed. Appropriate quality control methods shall be maintained over compounding methods at all times to ensure proper aseptic technique and compliance with all applicable state and federal law.

A. CSPs shall only be compounded pursuant to a valid patient-specific prescription, prescription drug order or medication order. However, drugs may be compounded in anticipation of a valid prescription/order based on a history of receiving valid prescriptions/orders that have been generated solely with an established pharmacist/patient/prescriber relationship and in an amount that does not exceed a **one (1) month, 45-day supply** for dispensing purposes.

B. Compounding in anticipation of receiving a prescription, prescription drug order or medication order without an appropriate history of such prescriptions/orders on file shall be considered manufacturing instead of compounding.

C. Any alteration, change or modification to the contents of a commercially manufactured over-the-counter medication shall require a valid prescription, prescription drug order or medication order from an authorized prescriber.

D. Pharmacists shall not offer CSPs to other pharmacies, practitioners or commercial entities for subsequent resale or administration, except pursuant to a patient specific prescription/order or as authorized by a Class J pharmacy permit.

E. A pharmacist or pharmacy may advertise or otherwise provide information concerning the provision of compounding services, however, no pharmacist or pharmacy shall attempt to solicit business by making specific claims about CSPs without specific testing of the CSP as compounded by the pharmacy to validate such claim.

F. Compounding of CSPs that are commercially available in the marketplace or that are essentially copies of commercially available FDA approved drug products is prohibited. This prohibition shall not apply if the drug is not commercially available due to circumstances beyond the licensee’s control (e.g., a drug shortage) or a specific medical need for a particular variation of a commercially available compound exists. Documentation of drug unavailability or the specific medical need for compounding a commercially available product shall be maintained in the pharmacy’s records.

G. The pharmacy shall maintain current drug reference materials related to CSPs that shall be electronically or physically available in the pharmacy for use and inspection by pharmacy staff.

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H. A third-party may be used to perform any testing or sampling required by this rule, provided the pharmacy and pharmacist-in-charge shall remain responsible for compliance with this rule and all applicable state/federal law.

I. Remedial Investigations: A remedial investigation shall be required if: (1) any sampling or testing required by this rule repeatedly demonstrates CFU counts that exceed USP Chapter 797 recommended action levels for the type of sampling/testing or (2) any sampling or testing demonstrates the presence of a highly pathogenic microorganism (e.g., Gram-negative rods, coagulase positive staphylococcus, molds, fungus or yeasts).

   1. 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.

   2. If highly pathogenic microorganisms are detected, the investigation shall be initiated with the assistance of a competent microbiologist, infection control professional, industrial hygienist or other competent staff and the source of contamination remedied, regardless of CFU count. The presence of a highly pathogenic microorganism shall be reported to the Board within seven (7) days after detection.

   3. Investigation procedures and any corrective/remediation methods taken shall be documented in the pharmacy’s records.

   (6) Policies and Procedures. Pharmacies shall establish and follow a written sterile compounding policy and procedure manual. The manual shall be current and shall be electronically or physically accessible to pharmacy staff. The pharmacist-in-charge shall annually review the manual for compliance and document the date of the required annual review in the pharmacy’s records. The required policy and procedure manual shall encompass all aspects of sterile compounding performed by the pharmacy and must include policies/procedures for:

   1. Compounding, labeling and dispensing CSPs;

   2. Storing, transporting and delivering CSPs;

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

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4. 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;

5. Beyond-use-dating;

6. Approved methods of sterilization and purification;

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

8. End-preparation testing, including, sampling plans;

9. Staff training and monitoring competency;

10. Reporting and investigating environmental deficiencies;

11. 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;

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

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

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

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

(7) Facility Design Requirements. Except as otherwise provided in section (8), CSPs shall be prepared in a compounding area that includes an ante area and buffer area(s).

A. Compounding Area Design Requirements: Compounding areas and surfaces shall be designed, maintained and controlled to minimize the risk of preparation contamination and the introduction, generation, accumulation and retention of particles. Compounding areas must be clean, well lit and designed in a manner that will allow effective cleaning and disinfection for the activities performed.
1. Junctures of ceilings to walls shall be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels shall be impregnated with a polymer to render them impervious and hydrophobic, and they shall be caulked around each perimeter to seal them to the support frame.

2. Dust-collecting overhangs must be avoided, such as ceiling utility pipes, ledges or windowsills.

3. Work surfaces and the surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, cleanable, non-shedding and resistant to damage by disinfectants.

4. Adequate provision for antiseptic hand cleansing shall be provided after entry into the ante area.

5. The buffer area shall not contain sources of water or floor drains. A sink with hot and cold water must be near, but not in, the buffer area.

6. The exterior lens surface of ceiling lighting fixtures shall be smooth, mounted flush or mounted/installed to promote easy cleaning.

7. Furniture in the compounding area shall be non-porous, smooth, non-shedding, impermeable, cleanable, and resistant to damage by disinfectants.

8. Temperature, humidity and pressure in the compounding area shall be controlled as necessary to ensure compliance with this rule.

