

Meeting Notice

Missouri Board of Pharmacy Sterile Compounding Rule Review

**December 18, 2015 9:00 a.m. to 4:00 p.m.
Professional Registration
3605 Missouri Blvd
Jefferson City, MO 65109**

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

If any member of the public wishes to attend the meeting, s/he should be present at the Division of Professional Registration, Executive Conference Room, 3605 Missouri Blvd, Jefferson City, Missouri, at 9:00 a.m. on December 18, 2015.

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

Please see attached tentative agenda for this meeting.

TENTATIVE AGENDA
December 18, 2015 9:00 a.m. to 4:00 p.m.

Missouri Board of Pharmacy
Sterile Compounding Rule Review

Professional Registration
3605 Missouri Blvd
Jefferson City, MO 65109

- 1 Review of Sterile Compounding Rule/Draft Revisions to 20 CSR 2220-2.200
- 2 Review of Proposed USP Chapter 797
- 3 Future Meeting Dates/Times

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

3
4 **Division 2220—State Board of Pharmacy**
5 **Chapter 2—General Rules**
6

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8 | **20 CSR 2220-2.200250 Sterile Compounding**

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

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

16			
17	(1) General Applicability	36	(18) Labeling
18	(2) Definitions	37	(19) Final Verification
19	(3) Risk Levels	38	(20) Beyond-Use Dating
20	(4) Low Risk CSPs with 12-Hour or Less Beyond-Use Date	39 40	(21) Point-of-Care Activated Systems
21	(5) General Compounding Requirements	41	(22) Storage
22	(6) Policies and Procedures	42	(23) Packaging and Delivery
23	(7) Facility Design Requirements	43	(24) Compounding Log
24	(8) Segregated Compounding Areas	44	(25) Aseptic Manipulation Training & Assessment
25	(9) ISO Certification	45	(26) Glove Fingertip Sampling
26	(10) Equipment	46	(27) Media-Fill Testing
27	(11) Primary Engineering Controls	47	(28) Environmental Sampling
28	(12) Ingredients & Supplies	48	(29) Facility Cleaning and Disinfection Requirements
29	(13) Standard Operating Procedures	49	(30) Quality Assurance
30	(14) Personal Cleansing and Garbing	50	(31) Recalls
31	(15) Aseptic Processing	51	(32) Record Keeping
32	(16) Additional Aseptic Technique Requirements for High Risk CSPs	52 53	(33) Hazardous Drugs
33	(17) End Preparation Testing	54	(34) Applicability
34			
35			
55			

56
57 [1]

***This document is a preliminary draft that has not been officially reviewed or approved by the Board. The Board will review the proposed draft and the recently released proposed changes to USP 797 during its 10/14/15 open session meeting. The public is invited to attend and to submit written comments. Comments should be submitted before 10/10/15 to MissouriBOP@pr.mo.gov.*

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

58 (2) **Definitions.**

- 59 (A) **Action Level:** A situation in which action must be taken in order to maintain
60 compliance with this rule, USP Chapter 797 or both.
- 61 (B) **Adverse Event:** Any incident related to or resulting from the compounding
62 process that did or may have resulted in an adverse patient outcome.
- 63 (C) **Ante-Area:** An area in which the concentration of airborne particles is controlled
64 to meet ISO Class 8 or better air quality and that provides assurance that pressure
65 relationships are constantly maintained so that air flows from clean to dirty areas.
- 66 (D) **Aseptic processing:** A mode of processing pharmaceutical and medical CSPs in
67 an ISO Class 5 area that involves procedures designed to produce a CSP that
68 meets a predetermined sterility assurance level and to preclude or prevent
69 contamination by microorganisms during processing or preparation.
- 70 (E) **Batch:** Batch compounding includes: (1) compounding multiple CSP units in a
71 single discrete process, by the same individual(s), carried out during one limited
72 time period, (2) compounding in advance of receiving a prescription and (3)
73 compounding a quantity in excess of the filling of an individual prescription or
74 medication order.
- 75 (F) **Beyond-Use Date:** For purposes of this rule, the date or time after which a CSP
76 should not be used.
- 77 (G) **Biological Safety Cabinet:** A ventilated cabinet for CSPs and for staff,
78 preparation and environmental protection that has an open front with inward
79 airflow for staff protection, downward high-efficiency particulate air (HEPA)
80 filtered laminar airflow for CSP protection, and HEPA-filtered exhausted air for
81 environmental protection.
- 82 (H) **Buffer Area:** An ISO 7 area where a primary engineering control is physically
83 located.
- 84 (I) **CFU:** Colony forming units.
- 85 (J) **Compounding:** The preparation, incorporation, mixing, packaging or labeling of a
86 drug or drug containing device: (1) as the result of a prescriber's prescription or
87 medication order based on the prescriber/patient/pharmacist relationship in the
88 course of professional practice, or (2) in anticipation of a prescription or
89 medication order as provided herein, or (3) for or incident to research, teaching or
90 chemical analysis and not for sale or dispensing purposes.
- 91 (K) **Compounding Area:** The area designated for preparing CSPs and includes the
92 ante-area and buffer area.

Comment [A1]: The Hospital Advisory Committee (HAC) indicated the BUD definition is consistent with current industry practice/understanding.

[2]

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- 93 (L) **Compounding Aseptic Containment Isolator (CACI):** A compounding aseptic
94 isolator (CAI) designed to provide worker protection from exposure to undesirable
95 levels of airborne drugs throughout the compounding and material transfer
96 processes and to provide an aseptic environment for CSPs.
- 97 (M) **Compounding Aseptic Isolator (CAI):** A form of isolator specifically designed
98 for compounding pharmaceutical ingredients or CSPs and to maintain an aseptic
99 compounding environment within the isolator throughout the compounding and
100 material transfer processes.
- 101 (N) **Compounding Equipment:** Equipment, instruments, apparatuses, and devices
102 used to compound CSPs.
- 103 (O) **Compounding Staff:** Any person who engages or participates in any aspect of
104 sterile compounding regardless of employment status.
- 105 (P) **Compounded Sterile Preparation (CSP):** Any low risk, medium risk or high
106 risk CSP prepared by a pharmacy, including:
107 a. Compounded biologics, diagnostics, drugs, nutrients, and
108 radiopharmaceuticals that must or are required to be sterile when they are
109 administered to patients, including, but not limited to the following dosage
110 forms: bronchial and inhaled nasal preparations intended for deposition in
111 the lung, baths and soaks for live organs and tissues, epidural and intrathecal
112 solutions, bladder/wound solutions, injectables, implantable devices and
113 dosage forms, inhalation solutions, intravenous solutions, irrigation
114 solutions, ophthalmic preparations, parenteral nutrition solutions, and
115 repackaged sterile preparations. Nasal sprays and irrigations intended for
116 deposit in the nasal passages may be prepared as nonsterile compounds;
- 117 b. An FDA approved manufactured sterile product that is either prepared
118 according to the manufacturers' approved labeling/recommendations or
119 prepared differently than published in such labeling; and
- 120 c. Assembling point-of-care activated systems.
- 121 (Q) **Controlled Room Temperature:** A controlled room temperature as defined by
122 USP.
- 123 (R) **Critical Area:** An ISO Class 5 environment.
- 124 (S) **Critical Site:** Any surface, pathway or opening (e.g., vial septa, injection ports,
125 beakers, needle hubs) that provides a direct pathway between a CSP or other
126 ingredient used to compound a CSP and the air, environment or moisture or that
127 poses a risk of touch contamination.

