

**OPEN MINUTES**  
**Missouri Board of Pharmacy**  
**Sterile Compounding Sub-Committee**  
**Telephone Conference Call**  
**September 23, 2015**

Members of the Missouri Board of Pharmacy met via conference call during the times and dates stated in the following minutes. A quorum of the Board was not present or anticipated for the meeting. However, public notice of the meeting was provided to ensure full compliance with Chapter 610, RSMo. The meeting was called to order by Executive Director Kimberly Grinston at 4:03 p.m. on September 23, 2015.

**Board Members Present**

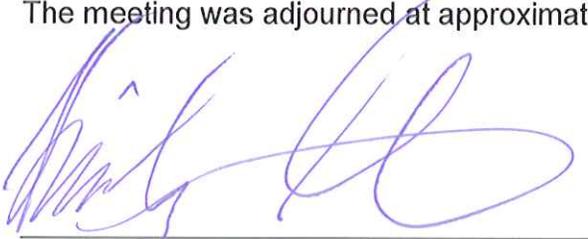
Douglas Lang, R.Ph.,  
Christian Tadrus, PharmD, Vice-President

**Staff Present**

Kimberly Grinston, Executive Director  
Tom Glenski, Chief Inspector

**DISCUSSION:** Kimberly Grinston reported that revisions from the 8/26/15 rule review meeting have been incorporated into the current proposed draft as well as additional changes by Ms. Grinston and Tom Glenski. Discussion was held. Substantive comments and suggested changes discussed during the meeting are included in the attached revised draft. Participating Board members agreed to submit the proposed draft for full Board review but noted several provisions were included for Board discussion purposes only and would likely be revised based on public/board comments.

The meeting was adjourned at approximately 8:07 p.m.



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KIMBERLY A. GRINSTON  
EXECUTIVE DIRECTOR

Date Approved: 1/12/2016

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

Division 2220—State Board of Pharmacy  
Chapter 2—General Rules

20 CSR 2220-2.200 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 (CSPs). The provisions of this rule are divided as follows:

(1) General Applicability	36	(18) Labeling
(2) Definitions	37	(19) Final Verification
(3) Risk Levels	38	(20) Beyond-Use Dating
(4) Low Risk CSPs with 12-Hour or Less Beyond-Use Date	38	(21) Point-of-Care Activated Systems
(5) General Compounding Requirements	40	(22) Storage
(6) Policies and Procedures	41	(23) Packaging and Delivery
(7) Facility Design Requirements	42	(24) Compounding Log
(8) Segregated Compounding Areas	43	(25) Aseptic Manipulation Training & Assessment
(9) ISO Certification	44	(26) Glove Fingertip Sampling
(10) Equipment	45	(27) Media-Fill Testing
(11) Primary Engineering Controls	46	(28) Environmental Sampling
(12) Ingredients & Supplies	47	(29) Facility Cleaning and Disinfection Requirements
(13) Standard Operating Procedures	48	(30) Quality Assurance
(14) Personal Cleansing and Garbing	49	(31) Recalls
(15) Aseptic Processing	50	(32) Record Keeping
(16) Additional Aseptic Technique Requirements for High Risk CSPs	51	(33) Hazardous Drugs
(17) End Preparation Testing	52	(34) Applicability
	53	
	54	

(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.

- 1 (C) **Ante-Area:** An area in which the concentration of airborne particles is controlled  
2 to meet ISO Class 8 or better air quality and that provides assurance that pressure  
3 relationships are constantly maintained so that air flows from clean to dirty areas.
- 4 (D) **Aseptic processing:** A mode of processing pharmaceutical and medical CSPs in  
5 an ISO Class 5 area that involves procedures designed to produce a CSP that  
6 meets a predetermined sterility assurance level and to preclude or prevent  
7 contamination by microorganisms during processing or preparation.
- 8 (E) **Batch:** Batch compounding includes: (1) compounding multiple CSP units in a  
9 single discrete process, by the same individual(s), carried out during one limited  
10 time period, (2) compounding in advance of receiving a prescription and (3)  
11 compounding a quantity in excess of the filling of an individual prescription or  
12 medication order.
- 13 (F) **Beyond-Use Date:** For purposes of this rule, the date or time after which a CSP  
14 should not be ~~dispensed, stored or transported~~ used.
- 15 (G) **Biological Safety Cabinet:** A ventilated cabinet for CSPs and for staff,  
16 preparation and environmental protection that has an open front with inward  
17 airflow for staff protection, downward high-efficiency particulate air (HEPA)  
18 filtered laminar airflow for CSP protection, and HEPA-filtered exhausted air for  
19 environmental protection.
- 20 (H) **Buffer Area:** An ISO 7 area where a primary engineering control is physically  
21 located.
- 22 (I) **CFU:** Colony forming units.
- 23 ~~(J) **Cold Temperature:** A temperature that is cold as defined by USP.~~
- 24 ~~(K)~~(J) **Compounding:** The preparation, incorporation, mixing, packaging or  
25 labeling of a drug or drug containing device: (1) as the result of a prescriber's  
26 prescription or prescription drug order based on the prescriber/patient/pharmacist  
27 relationship in the course of professional practice, or (2) in anticipation of a  
28 prescription drug or medication order as provided herein, or (3) for or incident to  
29 research, teaching or chemical analysis and not for sale or dispensing purposes.
- 30 ~~(L)~~(K) **Compounding Area:** The area designated for preparing CSPs and includes  
31 the ante-area and buffer area.
- 32 ~~(M)~~(L) **Compounding Aseptic Containment Isolator (CACI):** A compounding  
33 aseptic isolator (CAI) designed to provide worker protection from exposure to  
34 undesirable levels of airborne drugs throughout the compounding and material  
35 transfer processes and to provide an aseptic environment for CSPs.
- 36 ~~(N)~~(M) **Compounding Aseptic Isolator (CAI):** A form of isolator specifically  
37 designed for compounding pharmaceutical ingredients or CSPs and to maintain an  
38 aseptic compounding environment within the isolator throughout the compounding  
39 and material transfer processes.

1 | ~~(O)~~(N) **Compounding Equipment:** Equipment, instruments, apparatuses, and  
2 | devices used to compound CSPs.

3 | ~~(P)~~(O) **Compounding Staff:** Any person who engages or participates in any aspect  
4 | of sterile compounding regardless of employment status.

5 | ~~(Q)~~(P) **Compounded Sterile Preparation (CSP):** Any low risk, medium risk or  
6 | high risk CSP prepared by a pharmacy, including:

7 | a. Compounded biologics, diagnostics, drugs, nutrients, and  
8 | radiopharmaceuticals that must or are required to be sterile when they are  
9 | administered to patients, including, but not limited to the following dosage  
10 | forms: bronchial and inhaled nasal preparations intended for deposition in  
11 | the lung, baths and soaks for live organs and tissues, epidural and intrathecal  
12 | solutions, bladder/wound solutions, injectables, implantable devices and  
13 | dosage forms, inhalation solutions, intravenous solutions, irrigation  
14 | solutions, ophthalmic preparations, parenteral nutrition solutions, and  
15 | repackaged sterile preparations. Nasal sprays and irrigations intended for  
16 | deposit in the nasal passages may be prepared as nonsterile compounds;

17 | b. An FDA approved manufactured sterile product that is either prepared  
18 | according to the manufacturers' approved labeling/recommendations or  
19 | prepared differently than published in such labeling; and

20 | c. Assembling point-of-care activated systems.