9. Compounding areas and CSP storage areas (e.g., refrigerators and freezers) must have an effective temperature measuring device. At a minimum, temperatures shall be recorded and documented each day that the pharmacy is open for pharmacy activities. Alternatively, a continuous temperature monitoring system may be maintained if the system maintains ongoing documentation of temperature recordings or, if applicable, temperature alerts that are reviewed daily. Documentation of the required review shall be maintained in the pharmacy’s records or otherwise accessible to the pharmacy.

**Environmental Quality & Controls:** The pharmacy shall establish and follow proper controls to ensure environmental quality and to prevent environmental contamination.

1. Ante-areas shall be maintained in an ISO Class 8 or better air quality under dynamic conditions. Buffer areas shall be maintained in an ISO Class 7 or better air quality under dynamic conditions. Critical areas shall be maintained in an ISO Class 5 or better air quality under dynamic conditions.
2. The supply of HEPA-filtered air shall be adequate to maintain the required air quality classification. HEPA-filtered air shall be introduced in compounding areas at the ceiling and returns shall be mounted low on the wall, creating a general top-down dilution of area air with HEPA-filtered make-up air. Pharmacies licensed on the effective date of this rule with ceiling mounted returns shall be authorized to continue operations if the pharmacy maintains documentation that it is able to maintain the required ISO class conditions and environmental quality, provided that compliance with this subsection shall be required if the compounding area is moved/relocated.

3. An accurate device shall be installed to monitor the pressure differential between the buffer area and ante-area, and between the ante-area and the general environment outside the compounding area. The cascading pressure between the ISO Class 7 buffer area and the ISO Class 7/8 ante area and the general pharmacy area shall not be less than 5 pascals (0.02 inch water column) each for a total of not less than .05-inch water column from the buffer area all the way to the general pharmacy area. At a minimum, pressure results shall be recorded and documented each day that the pharmacy is open for pharmacy activities. Alternatively, a continuous monitoring system may be maintained if the system maintains ongoing documentation of pressure recordings or, if applicable, pressure alerts that are reviewed daily. Documentation of the required review shall be maintained in the pharmacy’s records or otherwise accessible to the pharmacy.

C. Relocation of or revisions to the compounding area shall constitute a pharmacy remodel and require compliance with 20 CSR 2220-2.020 remodeling requirements. Revisions include any structural changes to or replacement of the ante/buffer area walls/ceilings, sink, HEPA filtration system or heating/ventilating/air conditioning system.

(8) Segregated Compounding Areas: In lieu of a compounding area that includes an ante area and buffer area, Low Risk and Medium Risk CSPs may be compounded in a segregated compounding area within the pharmacy that complies with the following:

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A. Segregated compounding areas shall be designed, maintained and controlled to minimize the risk of preparation contamination and the introduction, generation and retention of particles inside the PEC. A segregated compounding area must be clean and well lit and designed in a manner that will allow effective cleaning and disinfection for the activities performed.

B. A line of demarcation must be established that defines and separates the segregated compounding area from other pharmacy activities/areas. The segregated compounding area shall be dedicated solely to activities directly related to sterile compounding. Segregated compounding areas shall not be used for non-sterile compounding.

C. Segregated compounding areas shall not include carpet or unsealed windows or doors that connect to the outdoors or be located in high traffic flow areas or areas in or adjacent to construction sites, warehouses, or food preparation or in any area with environmental air disturbances that may affect the PEC.

D. Areas and surfaces within the segregated compounding area shall be constructed and maintained in a manner that will minimize spaces in which microorganisms and other contaminants may accumulate. All surfaces shall be smooth, impervious, cleanable, nonshedding and resistant to damage by disinfectants, including, but not limited to, fixtures, shelving, counters, ceilings, walls and floors.

E. The segregated compounding area shall not contain sources of water or floor drains. A sink with hot and cold water must be available outside of the segregated compounding area. Sinks must be a minimum of three (3) feet but no farther than twenty-five (25) feet away from the PEC.

F. Adequate provision for performing antiseptic hand hygiene shall be provided before entry into the PEC.

G. CSP storage areas (e.g., refrigerators and freezers) must have an effective temperature measuring device. At a minimum, temperatures shall be recorded and documented each day that the pharmacy is open for pharmacy activities. Alternatively, a continuous temperature monitoring system may be maintained if the system maintains ongoing documentation of temperature recordings that are reviewed daily by pharmacy staff. The required daily staff review shall be documented in the pharmacy’s records.

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H. Low and medium risk CSPs compounded in a segregated compounding area
must be assigned a beyond-use date in compliance with section (21). The
assigned beyond-use date must be 12-hours or less unless the CSP is
compounded in a CAI or CACI that meets the following:
1. The CAI/CACI must provide isolation from the room and maintain ISO
   Class 5 air quality during dynamic operating conditions;
2. The manufacturer documents or verifies that the CAI/CACI will meet the
   requirements of this subsection when located in environments where the
   background particle counts exceed ISO Class 8 for 0.5 µm and larger
   particles; and
3. Documentation of compliance and the manufacturer’s verification is
   maintained in the pharmacy’s records.

I. Except as otherwise provided in this subsection (8), segregated compounding areas
shall comply with all other applicable provisions of this rule.

J. High Risk CSPs may not be compounded in a segregated compounding area.

K. Relocation of the segregated compounding area shall constitute a pharmacy remodel
and require compliance with 20 CSR 2220-2.020.

