

OPEN MINUTES
Missouri Board of Pharmacy
Sterile Compounding Sub-Committee
August 26, 2015

Members of the Missouri Board of Pharmacy met in open session 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 9:00 a.m. on August 26, 2015.

Board Members Present

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

Staff Present

Kimberly Grinston, Executive Director
Tom Glenski, Chief Inspector

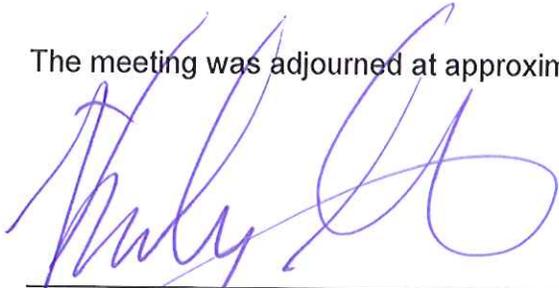
Others Present

Kevin Kinkade, R.Ph.

DISCUSSION: Kimberly Grinston reported available Board members were asked to review the current sterile compounding rule draft (20 CSR 2220-2.200) and to prepare a suggested draft for full Board review. Ms. Grinston reported that board members previously indicated they did not have recent sterile compounding or USP 797 experience, with the exception of Barbara Bilek. Kimberly Grinston reported the Board agreed by consensus to retain Kevin Kinkade to assist the Board's review due to his sterile compounding and regulatory background. Ms. Grinston expressed concerns regarding the length of the rule and the potential impact on small business. Christian Tadrus and Kevin Kinkade also expressed concerns regarding the impact on small business and indicated the rule should be understandable.

Staff and participating board members proceeded to review the draft rule. Substantive comments and suggested changes discussed during the meeting are included in the attached revised draft. Kimberly Grinston indicated the draft would be revised and returned to participating board members for finalization. Participating Board members agreed by consensus to review the next draft by conference call.

The meeting was adjourned at approximately 3:43 p.m.



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. Except as otherwise provided herein, 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 (2) Definitions (3) Risk Levels (4) Low Risk Preparations with 12-Hour or Less Beyond-Use Date (5) General Compounding Requirements (6) Policies and Procedures (7) Facility Design Requirements (8) Segregated Compounding Areas (9) ISO Certification (10) Equipment (11) Primary Engineering Controls (12) Ingredients & Supplies (13) Standard Operating Procedures (14) Cleansing and Garbing (15) Aseptic Processing (16) Additional Aseptic Technique Requirements for High Risk Preparations (17) End Preparation Testing (18) Labeling (19) Final Verification (20) Beyond-Use Dating (21) Point-of-Care Activated Systems (22) Storage (23) Packaging and Delivery (24) Compounding Log (25) Aseptic Manipulation Training & Assessment (26) Glove Fingerprint Sampling (27) Media-Fill Testing (28) General Cleaning and Disinfection Requirements (29) Quality Assurance (30) Recalls (31) Record Keeping (32) Hazardous Drugs and Radiopharmaceuticals (33) Preemption

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

Comment [A1]:
 USP defines "Cold" in 10.30.20, as:
Any temperature not exceeding 8° (46°F) is "cold." A "refrigerator" is a cold place in which the temperature is maintained thermostatic between 2° and 8° (36° and 46°F).

The definition of "controlled cold temperature" includes the 2° and 8° language that the group discussed referencing to distinguish "cold temperature" from "freezing" which one should incorporate here?

- 1 aseptic compounding environment within the isolator throughout the compounding
2 and material transfer processes.
- 3 (O) **Compounding Equipment:** Equipment, instruments, apparatuses, and devices
4 used to compound sterile preparations
- 5 (P) **Compounding Staff:** Any person who engages or participates in any aspect of
6 sterile compounding regardless of employment status.
- 7 (Q) **Compounded Sterile Preparation (CSP):** Any low risk, medium risk or high
8 risk compounded sterile preparation, including:
- 9 a. Compounded biologics, diagnostics, drugs, nutrients, and
10 radiopharmaceuticals that must or are required to be sterile when they are
11 administered to patients, including, but not limited to the following dosage
12 forms: aqueous bronchial and inhaled nasal preparations intended for
13 deposition in the lung, baths and soaks for live organs and tissues, epidural
14 and intrathecal solutions, bladder/wound solutions, injectables, implantable
15 devices and dosage forms, inhalation solutions, intravenous solutions,
16 irrigation solutions, ophthalmic preparations, parenteral nutrition solutions,
17 and repackaged sterile preparations. Nasal sprays and irrigations intended
18 for deposit in the nasal passages may be prepared as nonsterile compounds;
- 19 b. An FDA approved manufactured sterile product that is either prepared
20 according to the manufacturers' approved labeling/recommendations or
21 prepared differently than published in such labeling; and
- 22 c. Assembling point-of-care activated systems.
- 23 (R) **Controlled Room Temperature:** A controlled room temperature as defined by
24 USP.
- 25 (S) **Critical Area:** An ISO Class 5 area where products, preparations, surfaces or
26 containers are exposed to the environment.
- 27 (T) **Critical Site:** Any surface, pathway or opening (i.e., vial septa, injection ports,
28 beakers, needle hubs) that provides a direct pathway between a sterile preparation
29 or other ingredient used to compound a sterile preparation and the air, environment
30 or moisture or that poses a risk of touch contamination.
- 31 (U) **Direct Compounding Area (DCA):** A critical area within an ISO Class 5
32 primary engineering control where critical sites are exposed to unidirectional
33 HEPA-filtered air also known as first air.
- 34 (V) **Disinfectant:** An agent applied to inanimate objects that frees from infection and
35 destroys disease-causing pathogens or other harmful microorganisms but may not
36 kill bacterial and fungal spores.
- 37 (W) **Experiential Training:** Training based on experience and observation.
- 38 (X) **First Air:** The air exiting a HEPA filter in a unidirectional air stream that is
39 essentially particle free.
- 40 (Y) **Frozen:** A "frozen" temperature as defined by USP.