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- 128 (T) **Direct Compounding Area (DCA):** An area within an ISO Class 5 primary
129 engineering control where critical sites are exposed to unidirectional HEPA-
130 filtered air also known as first air.
- 131 (U) **Disinfectant:** An agent applied to inanimate objects that frees from infection and
132 destroys disease-causing pathogens or other harmful microorganisms but may not
133 kill bacterial and fungal spores.
- 134 (V) **Experiential Training:** Training based on experience and observation.
- 135 (W) **First Air:** The air exiting a HEPA filter in a unidirectional air stream that is
136 essentially particle free.
- 137 (X) **Frozen:** The temperature range for a freezer as defined by USP.
- 138 (Y) **Hazardous Drugs:** A hazardous drug as indicated on the National Institute for
139 Occupational Safety and Health's (NIOSH) List of Antineoplastic and Other
140 Hazardous Drugs in Healthcare Settings.
- 141 (Z) **High-Efficiency Particulate Air (HEPA) filter:** A particulate filter that directs
142 the flow of air forced through the filter in a uniform parallel flow and that is: (1)
143 capable of retaining airborne particles and microorganisms while allowing gases to
144 pass freely through and, (2) a minimum of 99.97% efficient when tested using 0.3-
145 µm thermally generated particles and a photometer or rated at their most
146 penetrating particle size using a particle counter.
- 147 (AA) **ISO Class 5:** An area with less than 3,520 particles (0.5 µm and larger in size)
148 per cubic meter.
- 149 (BB) **ISO Class 7:** An area with less than 352,000 particles (0.5 µm and larger in size)
150 per cubic meter.
- 151 (CC) **ISO Class 8:** An area with less than 3,520,000 particles (0.5 µm and larger in
152 size) per cubic meter.
- 153 (DD) **Line of Demarcation:** A visible line or barrier on the floor that separates a room
154 into distinct and identifiable separate areas for the performance of sterile
155 compounding from general pharmacy activities.
- 156 (EE) **Media-Fill Test:** A test using a growth medium to verify aseptic compounding
157 techniques or processes that are able to produce a CSP without microbial
158 contamination.
- 159 (FF) **Multiple-Dose Container:** A multiple-unit container for articles or CSPs that
160 contains more than one dose of medication and an antimicrobial preservative.
- 161 (GG) **Parenteral:** A CSP intended for injection through one (1) or more layers of skin.
- 162 (HH) **Peer-Reviewed Literature:** Literature that has been evaluated by other qualified
163 scientific, academic or qualified professionals for quality or accuracy and has been

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164 nationally published in a pharmaceutical, scientific, compendial or other medical
165 publication.

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

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168 ~~(H)~~(JJ) **Point of Care Activated System:** A closed system device that creates a
169 physical barrier between diluents, fluids or other drug components and is designed
170 to be activated by the end user by allowing the components to mix prior to
171 administration.

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

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

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

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

185 ~~(NN)~~(OO) **Single-Dose/Single-Unit Container/vial:** A container/vial of medication
186 intended for administration that is meant for use in a single patient for a single
187 case, procedure or injection.

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

Comment [A2]: During drafting, concerns were raised about requiring sterile alcohol or something equivalent/superior, throughout the rule. Several HAC members indicated sterile alcohol is the "gold standard" and should be included.

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

193 ~~(QQ)~~(RR) **Terminal Sterilization:** The application of a lethal process for the purpose
194 of achieving a predetermined sterility assurance level of less than 10⁻⁶, or a
195 probability of less than one nonsterile unit in one million units.

196 ~~(RR)~~(SS) **USP:** The United States Pharmacopeia and the National Formulary (USP-
197 NF) as adopted and published by the United States Pharmacopeial Convention,
198 effective May 2013. Copies of the USP-NF are published by, and available from,
199 USP, 12601 Twinbrook Parkway, Rockville, MD 20852-1790 or online at

200 <http://www.usp.org/>. The USP-NF is incorporated herein by reference. This rule
201 does not include any later amendments or additions to the USP-NF.

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

205
206 (3) **Risk Levels.** The following contamination risk levels shall be established for CSPs:

- 207 A. **Low Risk:** CSPs compounded under the following conditions:
- 208 1. CSPs compounded with aseptic manipulations entirely within an ISO
209 Class 5 or better air quality using only sterile ingredients, products,
210 components and devices;
 - 211 2. Compounding involving the transfer, measuring, mixing or manipulation
212 of no more than three commercially manufactured packages of sterile
213 products and no more than two entries into any one sterile container or
214 package (e.g., bag, vial) of sterile product or administration
215 container/device;
 - 216 3. Compounding manipulations are limited to aseptically opening ampules,
217 penetrating disinfected stoppers on vials with sterile needles/syringes,
218 and transferring sterile liquids in sterile syringes to sterile administration
219 devices or package containers of other sterile products/containers for
220 storage and dispensing;
 - 221 4. CSPs prepared by closed-system aseptic transfer of sterile, non-
222 pyrogenic finished pharmaceuticals obtained from licensed
223 manufacturers into sterile final containers obtained from licensed
224 manufacturers, or;
 - 225 5. Assembly of point-of-care activated systems.