(9) **ISO Certification.** All ISO classified areas and each PEC shall be certified to
ensure compliance with requirements of this rule. Certification shall be performed by
qualified individuals using recognized and appropriate certification and testing equipment:
A. Certification shall be performed prior to beginning sterile compounding activities
and every six (6) months thereafter. Recertification shall be completed whenever
the physical structure of the buffer area or ante-area has been altered or any other
facility changes or any changes to the PEC occur that may affect airflow or pressure
differential. PECs shall also be recertified when the device is relocated or altered or
major service to the PEC is performed.

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B. Certification/re-certification shall be conducted in accordance with the Controlled Environment Testing Association Certification Guide for Sterile Compounding Facilities (2008), which is incorporated herein by reference. Copies of the Certification Guide for Sterile Compounding Facilities (2008) are published by, and available from, Controlled Environment Testing Association, 1500 Sunday Drive, Suite 102, Raleigh, NC 27607 or online at http://www.cetainternational.org/. This rule does not include any later amendments or additions to the Certification Guide. The pharmacy shall maintain an attestation or statement from the certifier verifying that certification/recertification was performed in compliance with Certification Guide guidelines.

C. Certification/recertification results shall be reviewed by a pharmacist once the completed results are received. Deficiencies or failures shall be investigated and corrected prior to further compounding. Corrections may include, but are not limited to, changes in the use of the affected PEC or the ongoing use/recall of CSPs. The identity of the pharmacist conducting the required review and the review date shall be documented in the pharmacy’s records.

D. An in situ air pattern analysis (e.g. smoke study) shall be required prior to initial compounding and whenever maintenance, repairs or changes to the PEC or compounding area occur that may affect the airflow pattern. The in situ air pattern analysis shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the CSP under dynamic conditions. For purposes of this section, maintenance does not include routine pre-filter changes.

(10) **Equipment.** Compounding equipment shall be clean, properly functioning and effective for their intended use and shall be consistently capable of operating properly and within acceptable limits.

A. Equipment or other supplies shall be used, maintained, calibrated and verified for accuracy according to manufacturer recommendations, unless otherwise provided by Board rules.

B. Surfaces of compounding equipment that contact ingredients or in-process materials shall not be reactive so as to alter the strength, stability, quality or purity of the CSP beyond that desired.

[15]
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C. Automated compounding devices shall be tested for content, volume and weight accuracy prior to both initial and daily use. 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.

D. In the event of improper or inaccurate functioning, the equipment/device shall not be used until the deficiency has been remedied.

E. If ingredients/CSPs with special precautions for contamination are involved (e.g., penicillin), appropriate measures must be utilized in order to prevent cross-contamination (e.g., restricting equipment use for other operations/compounding or proper cleaning).

(11) **Primary Engineering Controls (PEC):** PECs shall be properly located, operated and maintained and shall comply with the following:

A. PECs must be located in a restricted access ISO Class 7 buffer area or in a segregated compounding area that complies with this rule and shall be placed in a manner to avoid conditions that could adversely affect their operation. PECs shall be located out of traffic patterns and away from conditions that could disrupt the 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 isolator 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. When volatile hazardous drugs are prepared, the exhaust air from the isolator shall be removed by properly designed building ventilation.
F. If an isolator is used, the recovery time to achieve ISO Class 5 air quality 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.

(12) **Ingredients and Supplies.** Compounding ingredients, supplies and containers shall be properly stored and secured in a clean, dry area to prevent contamination and to maintain the CSP’s strength, quality and purity. Ingredients, drugs and supplies must be stored according to manufacturer or USP requirements and conditions.

A. Except as otherwise provided by the board by rule, pharmacists/pharmacies shall only receive, store or use drugs or active ingredients for compounding that have been received from a Missouri licensed pharmacy or drug distributor. Active ingredients must be manufactured in an FDA registered facility. Expired, misbranded, adulterated or contaminated ingredients shall not be used in compounding.

B. Active ingredients and added substances or excipients for CSPs shall be compendial grade articles or shall be accompanied by a certificate of analysis from their supplier which shall be retained in the pharmacy’s records.

C. Drugs, ingredients and supplies shall be shelved off the floor. Bulk or unformulated drug substances and added substances or excipients shall be stored in adequately labeled and tightly closed containers under temperature, humidity, and lighting conditions that are either indicated in official monographs or approved by the manufacturer.

D. Ingredients that lack a supplier's expiration date cannot be used after one (1) year after receipt. The receipt date shall be recorded on the container of the ingredient.

E. Ingredient containers and container closures shall not be reactive, so as to alter the strength, stability, quality or purity of the compounded drug beyond the desired result. Container systems shall provide adequate protection against foreseeable external factors that can cause deterioration or contamination of the CSP.

F. **Single-Dose, Multiple Dose and Pharmacy Bulk Vials/Containers.**

Single, multiple-dose and pharmacy bulk vials/containers used in compounding shall be labeled with the beyond-use date and time after which time the vial/container shall not be used.

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1. Single-dose vials/containers and pharmacy bulk vial containers exposed to ISO Class 5 or cleaner air may be used until the assigned beyond-use date which shall not exceed six (6) hours after initial needle puncture, unless otherwise specified by the manufacturer.