- 1 (Z) **Hazardous Drugs:** A drug that exhibits one or more of the following
2 characteristics in humans or animals: (1) carcinogenicity, (2) teratogenicity or
3 other developmental toxicity, (3) reproductive toxicity, (4) serious organ toxicity
4 at low doses, (5) genotoxicity or (6) structure and toxicity profiles of new drugs
5 that mimic existing drugs determined hazardous by the previous
6 criteria/characteristics.
- 7 (AA) **High-Efficiency Particulate Air (HEPA) filter:** A particulate filter that directs
8 the flow of air forced through the filter in a uniform parallel flow and that is: (1)
9 capable of retaining airborne particles and microorganisms while allowing gases to
10 pass freely through and, (2) a minimum of 99.97% efficient when tested using 0.3-
11 μm thermally generated particles and a photometer or rated at their most
12 penetrating particle size using a particle counter.
- 13 (BB) **ISO Class 5:** An area with less than 3,520 particles (0.5 μm) per cubic meter.
- 14 (CC) **ISO Class 7:** An area with less than 352,000 particles (0.5 μm) per cubic meter.
- 15 (DD) **ISO Class 8:** An area with less than 3,520,000 particles (0.5 μm) per cubic meter.
- 16 (EE) **Line of Demarcation:** A visible line or barrier on the floor that separates a room
17 into distinct and identifiable separate areas for the performance of sterile
18 compounding from general pharmacy activities.
- 19 (FF) **Media Fill Test:** A test using a growth medium to verify aseptic compounding
20 techniques or processes are able to produce a compounded sterile preparation
21 without microbial contamination.
- 22 (GG) **Multiple-Dose Container:** A multiple-unit container for articles or preparations
23 that contains more than one dose of medication.
- 24 (HH) **Parenteral:** A drug preparation intended for injection through one (1) or more
25 layers of skin.
- 26 (II) **Peer-Reviewed Literature:** Literature that has been evaluated by other qualified
27 scientific, academic or qualified professionals for quality or accuracy and has been
28 nationally published in a pharmaceutical, scientific, compendial or other medical
29 publication.
- 30 (JJ) **Point of Care Activated System:** A closed system device that creates a physical
31 barrier between diluents, fluids or other drug components and is designed to be
32 activated by the end user by allowing the components to mix prior to
33 administration.
- 34 (KK) **Preparation:** A preparation, or a compounded sterile preparation, that is a sterile
35 drug or nutrient compounded in a licensed pharmacy pursuant to a lawful
36 prescription or medication order. The article may or may not contain sterile
37 products.
- 38 (LL) **Primary Engineering Control (PEC):** A device that provides an ISO Class 5
39 environment for the exposure of critical sites when compounding sterile
40 preparations. PECs include, but may not be limited to, laminar airflow

1 workbenches, biological safety cabinets, compounding aseptic isolators (CAIs)
2 and compounding aseptic containment isolators (CACIs).

3 (MM) **Refrigerator:** A “refrigerator” temperature as defined by USP.

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

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

10 (PP) **Sterile Alcohol:** Alcohol that contains 70% by volume USP grade Isopropanol
11 (isopropyl alcohol) and 30% USP purified water.

12 (QQ) **Sterilization:** A validated USP recognized process used to render a preparation
13 free of viable organisms.

14 (RR) **Terminal Sterilization:** The application of a lethal process (i.e., steam under
15 pressure or autoclaving) to sealed containers for the purpose of achieving a
16 predetermined sterility assurance level of less than 10^{-6} , or a probability of less
17 than one nonsterile unit in one million units.

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

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

27
28 (3) **Risk Levels.** The following contamination risk levels shall be established for
29 compounded sterile preparations:

30 A. **Low Risk:** Sterile preparations compounded under the following conditions:

- 31 1. Sterile preparations compounded with aseptic manipulations entirely
32 within an ISO Class 5 or better air quality using only sterile ingredients,
33 products, components and devices;
- 34 2. Compounding involving the transfer, measuring, mixing or manipulation
35 of no more than three commercially manufactured packages of sterile
36 products and no more than two entries into any one sterile container or
37 package (i.e., bag, vial) of sterile product or administration
38 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. Preparations 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:** Sterile preparations compounded under any of the following
12 conditions:
- 13 1. Compounding involving the transfer, measuring, or mixing
14 manipulations of more than three commercially manufactured
15 packages/vials of sterile products or involving more than two entries into
16 any one sterile container or package (i.e., bag, vial) of sterile product or
17 administration container/device;
 - 18 2. Multiple individual or small doses of sterile products are combined or
19 pooled to prepare a compounded sterile preparation that will be
20 administered either to multiple patients or to one patient on multiple
21 occasions;
 - 22 3. Preparations compounded with a medium risk product/preparation, or
 - 23 4. The compounding process includes complex aseptic manipulations other
24 than single-volume transfer and the preparation does not otherwise meet
25 the definition of a high risk sterile preparation.
 - 26 5. Medium Risk preparations shall remain medium risk for the life of the
27 preparation.
- 28 **C. High Risk:** Sterile preparations compounded under any of the following
29 conditions:
- 30 1. Preparations compounded from nonsterile ingredients including, but not
31 limited to, manufactured products not intended for sterile routes of
32 administration (i.e., oral);
 - 33 2. Compounding using nonsterile components, containers, devices or
34 equipment before terminal sterilization. If any nonsterile components are
35 used to make a sterile preparation, the preparation shall be deemed high
36 risk;

- 1 3. Confirmed or suspected exposure of any of the following to worse than
2 ISO Class 5 air quality for more than one (1) hour: (1) sterile contents of
3 commercially manufactured products, (2) compounded sterile
4 preparations that lack effective antimicrobial preservatives or (3) any
5 sterile surface of a device or container used for the preparation, transfer,
6 sterilization or packaging of compounded sterile preparations;
- 7 4. Preparations prepared by using an open-system transfer or open reservoir
8 before terminal sterilization;
- 9 5. Preparations compounded with other high risk products/preparations, or;
- 10 6. Nonsterile water-containing preparations that are stored for more than 6
11 hours before being sterilized.
- 12 7. High Risk preparations shall remain high risk for the life of the
13 preparation.
14

15 (4) **Low-Risk or Medium Risk preparations with a 12-Hour or Less Beyond-use**

16 **Date:** A Low Risk or Medium Risk preparation may be compounded in a segregated
17 compounding area if:

- 18 (A) The preparation is compounded in a PEC that complies with section (11) of this
19 rule;
- 20 (B) The preparation is assigned the lesser of a 12-hour beyond-use date or the
21 beyond-use date recommended in the manufacturers' package insert. The
22 preparation may not be dispensed or distributed after the assigned beyond-use
23 date;
- 24 (C) Individuals engaged in, or assisting with, sterile compounding follow proper
25 hand hygiene, garbing and aseptic technique in the segregated compounding
26 area as required by this rule; and
- 27 (D) Routine disinfection of the direct compounding area (DCA) is conducted to
28 minimize microbial surface contamination and maintain ISO Class 5 air quality.
29 At a minimum, the DCA shall be cleaned and disinfected prior to compounding,
30 between batches and whenever contamination is suspected using sterile alcohol
31 or an equivalent or superior agent which is allowed to dry immediately prior to
32 compounding.
33

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

- 1 A. Pharmacists shall only compound drugs pursuant to a valid prescription,
2 prescription drug order or medication order. However, drugs may be
3 compounded in limited quantities in anticipation of a valid prescription/order
4 based on a history of receiving valid prescriptions/orders that have been
5 generated solely with an established pharmacist/patient/prescriber relationship.
6 "Limited quantities" is defined as an amount of a batched preparation that does
7 not exceed a one (1) month supply.
- 8 B. Compounding in anticipation of receiving a prescription, prescription drug order
9 or medication order without an appropriate history of such prescriptions/orders
10 on file shall be considered manufacturing instead of compounding.
- 11 C. Any alteration, change or modification to the contents of a commercially
12 manufactured over-the-counter medication shall require a valid prescription,
13 prescription drug order or medication order from an authorized prescriber.
- 14 D. Pharmacists shall not offer compounded drug preparations to other pharmacies,
15 practitioners or commercial entities for subsequent resale or administration,
16 except pursuant to a patient specific prescription or as authorized by a Class J
17 pharmacy permit.
- 18 E. A pharmacist or pharmacy may advertise or otherwise provide information
19 concerning the provision of compounding services, however, no pharmacist or
20 pharmacy shall attempt to solicit business by making specific claims about
21 compounded preparations without specific testing of the preparation as
22 compounded by the pharmacy to validate such claim.
- 23 F. Compounding of drug products that are commercially available in the
24 marketplace or that are essentially copies of commercially available FDA
25 approved drug products is prohibited. This prohibition shall not apply if the drug
26 is not commercially available due to circumstances beyond the licensee's control
27 (i.e., a drug shortage) or a specific medical need for a particular variation of a
28 commercially available compound exists. Documentation of drug unavailability
29 or the specific medical need for compounding a commercially available product
30 shall be maintained in the pharmacy's records.
- 31 G. The pharmacy shall maintain current drug reference materials related to sterile
32 preparations that shall be electronically or physically available in the pharmacy
33 for use and inspection by pharmacy staff.
- 34 H. A third-party may be used to perform any testing or sampling required by this
35 rule, provided the pharmacy and pharmacist-in-charge shall remain responsible
36 for compliance with this rule and all applicable state/federal law.