- 226 B. **Medium Risk:** CSPs compounded under any of the following conditions:
- 227 1. Compounding involving the transfer, measuring, or mixing
228 manipulations of more than three commercially manufactured
229 packages/vials of sterile products or involving more than two entries into
230 any one sterile container or package (e.g., bag, vial) of sterile product or
231 administration container/device;
 - 232 2. Multiple individual or small doses of sterile products are combined or
233 pooled to prepare a CSP that will be administered either to multiple
234 patients or to one patient on multiple occasions;
 - 235 3. CSPs compounded with a medium risk CSP, or

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4. The compounding process includes complex aseptic manipulations other than single-volume transfer and the CSP does not otherwise meet the definition of a high risk sterile CSP.
 5. Medium Risk CSPs shall remain medium risk for the life of the CSP.
- C. **High Risk:** CSPs compounded under any of the following conditions:
1. CSPs compounded from nonsterile ingredients including, but not limited to, manufactured products not intended for sterile routes of administration (e.g., oral);
 2. Compounding using nonsterile components, containers, devices or equipment before terminal sterilization. If any nonsterile components are used to make a CSP, the CSP shall be deemed high risk;
 3. Confirmed or suspected exposure of any of the following to worse than ISO Class 5 air quality for more than one (1) hour: (1) sterile contents of commercially manufactured products, (2) CSPs that lack effective antimicrobial preservatives or (3) any sterile surface of a device or container used for the preparation, transfer, sterilization or packaging of CSPs;
 4. CSPs prepared by using an open-system transfer or open reservoir before terminal sterilization;
 5. CSPs compounded with a high risk CSP, or;
 6. Nonsterile water-containing CSPs that are stored for more than 6 hours before being sterilized.
 7. High Risk CSPs shall remain high risk for the life of the CSP.
- (4) **Low-Risk or Medium Risk CSP with a 12-Hour or Less Beyond-use Date:** A Low Risk or Medium Risk CSP may be compounded in a segregated compounding area if:
- (A) The CSP is compounded in a PEC that complies with section (11) of this rule;
 - (B) The CSP is assigned the lesser of a 12-hour beyond-use date or the beyond-use date recommended in the manufacturers' package insert. The CSP may not be dispensed or distributed after the assigned beyond-use date;
 - (C) Individuals engaged in, or assisting with, sterile compounding follow proper hand hygiene, garbing and aseptic technique in the segregated compounding area as required by this rule; and
 - (D) The PEC shall be cleaned and disinfected as required by this rule.

Comment [A3]: Barbara suggested PECs should also be decontaminated weekly.

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- 271 (5) **General Compounding Requirements.** CSPs shall be correctly packaged, handled,
272 transported, stored, dispensed and distributed. Appropriate quality control methods
273 shall be maintained over compounding methods at all times to ensure proper aseptic
274 technique and compliance with all applicable state and federal law.
- 275 A. CSPs shall only be compounded pursuant to a valid patient-specific prescription,
276 prescription drug order or medication order. However, drugs may be
277 compounded in anticipation of a valid prescription/order based on a history of
278 receiving valid prescriptions/orders that have been generated solely with an
279 established pharmacist/patient/prescriber relationship and in an amount that does
280 not exceed a ~~one (1) month~~ 45-day supply for dispensing purposes.
- 281 B. Compounding in anticipation of receiving a prescription, prescription drug order
282 or medication order without an appropriate history of such prescriptions/orders
283 on file shall be considered manufacturing instead of compounding.
- 284 C. Any alteration, change or modification to the contents of a commercially
285 manufactured over-the-counter medication shall require a valid prescription,
286 prescription ~~drug order~~ or medication order from an authorized prescriber.
- 287 D. Pharmacists shall not offer CSPs to other pharmacies, practitioners or
288 commercial entities for subsequent resale or administration, except pursuant to a
289 patient specific prescription/order or as authorized by a Class J pharmacy permit.
- 290 E. A pharmacist or pharmacy may advertise or otherwise provide information
291 concerning the provision of compounding services, however, no pharmacist or
292 pharmacy shall attempt to solicit business by making specific claims about CSPs
293 without specific testing of the CSP as compounded by the pharmacy to validate
294 such claim.
- 295 F. Compounding of CSPs that are commercially available in the marketplace or
296 that are essentially copies of commercially available FDA approved drug
297 products is prohibited. This prohibition shall not apply if the drug is not
298 commercially available due to circumstances beyond the licensee's control (e.g.,
299 a drug shortage) or a specific medical need for a particular variation of a
300 commercially available compound exists. Documentation of drug unavailability
301 or the specific medical need for compounding a commercially available product
302 shall be maintained in the pharmacy's records.
- 303 G. The pharmacy shall maintain current drug reference materials related to CSPs
304 that shall be electronically or physically available in the pharmacy for use and
305 inspection by pharmacy staff.

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

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

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

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

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

329
330 (6) Policies and Procedures. Pharmacies shall establish and follow a written sterile
331 compounding policy and procedure manual. The manual shall be current and shall be
332 electronically or physically accessible to pharmacy staff. The pharmacist-in-charge
333 shall annually review the manual for compliance and document the date of the required
334 annual review in the pharmacy's records. The required policy and procedure manual
335 shall encompass all aspects of sterile compounding performed by the pharmacy and
336 must include policies/procedures for:

- 337 1. Compounding, labeling and dispensing CSPs;
338 2. Storing, transporting and delivering CSPs;
339 3. Cleaning and disinfection. Policies and procedures shall identify authorized
340 cleaning/disinfecting agents and materials, schedules of use and methods of
341 application;

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Comment [A4]: A HAC member suggested reporting of highly pathogenic microorganisms should only be required if the microorganism is actually found in a preparation.

Other members suggested defining a "highly pathogenic microorganism" and/or clarifying what remediation efforts are required.

- 342 4. Maintaining, verifying and testing the accuracy and functioning of
343 compounding equipment, including, time frames for calibration, testing,
344 equipment monitoring and both annual and routine maintenance;
345 5. Beyond-use-dating;
346 6. Approved methods of sterilization and purification;
347 7. Environmental sampling, including, specified time frames and locations;
348 8. End-preparation testing, including, sampling plans;
349 9. Staff training and monitoring competency;
350 10. Reporting and investigating environmental deficiencies;
351 11. Media-fill testing. Policies and procedures shall address/identify media-fill
352 procedures, media selection, fill volume, incubation requirements, time and
353 temperature requirements, testing documentation, analyzing results, and any
354 corrective action guidelines or procedures;
355 12. Measures for preventing cross-contamination when compounding activities
356 require the manipulation of a patient's blood-derived or other biological
357 material (e.g., radiolabeling a patient's or donor's white blood cells);
358 13. Recall procedures which must include procedures for identifying and
359 notifying affected patients, prescribers and regulators when applicable;
360 14. Handling and reporting accidental exposures or spills of hazardous CSPs,
361 including, reporting methods and timeframes;
362 15. Reporting and investigating any real or suspected adverse event or any real
363 or suspected contaminated, non-sterile or defective final CSP, and;
364 16. Educating patients and/or caregivers concerning the appropriate storage, use
365 and control of CSPs, when applicable.