2. Unless otherwise specified by the manufacturer, multiple-dose vials/containers may be used until the assigned beyond-use date which shall not exceed twenty-eight (28) days after initially entering or opening (e.g., needle-puncture).

(13) **Standard Operating Procedures.** The following standard operating procedures shall be applicable to and observed in both compounding areas and segregated compounding areas:

A. Traffic flow in or around the compounding and segregated compounding areas shall be minimized and controlled.

B. Food items, chewing gum, eating, drinking and smoking are prohibited.

C. Nonessential objects that shed particles shall not be brought into the areas, including, but not limited to, pencils, cardboard cartons, paper towels, and cotton items (e.g., gauze pads).

D. Furniture, carts, supplies and equipment shall be removed from shipping cartons/containers and properly cleaned and disinfected before entering the compounding area or segregated compounding area. No shipping or other external cartons may be taken into the areas.

E. Carts/conveyances must be cleaned and disinfected before entering or returning to the ante area or buffer area.

F. Supplies and equipment shall be disinfected before entering the ISO 5 PEC by wiping the outer surface with sterile alcohol or an equivalent or superior non-residue generating disinfectant.

G. Only supplies essential for compounding shall be stored in the buffer area. Supplies or other non-essential equipment shall not be stored in the PEC.

(14) **Personal Cleansing and Garbing.** Individuals engaged in, or assisting with, CSPs shall be trained and demonstrate competence in proper personal cleansing, garbing and gloving procedures. Competence must be documented and assessed through direct observation.

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1. Except as otherwise provided herein, personal cleansing and garbing shall comply with USP Chapter 797. **Sterile gloves shall be worn when compounding, including, over isolator gloves if applicable.**

2. In lieu of full garbing At a minimum, compounding personnel using a CAI or CACI to compound non-hazardous drugs shall at a minimum don facial masks, non-shedding gowns and sterile gloves over the isolator gloves during compounding. Non-shedding gowns and gloves shall also be used during material handling. This section shall only be applicable if the CAI/CACI provides isolation from the room and is certified to maintain ISO Class 5 air quality during dynamic operating conditions as defined in 8 (G).

(15) Aseptic Processing. CSPs shall be prepared in a manner that maintains sterility and minimizes contamination and the introduction of particulate matter. Appropriate aseptic technique shall be utilized at all times.

A. Aseptic processing must be performed in at least ISO Class 5 conditions. Critical sites shall not be exposed to touch/contact contamination or worse than ISO Class 5 air.

B. Prior to compounding, ingredients and packaging shall undergo a visual unit-by-unit inspection to verify the components are free from defects and otherwise suitable for their intended use. Ingredients shall not be used if: (1) evidence of deterioration or contamination exists or is suspected, (2) an unauthorized break in any container, closure or seal is detected, (3) the contents do not have the expected appearance, aroma, or texture or (4) the beyond-use date or expiration date has been exceeded.

C. Items/equipment must be disinfected before placement in the PEC. Syringes, needles and tubing in outer wraps designed to keep them sterile until opening are not required to be individually disinfected if opened in an ISO Class 5 work area.

D. Only materials and equipment essential for aseptic compounding shall be placed in the primary engineering control. Materials and equipment shall be arranged in the DCA to allow a clear, uninterrupted path of HEPA-filtered air over critical sites at all times during compounding. Compounding staff shall not interrupt, impede, or divert flow of first-air from HEPA filters to critical sites.

E. All critical sites shall be wiped vigorously in one direction with sterile alcohol and allowed to air dry before being punctured or used.

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F. Wetted gauze pads or other particle-generating material shall not be used to
disinfect sterile entry points. If sterile, single-use alcohol prep pads are used, the
surface of the pad shall not contact any other object before contacting the surface
of the entry point.

G. Before compounding, staff shall visually confirm that ingredients used and
measured in syringes match the prescription or medication order being
compounded. Density or specific gravity values programmed in automated
compounding devices shall be confirmed to be correct before and after
delivering volumes of the liquids assigned to each channel or port.

(16) Additional Aseptic Technique Requirements for High Risk CSPs. In addition to
section (15), the following requirements for high risk CSPs are applicable:

A. Presterilization procedures for High Risk CSPs, such as weighing and mixing,
shall be completed in no worse than an ISO Class 8 environment.

B. All non-sterile equipment that is to come in contact with the sterilized final high
risk CSP shall be sterilized before introduction into the buffer area.
Additionally, all nonsterile measuring, mixing and purifying devices shall be
rinsed thoroughly with sterile water for irrigation, disinfected and thoroughly
drained or dried before being used to compound.

C. All high risk CSPs must be sterilized before dispensing or distribution via a
method recognized for the CSP type by USP Chapter 1211.

1. Water-containing CSPs that are nonsterile during any phase of the
compounding procedure shall be sterilized within 6 hours after completing
the CSP.

2. 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.

3. Commercially available filters shall be approved for human use
applications in sterilizing pharmaceutical fluids. Sterile filters used to
sterilize CSPs shall be pyrogen free and a pore size of 0.20 to 0.22
microns. They shall be certified by the manufacturer to retain at least 10 to
the seventh microorganisms of a strain of Brevundimonas (pseudomonas)
diminue. The pharmacy must maintain this documentation for each filter
utilized in the sterilization of CSPs.