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

7 1. Compounded preparations and any ingredients used within the compounding
8 process that are part of the remedial investigation shall be quarantined until
9 the results of the investigation are known. All affected areas shall be
10 resampled to ensure a suitable state of microbial control prior to further
11 compounding. The pharmacy shall ensure that no misbranded, contaminated
12 or adulterated product is administered or dispensed for patient use.

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

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

21
22 (6) Policies and Procedures. Pharmacies shall establish and follow a written sterile
23 compounding policy and procedure manual. The manual shall be current and shall be
24 electronically or physically accessible to pharmacy staff. The pharmacist-in-charge
25 shall annually review the manual for compliance and document the date of the required
26 annual review in the pharmacy's records. The required policy and procedure manual
27 shall encompass all aspects of sterile compounding performed by the pharmacy and
28 must include policies/procedures for:

- 29 1. Compounding, labeling, sterilizing and dispensing sterile preparations;
- 30 2. Storing, transporting and delivering sterile preparations;
- 31 3. Cleaning and disinfection. Policies and procedures shall identify authorized
32 cleaning/disinfecting agents and materials, schedules of use and methods of
33 application;
- 34 4. Maintaining, verifying and testing the accuracy and functioning of
35 compounding equipment, including, time frames for calibration, testing,
36 equipment monitoring and both annual and routine maintenance;
- 37 5. Beyond-use-dating;
- 38 6. Approved methods of sterilization and purification;
- 39 7. Environmental sampling, including, specified time frames and locations;
- 40 8. End-preparation testing, including, sampling plans;

- 1 9. Staff training and monitoring competency;
- 2 10. Reporting and investigating environmental deficiencies and conducting
- 3 remedial investigations;
- 4 11. Media-fill testing. Policies and procedures shall address/identify media-fill
- 5 procedures, media selection, fill volume, incubation requirements, time and
- 6 temperature requirements, testing documentation, analyzing results, and any
- 7 corrective action guidelines or procedures;
- 8 12. Measures for preventing cross-contamination when compounding activities
- 9 require the manipulation of a patient's blood-derived or other biological
- 10 material (i.e., radiolabeling a patient's or donor's white blood cells);
- 11 13. Recall procedures which must include procedures for identifying and
- 12 notifying affected patients, prescribers and regulators when applicable;
- 13 14. Handling and reporting accidental exposures or spills of hazardous sterile
- 14 preparations, including, reporting methods and timeframes;
- 15 15. Reporting and investigating any real or suspected adverse event or any real
- 16 or suspected contaminated, non-sterile or defective final preparation, and;
- 17 16. Educating patients and/or caregivers concerning the appropriate storage, use
- 18 and control of sterile compounded preparations when applicable.
- 19

20 (7) **Facility Design Requirements.** Sterile preparations shall be prepared in a
21 compounding area that includes an ante area and buffer area(s) or in a segregated
22 compounding area that complies with section 8 of this rule.

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

28 1. ~~Areas and surfaces within the compounding area shall be constructed and~~
29 ~~maintained in a manner that will minimize spaces in which microorganisms~~
30 ~~and other contaminants may accumulate. The Compounding areas and~~
31 ~~surfaces shall be resistant to damage by disinfectant agents.~~ Junctures of
32 ceilings to walls shall be coved or caulked to avoid cracks and crevices
33 where dirt can accumulate. If ceilings consist of inlaid panels, the panels
34 shall be impregnated with a polymer to render them impervious and
35 hydrophobic, and they shall be caulked around each perimeter to seal them to
36 the support frame

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

- 1 3. Work surfaces and the surfaces of ceilings, walls, floors, fixtures, shelving,
2 counters, and cabinets shall be smooth, impervious, free from cracks and
3 crevices, cleanable, non-shedding and resistant to damage by disinfectants.
- 4 4. Adequate provision for antiseptic hand cleansing shall be provided after
5 entry into the ante area.
- 6 5. The buffer area shall not contain sources of water or floor drains. A sink with
7 hot and cold water must be near, but not in, the buffer area.
- 8 6. The exterior lens surface of ceiling lighting fixtures shall be smooth,
9 mounted flush or mounted/installed to promote easy cleaning.
- 10 7. Furniture in the compounding area shall be nonporous, smooth, non-
11 shedding, impermeable, cleanable, and resistant to damage by disinfectants.
- 12 8. Temperature, humidity and pressure in the compounding area shall be
13 controlled as necessary to ensure compliance with this rule.
- 14 9. Compounding areas and compounded preparation storage areas (i.e.,
15 refrigerators and freezers) must have an effective temperature control device.
16 At a minimum, temperatures shall be recorded and documented each day that
17 the pharmacy is open for pharmacy activities. Alternatively, a continuous
18 temperature monitoring system may be maintained if the system maintains
19 ongoing documentation of temperature recordings that are reviewed daily by
20 pharmacy staff. The required daily staff review shall be documented in the
21 pharmacy's records.
- 22 10. Segregated compounding areas shall comply with section (8) of this rule.

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

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

1 3. An accurate device shall be installed to monitor the pressure differential
2 between the buffer area and ante-area, and between the ante-area and the
3 general environment outside the compounding area. The cascading pressure
4 between the ISO Class 7 buffer area and the ISO Class 7/8 ante area and the
5 general pharmacy area shall not be less than 5 pascals (0.02 inch water
6 column) each for a total of not less than .05-inch water column from the
7 buffer area all the way to the general pharmacy area. Results shall be
8 reviewed and documented on a log at least daily. Alternatively, a
9 continuous recording device may be used to document pressure differential,
10 provided the results are reviewed at least daily.

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

13
14 (8) **Segregated Compounding Areas:** In lieu of a compounding area that includes an
15 ante area and buffer area, Low Risk and Medium Risk sterile preparations may be
16 compounded in a segregated compounding area that complies with the following:

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

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

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

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

37 E. A sink with hot and cold water must be available outside of the segregated
38 compounding area. Sinks must be a minimum of three (3) feet but no farther
39 than twenty-five (25) feet away from the PEC.