21 | ~~(R)~~(Q) **Controlled Room Temperature:** A controlled room temperature as defined  
22 | by USP.

23 | ~~(S)~~(R) **Critical Area:** An ISO Class 5 area where products, CSPs, surfaces or  
24 | containers are exposed to the environment.

25 | ~~(T)~~(S) **Critical Site:** Any surface, pathway or opening (i.e., vial septa, injection  
26 | ports, beakers, needle hubs) that provides a direct pathway between a CSP or other  
27 | ingredient used to compound a CSP and the air, environment or moisture or that  
28 | poses a risk of touch contamination.

29 | ~~(U)~~(T) **Direct Compounding Area (DCA):** A critical area within an ISO Class 5  
30 | primary engineering control where critical sites are exposed to unidirectional  
31 | HEPA-filtered air also known as first air.

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

35 | ~~(W)~~(V) **Experiential Training:** Training based on experience and observation.

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

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

1 | ~~(Z)~~(Y) **Hazardous Drugs:** A hazardous drug as indicated on the National Institute  
2 | for Occupational Safety and Health's (NIOSH) List of Antineoplastic and Other  
3 | Hazardous Drugs in Healthcare Settings.

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

10 | ~~(BB)~~(AA) **ISO Class 5:** An area with less than 3,520 particles (0.5  $\mu$ m and larger in  
11 | size) per cubic meter.

12 | ~~(CC)~~(BB) **ISO Class 7:** An area with less than 352,000 particles (0.5  $\mu$ m and larger in  
13 | size) per cubic meter.

14 | ~~(DD)~~(CC) **ISO Class 8:** An area with less than 3,520,000 particles (0.5  $\mu$ m and larger  
15 | in size) per cubic meter.

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

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

22 | ~~(GG)~~(FF) **Multiple-Dose Container:** A multiple-unit container for articles or CSPs  
23 | that contains more than one dose of medication.

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

26 | ~~(I)~~(HH) **Peer-Reviewed Literature:** Literature that has been evaluated by other  
27 | qualified scientific, academic or qualified professionals for quality or accuracy and  
28 | has been nationally published in a pharmaceutical, scientific, compendial or other  
29 | medical publication.

30 | ~~(J)~~(II) **Point of Care Activated System:** A closed system device that creates a  
31 | physical barrier between diluents, fluids or other drug components and is designed  
32 | to be activated by the end user by allowing the components to mix prior to  
33 | administration.

34 | ~~(KK)~~ **Preparation:** A compounded sterile preparation prepared by a pharmacy.

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

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

4 | ~~(MM)~~(LL) **Refrigerated.** A cold place in which the temperature is maintained  
 5 | thermostatically between 2° and 8° (36°C and 46°F).

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

9 | ~~(OO)~~(NN) **Single-Dose/Single-Unit Container/vial:** A container/vial of liquid  
 10 | medication intended for ~~parenteral~~ administration that is meant for use in a single  
 11 | patient for a single case, procedure or injection.

12 | ~~(PP)~~(OO) **Sterile Alcohol:** Alcohol that contains 70% by volume USP grade  
 13 | Isopropanol (isopropyl alcohol) and 30% USP purified water and is free of viable  
 14 | organisms.

15 | ~~(QQ)~~(PP) **Sterilization:** A validated USP recognized process used to render a CSP free  
 16 | of viable organisms.

17 | ~~(RR)~~(QQ) **Terminal Sterilization:** The application of a lethal process for the purpose  
 18 | of achieving a predetermined sterility assurance level of less than  $10^{-6}$ , or a  
 19 | probability of less than one nonsterile unit in one million units.

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

26 | ~~(TT)~~(SS) **Unidirectional Flow:** An airflow moving in a single direction in a robust  
 27 | and uniform manner and at a sufficient speed to reproducibly sweep particles away  
 28 | from the critical processing or testing area.

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

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

- 32 | 1. CSPs compounded with aseptic manipulations entirely within an ISO  
 33 | Class 5 or better air quality using only sterile ingredients, products,  
 34 | components and devices;
- 35 | 2. Compounding involving the transfer, measuring, mixing or manipulation  
 36 | of no more than three commercially manufactured packages of sterile  
 37 | products and no more than two entries into any one sterile container or  
 38 | package (i.e., bag, vial) of sterile product or administration  
 39 | container/device;

- 1 3. Compounding manipulations are limited to aseptically opening ampules,  
2 penetrating disinfected stoppers on vials with sterile needles/syringes,  
3 and transferring sterile liquids in sterile syringes to sterile administration  
4 devices or package containers of other sterile products/containers for  
5 storage and dispensing;
- 6 4. CSPs prepared by closed-system aseptic transfer of sterile, non-  
7 pyrogenic finished pharmaceuticals obtained from licensed  
8 manufacturers into sterile final containers obtained from licensed  
9 manufacturers, or;
- 10 5. Assembly of point-of-care activated systems.

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

- 12 1. Compounding involving the transfer, measuring, or mixing  
13 manipulations of more than three commercially manufactured  
14 packages/vials of sterile products or involving more than two entries into  
15 any one sterile container or package (i.e., bag, vial) of sterile product or  
16 administration container/device;
- 17 2. Multiple individual or small doses of sterile products are combined or  
18 pooled to prepare a CSP that will be administered either to multiple  
19 patients or to one patient on multiple occasions;
- 20 3. CSPs compounded with a medium risk product/CSP, or
- 21 4. The compounding process includes complex aseptic manipulations other  
22 than single-volume transfer and the CSP does not otherwise meet the  
23 definition of a high risk sterile CSP.
- 24 5. Medium Risk CSPs shall remain medium risk for the life of the CSP.

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

- 26 1. CSPs compounded from nonsterile ingredients including, but not limited  
27 to, manufactured products not intended for sterile routes of  
28 administration (i.e., oral);
- 29 2. Compounding using nonsterile components, containers, devices or  
30 equipment before terminal sterilization. If any nonsterile components are  
31 used to make a CSP, the CSP shall be deemed high risk;
- 32 3. Confirmed or suspected exposure of any of the following to worse than  
33 ISO Class 5 air quality for more than one (1) hour: (1) sterile contents of  
34 commercially manufactured products, (2) CSPs that lack effective  
35 antimicrobial preservatives or (3) any sterile surface of a device or  
36 container used for the preparation, transfer, sterilization or packaging of  
37 CSPs;
- 38 4. CSPs prepared by using an open-system transfer or open reservoir before  
39 terminal sterilization;
- 40 5. CSPs compounded with a high risk products/CSP, or;

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

3                   7. High Risk CSPs shall remain high risk for the life of the CSP.  
4

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

- 7 (A) The CSP is compounded in a PEC that complies with section (11) of this rule;
- 8 (B) The CSP is assigned the lesser of a 12-hour beyond-use date or the beyond-use  
9 date recommended in the manufacturers' package insert. The CSP may not be  
10 dispensed or distributed after the assigned beyond-use date;
- 11 (C) Individuals engaged in, or assisting with, sterile compounding follow proper  
12 hand hygiene, garbing and aseptic technique in the segregated compounding  
13 area as required by this rule; and
- 14 (D) The PEC shall be cleaned and disinfected as required by this rule.  
15