[20]
D. Final containers used for high risk CSPs must be sterile and capable of maintaining
CSP integrity until the beyond-use date. Sterilization methods must be based on
the properties of the CSP.

(17) **End Preparation Testing.** End preparation testing for CSPs shall be conducted as
required by this section. Finished CSPs must be quarantined pending results of any
required testing. Except as otherwise allowed by this rule, CSPs shall not be
dispensed until all end-preparation testing results are final and meet required results.
Quarantine dates and time periods must be documented in the pharmacy’s records.
The results of any end preparation testing (e.g., sterility, endotoxin and potency) shall
be reviewed by a pharmacist

A. **Low Risk:** Low Risk CSPs shall undergo sterility testing if the beyond-use date
exceeds 48 hours at controlled room temperature, 14 days at refrigerated
temperature, or 45 days in solid frozen state at -25° to -10° Celsius or colder.

B. **Medium Risk:** Medium Risk CSPs shall undergo sterility testing if the beyond-
use date exceeds more than 30 hours at controlled room temperature, 9 days at
refrigerated temperature, or 45 days in solid frozen state at - 25° to -10° Celsius
or colder.

C. **High Risk:** At a minimum, the following testing shall be required for high risk
CSPs:

1. **Sterility Testing:** All High Risk CSPs must be tested for sterility
without exception in accordance with a method recommended or
required by USP Chapter 71. Samples for sterility testing shall be
collected immediately after CSP completion. The sampling plan shall
comply with USP Chapter 71, Tables 2 and 3.

2. **Bacterial Endotoxin (Pyrogen) Testing:** All high risk parenteral,
epidural or intrathecal CSPs shall be tested for bacterial endotoxins using
a USP Chapter 85 recognized method for bacterial endotoxin testing.

3. **Potency Testing:** Final potency shall be confirmed by validated
instrumental analysis for each CSP that has been assigned a beyond-use
date of more than thirty (30) days. The final CSP shall maintain a
potency within monograph limits for USP articles or, in the absence of a
monograph, of +/− 10%. Testing of each CSP/batch is not required once
potency has been established for the specific CSP if no modifications
have been made to the compounding procedure, process or formula (e.g.,
ingredient sources, batch size or equipment).

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4. **Antimicrobial Effectiveness Testing**: All high risk multiple dose CSPs must be tested for antimicrobial effectiveness. Testing must comply with USP Chapter 51. Testing of each CSP/batch is not required once antimicrobial effectiveness has been established for the specific CSP if no modifications have been made to the compounding procedure, process or formula (e.g., ingredient sources, batch size or equipment).

D. **Emergency Dispensing**: CSPs may be dispensed for immediate administration to a patient prior to receiving the results of the testing required by this rule if:

1. No alternative product/CSP is available and the patient will be exposed to negative risks if therapy is delayed. The reason for the emergency dispensing shall be documented in the pharmacy’s records; and

2. The prescriber/ordering health care provider is informed the CSP will be dispensed prior to receiving test results and approves the dispensing. Prescriber/provider approval shall be documented in the pharmacy’s records. A separate authorization from the prescriber/provider is required for each emergency dispensing.

3. This section shall not be construed to exempt any person or entity from performing any testing required by this rule.

(18) **Labeling**. Except as otherwise provided herein, CSPs dispensed to patients shall be labeled in accordance with section 338.059, RSMo, and with the following supplemental information affixed to the CSP:

A. Beyond-use date;

B. Compounding date, if different from the date the prescription is filled;

C. The actual name of each active or therapeutic ingredient;

D. The amounts or concentration of all active or therapeutic ingredients;

E. Total volume;

F. Storage requirements;

G. If given to a patient, the pharmacy’s phone number and a statement indicating “This is a compounded preparation”;

H. Any CSP or device specific instructions for use including the route of administration and the rate of administration, and;

I. Auxiliary labels when applicable.

J. When a CSP is packaged in individual containers and dispensed to the patient in a labeled outer container as required above, the individual containers must be labeled with the CSP name, lot number and beyond use date.

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Final Verification. Prior to dispensing, a pharmacist shall physically verify that the CSP has been properly prepared, sterilized, packaged and labeled and that all required end-preparation testing has been performed and documented. The following quality assurance measures shall be performed by a pharmacist before a CSP is dispensed or distributed:

1. Compounding records shall be reviewed to verify that the correct measurements, volumes, quantities, calculations and sterilization procedures were used. If an automated compounding device was used, a pharmacist must verify proper calibration and verify that data entered into the device was correct and accurate, including, but not limited to, density or specific gravity values.

2. The final CSP must be visually inspected for physical integrity, clarity and expected appearance. Additionally, each compounded unit shall be inspected against lighted white or black background or both for evidence of visible particulates or other foreign matter. Visual inspection shall not be required for hazardous drugs if the inspection may be harmful.

Beyond-Use Dating. All CSPs must be assigned a beyond-use date. Beyond-use dates shall be determined from the date or time the CSP is compounded. The nature of the drug and its degradation mechanism, drug stability, sterility considerations, antimicrobial effective testing results, container packaging, storage conditions and the intended duration of therapy shall be considered. CSPs shall not be dispensed past the assigned beyond-use date.