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

3 G. Low and medium risk preparations compounded in a segregated compounding
4 area must be assigned a beyond-use date in compliance with section (21). The
5 assigned beyond-use date must be 12-hours or less unless the preparation is
6 compounded in a CAI or CACI that meets the following:

- 7 1. The CAI/CACI must provide isolation from the room and maintain ISO
8 Class 5 air quality during dynamic operating conditions;
- 9 2. The manufacturer documents or verifies that the CAI/CACI will meet the
10 requirements of this subsection when located in environments where the
11 background particle counts exceed ISO Class 8 for 0.5 µm and larger
12 particles; and
- 13 3. Documentation of compliance and the manufacturer's verification is
14 maintained in the pharmacy's records.

Formatted: Pattern: Clear

15 H. Segregated compounding areas shall comply with all other applicable provisions of
16 this rule, including, all applicable testing, cleaning and disinfection requirements.

17 I. High Risk preparations may not be compounded in a segregated compounding area.

Comment [A2]: I think we still need to ck what is required in an SCA.

18
19 (9) **ISO Certification.** All ISO classified areas and each PEC shall be certified to
20 ensure compliance with requirements of this rule. Certification shall be performed by
21 qualified individuals using recognized and appropriate certification and testing equipment:

22 A. Certification shall be performed before initially beginning sterile compounding
23 activities and every six (6) months thereafter. Recertification shall be completed
24 whenever the physical structure of the buffer area or ante-area has been altered or
25 any other facility changes or any changes to the PEC occur that may affect airflow
26 or pressure differential. PECs shall also be recertified when the device is relocated
27 or altered or major service to the PEC is performed.

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

- 1 C. Certification/recertification results shall be reviewed by a pharmacist once the
2 completed results are received to ensure compliance with this rule. Deficiencies or
3 failures shall be investigated and corrected prior to further compounding.
4 Corrections may include, but are not limited to, changes in the use of the affected
5 PEC or the ongoing use/recall of compounded preparations. The identity of the
6 pharmacist conducting the required review and the review date shall be documented
7 in the pharmacy's records.
- 8 D. An in situ air pattern analysis (i.e. smoke study) shall be required prior to initial
9 compounding and whenever maintenance, repairs or changes to the PEC or
10 compounding area occur that may affect the airflow pattern. The in situ air pattern
11 analysis shall be conducted at the critical area to demonstrate unidirectional airflow
12 and sweeping action over and away from the preparation under dynamic conditions.
13 For purposes of this section, maintenance does not include routine pre-filter
14 changes.
- 15
- 16 (10) **Equipment**. Compounding equipment shall be clean, accurate, and effective for
17 their intended use and shall be consistently capable of operating properly and within
18 acceptable limits.
- 19 A. Equipment or other supplies shall be used, maintained, calibrated and verified
20 for accuracy according to manufacturer recommendations, unless otherwise
21 provided by Board rules.
- 22 B. Surfaces of compounding equipment that contact ingredients, in-process
23 materials or drug products shall not be reactive, additive or absorptive so as to
24 alter the ~~safety, identity,~~ strength, quality or purity of the drug
25 product/preparation beyond that desired.
- 26 C. Automated compounding devices shall be tested for content, volume and
27 weight accuracy prior to both initial and daily use. Test results shall be
28 promptly reviewed by a pharmacist to ensure compliance. The identity of the
29 reviewing pharmacist and the review date shall be documented in the
30 pharmacy's records.
- 31 D. In the event of improper or inaccurate functioning, the equipment/device shall
32 not be used until the deficiency has been remedied.
- 33 E. If drug products/preparations with special precautions for contamination are
34 involved (i.e., penicillin), appropriate measures must be utilized in order to
35 prevent cross-contamination (i.e., restricting equipment use for other
36 operations/compounding or proper cleaning).
- 37
- 38 (11) **Primary Engineering Controls (PEC)**: PECs shall be properly located, operated
39 and maintained and shall comply with the following:

Comment [A3]: "Promptly" isn't defined.
Suggestions? Should it be included here?

- 1 A. PECs must be located in a restricted access ISO Class 7 buffer area or in a
2 segregated compounding area that complies with this rule and shall be placed in
3 a manner to avoid conditions that could adversely affect their operation. PECs
4 shall be located out of traffic patterns and away from ~~room air currents~~
5 conditions that could disrupt the intended airflow patterns (i.e., ventilation
6 systems or cross-drafts).
- 7 B. PECs shall maintain ISO Class 5 or better conditions during dynamic operating
8 conditions and while compounding sterile preparations, including, when
9 transferring ingredients into and out of the isolator and during exposure of
10 critical sites;
- 11 C. PECs shall provide unidirectional (laminar flow) HEPA air at a velocity
12 sufficient to prevent airborne particles from contacting critical sites.
- 13 D. Compounding Aseptic Isolators (CAI): Air exchange into the isolator from the
14 surrounding environment shall not occur unless the air has first passed through a
15 microbial retentive HEPA filter.
- 16 E. Compounding Aseptic Containment Isolators (CACI): Air exchange with the
17 surrounding environment shall not occur unless the air is first passed through a
18 microbial retentive HEPA filter system capable of containing airborne
19 concentrations of the physical size and state of the drug being compounded.
20 When volatile hazardous drugs are prepared, the exhaust air from the isolator
21 shall be removed by properly designed building ventilation.
- 22 F. If an isolator is used, the recovery time to achieve ISO Class 5 air quality shall
23 be identified in the pharmacy's policies and procedures and internal procedures
24 developed to ensure adequate recovery time is allowed after material transfer
25 and before or during compounding operations.

26
27 (12) **Ingredients and Supplies.** Compounding ingredients, supplies and containers shall
28 be properly stored and secured in a clean, dry area to prevent contamination and to
29 maintain preparation strength, quality and purity. Ingredients, drugs and supplies
30 must be stored according to manufacturer or USP requirements and conditions.

- 31 A. Except as otherwise provided by the board by rule, pharmacists/pharmacies
32 shall only receive, store or use drugs or active ingredients for compounding
33 that have been received from a Missouri licensed pharmacy or drug
34 distributor. Active ingredients must be manufactured in an FDA registered
35 facility. Expired, misbranded, adulterated or contaminated products shall not
36 be used in compounding.
- 37 B. Active ingredients and added substances or excipients for CSPs shall be
38 compendial grade articles or shall be accompanied by a certificate of analysis
39 from their supplier which shall be retained in the pharmacy's records. Tom
40 will research if all are compendial grade.