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

- 20 A. CSPs shall only be compounded pursuant to a valid patient-specific prescription,  
21 prescription drug order or medication order. However, drugs may be  
22 compounded ~~in limited quantities~~ in anticipation of a valid prescription/order  
23 based on a history of receiving valid prescriptions/orders that have been  
24 generated solely with an established pharmacist/patient/prescriber relationship  
25 and in an amount that does not exceed a one (1) month supply for dispensing  
26 purposes. ~~“Limited quantities” is defined as an amount of a batched preparation~~  
27 ~~that does not exceed a one (1) month supply needed for dispensing purposes.~~
- 28 B. Compounding in anticipation of receiving a prescription, prescription drug order  
29 or medication order without an appropriate history of such prescriptions/orders  
30 on file shall be considered manufacturing instead of compounding.
- 31 C. Any alteration, change or modification to the contents of a commercially  
32 manufactured over-the-counter medication shall require a valid prescription,  
33 prescription drug order or medication order from an authorized prescriber.
- 34 D. Pharmacists shall not offer CSPs to other pharmacies, practitioners or  
35 commercial entities for subsequent resale or administration, except pursuant to a  
36 patient specific prescription/order or as authorized by a Class J pharmacy permit.

- 1 E. A pharmacist or pharmacy may advertise or otherwise provide information  
2 concerning the provision of compounding services, however, no pharmacist or  
3 pharmacy shall attempt to solicit business by making specific claims about CSPs  
4 without specific testing of the CSP as compounded by the pharmacy to validate  
5 such claim.
- 6 F. Compounding of ~~drug products~~ CSPs that are commercially available in the  
7 marketplace or that are essentially copies of commercially available FDA  
8 approved drug products is prohibited. This prohibition shall not apply if the drug  
9 is not commercially available due to circumstances beyond the licensee's control  
10 (i.e., a drug shortage) or a specific medical need for a particular variation of a  
11 commercially available compound exists. Documentation of drug unavailability  
12 or the specific medical need for compounding a commercially available product  
13 shall be maintained in the pharmacy's records.
- 14 G. The pharmacy shall maintain current drug reference materials related to CSPs  
15 that shall be electronically or physically available in the pharmacy for use and  
16 inspection by pharmacy staff.
- 17 H. A third-party may be used to perform any testing or sampling required by this  
18 rule, provided the pharmacy and pharmacist-in-charge shall remain responsible  
19 for compliance with this rule and all applicable state/federal law.
- 20 I. Remedial Investigations: A remedial investigation shall be required if: (1) any  
21 sampling or testing required by this rule repeatedly demonstrates CFU counts that  
22 exceed USP Chapter 797 recommended action levels for the type of  
23 sampling/testing or (2) any sampling or testing demonstrates the presence of a  
24 highly pathogenic microorganism (i.e., Gram-negative rods, coagulase positive  
25 staphylococcus, molds, fungus or yeasts).
- 26 1. CSPs and any ingredients used within the compounding process that are part  
27 of the remedial investigation shall be quarantined until the results of the  
28 investigation are known. All affected areas shall be resampled to ensure a  
29 suitable state of microbial control prior to further compounding. The  
30 pharmacy shall ensure that no misbranded, contaminated or adulterated  
31 product is administered or dispensed for patient use.
  - 32 2. If highly pathogenic microorganisms are detected, the investigation shall be  
33 initiated with the assistance of a competent microbiologist, infection control  
34 professional, industrial hygienist or other competent staff and the source of  
35 contamination remedied, regardless of CFU count. The presence of a highly  
36 pathogenic microorganism shall be reported to the Board within seven (7)  
37 days after detection.
  - 38 3. Investigation procedures and any corrective/remediation methods taken shall  
39 be documented in the pharmacy's records.
- 40

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

- 8 1. Compounding, labeling, ~~sterilizing~~ and dispensing CSPs;
- 9 2. Storing, transporting and delivering CSPs;
- 10 3. Cleaning and disinfection. Policies and procedures shall identify authorized  
11 cleaning/disinfecting agents and materials, schedules of use and methods of  
12 application;
- 13 4. Maintaining, verifying and testing the accuracy and functioning of  
14 compounding equipment, including, time frames for calibration, testing,  
15 equipment monitoring and both annual and routine maintenance;
- 16 5. Beyond-use-dating;
- 17 6. Approved methods of sterilization and purification;
- 18 7. Environmental sampling, including, specified time frames and locations;
- 19 8. End-preparation testing, including, sampling plans;
- 20 9. Staff training and monitoring competency;
- 21 10. Reporting and investigating environmental deficiencies ~~and conducting~~  
22 ~~remedial investigations~~;
- 23 11. Media-fill testing. Policies and procedures shall address/identify media-fill  
24 procedures, media selection, fill volume, incubation requirements, time and  
25 temperature requirements, testing documentation, analyzing results, and any  
26 corrective action guidelines or procedures;
- 27 12. Measures for preventing cross-contamination when compounding activities  
28 require the manipulation of a patient's blood-derived or other biological  
29 material (i.e., radiolabeling a patient's or donor's white blood cells);
- 30 13. Recall procedures which must include procedures for identifying and  
31 notifying affected patients, prescribers and regulators when applicable;
- 32 14. Handling and reporting accidental exposures or spills of hazardous CSPs,  
33 including, reporting methods and timeframes;
- 34 15. Reporting and investigating any real or suspected adverse event or any real  
35 or suspected contaminated, non-sterile or defective final CSP, and;
- 36 16. Educating patients and/or caregivers concerning the appropriate storage, use  
37 and control of CSPs, when applicable.

38  
39 (7) **Facility Design Requirements.** Except as otherwise provided in section (8), CSPs shall  
40 be prepared in a compounding area that includes an ante area and buffer area(s).

1       A. **Compounding Area Design Requirements:** Compounding areas and surfaces  
2 shall be designed, maintained and controlled to minimize the risk of preparation  
3 contamination and the introduction, generation, accumulation and retention of  
4 particles. Compounding areas must be clean, well lit and designed in a manner that  
5 will allow effective cleaning and disinfection for the activities performed.

6           1. Junctures of ceilings to walls shall be coved or caulked to avoid cracks and  
7           crevices where dirt can accumulate. If ceilings consist of inlaid panels, the  
8           panels shall be impregnated with a polymer to render them impervious and  
9           hydrophobic, and they shall be caulked around each perimeter to seal them to  
10          the support frame.

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

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

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

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

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

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

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

26          9. Compounding areas and CSP storage areas (i.e., refrigerators and freezers)  
27          must have an effective temperature measuring device. At a minimum,  
28          temperatures shall be recorded and documented each day that the pharmacy  
29          is open for pharmacy activities. Alternatively, a continuous temperature  
30          monitoring system may be maintained if the system maintains ongoing  
31          documentation of temperature recordings or, if applicable, temperature alerts  
32          that are reviewed daily ~~by pharmacy staff. The required daily staff review~~  
33          ~~shall be documented and maintained in the pharmacy's records or accessible~~  
34          ~~to the pharmacy. Documentations of the required review shall be maintained~~  
35          in the pharmacy's records or otherwise accessible to the pharmacy.