A. For Low and Medium Risk CSPs, beyond-use dates shall be assigned based on any of the following resources: USP Chapter 797, the manufacturer’s labeling, direct testing using validated testing methods, compendial references or peer-reviewed literature based on CSP-specific experimental studies/testing.
B. High Risk CSPs: Beyond-use dates not specifically referenced in the manufacturer’s approved labeling or in a USP monograph or not established by CSP specific instrumental analysis shall be limited to thirty (30) days after compounding. High risk CSPs with beyond-use dates greater than thirty (30) days shall undergo laboratory testing using validated methods prior to release to verify stability (sterility and potency) for the maximum beyond-use date. Testing of each CSP/batch is not required once stability has been established for the specific CSP as required by this subsection and no modifications have been made to the compounding procedure, process or formula.

(21) **Point-of-Care Activated Systems.** In addition to other applicable requirements:

A. Point-of-Care activated systems shall be assembled within an ISO Class 5 environment and assigned a beyond-use date in accordance with the manufacturer’s recommendations or labeling.

B. 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. 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.

C. Point of care activated systems shall be stored in accordance with the manufacturer’s labeling and recommendations.

(22) **Storage.** CSPs shall be stored strictly in accordance with the conditions stated on the ingredient label, if applicable. Adulterated, misbranded, expired or contaminated CSPs shall be segregated and quarantined from the compounding area and other drug inventory and properly disposed of.

A. If storage at controlled room temperature is directed, an article may alternatively be stored and distributed in a cool place as defined by USP, unless otherwise specified in the individual USP monograph or on the label.

B. Temperature excursions shall be allowed as permitted or recognized by USP.

C. Any excess CSP shall be stored and accounted for under conditions dictated by the CSP’s composition and stability characteristics to ensure its strength, quality and purity. Excess CSPs shall be labeled with the name and strength of the drug(s), an in-house lot number, compounding date, volume and beyond-use date.

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(23) **Packaging and Delivery.** CSPs shall be packaged, stored, transported and delivered in a manner that will preserve the physical integrity, sterility, stability, and purity of the CSP. Packaging shall be selected that simultaneously protects CSPs from damage, leakage, contamination, and degradation and protects individuals transporting packed CSPs from harm. Prescription delivery shall comply with applicable provisions of 20 CSR 2220-2.013. The pharmacy shall establish a mechanism for the patient/ultimate user to report packaging or transporting concerns to the pharmacy and documenting any reports received.

(24) **Compounding Log:** A compounding log shall be maintained that records/documents each CSP made. The compounding log shall be maintained at the pharmacy separate from the prescription record, either electronically or in writing, and shall be immediately available upon request. Each compounding entry shall be verified and manually or electronically signed or initialed by the verifying pharmacist. The following information shall be recorded in the compounding log for each CSP:

(A) Compounding date;
(B) The identity of the compounder and the pharmacist performing the final verification required by section (19) of this rule, if different;
(C) A list of ingredients and their amounts by weight or volume;
(D) Description of the compounding process, including, the compounding method, formula or recipe and, if necessary for proper compounding, the order of adding ingredients. For High Risk CSPs, the log must also include sterilization and testing methods. The information required by this subsection may be separately maintained in the pharmacy’s records if immediately available on request;
(E) The identity of the source, lot number and the expiration or beyond-use date of each ingredient, as well as an in-house lot number and a beyond-use date for batch bulk CSPs;
(F) An identifying prescription number or a readily retrievable unique identifier;
(G) The beyond-use date assigned to the CSP and placed on the label;
(H) For High Risk CSPs, the type of container and container lot number, if applicable; and
(I) Any CSP storage conditions included on the CSP label or in materials provided to the patient.

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Aseptic Manipulation Training and Assessment. Compounding staff shall be skilled and trained to accurately and competently perform the duties assigned and to operate any equipment used. At a minimum, compounding staff must undergo Aseptic Competency Training and an Aseptic Technique Skill Assessment as follows:

A. Aseptic Competency Training: Aseptic competency training shall include both didactic and experiential training and may be tailored to the pharmacy’s activities. Didactic training must include an instructional component along with a testing or evaluation method to verify competency. Staff shall be trained to perform the duties assigned when the level of sterile activity or sterile compounding methods change. Aseptic competency training must be completed for all risk levels prior to initial compounding and every twelve (12) months thereafter.

B. Aseptic Technique Skill Assessment: A practical aseptic technique skill assessment shall be completed for all individuals compounding sterile preparations to verify aseptic competency. The assessment must include glove fingertip sampling, media-fill testing and a direct visual evaluation of the individual’s competency. The 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;


C. The required Aseptic Technique Skill Assessment must be completed for staff compounding low or medium risk CSPs prior to initial compounding and every twelve (12) months thereafter. For staff compounding high risk CSPs, the assessment must be completed prior to initial compounding and every six (6) months thereafter.
D. Compounding staff shall successfully pass all training and assessments. Staff who fail to demonstrate competency or whose glove fingertip sampling or media-fill tests demonstrate one or more units of visible microbial contamination shall be retrained and re-evaluated to ensure correction of all deficiencies prior to beginning or continuing any further compounding. The retraining and revaluation shall be documented in the pharmacy’s records.