- 367 (7) **Facility Design Requirements.** Except as otherwise provided in section (8), CSPs shall
368 be prepared in a compounding area that includes an ante area and buffer area(s).
369 A. **Compounding Area Design Requirements:** Compounding areas and surfaces
370 shall be designed, maintained and controlled to minimize the risk of preparation
371 contamination and the introduction, generation, accumulation and retention of
372 particles. Compounding areas must be clean, well lit and designed in a manner that
373 will allow effective cleaning and disinfection for the activities performed.

Comment [A5]: Members of the HAC indicated the rule and new facility design requirements may have a significant financial impact on hospital owned pharmacies, especially Critical Access Hospitals. The HAC suggested that the rule allow pharmacies/hospitals to submit a variance request to the Board for the facility/design requirements (see section 34).

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1. Junctures of ceilings to walls shall be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels shall be impregnated with a polymer to render them impervious and hydrophobic, and they shall be caulked around each perimeter to seal them to the support frame.
 2. Dust-collecting overhangs must be avoided, such as ceiling utility pipes, ledges or windowsills.
 3. Work surfaces and the surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, cleanable, non-shedding and resistant to damage by disinfectants.
 4. Adequate provision for antiseptic hand cleansing shall be provided after entry into the ante area.
 5. The buffer area shall not contain sources of water or floor drains. A sink with hot and cold water must be near, but not in, the buffer area.
 6. The exterior lens surface of ceiling lighting fixtures shall be smooth, mounted flush or mounted/installed to promote easy cleaning.
 7. Furniture in the compounding area shall be nonporous, smooth, non-shedding, impermeable, cleanable, and resistant to damage by disinfectants.
 8. Temperature, humidity and pressure in the compounding area shall be controlled as necessary to ensure compliance with this rule.
 9. Compounding areas and CSP storage areas (e.g., refrigerators and freezers) must have an effective temperature measuring device. At a minimum, temperatures shall be recorded and documented each day that the pharmacy is open for pharmacy activities. Alternatively, a continuous temperature monitoring system may be maintained if the system maintains ongoing documentation of temperature recordings or, if applicable, temperature alerts that are reviewed daily. Documentation of the required review shall be maintained in the pharmacy's records or otherwise accessible to the pharmacy.

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

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408
409
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.

[11]

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410 2. The supply of HEPA-filtered air shall be adequate to maintain the required
411 air quality classification. HEPA-filtered air shall be introduced in
412 compounding areas at the ceiling and returns shall be mounted low on the
413 wall, creating a general top-down dilution of area air with HEPA-filtered
414 make-up air. Pharmacies licensed on the effective date of this rule with
415 ceiling mounted returns shall be authorized to continue operations if the
416 pharmacy maintains documentation that it is able to maintain the required
417 ISO class conditions and environmental quality, provided that compliance
418 with this subsection shall be required if the compounding area is
419 moved/relocated.

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

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

439
440 (8) **Segregated Compounding Areas:** In lieu of a compounding area that includes an
441 ante area and buffer area, Low Risk and Medium Risk CSPs may be compounded in a
442 segregated compounding area within the pharmacy that complies with the following:

Comment [A6]: The change was suggested to clarify the rule would only apply to compounding within an SCA that is in the pharmacy and not to nursing compounding activities that happen on the floor.

[12]

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- 443 A. Segregated compounding areas shall be designed, maintained and controlled to
444 minimize the risk of preparation contamination and the introduction,
445 generation and retention of particles inside the PEC. A segregated
446 compounding area must be clean and well lit and designed in a manner that
447 will allow effective cleaning and disinfection for the activities performed.
- 448 B. A line of demarcation must be established that defines and separates the
449 segregated compounding area from other pharmacy activities/areas. The
450 segregated compounding area shall be dedicated solely to activities directly
451 related to sterile compounding. Segregated compounding areas shall not be
452 used for non-sterile compounding.
- 453 C. Segregated compounding areas shall not include carpet or unsealed windows
454 or doors that connect to the outdoors or be located in high traffic flow areas or
455 areas in or adjacent to construction sites, warehouses, or food preparation or in
456 any area with environmental air disturbances that may affect the PEC.
- 457 D. Areas and surfaces within the segregated compounding area shall be
458 constructed and maintained in a manner that will minimize spaces in which
459 microorganisms and other contaminants may accumulate. All surfaces shall be
460 smooth, impervious, cleanable, nonshedding and resistant to damage by
461 disinfectants, including, but not limited to, fixtures, shelving, counters,
462 ceilings, walls and floors.
- 463 E. The segregated compounding area shall not contain sources of water or floor
464 drains. A sink with hot and cold water must be available outside of the
465 segregated compounding area. Sinks must be a minimum of three (3) feet but
466 no farther than twenty-five (25) feet away from the PEC.
- 467 F. Adequate provision for performing antiseptic hand hygiene shall be provided
468 before entry into the PEC.
- 469 G. CSP storage areas (e.g., refrigerators and freezers) must have an effective
470 temperature measuring device. At a minimum, temperatures shall be recorded
471 and documented each day that the pharmacy is open for pharmacy activities.
472 Alternatively, a continuous temperature monitoring system may be maintained
473 if the system maintains ongoing documentation of temperature recordings that
474 are reviewed daily by pharmacy staff. The required daily staff review shall be
475 documented in the pharmacy's records.