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

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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 ~~or segregated 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. Results shall be reviewed and documented on a log at least daily. Alternatively, a continuous recording device may be used to document pressure differential, provided the results are reviewed at least daily.
- 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 that complies with the following:
- 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.

- 1 B. A line of demarcation must be established that defines and separates the  
2 segregated compounding area from other pharmacy activities/areas. The  
3 segregated compounding area shall be dedicated solely to activities directly  
4 related to sterile compounding. Segregated compounding areas shall not be  
5 used for non-sterile compounding.
- 6 C. Segregated compounding areas shall not include carpet or unsealed windows  
7 or doors that connect to the outdoors or be located in high traffic flow areas or  
8 areas in or adjacent to construction sites, warehouses, or food preparation or in  
9 any area with environmental air disturbances that may affect the PEC.
- 10 D. Areas and surfaces within the segregated compounding area shall be  
11 constructed and maintained in a manner that will minimize spaces in which  
12 microorganisms and other contaminants may accumulate. All surfaces ~~inside~~  
13 ~~the line of demarcation~~ shall be smooth, impervious, cleanable, nonshedding  
14 and resistant to damage by disinfectants, including, but not limited to, fixtures,  
15 shelving, counters, ceilings, walls and floors.
- 16 E. The segregated compounding area shall not contain sources of water or floor  
17 drains. A sink with hot and cold water must be available outside of the  
18 segregated compounding area. Sinks must be a minimum of three (3) feet but  
19 no farther than twenty-five (25) feet away from the PEC.
- 20 F. Adequate provision for performing antiseptic hand hygiene shall be provided  
21 before entry into the PEC.
- 22 G. CSP storage areas (i.e., refrigerators and freezers) must have an effective  
23 temperature measuring device. At a minimum, temperatures shall be recorded  
24 and documented each day that the pharmacy is open for pharmacy activities.  
25 Alternatively, a continuous temperature monitoring system may be maintained  
26 if the system maintains ongoing documentation of temperature recordings that  
27 are reviewed daily by pharmacy staff. The required daily staff review shall be  
28 documented in the pharmacy's records.
- 29 H. Low and medium risk CSPs compounded in a segregated compounding area  
30 must be assigned a beyond-use date in compliance with section (21). The  
31 assigned beyond-use date must be 12-hours or less unless the CSP is  
32 compounded in a CAI or CACI that meets the following:
- 33 1. The CAI/CACI must provide isolation from the room and maintain ISO  
34 Class 5 air quality during dynamic operating conditions;
  - 35 2. The manufacturer documents or verifies that the CAI/CACI will meet the  
36 requirements of this subsection when located in environments where the  
37 background particle counts exceed ISO Class 8 for 0.5 µm and larger  
38 particles; and
  - 39 3. Documentation of compliance and the manufacturer's verification is  
40 maintained in the pharmacy's records.

- 1 I. Except as otherwise provided in this subsection (8), segregated compounding areas  
2 shall comply with all other applicable provisions of this rule.  
3 J. High Risk CSPs may not be compounded in a segregated compounding area.  
4 | K. Relocation of the ~~compounding area or~~ segregated compounding area shall  
5 constitute a pharmacy remodel and require compliance with 20 CSR 2220-2.020.  
6

7 (9) **ISO Certification.** All ISO classified areas and each PEC shall be certified to  
8 ensure compliance with requirements of this rule. Certification shall be performed by  
9 qualified individuals using recognized and appropriate certification and testing equipment:

- 10 | A. Certification shall be performed ~~before initially~~ prior to beginning sterile  
11 compounding activities and every six (6) months thereafter. Recertification shall be  
12 completed whenever the physical structure of the buffer area or ante-area has been  
13 altered or any other facility changes or any changes to the PEC occur that may affect  
14 airflow or pressure differential. PECs shall also be recertified when the device is  
15 relocated or altered or major service to the PEC is performed.  
16 B. Certification/re-certification shall be conducted in accordance with the Controlled  
17 Environment Testing Association Certification Guide for Sterile Compounding  
18 Facilities (2008), which is incorporated herein by reference. Copies of the  
19 Certification Guide for Sterile Compounding Facilities (2008) are published by, and  
20 available from, Controlled Environment Testing Association, 1500 Sunday Drive,  
21 Suite 102, Raleigh, NC 27607 or online at <http://www.cetainternational.org/>. This  
22 rule does not include any later amendments or additions to the Certification Guide.  
23 The pharmacy shall maintain an attestation or statement from the certifier verifying  
24 that certification/recertification was performed in compliance with Certification  
25 Guide guidelines.  
26 C. Certification/recertification results shall be reviewed by a pharmacist once the  
27 | completed results are received ~~to ensure compliance with this rule~~. Deficiencies or  
28 failures shall be investigated and corrected prior to further compounding.  
29 Corrections may include, but are not limited to, changes in the use of the affected  
30 PEC or the ongoing use/recall of CSPs. The identity of the pharmacist conducting  
31 the required review and the review date shall be documented in the pharmacy's  
32 records.  
33 D. An in situ air pattern analysis (i.e. smoke study) shall be required prior to initial  
34 compounding and whenever maintenance, repairs or changes to the PEC or  
35 compounding area occur that may affect the airflow pattern. The in situ air pattern  
36 analysis shall be conducted at the critical area to demonstrate unidirectional airflow  
37 and sweeping action over and away from the CSP under dynamic conditions. For  
38 purposes of this section, maintenance does not include routine pre-filter changes.  
39

- 1 (10) **Equipment**. Compounding equipment shall be clean, properly functioning and  
2 effective for their intended use and shall be consistently capable of operating  
3 properly and within acceptable limits.
- 4 A. Equipment or other supplies shall be used, maintained, calibrated and verified  
5 for accuracy according to manufacturer recommendations, unless otherwise  
6 provided by Board rules.
- 7 B. Surfaces of compounding equipment that contact ingredients, in-process  
8 materials or drug products shall not be reactive, ~~additive, adsorptive or~~  
9 ~~absorptive~~ so as to alter the strength, stability, quality or purity of the drug  
10 product/CSP beyond that desired.
- 11 C. Automated compounding devices shall be tested for content, volume and  
12 weight accuracy prior to both initial and daily use. Test results shall be  
13 reviewed by a pharmacist to ensure compliance. The identity of the reviewing  
14 pharmacist and the review date shall be documented in the pharmacy's  
15 records.
- 16 D. In the event of improper or inaccurate functioning, the equipment/device shall  
17 not be used until the deficiency has been remedied.
- 18 E. If drug products/CSPs with special precautions for contamination are involved  
19 (i.e., penicillin), appropriate measures must be utilized in order to prevent  
20 cross-contamination (i.e., restricting equipment use for other  
21 operations/compounding or proper cleaning).
- 22
- 23 (11) **Primary Engineering Controls (PEC)**: PECs shall be properly located, operated  
24 and maintained and shall comply with the following:
- 25 A. PECs must be located in a restricted access ISO Class 7 buffer area or in a  
26 segregated compounding area that complies with this rule and shall be placed in  
27 a manner to avoid conditions that could adversely affect their operation. PECs  
28 shall be located out of traffic patterns and away from conditions that could  
29 disrupt the intended airflow patterns (i.e., ventilation systems or cross-drafts).
- 30 B. PECs shall maintain ISO Class 5 or better conditions during dynamic operating  
31 conditions and while compounding sterile preparations, including, when  
32 transferring ingredients into and out of the isolator and during exposure of  
33 critical sites;
- 34 C. PECs shall provide unidirectional (laminar flow) HEPA air at a velocity  
35 sufficient to prevent airborne particles from contacting critical sites.
- 36 D. Compounding Aseptic Isolators (CAI): Air exchange into the isolator from the  
37 surrounding environment shall not occur unless the air has first passed through a  
38 microbial retentive HEPA filter.