- 1 C. Upon receipt of each lot of sterile compounding ingredients and prior to
2 compounding, a visual inspection of the lot shall be conducted for evidence
3 of unacceptable condition or quality.
- 4 D. Drugs, ingredients and supplies shall be shelved off the floor. Bulk or
5 unformulated drug substances and added substances or excipients shall be
6 stored in adequately labeled and tightly closed containers under temperature,
7 humidity, and lighting conditions that are either indicated in official
8 monographs or approved by the manufacturer.
- 9 E. Products or ingredients that lack a supplier's expiration date cannot be used
10 after one (1) year after receipt. The receipt date shall be recorded on the
11 container of the product/ingredient.
- 12 F. Ingredient containers and container closures shall not be reactive, additive or
13 absorptive so as to alter the ~~safety, identity~~, strength, quality or purity of the
14 compounded drug beyond the desired result. Container systems shall provide
15 adequate protection against foreseeable external factors that can cause
16 deterioration or contamination of the compounded preparation.
- 17 G. Single-Dose and Multiple Dose Containers. Single and multiple-dose
18 containers shall be labeled to indicate the date and time of initial entering or
19 opening. A beyond-use date must be assigned for the use of single-dose and
20 multiple-dose containers after initial entering or opening.
 - 21 1. Single-dose vials exposed to ISO Class 5 or cleaner air may be used
22 up to six (6) hours after initial needle puncture. Opened single-dose
23 ampules shall not be stored for any time period.
 - 24 2. Multiple-dose containers may be used up to twenty-eight (28) days
25 after initially entering or opening (i.e., needle-puncture) unless
26 otherwise specified by the manufacturer.
- 27
- 28 (13) Standard Operating Procedures. The following standard operating procedures
29 shall be applicable to and observed in both compounding areas and segregated
30 compounding areas:
 - 31 A. Traffic flow in or around the compounding and segregated compounding areas shall
32 be minimized and controlled.
 - 33 B. Food items, chewing gum, eating, drinking and smoking are prohibited.
 - 34 C. Nonessential objects that shed particles shall not be brought into the areas,
35 including, but not limited to, pencils, cardboard cartons, paper towels, and cotton
36 items (i.e., gauze pads).
 - 37 D. Furniture, carts, supplies and equipment shall be removed from shipping
38 cartons/containers and properly cleaned and disinfected before entering the
39 compounding area or segregated compounding area. No shipping or other external
40 cartons may be taken into the areas.

1 E. Packaged compounding supplies and components (i.e., needles, syringes and tubing
2 sets) shall be opened and wiped down with a non-residue generating disinfecting
3 agent before being passed into the buffer area or segregated compounding area.
4 Supplies and equipment shall be decontaminated once again before entering the
5 ISO 5 PEC by wiping the outer surface with sterile alcohol or an equivalent or
6 superior disinfectant that does not leave residue.

7 F. Only supplies essential for compounding shall be stored in the buffer area. Supplies
8 or other equipment shall not be stored in the PEC.
9

10 (14) **Cleansing and Garbing.** Individuals engaged in, or assisting with, compounding
11 sterile preparations shall be trained and demonstrate competence in proper cleansing,
12 garbing and gloving procedures. Competence must be documented and assessed
13 through direct observation.

14 1. Except as otherwise provided herein, cleansing and garbing shall comply with
15 USP Chapter 797.

16 2. In lieu of full garbing, compounding personnel using a CAI or CACI to
17 compound non-hazardous drugs shall at a minimum don facial masks, non-
18 shedding gowns and sterile gloves over the isolator gloves during compounding.
19 Non-shedding gowns and gloves shall also be used during material handling.
20 This section shall only be applicable if the CAI/CACI provides isolation from
21 the room and is certified to maintain ISO Class 5 air quality during dynamic
22 operating conditions.
23

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

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

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

- 1 C. Only materials and equipment essential for aseptic compounding shall be placed
2 in the primary engineering control. Materials and equipment shall be arranged
3 in the DCA to allow a clear, uninterrupted path of HEPA-filtered air over critical
4 sites at all times during compounding. Compounding staff shall not interrupt,
5 impede, or divert flow of first-air from HEPA filters to critical sites. ~~No objects~~
6 ~~may be placed between the first air from HEPA filters and an exposed critical~~
7 ~~site.~~
- 8 D. All critical sites shall be wiped vigorously in one direction with sterile alcohol
9 and allowed to dry before being punctured or used.
- 10 E. Wetted gauze pads or other particle-generating material shall not be used to
11 disinfect sterile entry points. If sterile, single-use alcohol prep pads are used, the
12 surface of the pad shall not contact any other object before contacting the surface
13 of the entry point.
- 14 F. When sterile supplies are received in sealed pouches designed to keep them
15 sterile until opening, the sterile item may be removed from the covering pouches
16 as the supplies are introduced into the ISO Class 5 PEC without disinfecting the
17 individual sterile supply items. However, syringes, needles, and tubing with an
18 outer wrap shall remain in their individual packaging and shall only be opened in
19 an ISO Class 5 work area.
- 20 G. Before compounding, staff shall visually confirm that ingredients used and
21 measured in syringes match the prescription or medication order being
22 compounded. Density or specific gravity values programmed in automated
23 compounding devices shall be confirmed to be correct before and after
24 delivering volumes of the liquids assigned to each channel or port.

25
26 **(16) Additional Aseptic Technique Requirements for High Risk Preparations.** In
27 addition to section (15), the following requirements for high risk preparations are
28 applicable:

- 29 A. Presterilization procedures for High Risk preparations, such as weighing and
30 mixing, shall be completed in no worse than an ISO Class 8 environment.
- 31 B. All non-sterile equipment that is to come in contact with the sterilized final high
32 risk preparation shall be sterilized before introduction into the buffer area.
33 Additionally, all nonsterile measuring, mixing and purifying devices shall be
34 rinsed thoroughly with sterile water for irrigation, disinfected and thoroughly
35 drained or dried before being used to compound.
- 36 C. All high risk preparations must be sterilized before dispensing or distribution via
37 a method recognized for the preparation type by USP Chapter 1211.
 - 38 1. Water-containing CSPs that are nonsterile during any phase of the
39 compounding procedure shall be sterilized within 6 hours after completing
40 the preparation.

- 1 2. Filters used for sterilization shall be tested for integrity (i.e., bubble point
2 testing) after use. Testing shall comply with manufacturer
3 recommendations. Testing dates and results must be documented in the
4 pharmacy's records and reviewed by a pharmacist prior to preparation
5 release.
- 6 3. Commercially available filters shall be approved for human use
7 applications in sterilizing pharmaceutical fluids. Sterile filters used to
8 sterilize CSPs shall be pyrogen free and a pore size of 0.20 to 0.22
9 microns. They shall be certified by the manufacturer to retain at least 10 to
10 the seventh microorganisms of a strain of *Brevundimonas* (*pseudomonas*)
11 diminute. The pharmacy must maintain this documentation for each filter
12 utilized in the sterilization of CSPs.
- 13 D. Final containers used for high risk preparations must be sterile and capable of
14 maintaining preparation integrity until the beyond-use date. Sterilization methods
15 must be based on the properties of the preparation.
- 16
- 17 (17) **End Preparation Testing.** End preparation testing for sterile CSPs shall be
18 conducted as required by this section. Finished preparations must be quarantined
19 pending results of any required testing. Except as otherwise allowed by this rule,
20 CSPs shall not be dispensed until all end-preparation testing results are final and meet
21 required results. Quarantine dates and time periods must be documented in the
22 pharmacy's records. The results of any end preparation testing (i.e., sterility,
23 endotoxin and potency) shall be reviewed by a pharmacist
- 24 A. **Low & Medium Risk:** Except as otherwise provided herein, low and medium
25 risk preparations shall undergo sterility testing if the beyond-use date is extended
26 beyond the storage limits in section (22).
- 27 B. **High Risk:** At a minimum, the following testing shall be required for high risk
28 preparations:
 - 29 1. **Sterility Testing:** All High Risk preparations must be tested for sterility
30 without exception in accordance with a method recommended or
31 required by USP Chapter 71. Samples for sterility testing shall be
32 collected immediately after preparation completion. The sampling plan
33 shall comply with USP Chapter 71, Tables 2 and 3.
 - 34 2. **Bacterial Endotoxin (Pyrogen) Testing:** All high risk parenteral sterile
35 preparations or compounded sterile preparations administered via
36 epidural or intrathecal route shall be tested for bacterial endotoxins using
37 a USP Chapter 85 recognized method for bacterial endotoxin testing.