E. Training and assessment dates along with the results of the required practical aseptic technique skill assessment, glove fingertip sampling and media-fill testing shall be reviewed and documented by the pharmacist-in-charge or his/her designee.

(26) **Glove Fingertip Sampling.** Compounding staff shall undergo and successfully complete both initial and ongoing glove fingertip sampling to assess compliance with gloving and aseptic processing. Initial and ongoing fingertip sampling shall be completed in accordance with USP Chapter 797 procedures, timeframes and methods. Glove fingertip sampling shall be conducted following each required media-fill test.

(27) **Media-Fill Testing.** Pharmacies shall establish and follow policies and procedures for conducting media-fill testing to assess the quality of aseptic skills/techniques of compounding staff. Media-Fill tests shall be conducted as part of the required aseptic technique skill assessment and shall include a minimum of three media-fill units using the same container or closure. Media-fill tests shall represent the most challenging or stressful conditions actually encountered by the personnel being evaluated. Initial and ongoing media-fill testing shall be completed in accordance with USP Chapter 797 recommended procedures and methods for the applicable risk level(s).

(28) **Environmental Sampling.** Environmental sampling shall be routinely conducted in all ISO classified areas to evaluate air quality compliance and microbial bio burden levels. Sampling shall be conducted during dynamic operating conditions in accordance with USP Chapter 797. Surface samples and viable airborne particle samples shall be tested for bacteria, fungus, mold and yeast. Sampling shall occur as follows:

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A. **Surface Sampling**: Surface sampling shall be conducted in accordance with USP Chapter 797 using both general growth media and fungal specific media. Surface sampling for pharmacies engaged in Low Risk and Medium Risk must be performed every thirty (30) days. For High Risk compounding, surface sampling shall be performed every fourteen (14) days.

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. Each sample location shall be tested with both general growth media (e.g., tryptic soy agar) and fungal specific media (e.g., malt extract agar or saboraud dextrose agar) on plates of at least 55mm in size. 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 of new facilities and equipment;
2. Whenever the physical structure of the compounding area has been altered;
3. As part of the recertification of facilities and equipment;
4. In response to identified problems with CSPs or end-preparation testing failure; and
5. Whenever maintenance, repairs or changes to the primary engineering control(s) or compounding area may affect the airflow pattern. The date and type of maintenance, repair or change shall be documented in the pharmacy’s records;

C. **Non-Viable Airborne Particle Testing**: Non-viable air sampling shall be performed using a volumetric device in compliance with USP Chapter 797. Non-Viable Airborne Particle Testing must be conducted prior to initial compounding and every six (6) months thereafter.

D. **Pressure Differential**: Pressure differential monitoring shall be required for all sterile compounding areas to ensure compliance with section (7)(B) of this rule.

(29) **General Cleaning and Disinfection Requirements**: The pharmacy shall establish and follow written policies and procedures governing all aspects of cleaning and disinfection. Except as otherwise provided herein, the following requirements shall be applicable:

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Comment [A11]: HAC members indicated the increased surface sampling requirements will be pricey as some pharmacies may have to outsource sampling. Other members indicated the cost would be minimal relative to the likely risk/liability. Members suggested matching any new USP recommendation for sampling.
A. Compounding areas and segregated compounding areas shall be free of infestation by insects, rodents and other vermin. Trash shall be disposed of in a timely and sanitary manner.

B. Cleaning and disinfection shall be performed and conducted in accordance with USP Chapter 797 timeframes and procedures, except as otherwise provided herein.

C. Individuals responsible for cleaning and disinfecting shall be trained in proper cleaning and disinfection procedures and mechanisms prior to performing cleaning/disinfection 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 retrained and successfully reevaluated prior to cleaning or disinfecting the compounding or segregated compounding area.

D. Cleaning, disinfection and mopping activities shall be performed using approved agents and procedures described in the pharmacy’s written policies and procedures. Cleaning and disinfecting agents shall be selected based on compatibility, effectiveness and the absence of inappropriate or toxic residues. Manufacturers' directions or published peer-reviewed literature for minimum contact time shall be followed.

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 DCA shall be cleaned and disinfected prior to compounding, between batches and whenever contamination is suspected using sterile alcohol or an equivalent or superior agent which is allowed to dry immediately prior to compounding.

G. Segregated Compounding Areas: Floors and work surfaces within the line of demarcation shall be cleaned and disinfected daily or immediately prior to compounding if not used daily. Shelving and storage areas shall be cleaned and disinfected monthly.

(30) Quality Assurance. Sterile compounding pharmacies shall establish and follow a written quality assurance program for monitoring and evaluating the quality of compounding activities.

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A. At a minimum, the quality assurance program shall include procedures for monitoring and tracking infection rates, adverse drug events, CSP recalls and complaints from prescribers, patients or other individuals or entities.

B. The quality assurance plan shall delineate the individuals responsible for each aspect of the quality assurance program either by name or position title.

C. The quality assurance plan shall be maintained at the pharmacy or readily retrievable upon request. The pharmacist-in-charge shall annually review the quality assurance program and document the review in the pharmacy’s records.

(31) **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).

A. Patient and prescriber notifications required by this section shall be made [initiated] as soon as reasonably practicable but in no event later than one (1) business day of the recall. The date and manner of notification shall be documented in the pharmacy’s records.