[13]

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- 476 H. Low and medium risk CSPs compounded in a segregated compounding area
477 must be assigned a beyond-use date in compliance with section (21). The
478 assigned beyond-use date must be 12-hours or less unless the CSP is
479 compounded in a CAI or CACI that meets the following:
- 480 1. The CAI/CACI must provide isolation from the room and maintain ISO
481 Class 5 air quality during dynamic operating conditions;
 - 482 2. The manufacturer documents or verifies that the CAI/CACI will meet the
483 requirements of this subsection when located in environments where the
484 background particle counts exceed ISO Class 8 for 0.5 µm and larger
485 particles; and
 - 486 3. Documentation of compliance and the manufacturer's verification is
487 maintained in the pharmacy's records.
- 488 I. Except as otherwise provided in this subsection (8), segregated compounding areas
489 shall comply with all other applicable provisions of this rule.
- 490 J. High Risk CSPs may not be compounded in a segregated compounding area.
- 491 K. Relocation of the segregated compounding area shall constitute a pharmacy remodel
492 and require compliance with 20 CSR 2220-2.020.
- 493
- 494 (9) **ISO Certification.** All ISO classified areas and each PEC shall be certified to
495 ensure compliance with requirements of this rule. Certification shall be performed by
496 qualified individuals using recognized and appropriate certification and testing equipment:
- 497 A. Certification shall be performed prior to beginning sterile compounding activities
498 and every six (6) months thereafter. Recertification shall be completed whenever
499 the physical structure of the buffer area or ante-area has been altered or any other
500 facility changes or any changes to the PEC occur that may affect airflow or pressure
501 differential. PECs shall also be recertified when the device is relocated or altered or
502 major service to the PEC is performed.

- 503 B. Certification/re-certification shall be conducted in accordance with the Controlled
504 Environment Testing Association Certification Guide for Sterile Compounding
505 Facilities (2008), which is incorporated herein by reference. Copies of the
506 Certification Guide for Sterile Compounding Facilities (2008) are published by, and
507 available from, Controlled Environment Testing Association, 1500 Sunday Drive,
508 Suite 102, Raleigh, NC 27607 or online at <http://www.cetainternational.org/>. This
509 rule does not include any later amendments or additions to the Certification Guide.
510 The pharmacy shall maintain an attestation or statement from the certifier verifying
511 that certification/recertification was performed in compliance with Certification
512 Guide guidelines.
- 513 C. Certification/recertification results shall be reviewed by a pharmacist once the
514 completed results are received. Deficiencies or failures shall be investigated and
515 corrected prior to further compounding. Corrections may include, but are not
516 limited to, changes in the use of the affected PEC or the ongoing use/recall of CSPs.
517 The identity of the pharmacist conducting the required review and the review date
518 shall be documented in the pharmacy's records.
- 519 D. An in situ air pattern analysis (e.g. smoke study) shall be required prior to initial
520 compounding and whenever maintenance, repairs or changes to the PEC or
521 compounding area occur that may affect the airflow pattern. The in situ air pattern
522 analysis shall be conducted at the critical area to demonstrate unidirectional airflow
523 and sweeping action over and away from the CSP under dynamic conditions. For
524 purposes of this section, maintenance does not include routine pre-filter changes.
525
- 526 (10) **Equipment.** Compounding equipment shall be clean, properly functioning and
527 effective for their intended use and shall be consistently capable of operating
528 properly and within acceptable limits.
- 529 A. Equipment or other supplies shall be used, maintained, calibrated and verified
530 for accuracy according to manufacturer recommendations, unless otherwise
531 provided by Board rules.
- 532 B. Surfaces of compounding equipment that contact ingredients or in-process
533 materials shall not be reactive so as to alter the strength, stability, quality or
534 purity of the CSP beyond that desired.

[15]

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- 535 C. Automated compounding devices shall be tested for content, volume and
536 weight accuracy prior to both initial and daily use. Test results shall be
537 reviewed by a pharmacist to ensure compliance. The identity of the reviewing
538 pharmacist and the review date shall be documented in the pharmacy's
539 records.
- 540 D. In the event of improper or inaccurate functioning, the equipment/device shall
541 not be used until the deficiency has been remedied.
- 542 E. If ingredients/CSPs with special precautions for contamination are involved
543 (e.g., penicillin), appropriate measures must be utilized in order to prevent
544 cross-contamination (e.g., restricting equipment use for other
545 operations/compounding or proper cleaning).
- 546
- 547 (11) **Primary Engineering Controls (PEC):** PECs shall be properly located, operated
548 and maintained and shall comply with the following:
- 549 A. PECs must be located in a restricted access ISO Class 7 buffer area or in a
550 segregated compounding area that complies with this rule and shall be placed in
551 a manner to avoid conditions that could adversely affect their operation. PECs
552 shall be located out of traffic patterns and away from conditions that could
553 disrupt the intended airflow patterns (e.g., ventilation systems or cross-drafts).
- 554 B. PECs shall maintain ISO Class 5 or better conditions during dynamic operating
555 conditions and while compounding sterile preparations, including, when
556 transferring ingredients into and out of the isolator and during exposure of
557 critical sites;
- 558 C. PECs shall provide unidirectional (laminar flow) HEPA air at a velocity
559 sufficient to prevent airborne particles from contacting critical sites.
- 560 D. Compounding Aseptic Isolators (CAI): Air exchange into the isolator from the
561 surrounding environment shall not occur unless the air has first passed through a
562 microbial retentive HEPA filter.
- 563 E. Compounding Aseptic Containment Isolators (CACI): Air exchange with the
564 surrounding environment shall not occur unless the air is first passed through a
565 microbial retentive HEPA filter system capable of containing airborne
566 concentrations of the physical size and state of the drug being compounded.
567 When volatile hazardous drugs are prepared, the exhaust air from the isolator
568 shall be removed by properly designed building ventilation.

[16]

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569 F. If an isolator is used, the recovery time to achieve ISO Class 5 air quality shall
570 be identified in the pharmacy's policies and procedures and internal procedures
571 developed to ensure adequate recovery time is allowed after material transfer
572 and before or during compounding operations.
573

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

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

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

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

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

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

600 F. **Single-Dose, Multiple Dose and Pharmacy Bulk Vials/Containers.**
601 Single, multiple-dose and pharmacy bulk vials/containers used in
602 compounding shall be labeled with the beyond-use date and time after which
603 time the vial/container shall not be used.

[17]

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- 604 1. Single-dose vials/containers and pharmacy bulk vial containers
605 exposed to ISO Class 5 or cleaner air may be used until the assigned
606 beyond-use date which shall not exceed six (6) hours after initial
607 needle puncture, unless otherwise specified by the manufacturer.
608 Opened single-dose ampules shall not be stored for any time period.
609 2. Unless otherwise specified by the manufacturer, multiple-dose
610 vials/containers may be used until the assigned beyond-use date
611 which shall not exceed twenty-eight (28) days after initially entering
612 or opening (e.g., needle-puncture).
613

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

- 617 A. Traffic flow in or around the compounding and segregated compounding areas shall
618 be minimized and controlled.
619 B. Food items, chewing gum, eating, drinking and smoking are prohibited.
620 C. Nonessential objects that shed particles shall not be brought into the areas,
621 including, but not limited to, pencils, cardboard cartons, paper towels, and cotton
622 items (e.g., gauze pads).
623 D. Furniture, carts, supplies and equipment shall be removed from shipping
624 cartons/containers and properly cleaned and disinfected before entering the
625 compounding area or segregated compounding area. No shipping or other external
626 cartons may be taken into the areas.
627 E. Carts/conveyances must be cleaned and disinfected before entering or returning to
628 the ante area or buffer area.
629 F. Supplies and equipment shall be disinfected before entering the ISO 5 PEC by
630 wiping the outer surface with sterile alcohol or an equivalent or superior non-
631 residue generating disinfectant.
632 G. Only supplies essential for compounding shall be stored in the buffer area. Supplies
633 or other non-essential equipment shall not be stored in the PEC.
634

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

Comment [A7]: See previous comment on concerns about requiring sterile alcohol.