- 1 E. Compounding Aseptic Containment Isolators (CACI): Air exchange with the  
 2 surrounding environment shall not occur unless the air is first passed through a  
 3 microbial retentive HEPA filter system capable of containing airborne  
 4 concentrations of the physical size and state of the drug being compounded.  
 5 When volatile hazardous drugs are prepared, the exhaust air from the isolator  
 6 shall be removed by properly designed building ventilation.
- 7 F. If an isolator is used, the recovery time to achieve ISO Class 5 air quality shall  
 8 be identified in the pharmacy's policies and procedures and internal procedures  
 9 developed to ensure adequate recovery time is allowed after material transfer  
 10 and before or during compounding operations.

11  
 12 (12) **Ingredients and Supplies.** Compounding ingredients, supplies and containers shall  
 13 be properly stored and secured in a clean, dry area to prevent contamination and to  
 14 maintain the CSP's strength, quality and purity. Ingredients, drugs and supplies  
 15 must be stored according to manufacturer or USP requirements and conditions.

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

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

25 ~~C. Upon receipt of each lot of sterile compounding ingredients and prior to~~  
 26 ~~compounding, a visual inspection of the lot shall be conducted for evidence~~  
 27 ~~of unacceptable condition or quality.~~

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

33 ~~E.D.~~ ~~Products or i~~Ingredients that lack a supplier's expiration date cannot  
 34 be used after one (1) year after receipt. The receipt date shall be recorded on  
 35 the container of the product/ingredient.

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

1 | G.F. Single-Dose and Multiple Dose Vials/Containers. Single and  
 2 | multiple-dose vials/containers used in compounding shall be labeled with the  
 3 | date and time of initial entering or opening and a beyond-use date after  
 4 | which the product shall not be used.

5 | 1. Single-dose vials/containers exposed to ISO Class 5 or cleaner air  
 6 | may be used until the assigned beyond-use date which shall not  
 7 | exceed six (6) hours after initial needle puncture, unless otherwise  
 8 | specified by the manufacturer. Opened single-dose ampules shall not  
 9 | be stored for any time period.

10 | 2. Unless otherwise specified by the manufacturer, multiple-dose ~~use~~  
 11 | vials/containers may be used until the assigned beyond-use date  
 12 | which shall not exceed twenty-eight (28) days after initially entering  
 13 | or opening (i.e., needle-puncture).  
 14 |

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

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

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

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

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

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

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

33 | F.G. Only supplies essential for compounding shall be stored in the buffer area.  
 34 | Supplies or other non-essential equipment shall not be stored in the PEC.  
 35 |

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

- 1 | 1. Except as otherwise provided herein, personal cleansing and garbing shall  
2 | comply with USP Chapter 797.
- 3 | 2. In lieu of full garbing, compounding personnel using a CAI or CACI to  
4 | compound non-hazardous drugs shall at a minimum don facial masks, non-  
5 | shedding gowns and sterile gloves over the isolator gloves during compounding.  
6 | Non-shedding gowns and gloves shall also be used during material handling.  
7 | This section shall only be applicable if the CAI/CACI provides isolation from  
8 | the room and is certified to maintain ISO Class 5 air quality during dynamic  
9 | operating conditions as defined in 8 (G).

10 |  
11 | (15) **Aseptic Processing**. CSPs shall be prepared in a manner that maintains sterility and  
12 | minimizes contamination and the introduction of particulate matter. Appropriate  
13 | aseptic technique shall be utilized at all times.

- 14 | A. Aseptic processing must be performed in at least ISO Class 5 conditions. Critical  
15 | sites shall not be exposed to touch/contact contamination or worse than ISO  
16 | Class 5 air.
- 17 | B. Prior to ~~use~~ compounding, drug products, ingredients and packaging shall  
18 | undergo a visual unit-by-unit inspection to verify the components are free from  
19 | defects and otherwise suitable for their intended use. Products or ingredients  
20 | shall not be used if: (1) evidence of deterioration or contamination exists or is  
21 | suspected, (2) an unauthorized break in any container, closure or seal is detected,  
22 | (3) the contents do not have the expected appearance, aroma, or texture or (4) the  
23 | beyond-use date or expiration date has been exceeded.
- 24 | C. Only materials and equipment essential for aseptic compounding shall be placed  
25 | in the primary engineering control. Materials and equipment shall be arranged  
26 | in the DCA to allow a clear, uninterrupted path of HEPA-filtered air over critical  
27 | sites at all times during compounding. Compounding staff shall not interrupt,  
28 | impede, or divert flow of first-air from HEPA filters to critical sites.
- 29 | D. All critical sites shall be wiped vigorously in one direction with sterile alcohol  
30 | and allowed to air dry before being punctured or used.
- 31 | E. Wetted gauze pads or other particle-generating material shall not be used to  
32 | disinfect sterile entry points. If sterile, single-use alcohol prep pads are used, the  
33 | surface of the pad shall not contact any other object before contacting the surface  
34 | of the entry point.

1 F. When sterile supplies are received in sealed pouches designed to keep them  
2 sterile until opening, ~~the sterile item may be removed from the covering pouches~~  
3 ~~as the supplies are introduced into the ISO Class 5 PEC without disinfecting the~~  
4 ~~individual sterile supply items~~ the outer wrap must be disinfected before  
5 placement in the PEC. ~~However,~~ sSyringes, needles, and tubing with an outer  
6 wrap shall remain in their individual packaging and shall only be opened in an  
7 ISO Class 5 work area.

8 G. Before compounding, staff shall visually confirm that ingredients used and  
9 measured in syringes match the prescription or medication order being  
10 compounded. Density or specific gravity values programmed in automated  
11 compounding devices shall be confirmed to be correct before and after  
12 delivering volumes of the liquids assigned to each channel or port.  
13

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

- 16 A. Presterilization procedures for High Risk CSPs, such as weighing and mixing,  
17 shall be completed in no worse than an ISO Class 8 environment.
- 18 B. All non-sterile equipment that is to come in contact with the sterilized final high  
19 risk CSP shall be sterilized before introduction into the buffer area.  
20 Additionally, all nonsterile measuring, mixing and purifying devices shall be  
21 rinsed thoroughly with sterile water for irrigation, disinfected and thoroughly  
22 drained or dried before being used to compound.
- 23 C. All high risk CSPs must be sterilized before dispensing or distribution via a  
24 method recognized for the CSP type by USP Chapter 1211.
- 25 1. Water-containing CSPs that are nonsterile during any phase of the  
26 compounding procedure shall be sterilized within 6 hours after completing  
27 the CSP.
  - 28 2. Filters used for sterilization shall be tested for integrity (i.e., bubble point  
29 testing) after use. Testing shall comply with manufacturer  
30 recommendations. Testing dates and results must be documented in the  
31 pharmacy's records and reviewed by a pharmacist prior to releasing the  
32 CSP.
  - 33 3. Commercially available filters shall be approved for human use  
34 applications in sterilizing pharmaceutical fluids. Sterile filters used to  
35 sterilize CSPs shall be pyrogen free and a pore size of 0.20 to 0.22  
36 microns. They shall be certified by the manufacturer to retain at least 10 to  
37 the seventh microorganisms of a strain of *Brevundimonas* (*pseudomonas*)  
38 *diminute*. The pharmacy must maintain this documentation for each filter  
39 utilized in the sterilization of CSPs.