B. If a patient recall notification is unsuccessful, the pharmacy shall mail notification to the patient within the required one (1) business day timeframe.

C. Recalls initiated pursuant to this section shall be reported to the board in writing within three (3) business days.

D. If recall notification cannot be conducted as required herein, the pharmacy may submit to the Board a written plan to extend the notification period. The request must include a description of the nature of the recall, the potential number of patients affected, the reason(s) supporting the extension request and a proposed timeframe for completing the required notifications.

**Comment [A12]:** Several HAC members indicated a 1-day business notification would be a hardship and potentially impossible for some hospitals/pharmacies. Concerns were specifically raised about hospitals serving large patient populations or serving indigent patients without a stable address. Suggestions included:

- Leave manner of notification open but require documentation when notification can’t be made.
- Only require notification to be “initiated” within 1 day.
A. Patient and prescriber notifications required by this section shall be made as soon as reasonably practicable. The date and manner of notification shall be documented in the pharmacy’s records.

B. Recalls initiated pursuant to this section shall be reported to the board in writing within three (3) business days. The request must include a description of the nature of the recall, the potential number of patients affected and a designation of when the required notifications were or will be made.
Record Keeping. The pharmacy shall maintain the following records:

A. Aseptic competency training and aseptic technique skill assessment dates and results;
B. Testing dates and results for glove fingertip sampling, media-fill tests and end-CSP testing;
C. Environmental sampling dates and results, including, any corrective efforts taken;
D. Required refrigerator and temperature logs;
E. Cleaning and disinfection records that document compliance with this rule;
F. Equipment calibration dates and results and maintenance reports;
G. Certificates of analysis for compounding ingredients, if applicable;
H. Certification records for PECs and sterile compounding areas;
I. Copies of any manufacturer equipment standards that are relied upon to maintain compliance with this rule;
J. Batch CSP files;
K. For high risk CSPs, sterilization, quarantine and ingredient validation records;
L. Emergency dispensing records as required by subsection (17), including, documentation of prescriber authorization and the dates of such authorization;
M. CSP recall records, including, dates, patients affected and any investigation, corrective actions or recall notifications made; and
N. All other records required by this rule or governing law.

Except as otherwise provided herein, records and reports required by this rule shall be either electronically or physically maintained for two (2) years. Records shall be readily retrievable and subject to inspection by the Board of Pharmacy or its agents upon request. 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.

P. Prescription records shall be maintained in compliance with Missouri law and the rules of the Board.

Hazardous Drugs. Hazardous drugs shall be prepared, stored and compounded in accordance with the USP-NF. Compounding staff engaged in handling, preparing or compounding hazardous drugs shall be trained as required by USP-NF and the rules of the Board. The following additional requirements shall be implemented to insure the protection of the staff involved:

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A. Hazardous drugs/CSPs shall be stored, handled and prepared under conditions that protect workers and other staff.

B. Appropriate disposal containers shall be available for used needles, syringes, and if applicable, hazardous waste from the CSP of chemotherapy agents and infectious waste. Disposal of hazardous waste shall comply with all applicable local, state and federal requirements;

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

D. Prepared doses of hazardous 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.

(34) **Applicability.** If a conflict between this rule and the applicable provisions of USP exists, the requirements of this rule shall apply unless otherwise indicated herein. In the interest of public protection, the use of an alternative technology, technique, material or procedure not specifically included in this rule or USP shall only be authorized if an exemption is approved by the Board. The exemption request must be in writing and must include:

(A) A description of the exemption requested and the reasons supporting the request;

(B) Testing or other scientific evidence demonstrating the technology, technique, material or procedure is equivalent or superior with statistical significance to those included in this rule or USP. Peer-reviewed literature shall be insufficient without actual proof of the testing or other scientific evidence methods and results supporting the request;

(C) A detailed statement of any hardship or public harm that will occur if the exemption is not granted, and;

(D) Any other evidence requested by the Board.
Effective Date. Compliance with this rule shall be required within six (6) months after this rule becomes effective. Pharmacies that hold a current and active pharmacy permit on the effective date of this rule shall be granted an additional one (1) year after such effective date to comply with the provisions of section (7) or (8) of this rule that require physical or structural changes to the pharmacy to be compliant. The one (1) year exemption shall not apply to pharmacies that undergo a change of ownership or change of location.

A pharmacy may submit a written request to the Board for a variance from the physical or structural requirements of this rule. The Board may revoke or deny a request if the requested variance would detrimentally impact the health, safety or welfare of patients, staff or the public or result in an unsterile product, as determined by the Board. If approved, the Board’s written determination shall identify a variance expiration date. The pharmacy shall inform the Board in writing within thirty (30) days of any change in the conditions warranting the variance request. Variance requests shall contain:

(A) The section number of the requirement(s) in question;

(B) Specific reasons why compliance with the requirement(s) would impose an undue hardship on the public or the pharmacy, including an estimate of any additional cost which might be involved;

(C) An explanation of any extenuating factors which may be relevant;

(D) A complete description of the steps, safeguards or processes that are in place or will be taken to ensure the sterility of CSPs or to safeguard the health, safety and welfare of the patient, staff or public if the variance request is granted; and

(E) The length of time the variance is requested.

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