- 639 1. Except as otherwise provided herein, personal cleansing and garbing shall
640 comply with USP Chapter 797. Sterile gloves shall be worn when
641 compounding, including, over isolator gloves if applicable.
642 2. ~~In lieu of full garbing~~ At a minimum, compounding personnel using a CAI or
643 CACI to compound non-hazardous drugs shall ~~at a minimum~~ don facial masks,
644 non-shedding gowns and sterile gloves over the isolator gloves during
645 compounding. Non-shedding gowns and gloves shall also be used during
646 material handling. This section shall only be applicable if the CAI/CACI
647 provides isolation from the room and is certified to maintain ISO Class 5 air
648 quality during dynamic operating conditions as defined in 8 (G).
649
650 (15) **Aseptic Processing**. CSPs shall be prepared in a manner that maintains sterility and
651 minimizes contamination and the introduction of particulate matter. Appropriate
652 aseptic technique shall be utilized at all times.
653 A. Aseptic processing must be performed in at least ISO Class 5 conditions. Critical
654 sites shall not be exposed to touch/contact contamination or worse than ISO
655 Class 5 air.
656 B. Prior to compounding, ingredients and packaging shall undergo a visual unit-by-
657 unit inspection to verify the components are free from defects and otherwise
658 suitable for their intended use. Ingredients shall not be used if: (1) evidence of
659 deterioration or contamination exists or is suspected, (2) an unauthorized break
660 in any container, closure or seal is detected, (3) the contents do not have the
661 expected appearance, aroma, or texture or (4) the beyond-use date or expiration
662 date has been exceeded.
663 C. Items/equipment must be disinfected before placement in the PEC. Syringes,
664 needles and tubing in outer wraps designed to keep them sterile until opening are
665 not required to be individually disinfected if opened in an ISO Class 5 work
666 area.
667 D. Only materials and equipment essential for aseptic compounding shall be placed
668 in the primary engineering control. Materials and equipment shall be arranged
669 in the DCA to allow a clear, uninterrupted path of HEPA-filtered air over critical
670 sites at all times during compounding. Compounding staff shall not interrupt,
671 impede, or divert flow of first-air from HEPA filters to critical sites.
672 E. All critical sites shall be wiped vigorously in one direction with sterile alcohol
673 and allowed to air dry before being punctured or used.

Comment [A8]: This language was added by staff because it is mentioned in 797 and was discussed in prior drafts. Should sterile gloves be required for all compounding?

Comment [A9]: Greg asked if the gowning/sterile glove requirements are necessary for a CAI/CACI, especially facial masks.

Neal indicated 797 only requires garbing if referenced by the manufacturer and suggested following 797's language. Other members indicated the proposed garbing will better protect the public.

[19]

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- 674 F. Wetted gauze pads or other particle-generating material shall not be used to
675 disinfect sterile entry points. If sterile, single-use alcohol prep pads are used, the
676 surface of the pad shall not contact any other object before contacting the surface
677 of the entry point.
- 678 G. Before compounding, staff shall visually confirm that ingredients used and
679 measured in syringes match the prescription or medication order being
680 compounded. Density or specific gravity values programmed in automated
681 compounding devices shall be confirmed to be correct before and after
682 delivering volumes of the liquids assigned to each channel or port.

683

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

- 686 A. Presterilization procedures for High Risk CSPs, such as weighing and mixing,
687 shall be completed in no worse than an ISO Class 8 environment.
- 688 B. All non-sterile equipment that is to come in contact with the sterilized final high
689 risk CSP shall be sterilized before introduction into the buffer area.
690 Additionally, all nonsterile measuring, mixing and purifying devices shall be
691 rinsed thoroughly with sterile water for irrigation, disinfected and thoroughly
692 drained or dried before being used to compound.
- 693 C. All high risk CSPs must be sterilized before dispensing or distribution via a
694 method recognized for the CSP type by USP Chapter 1211.
- 695 1. Water-containing CSPs that are nonsterile during any phase of the
696 compounding procedure shall be sterilized within 6 hours after completing
697 the CSP.
- 698 2. Filters used for sterilization shall be tested for integrity (e.g., bubble point
699 testing) after use. Testing shall comply with manufacturer
700 recommendations. Testing dates and results must be documented in the
701 pharmacy's records and reviewed by a pharmacist prior to releasing the
702 CSP.
- 703 3. Commercially available filters shall be approved for human use
704 applications in sterilizing pharmaceutical fluids. Sterile filters used to
705 sterilize CSPs shall be pyrogen free and a pore size of 0.20 to 0.22
706 microns. They shall be certified by the manufacturer to retain at least 10
707 to the seventh microorganisms of a strain of *Brevundimonas* (*pseudomonas*)
708 diminute. The pharmacy must maintain this documentation for each filter
709 utilized in the sterilization of CSPs.

[20]

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710 D. Final containers used for high risk CSPs must be sterile and capable of maintaining
711 CSP integrity until the beyond-use date. Sterilization methods must be based on
712 the properties of the CSP.
713

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

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

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

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

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

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

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

[21]

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

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

- 754 1. No alternative product/CSP is available and the patient will be exposed
755 to negative risks if therapy is delayed. The reason for the emergency
756 dispensing shall be documented in the pharmacy's records; and
757 2. The prescriber/ordering health care provider is informed the CSP will be
758 dispensed prior to receiving test results and approves the dispensing.
759 Prescriber/provider approval shall be documented in the pharmacy's
760 records. A separate authorization from the prescriber/provider is
761 required for each emergency dispensing.
762 3. This section shall not be construed to exempt any person or entity from
763 performing any testing required by this rule.
764

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

- 768 A. Beyond-use date;
769 B. Compounding date, if different from the date the prescription is filled;
770 C. The actual name of each active or therapeutic ingredient;
771 D. The amounts or concentration of all active or therapeutic ingredients;
772 E. Total volume;
773 F. Storage requirements;
774 ~~F.G. If given to a patient, the pharmacy's phone number and a statement~~
775 ~~indicating "This is a compounded preparation";~~
776 ~~G.H. Any CSP or device specific instructions for use including the route of~~
777 ~~administration and the rate of administration, and;~~
778 ~~H.I. Auxiliary labels when applicable.~~
779 H.J. When a CSP is packaged in individual containers and dispensed to the patient
780 in a labeled outer container as required above, the individual containers must
781 be labeled with the CSP name, lot number and beyond use date.