1 3. **Potency Testing:** Final potency shall be confirmed by validated
2 instrumental analysis for each sterile preparation that has been assigned a
3 beyond-use date of more than thirty (30) days. Testing of each
4 preparation/batch is not required once potency has been established for
5 the specific preparation if no modifications have been made to the
6 compounding procedure, process or formula (i.e., ingredient sources,
7 batch size or equipment).

8 4. **Antimicrobial Effectiveness Testing:** Antimicrobial effectiveness must
9 be demonstrated for aqueous-based, multiple-dose topical and oral
10 dosage forms and for other dosage forms such as ophthalmic, otic, nasal,
11 irrigation and dialysis fluids. For purposes of this section, aqueous is
12 defined as a water activity of more than 0.6. Testing must comply with
13 USP Chapter 51. [My notes say Tom will provide language: "reference
14 USP w/ potency for multidose." I added this language from Chapter 51.]

15 C. **Emergency Dispensing:** Sterile preparations may be dispensed for immediate
16 administration to a patient prior to receiving the results of the testing required by
17 this rule if:

- 18 1. No alternative product/preparation is available and the patient will be
19 exposed to negative risks if therapy is delayed. The reason for the
20 emergency dispensing shall be documented in the pharmacy's records;
21 and
- 22 2. The prescriber/ordering health care provider is informed the preparation
23 will be dispensed prior to receiving test results and approves the
24 dispensing. Prescriber/provider approval shall be documented in the
25 pharmacy's records. A separate authorization from the
26 prescriber/provider is required for each emergency dispensing.
- 27 3. This section shall not be construed to exempt any person or entity from
28 performing any testing required by this rule.

29
30 (18) **Labeling.** Except as otherwise provided herein, sterile preparations dispensed to
31 patients shall be labeled in accordance with section 338.059, RSMo, and with the
32 following supplemental information affixed to the preparation:

- 33 A. Beyond-use date;
- 34 B. Date of preparation
- 35 C. The actual name of each active or therapeutic ingredient;
- 36 D. The amounts or concentration of active or therapeutic ingredients. For
37 injectables, the amounts or concentration of all active ingredients;
- 38 E. Total volume;
- 39 F. Storage requirements;

1 G. Any preparation or device specific instructions for use including the route of
2 administration and the rate of administration, and;

3 H. Auxiliary labels when applicable.

4 I. When a preparation is packaged in individual containers and dispensed to the
5 patient in a labeled outer container as required above, the individual containers
6 must be labeled with the preparation name, lot number and beyond use date.
7

8 (19) **Final Verification.** Prior to dispensing, a pharmacist shall physically verify that the
9 compounded preparation has been properly prepared, sterilized, packaged and labeled
10 and that all required end preparation testing has been performed and documented. The
11 following quality assurance measures shall be performed by a pharmacist before a
12 sterile preparation is dispensed or distributed:

- 13 1. Compounding records shall be reviewed to verify that the correct
14 measurements, volumes, quantities, calculations and sterilization procedures
15 were used. If an automated compounding device was used, a pharmacist
16 must verify that data entered into the device was correct and accurate,
17 including, but not limited to, density or specific gravity values.
18 2. The final preparation must be visually inspected for physical integrity, clarity
19 and expected appearance. Additionally, each compounded unit shall be
20 inspected against lighted white or black background or both for evidence of
21 visible particulates or other foreign matter. Visual inspection shall not be
22 required for hazardous drugs if the inspection may be harmful.
23

24 (20) **Beyond-Use Dating.** All sterile preparations must be assigned a beyond-use date.
25 Beyond-use dates shall be determined from the date or time the preparation is
26 compounded. The nature of the drug and its degradation mechanism, drug stability,
27 sterility considerations, container packaging, storage conditions and the intended
28 duration of therapy shall be considered.

- 29 A. For Low and Medium Risk preparations, beyond-use dates shall be assigned
30 based on any of the following resources: USP Chapter 797, the manufacturer's
31 labeling, direct testing using validated testing methods, compendial references or
32 peer-reviewed literature based on preparation-specific experimental
33 studies/testing.

Comment [A4]: I checked the DQSA for additional labeling requirements. It appears 503(b) outsourcers have to include "this is compounded drug" and "not for resale" on labels. See 503(b) <http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section353b&num=0&edition=prelim>

I didn't find any labeling changes for pharmacies operating under 503(a). Do we need to add anything else here?

1 B. High Risk preparations: Beyond-use dates not specifically referenced in the
2 manufacturer's approved labeling or not established by preparation specific
3 instrumental analysis shall be limited to thirty (30) days after compounding.
4 High risk preparations with beyond-use dates greater than thirty (30) days shall
5 undergo laboratory testing using validated methods prior to release to verify
6 stability (sterility and potency) for the maximum beyond-use date. Testing of
7 each preparation/batch is not required once stability has been established for the
8 specific preparation as required by this subsection and no modifications have
9 been made to the compounding procedure, process or formula.

10
11 (21) Point-of-Care Activated Systems. In addition to other applicable requirements:

- 12 A. Point-of-Care activated systems shall be assembled within an ISO Class 5
13 environment and assigned a beyond-use date in accordance with the
14 manufacturer's recommendations or labeling.
15 B. The beyond-use date of an assembled non-activated system shall be limited to a
16 maximum of fifteen (15) days unless the pharmacy has documentation from the
17 system's manufacturer that a longer date is acceptable. When dispensed, an
18 assembled non-activated system shall be labeled with beyond-use dates for both
19 activated and non-activated states. The compounding record must document
20 both dates.
21 C. Point of care activated systems shall be stored in accordance with the
22 manufacturer's labeling and recommendations.

23
24 (22) Storage. Sterile preparations shall be properly stored and maintained. Preparations
25 shall be stored strictly in accordance with the conditions stated on the ingredient label,
26 if applicable. Adulterated, misbranded, expired or contaminated preparations shall be
27 segregated and quarantined from the compounding area and other drug inventory. In
28 the absence of passing a sterility test, compounded sterile preparations shall be stored
29 as follows:

- 30 A. Low Risk: Shall be stored for no more than 48 hours at controlled room
31 temperature, 14 days at cold temperature, and 45 days in solid frozen state at -25° to
32 -10° Celsius or colder.
33 B. Medium Risk: Shall be stored for no more than 30 hours at controlled room
34 temperature, 9 days at cold temperature, and 45 days in solid frozen state at -25° to
35 -10° Celsius or colder.
36 C. High Risk: Shall be stored for no more than 24 hours at controlled room
37 temperature, 3 days at cold temperature, and 45 days in solid frozen state at -25° to -
38 10° Celsius or colder.