1 D. Final containers used for high risk CSPs must be sterile and capable of maintaining  
2 CSP integrity until the beyond-use date. Sterilization methods must be based on  
3 the properties of the CSP.  
4

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

12 A. **Low Risk:** Low Risk CSPs shall undergo sterility testing if ~~the preparation is~~  
13 ~~stored for more than~~ the beyond-use date exceeds 48 hours at controlled room  
14 temperature, 14 days at ~~each~~ refrigerated temperature, and 45 days in solid  
15 frozen state at -25° to -10° Celsius or colder.

16 B. **Medium Risk:** Medium Risk CSPs shall undergo sterility testing if ~~the CSP is~~  
17 ~~stored for beyond-use date exceeds~~ more than 30 hours at controlled room  
18 temperature, 9 days at ~~each~~ refrigerated temperature, and 45 days in solid frozen  
19 state at - 25° to -10° Celsius or colder.

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

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

27 2. **Bacterial Endotoxin (Pyrogen) Testing:** All high risk parenteral,  
28 ~~epidural or intrathecal sterile preparations or administered via epidural or~~  
29 ~~intrathecal route~~ CSPs shall be tested for bacterial endotoxins using a  
30 USP Chapter 85 recognized method for bacterial endotoxin testing.

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

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

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

- 9           1. No alternative product/CSP is available and the patient will be exposed  
 10           to negative risks if therapy is delayed. The reason for the emergency  
 11           dispensing shall be documented in the pharmacy's records; and
- 12           2. The prescriber/ordering health care provider is informed the CSP will be  
 13           dispensed prior to receiving test results and approves the dispensing.  
 14           Prescriber/provider approval shall be documented in the pharmacy's  
 15           records. A separate authorization from the prescriber/provider is  
 16           required for each emergency dispensing.
- 17           3. This section shall not be construed to exempt any person or entity from  
 18           performing any testing required by this rule.

19  
 20           (18) **Labeling.** Except as otherwise provided herein, CSPs dispensed to patients shall be  
 21           labeled in accordance with section 338.059, RSMo, and with the following  
 22           supplemental information affixed to the CSP:

- 23           A. Beyond-use date;
- 24           B. ~~Date of preparation~~compounding Compounding date, if different from the date  
 25           the prescription is filled;
- 26           C. The actual name of each active or therapeutic ingredient;
- 27           D. The amounts or concentration of all active or therapeutic ingredients;
- 28           E. Total volume;
- 29           E.F. The pharmacy's phone number;
- 30           G. Storage requirements;
- 31           F.H. If given to a patient, a statement indicating "This is a compounded  
 32           preparation";
- 33           G.I. Any CSP or device specific instructions for use including the route of  
 34           administration and the rate of administration, and;
- 35           H.J. Auxiliary labels when applicable.
- 36           I.K. When a CSP is packaged in individual containers and dispensed to the  
 37           patient in a labeled outer container as required above, the individual containers  
 38           must be labeled with the CSP name, lot number and beyond use date.

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

- 6 1. Compounding records shall be reviewed to verify that the correct  
7 measurements, volumes, quantities, calculations and sterilization procedures  
8 were used. If an automated compounding device was used, a pharmacist  
9 must verify proper calibration and verify that data entered into the device  
10 was correct and accurate, including, but not limited to, density or specific  
11 gravity values.
- 12 2. The final CSP must be visually inspected for physical integrity, clarity and  
13 expected appearance. Additionally, each compounded unit shall be  
14 inspected against lighted white or black background or both for evidence of  
15 visible particulates or other foreign matter. Visual inspection shall not be  
16 required for hazardous drugs if the inspection may be harmful.

17  
18 (20) **Beyond-Use Dating.** All CSPs must be assigned a beyond-use date. Beyond-use  
19 dates shall be determined from the date or time the CSP is compounded. The nature  
20 of the drug and its degradation mechanism, drug stability, sterility considerations,  
21 antimicrobial effective testing results, container packaging, storage conditions and the  
22 intended duration of therapy shall be considered. CSPs shall not be dispensed past the  
23 assigned beyond-use date.

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

37  
38 (21) **Point-of-Care Activated Systems.** In addition to other applicable requirements:

- 1 A. Point-of-Care activated systems shall be assembled within an ISO Class 5  
2 environment and assigned a beyond-use date in accordance with the  
3 manufacturer's recommendations or labeling.
- 4 B. The beyond-use date of an assembled non-activated system shall be limited to a  
5 maximum of fifteen (15) days unless the pharmacy has documentation from the  
6 system's manufacturer that a longer date is acceptable. When dispensed, an  
7 assembled non-activated system shall be labeled with beyond-use dates for both  
8 activated and non-activated states. The compounding record must document  
9 both dates.
- 10 C. Point of care activated systems shall be stored in accordance with the  
11 manufacturer's labeling and recommendations.

12  
13 (22) ~~Storage. Sterile preparations shall be properly stored and maintained. Preparations~~  
14 CSPs shall be stored strictly in accordance with the conditions stated on the ingredient  
15 label, if applicable. Adulterated, misbranded, expired or contaminated CSPs shall be  
16 segregated and quarantined from the compounding area and other drug inventory and  
17 properly disposed of.

- 18 A. If storage at controlled room temperature is directed, an article may alternatively  
19 be stored and distributed in a cool place as defined by USP, unless otherwise  
20 specified in the individual USP monograph or on the label.
- 21 B. Temperature excursions shall be allowed as permitted or recognized by USP.
- 22 C. Any excess CSP shall be stored and accounted for under conditions dictated by  
23 the CSP's composition and stability characteristics to ensure its strength, quality  
24 and purity. Excess CSPs shall be labeled with the name and strength of the  
25 drug(s), an in-house lot number, date of ~~preparation~~ compounding, volume and  
26 beyond-use date.

27  
28 (23) Packaging and Delivery. CSPs shall be packaged, stored, transported and delivered  
29 in a manner that will preserve the physical integrity, sterility, stability, and purity of  
30 the CSP. Packaging shall be selected that simultaneously protects CSPs from damage,  
31 leakage, contamination, and degradation and protects individuals transporting packed  
32 CSPs from harm. Prescription delivery shall comply with applicable provisions of 20  
33 CSR 2220-2.013. The pharmacy shall establish a mechanism for the patient/ultimate  
34 user to report packaging or transporting concerns to the pharmacy and documenting  
35 any reports received.