[22]

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- 782
783 (19) **Final Verification.** Prior to dispensing, a pharmacist shall physically verify that the
784 CSP has been properly prepared, sterilized, packaged and labeled and that all required
785 end-preparation testing has been performed and documented. The following quality
786 assurance measures shall be performed by a pharmacist before a CSP is dispensed or
787 distributed:
788 1. Compounding records shall be reviewed to verify that the correct
789 measurements, volumes, quantities, calculations and sterilization procedures
790 were used. If an automated compounding device was used, a pharmacist
791 must verify proper calibration and verify that data entered into the device
792 was correct and accurate, including, but not limited to, density or specific
793 gravity values.
794 2. The final CSP must be visually inspected for physical integrity, clarity and
795 expected appearance. Additionally, each compounded unit shall be
796 inspected against lighted white or black background or both for evidence of
797 visible particulates or other foreign matter. Visual inspection shall not be
798 required for hazardous drugs if the inspection may be harmful.
799
- 800 (20) **Beyond-Use Dating.** All CSPs must be assigned a beyond-use date. Beyond-use
801 dates shall be determined from the date or time the CSP is compounded. The nature
802 of the drug and its degradation mechanism, drug stability, sterility considerations,
803 antimicrobial effective testing results, container packaging, storage conditions and the
804 intended duration of therapy shall be considered. CSPs shall not be dispensed past the
805 assigned beyond-use date.
806 A. For Low and Medium Risk CSPs, beyond-use dates shall be assigned based on
807 any of the following resources: USP Chapter 797, the manufacturer's labeling,
808 direct testing using validated testing methods, compendial references or peer-
809 reviewed literature based on CSP-specific experimental studies/testing.

[23]

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810 B. High Risk CSPs: Beyond-use dates not specifically referenced in the
811 manufacturer's approved labeling or in a USP monograph or not established by
812 CSP specific instrumental analysis shall be limited to thirty (30) days after
813 compounding. High risk CSPs with beyond-use dates greater than thirty (30)
814 days shall undergo laboratory testing using validated methods prior to release to
815 verify stability (sterility and potency) for the maximum beyond-use date.
816 Testing of each CSP/batch is not required once stability has been established for
817 the specific CSP as required by this subsection and no modifications have been
818 made to the compounding procedure, process or formula.
819

Comment [A10]: Members commented a 30-day BUD is too long for High Risk if there isn't specific data.

- 820 (21) **Point-of-Care Activated Systems.** In addition to other applicable requirements:
- 821 A. Point-of-Care activated systems shall be assembled within an ISO Class 5
822 environment and assigned a beyond-use date in accordance with the
823 manufacturer's recommendations or labeling.
- 824 B. The beyond-use date of an assembled non-activated system shall be limited to a
825 maximum of fifteen (15) days unless the pharmacy has documentation from the
826 system's manufacturer that a longer date is acceptable. When dispensed, an
827 assembled non-activated system shall be labeled with beyond-use dates for both
828 activated and non-activated states. The compounding record must document
829 both dates.
- 830 C. Point of care activated systems shall be stored in accordance with the
831 manufacturer's labeling and recommendations.
832
- 833 (22) **Storage.** CSPs shall be stored strictly in accordance with the conditions stated on the
834 ingredient label, if applicable. Adulterated, misbranded, expired or contaminated
835 CSPs shall be segregated and quarantined from the compounding area and other drug
836 inventory and properly disposed of.
- 837 A. If storage at controlled room temperature is directed, an article may alternatively
838 be stored and distributed in a cool place as defined by USP, unless otherwise
839 specified in the individual USP monograph or on the label.
- 840 B. Temperature excursions shall be allowed as permitted or recognized by USP.
- 841 C. Any excess CSP shall be stored and accounted for under conditions dictated by
842 the CSP's composition and stability characteristics to ensure its strength, quality
843 and purity. Excess CSPs shall be labeled with the name and strength of the
844 drug(s), an in-house lot number, compounding date, volume and beyond-use
845 date.

[24]

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- 846
847 (23) **Packaging and Delivery**. CSPs shall be packaged, stored, transported and delivered
848 in a manner that will preserve the physical integrity, sterility, stability, and purity of
849 the CSP. Packaging shall be selected that simultaneously protects CSPs from damage,
850 leakage, contamination, and degradation and protects individuals transporting packed
851 CSPs from harm. Prescription delivery shall comply with applicable provisions of 20
852 CSR 2220-2.013. The pharmacy shall establish a mechanism for the patient/ultimate
853 user to report packaging or transporting concerns to the pharmacy and documenting
854 any reports received.
855
- 856 (24) **Compounding Log**: A compounding log shall be maintained that records/documents
857 each CSP made. The compounding log shall be maintained at the pharmacy separate
858 from the prescription record, either electronically or in writing, and shall be
859 immediately available upon request. Each compounding entry shall be verified and
860 manually or electronically signed or initialed by the verifying pharmacist. The
861 following information shall be recorded in the compounding log for each CSP:
862 (A) Compounding date;
863 (B) The identity of the compounder and the pharmacist performing the final
864 verification required by section (19) of this rule , if different;
865 (C) A list of ingredients and their amounts by weight or volume;
866 (D) Description of the compounding process, including, the compounding
867 method, formula or recipe and, if necessary for proper compounding, the
868 order of adding ingredients. For High Risk CSPs, the log must also include
869 sterilization and testing methods. The information required by this
870 subsection may be separately maintained in the pharmacy's records if
871 immediately available on request;
872 (E) The identity of the source, lot number and the expiration or beyond-use
873 date of each ingredient, as well as an in-house lot number and a beyond-
874 use date for batch bulk CSPs;
875 (F) An identifying prescription number or a readily retrievable unique
876 identifier;
877 (G) The beyond-use date assigned to the CSP and placed on the label;
878 (H) For High Risk CSPs, the type of container and container lot number, if
879 applicable; and
880 (I) Any CSP storage conditions included on the CSP label or in materials
881 provided to the patient.