- 1 D. If storage at controlled room temperature is directed, an article may alternatively be
2 stored and distributed in a cool place as defined by USP, unless otherwise specified
3 in the individual USP monograph or on the label.
4 E. Temperature excursions shall be allowed as permitted or recognized by USP.
5 F. Any excess compounded preparation shall be stored and accounted for under
6 conditions dictated by the preparation's composition and stability characteristics to
7 ensure its strength, quality and purity. Excess preparations shall be labeled with the
8 name and strength of the drug(s), an in-house lot number, date of preparation,
9 volume and beyond-use date.

10
11 (23) **Packaging and Delivery.** Compounded sterile preparations shall be packaged, stored,
12 transported and delivered in a manner that will preserve the physical integrity,
13 sterility, stability, and purity of the preparation. Packaging shall be selected that
14 simultaneously protects CSPs from damage, leakage, contamination, and degradation
15 and protects individuals transporting packed CSPs from harm. The final preparation
16 shall maintain a potency of $\pm 10\%$ within monograph limits for USP articles.
17 Prescription delivery shall comply with applicable provisions of 20 CSR 22202.013.
18 The pharmacy shall establish a mechanism for patient reporting of packaging or
19 transporting concerns to the pharmacy and documenting any reports received.
20

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

- 28 1. Compounding date;
- 29 2. The identity of the compounder and the final verification pharmacist, if
30 different;
- 31 3. A list of ingredients and their amounts by weight or volume;
- 32 4. Description of the compounding process and, if necessary for proper
33 compounding, the order of adding drug products and ingredients. The
34 method, formula or recipe for compounding, provided this information
35 may be separately maintained in the pharmacy's records if immediately
36 upon request;
- 37 5. The identity of the source, lot number and the expiration or beyond-use
38 date of each ingredient, as well as an in-house lot number and a beyond-
39 use date for batch bulk CSPs;
- 40 6. An identifying prescription number or a readily retrievable unique
41 identifier;

- 1 7. The beyond-use date assigned to the preparation and placed on the label;
- 2 8. For High Risk preparations, the type of container and container lot
- 3 number, if applicable; and
- 4 9. Any preparation storage conditions included on the patient label or in
- 5 materials provided to the patient.

6
7 (25) **Aseptic Manipulation Training and Assessment.** Compounding staff shall be
8 skilled and trained to accurately and competently perform the duties assigned and to
9 operate any equipment used. At a minimum, compounding staff must undergo
10 Aseptic Competency Training and an Aseptic Technique Skill Assessment as follows:

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

19 B. **Aseptic Technique Skill Assessment:** A practical aseptic technique skill
20 assessment shall be completed for all individuals compounding sterile
21 preparations to verify aseptic competency. The assessment must include glove
22 fingertip sampling, media fill testing and a direct visual evaluation of the
23 individual's competency. The visual observation shall assess:

- 24 1. Proper aseptic technique, manipulations and work practices, including,
25 but not limited to, avoiding touch contamination, proper use of first air
26 and if applicable, sterilizing high risk preparations;
- 27 2. Sanitation and disinfection;
- 28 3. Hand hygiene, gloving and garbing;
- 29 4. Identifying, weighing, and measuring of ingredients;
- 30 5. Maintaining and achieving sterility in ISO Class 5 areas and within
31 primary engineering controls, and;
- 32 6. Labeling and inspecting CSPs for quality.

33 C. The required Aseptic Technique Skill Assessment must be completed for staff
34 compounding low or medium risk preparations prior to initial compounding and
35 every twelve (12) months thereafter. For staff compounding high risk
36 preparations, the assessment must be completed prior to initial compounding and
37 every six (6) months thereafter.

1 D. Compounding staff shall successfully pass all training and assessments. Staff
2 who fail to demonstrate competency or whose glove fingertip sampling or
3 media-fill tests demonstrate one or more units of visible microbial contamination
4 shall be reinstructed and re-evaluated to ensure correction of all deficiencies
5 prior to beginning or continuing any further compounding. The reinstruction and
6 reevaluation shall be documented in the pharmacy's records.

7 E. Training and assessment dates along with the results of the required practical
8 aseptic technique skill assessment, glove fingertip sampling and media fill
9 testing shall be documented and maintained in the pharmacy's records and
10 reviewed by the pharmacist-in-charge to ensure compliance.
11

12 (26) **Glove Fingertip Sampling.** Compounding staff shall undergo and successfully
13 complete both initial and ongoing glove fingertip sampling to assess compliance with
14 gloving and aseptic processing. Initial and ongoing fingertip sampling shall be
15 completed in accordance with USP Chapter 797 procedures, timeframes and methods.
16 Sampling shall be conducted following each required media fill test as part of the
17 practical aseptic technique skill assessment. In addition to USP requirements, samples
18 must be tested for mold, yeast, bacteria and fungus.
19

20 (27) **Media-Fill Testing.** Pharmacies shall establish and follow policies and procedures
21 for conducting media-fill testing to assess the quality of aseptic skills/techniques of
22 compounding staff. Media fill tests shall be conducted as part of the required aseptic
23 technique skill assessment and shall include a minimum of three media fill units using
24 the same container or closure. Initial and ongoing media-fill testing shall be
25 completed in accordance with USP Chapter 797 recommended procedures and
26 methods for the risk level(s) of sterile compounding performed.
27

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

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

- 1 B. **Viable Airborne Particle Testing:** Volumetric viable air sampling by
2 impaction shall be conducted in all ISO classified environments. Each viable
3 air sample shall sample 1,000 liters for all ISO Class 5 areas and 500 liters
4 for other ISO classified areas. Each sample location shall be tested with both
5 general growth media (i.e., tryptic soy agar) and fungal specific media (i.e.,
6 malt extract agar or saboraud dextrose agar) on plates of at least 55mm in
7 size. Use of settling plates alone shall not be sufficient. Viable Airborne
8 Particle Testing must be conducted prior to initial compounding and every
9 six (6) months thereafter. Testing shall also occur:
- 10 1. As part of the initial certification of new facilities and equipment;
 - 11 2. Whenever the physical structure of the compounding area has been
12 altered;
 - 13 3. As part of the recertification of facilities and equipment;
 - 14 4. In response to identified problems with sterile preparations or end-
15 preparation testing failure; and
 - 16 5. Whenever maintenance, repairs or changes to the primary
17 engineering control(s) or compounding area may affect the airflow
18 pattern. The date and type of maintenance, repair or change shall be
19 documented in the pharmacy's records;
- 20 C. **Non-Viable Airborne Particle Testing.** Non-viable air sampling shall be
21 performed using a volumetric device in compliance with USP Chapter 797.
22 Non-Viable Airborne Particle Testing must be conducted prior to initial
23 compounding and every six (6) months thereafter.
- 24 D. **Pressure Differential:** Pressure differential monitoring shall be required for
25 all sterile compounding areas to ensure compliance with section (7)(B) of
26 this rule. Pressure differential monitoring results shall be documented in
27 writing and reviewed daily.
- 28
- 29 (29) **General Cleaning and Disinfection Requirements.** The pharmacy shall establish
30 and follow written policies and procedures governing all aspects of cleaning and
31 disinfection. Except as otherwise provided herein, the following requirements shall
32 be applicable:
- 33 A. Compounding areas and segregated compounding areas shall be free of
34 infestation by insects, rodents and other vermin. Trash shall be disposed of in a
35 timely and sanitary manner.
 - 36 B. Cleaning and disinfection shall be performed and conducted in accordance with
37 USP Chapter 797 timeframes and procedures, except as otherwise provided
38 herein.