36

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

7 (A) Compounding date;

8 (B) The identity of the compounder and the pharmacist performing the final  
9 verification required by section (19) of this rule ~~pharmacist~~, if different;

10 (C) A list of ingredients and their amounts by weight or volume;

11 (D) Description of the compounding process, including, the compounding  
12 method, formula or recipe and, if necessary for proper compounding, the  
13 order of adding drug products and ingredients. For High Risk CSPs, the  
14 log must also include sterilization and testing methods. The information  
15 required by this subsection may be separately maintained in the  
16 pharmacy's records if immediately available on request;

17 (E) The identity of the source, lot number and the expiration or beyond-use  
18 date of each ingredient, as well as an in-house lot number and a beyond-  
19 use date for batch bulk CSPs;

20 (F) An identifying prescription number or a readily retrievable unique  
21 identifier;

22 (G) The beyond-use date assigned to the CSP and placed on the label;

23 (H) For High Risk CSPs, the type of container and container lot number, if  
24 applicable; and

25 (I) Any CSP storage conditions included on the CSP label or in materials  
26 provided to the patient.

27  
28 (25) **Aseptic Manipulation Training and Assessment**. Compounding staff shall be  
29 skilled and trained to accurately and competently perform the duties assigned and to  
30 operate any equipment used. At a minimum, compounding staff must undergo  
31 Aseptic Competency Training and an Aseptic Technique Skill Assessment as follows:

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

- 1 B. Aseptic Technique Skill Assessment: A practical aseptic technique skill  
2 assessment shall be completed for all individuals compounding sterile  
3 preparations to verify aseptic competency. The assessment must include glove  
4 fingertip sampling, media-fill testing and a direct visual evaluation of the  
5 individual's competency. The visual observation shall assess:
- 6 1. Proper aseptic technique, manipulations and work practices, including,  
7 but not limited to, avoiding touch contamination, proper use of first air  
8 and if applicable, sterilizing high risk CSPs;
  - 9 2. Sanitation and disinfection;
  - 10 3. Hand hygiene, gloving and garbing;
  - 11 4. Identifying, weighing, and measuring of ingredients;
  - 12 5. Maintaining and achieving sterility in ISO Class 5 areas and within  
13 primary engineering controls, and;
  - 14 6. Labeling and inspecting CSPs for quality.
- 15 C. The required Aseptic Technique Skill Assessment must be completed for staff  
16 compounding low or medium risk CSPs prior to initial compounding and every  
17 twelve (12) months thereafter. For staff compounding high risk CSPs, the  
18 assessment must be completed prior to initial compounding and every six (6)  
19 months thereafter.
- 20 D. Compounding staff shall successfully pass all training and assessments. Staff  
21 who fail to demonstrate competency or whose glove fingertip sampling or  
22 media-fill tests demonstrate one or more units of visible microbial contamination  
23 shall be re-instructed and re-evaluated to ensure correction of all deficiencies  
24 prior to beginning or continuing any further compounding. The re-instruction and  
25 reevaluation shall be documented in the pharmacy's records.
- 26 E. Training and assessment dates along with the results of the required practical  
27 aseptic technique skill assessment, glove fingertip sampling and media-fill  
28 testing shall be reviewed and documented ~~and maintained in the pharmacy's~~  
29 ~~records and reviewed by the pharmacist-in-charge to ensure compliance or~~  
30 his/her/their designee.

31  
32 **(26) Glove Fingertip Sampling.**

33 Compounding staff shall undergo and successfully complete both initial and ongoing glove  
34 fingertip sampling to assess compliance with gloving and aseptic processing. Initial and  
35 ongoing fingertip sampling shall be completed in accordance with USP Chapter 797  
36 procedures, timeframes and methods. Glove fingertip sampling ~~Ongoing sampling~~ shall be  
37 conducted following each required media-fill test. ~~In addition to USP requirements,~~  
38 ~~samples must be tested for mold, yeast, bacteria and fungus.~~

1 (27) **Media-Fill Testing.** Pharmacies shall establish and follow policies and procedures  
2 for conducting media-fill testing to assess the quality of aseptic skills/techniques of  
3 compounding staff. Media-Fill tests shall be conducted as part of the required aseptic  
4 technique skill assessment and shall include a minimum of three media-fill units using  
5 the same container or closure. Media-fill tests shall represent the most challenging or  
6 stressful conditions actually encountered by the personnel being evaluated. Initial and  
7 ongoing media-fill testing shall be completed in accordance with USP Chapter 797  
8 recommended procedures and methods for the applicable risk level(s). ~~In addition to~~  
9 ~~USP requirements, samples must be tested for mold, yeast, bacteria and fungus.~~

10  
11 (28) **Environmental Sampling.** Environmental sampling shall be routinely conducted in  
12 all ISO classified areas to evaluate air quality compliance and microbial bio burden  
13 levels. Sampling shall be conducted during dynamic operating conditions in  
14 accordance with USP Chapter 797. Surface samples and viable airborne particle  
15 samples shall be tested for bacteria, fungus, mold and yeast. Sampling shall occur as  
16 follows:

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

22 B. **Viable Airborne Particle Testing:** Volumetric viable air sampling by  
23 impaction shall be conducted in all ISO classified environments. Each viable  
24 air sample shall sample 1,000 liters for all ISO areas ~~Class 5 areas and 500~~  
25 ~~liters for other ISO classified areas.~~ Each sample location shall be tested  
26 with both general growth media (i.e., tryptic soy agar) and fungal specific  
27 media (i.e., malt extract agar or saboraaud dextrose agar) on plates of at least  
28 55mm in size. Use of settling plates alone shall not be sufficient. Viable  
29 Airborne Particle Testing must be conducted prior to initial compounding  
30 and every six (6) months thereafter. Testing shall also occur:

- 31 1. As part of the initial certification of new facilities and equipment;
- 32 2. Whenever the physical structure of the compounding area has been  
33 altered;
- 34 3. As part of the recertification of facilities and equipment;
- 35 4. In response to identified problems with CSPs or end-preparation  
36 testing failure; and
- 37 5. Whenever maintenance, repairs or changes to the primary  
38 engineering control(s) or compounding area may affect the airflow  
39 pattern. The date and type of maintenance, repair or change shall be  
40 documented in the pharmacy's records;

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

5 D. **Pressure Differential:** Pressure differential monitoring shall be required for  
6 all sterile compounding areas to ensure compliance with section (7)(B) of  
7 this rule. Alternatively, a continuous pressure monitoring system may be  
8 maintained if the system maintains ongoing documentation of pressure  
9 recordings, or if applicable, pressure alerts/notifications that are reviewed  
10 daily. ~~Pressure differential monitoring results shall be documented in~~  
11 ~~writing and reviewed daily.~~ Documentation of the required review shall be  
12 maintained in the pharmacy's records or otherwise accessible to the  
13 pharmacy.

14  
15 (29) **General Cleaning and Disinfection Requirements.** The pharmacy shall establish  
16 and follow written policies and procedures governing all aspects of cleaning and  
17 disinfection. Except as otherwise provided herein, the following requirements shall  
18 be applicable:

19 A. Compounding areas and segregated compounding areas shall be free of  
20 infestation by insects, rodents and other vermin. Trash shall be disposed of in a  
21 timely and sanitary manner.

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

25 C. Individuals responsible for cleaning and disinfecting shall be trained in proper  
26 cleaning and disinfection procedures and mechanisms prior to performing  
27 cleaning/disinfection activities. Training shall include direct visual observation  
28 of the individual's cleaning and disinfecting process by qualified staff. The  
29 individual shall be annually reassessed for competency through direct visual  
30 observation. Documentation of the required training and training dates shall be  
31 maintained in the pharmacy's records. Individuals who fail to demonstrate  
32 competency shall be instructed and successfully reevaluated prior to cleaning  
33 or disinfecting the compounding or segregated compounding area.

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

- 1 | E. Primary engineering controls shall be cleaned with a germicidal ~~detergent-agent~~  
2 | followed by sterile alcohol. Sterile water for irrigation shall be used to dilute  
3 | germicidal agents used inside the PEC that require dilution.
- 4 | F. Routine disinfection of the direct compounding area (DCA) is conducted to  
5 | minimize microbial surface contamination and maintain ISO Class 5 air quality.  
6 | At a minimum, the DCA shall be cleaned and disinfected prior to compounding,  
7 | between batches and whenever contamination is suspected using sterile alcohol  
8 | or an equivalent or superior agent which is allowed to dry immediately prior to  
9 | compounding.
- 10 | G. *Segregated Compounding Areas*: Floors and work surfaces within the line of  
11 | demarcation shall be cleaned and disinfected daily or immediately prior to  
12 | compounding if not used daily. Shelving and storage areas shall be cleaned and  
13 | disinfected monthly.
- 14 |
- 15 | (30) **Quality Assurance**. Sterile compounding pharmacies shall establish and follow a  
16 | written quality assurance program for monitoring and evaluating the quality of  
17 | compounding activities.
- 18 | A. At a minimum, the quality assurance program shall include procedures for  
19 | monitoring and tracking infection rates, adverse drug events, CSP recalls and  
20 | complaints from prescribers, patients or other individuals or entities.
- 21 | B. The quality assurance plan shall delineate the individuals responsible for each  
22 | aspect of the quality assurance program either by name or position title.
- 23 | C. The quality assurance plan shall be maintained at the pharmacy or readily  
24 | retrievable upon request. The pharmacist-in-charge shall annually review the  
25 | quality assurance program and document the review in the pharmacy's records.  
26 |
- 27 | (31) **Recalls**. A recall must be initiated when a ~~dispensed or distributed~~ **CSP** is deemed to  
28 | be misbranded, adulterated or non-sterile or if end-preparation testing results are out  
29 | of specification. The pharmacy shall notify the prescriber of the nature of the recall,  
30 | the problem(s) identified and any recommended actions to ensure public health and  
31 | safety. In cases where the CSP has the potential to harm the patient, the same  
32 | notification shall be provided to all patients that received the recalled CSP(s).
- 33 | A. Patient and prescriber notifications required by this section shall be made as soon  
34 | as reasonably practicable but in no event later than one (1) business day of the  
35 | recall. The date and manner of notification shall be documented in the pharmacy's  
36 | records.
- 37 | B. If a patient recall notification is unsuccessful, the pharmacy shall mail notification  
38 | to the patient within the required one (1) business day timeframe.
- 39 | C. Recalls initiated pursuant to this section shall be reported to the board in writing  
40 | within three (3) business days.

1 D. If recall notification cannot be conducted as required herein, the pharmacy may  
2 submit to the Board a written plan to extend the notification period. The request  
3 must include a description of the nature of the recall, the potential number of  
4 patients affected, the reason(s) supporting the extension request and a proposed  
5 timeframe for completing the required notifications.  
6

7 (32) **Record Keeping**. The pharmacy shall maintain the following records:

- 8 A. Aseptic competency training and aseptic technique skill assessment dates and  
9 results;
- 10 B. Testing dates and results for glove fingertip sampling, media-fill tests and end-  
11 CSP testing;
- 12 C. Environmental sampling dates and results, including, any corrective efforts  
13 taken;
- 14 D. Cleaning and disinfection evaluation dates and results;
- 15 E. Required refrigerator and temperature logs;
- 16 F. Cleaning and disinfection records that document compliance with this rule;
- 17 G. Equipment calibration dates and results and maintenance reports;
- 18 H. Certificates of analysis for compounding ingredients, if applicable;
- 19 I. Certification records for PECs and sterile compounding areas;
- 20 J. Copies of any manufacturer equipment standards that are relied upon to  
21 maintain compliance with this rule;
- 22 K. Batch CSP files;
- 23 L. For high risk CSPs, sterilization, quarantine and ingredient validation records;
- 24 M. Emergency dispensing records as required by subsection (17), including,  
25 documentation of prescriber authorization and the dates of such authorization;
- 26 N. CSP recall records, including, dates, patients affected and any investigation,  
27 corrective actions or recall notifications made; and
- 28 O. All other records required by this rule or governing law.
- 29 P. Except as otherwise provided herein, records and reports required by this rule  
30 shall be either electronically or physically maintained for two (2) years.  
31 Records shall be readily retrievable and subject to inspection by the Board of  
32 Pharmacy or its agents upon request. At a minimum, records shall be  
33 physically or electronically produced immediately or within two (2) hours of a  
34 request from the Board or the Board's authorized designee.
- 35 Q. Prescription records shall be maintained in compliance with Missouri law and  
36 the rules of the Board.  
37

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

- 6 A. Hazardous drugs/CSPs shall be stored, handled and prepared under  
7 conditions that protect workers and other staff.
- 8 B. Appropriate disposal containers shall be available for used needles, syringes,  
9 and if applicable, hazardous waste from the CSP of chemotherapy agents and  
10 infectious waste. Disposal of hazardous waste shall comply with all  
11 applicable local, state and federal requirements;
- 12 C. Written procedures for handling major and minor spills and generated waste  
13 of hazardous agents must be developed and must be included in the policy  
14 and procedure manual, and;
- 15 D. Prepared doses of hazardous drugs must be labeled with proper precautions  
16 inside and outside, and shipped in a manner to minimize the risk of  
17 accidental rupture of the primary container.

18  
19 (34) **Applicability.** If a conflict between this rule and the applicable provisions of  
20 USP exists, the requirements of this rule shall apply unless otherwise indicated  
21 herein. In the interest of public protection, the use of an alternative technology,  
22 technique, material or procedure not specifically included in this rule or USP  
23 shall only be authorized if an exemption is approved by the Board. The  
24 exemption request must be in writing and must include:

- 25 (A) A description of the exemption requested and the reasons supporting the  
26 request;
- 27 (B) Testing or other scientific evidence demonstrating the technology,  
28 technique, material or procedure is equivalent or superior with statistical  
29 significance to those included in this rule or USP. Peer-reviewed  
30 literature shall be insufficient without actual proof of the testing or other  
31 scientific evidence methods and results supporting the request;
- 32 (C) A detailed statement of any hardship or public harm that will occur if  
33 the exemption is not granted, and;
- 34 (D) Any other evidence requested by the Board.

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(35) 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.