- 1 C. Individuals responsible for cleaning and disinfecting shall be trained in proper
2 cleaning and disinfection procedures and mechanisms prior to performing
3 cleaning/disinfection activities. Training shall include direct visual observation
4 of the individual's cleaning and disinfecting process by qualified staff. The
5 individual shall be annually reassessed for competency through direct visual
6 observation. Documentation of the required training and training dates shall be
7 maintained in the pharmacy's records. Individuals who fail to demonstrate
8 competency shall be re-instructed and successfully reevaluated prior to cleaning
9 or disinfecting the compounding or segregated compounding area.
- 10 D. Cleaning, disinfection and mopping activities shall be performed using approved
11 agents and procedures described in the pharmacy's written policies and
12 procedures. Cleaning and disinfecting agents shall be selected based on
13 compatibility, effectiveness and the absence of inappropriate or toxic residues.
14 Manufacturers' directions or published peer-reviewed literature for minimum
15 contact time shall be followed.
- 16 E. Primary engineering controls shall be cleaned with a germicidal detergent
17 followed by sterile alcohol. Sterile water for irrigation shall be used to dilute
18 germicidal agents used inside the PEC that require dilution.
- 19 F. *Segregated Compounding Areas*: Floors and work surfaces within the line of
20 demarcation shall be cleaned and disinfected daily or immediately prior to
21 compounding if not used daily. Shelving and storage areas shall be cleaned and
22 disinfected monthly.

23
24 (30) **Quality Assurance**. Sterile compounding pharmacies shall establish and follow a
25 written quality assurance program for monitoring and evaluating the quality of
26 compounding activities.

- 27 A. At a minimum, the quality assurance program shall include procedures for
28 monitoring and tracking infection rates, adverse drug events, preparation
29 recalls and complaints from prescribers, patients or other individuals or
30 entities.
- 31 B. The quality assurance plan shall delineate the individuals responsible for each
32 aspect of the quality assurance program either by name or position title.
- 33 C. The quality assurance plan shall be maintained at the pharmacy or readily
34 retrievable upon request. The pharmacist-in-charge shall annually review the
35 quality assurance program and document the review in the pharmacy's records.
36

- 1 (31) **Recalls.** A recall must be initiated when a dispensed or distributed preparation is
2 deemed to be misbranded, adulterated or non-sterile or if end-preparation testing
3 results are out of specification. The pharmacy shall notify the prescriber of the nature
4 of the recall, the problem(s) identified and any recommended actions to ensure public
5 health and safety. In cases where the compounded preparation has the potential to
6 harm the patient, the same notification shall be provided to all patients that received
7 the recalled preparation(s).
- 8 A. Patient and prescriber notifications required by this section shall be made as soon
9 as reasonably practicable but in no event later than one (1) business day of the
10 recall. The date and manner of notification shall be documented in the pharmacy's
11 records.
- 12 B. If a patient recall notification is unsuccessful, the pharmacy shall mail notification
13 to the patient within the required one (1) business day timeframe.
- 14 C. Recalls initiated pursuant to this section shall be reported to the board in writing
15 within three (3) business days, in a form approved by the Board.
- 16 D. If recall notification cannot be conducted as required herein, the pharmacy may
17 submit to the Board a written plan to extend the notification period. The request
18 must include a description of the nature of the recall, the potential number of
19 patients affected, the reason(s) supporting the extension request and a proposed
20 timeframe for completing the required notifications.
- 21
- 22 (32) **Record Keeping.** The pharmacy shall maintain the following records:
- 23 A. Aseptic competency training and aseptic technique skill assessment dates and
24 results;
- 25 B. Testing dates and results for glove fingertip sampling, media-fill tests and end-
26 preparation testing;
- 27 C. Environmental sampling dates and results, including, any corrective efforts
28 taken;
- 29 D. Cleaning and disinfection evaluation dates and results;
- 30 E. Required refrigerator and temperature logs;
- 31 F. Cleaning and disinfection records that document compliance with this rule;
- 32 G. Equipment calibration dates and results and maintenance reports;
- 33 H. Certificates of analysis for compounding ingredients;
- 34 I. Certification records for PECs and sterile compounding areas;
- 35 J. Copies of any manufacturer equipment standards that are relied upon to
36 maintain compliance with this rule;
- 37 K. Batch preparation files;
- 38 L. For high risk preparations, sterilization, quarantine and ingredient validation
39 records;

Comment [A5]: I revised this section to r
closely match 2220-2.040(8)(C). My notes
didn't have a firm recommendation on the
timeframe. What should be included here?

- 1 M. Emergency dispensing records as required by subsection (17), including,
2 documentation of prescriber authorization and the dates of such authorization;
- 3 N. Preparation recall records, including, dates, patients affected and any
4 investigation, corrective actions or recall notifications made; and
- 5 O. All other records required by this rule or governing law.
- 6 P. Except as otherwise provided herein, records and reports required by this rule
7 shall be either electronically or physically maintained for two (2) years.
8 Records shall be readily retrievable and subject to inspection by the Board of
9 Pharmacy or its agents upon request. At a minimum, records shall be
10 physically or electronically produced immediately or within two (2) hours of a
11 request from the Board or the Board's authorized designee.
- 12 Q. Prescription records shall be maintained in compliance with Missouri law and
13 the rules of the Board.

14
15 (33) **Hazardous Drugs and Radiopharmaceuticals.** Hazardous CSPs and
16 radiopharmaceuticals shall be prepared, stored and compounded in accordance with
17 USP 797. Compounding staff engaged in handling, preparing or compounding
18 hazardous drugs or radiopharmaceuticals shall be trained as required by USP Chapter
19 797. The following additional requirements shall be implemented to insure the
20 protection of the staff involved:

- 21 A. Hazardous drugs/preparations shall be stored, handled and prepared under
22 conditions that protect workers and other staff.
- 23 B. Appropriate disposal containers shall be available for used needles, syringes,
24 and if applicable, hazardous waste from the preparation of chemotherapy
25 agents and infectious waste. Disposal of hazardous waste shall comply with
26 all applicable local, state and federal requirements;
- 27 C. Written procedures for handling major and minor spills and generated waste
28 of hazardous agents must be developed and must be included in the policy
29 and procedure manual, and;
- 30 D. Prepared doses of hazardous drugs must be labeled with proper precautions
31 inside and outside, and shipped in a manner to minimize the risk of
32 accidental rupture of the primary container.
- 33 E. Notwithstanding any provision of this rule or USP Chapter 797, low risk
34 radiopharmaceutical preparations prepared in a segregated compounding
35 area may be assigned an eighteen (18) hour or lesser beyond-use date.

36
37 (34) **Applicability.** If a conflict between this rule and the applicable provisions of USP
38 exists, the requirements of this rule shall apply unless otherwise indicated herein.