[25]

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882
883 (25) **Aseptic Manipulation Training and Assessment**. Compounding staff shall be
884 skilled and trained to accurately and competently perform the duties assigned and to
885 operate any equipment used. At a minimum, compounding staff must undergo
886 Aseptic Competency Training and an Aseptic Technique Skill Assessment as follows:
887 A. **Aseptic Competency Training**: Aseptic competency training shall include both
888 didactic and experiential training and may be tailored to the pharmacy's
889 activities. Didactic training must include an instructional component along with
890 a testing or evaluation method to verify competency. Staff shall be trained to
891 perform the duties assigned when the level of sterile activity or sterile
892 compounding methods change. Aseptic competency training must be completed
893 for all risk levels prior to initial compounding and every twelve (12) months
894 thereafter.
895 B. **Aseptic Technique Skill Assessment**: A practical aseptic technique skill
896 assessment shall be completed for all individuals compounding sterile
897 preparations to verify aseptic competency. The assessment must include glove
898 fingertip sampling, media-fill testing and a direct visual evaluation of the
899 individual's competency. The visual observation shall assess:
900 1. Proper aseptic technique, manipulations and work practices, including,
901 but not limited to, avoiding touch contamination, proper use of first air
902 and if applicable, sterilizing high risk CSPs;
903 2. Cleaning and disinfection;
904 3. Hand hygiene, gloving and garbing;
905 4. Identifying, weighing, and measuring of ingredients;
906 5. Maintaining and achieving sterility in ISO Class 5 areas and within
907 primary engineering controls, and;
908 6. Labeling and inspecting CSPs for quality.
909 C. The required Aseptic Technique Skill Assessment must be completed for staff
910 compounding low or medium risk CSPs prior to initial compounding and every
911 twelve (12) months thereafter. For staff compounding high risk CSPs, the
912 assessment must be completed prior to initial compounding and every six (6)
913 months thereafter.

[26]

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- 914 D. Compounding staff shall successfully pass all training and assessments. Staff
915 who fail to demonstrate competency or whose glove fingertip sampling or
916 media-fill tests demonstrate one or more units of visible microbial contamination
917 shall be reinstructed and re-evaluated to ensure correction of all deficiencies
918 prior to beginning or continuing any further compounding. The reinstruction and
919 reevaluation shall be documented in the pharmacy's records.
- 920 E. Training and assessment dates along with the results of the required practical
921 aseptic technique skill assessment, glove fingertip sampling and media-fill
922 testing shall be reviewed and documented by the pharmacist-in-charge or his/her
923 designee.
- 924
- 925 (26) **Glove Fingertip Sampling.** Compounding staff shall undergo and successfully
926 complete both initial and ongoing glove fingertip sampling to assess compliance with
927 gloving and aseptic processing. Initial and ongoing fingertip sampling shall be
928 completed in accordance with USP Chapter 797 procedures, timeframes and methods.
929 Glove fingertip sampling shall be conducted following each required media-fill test
930
- 931 (27) **Media-Fill Testing.** Pharmacies shall establish and follow policies and procedures
932 for conducting media-fill testing to assess the quality of aseptic skills/techniques of
933 compounding staff. Media-Fill tests shall be conducted as part of the required aseptic
934 technique skill assessment and shall include a minimum of three media-fill units using
935 the same container or closure. Media-fill tests shall represent the most challenging or
936 stressful conditions actually encountered by the personnel being evaluated Initial and
937 ongoing media-fill testing shall be completed in accordance with USP Chapter 797
938 recommended procedures and methods for the applicable risk level(s).
939
- 940 (28) **Environmental Sampling.** Environmental sampling shall be routinely conducted in
941 all ISO classified areas to evaluate air quality compliance and microbial bio burden
942 levels. Sampling shall be conducted during dynamic operating conditions in
943 accordance with USP Chapter 797. Surface samples and viable airborne particle
944 samples shall be tested for bacteria, fungus, mold and yeast. Sampling shall occur as
945 follows:

[27]

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- 946 A. **Surface Sampling:** Surface sampling shall be conducted in accordance
947 with USP Chapter 797 using both general growth media and fungal specific
948 media. Surface sampling for pharmacies engaged in Low Risk and Medium
949 Risk must be performed every thirty (30) days. For High Risk compounding,
950 surface sampling shall be performed every fourteen (14) days.
- 951 B. **Viable Airborne Particle Testing:** Volumetric viable air sampling by
952 impaction shall be conducted in all ISO classified environments. Each viable
953 air sample shall sample 1,000 liters for all ISO areas. Each sample location
954 shall be tested with both general growth media (e.g., tryptic soy agar) and
955 fungal specific media (e.g., malt extract agar or saboraud dextrose agar) on
956 plates of at least 55mm in size. Use of settling plates alone shall not be
957 sufficient. Viable Airborne Particle Testing must be conducted prior to
958 initial compounding and every six (6) months thereafter. Testing shall also
959 occur:
- 960 1. As part of the initial certification of new facilities and equipment;
 - 961 2. Whenever the physical structure of the compounding area has been
962 altered;
 - 963 3. As part of the recertification of facilities and equipment;
 - 964 4. In response to identified problems with CSPs or end-preparation
965 testing failure; and
 - 966 5. Whenever maintenance, repairs or changes to the primary
967 engineering control(s) or compounding area may affect the airflow
968 pattern. The date and type of maintenance, repair or change shall be
969 documented in the pharmacy's records;
- 970 C. **Non-Viable Airborne Particle Testing:** Non-viable air sampling shall be
971 performed using a volumetric device in compliance with USP Chapter 797.
972 Non-Viable Airborne Particle Testing must be conducted prior to initial
973 compounding and every six (6) months thereafter.
- 974 D. **Pressure Differential:** Pressure differential monitoring shall be required for
975 all sterile compounding areas to ensure compliance with section (7)(B) of
976 this rule.
- 977
- 978 (29) **General Cleaning and Disinfection Requirements.** The pharmacy shall establish
979 and follow written policies and procedures governing all aspects of cleaning and
980 disinfection. Except as otherwise provided herein, the following requirements shall
981 be applicable:

Comment [A11]: HAC members indicated the increased surface sampling requirements will be pricey as some pharmacies may have to outsource sampling. Other members indicated the cost would be minimal relative to the likely risk/liability. Members suggested matching any new USP recommendation for sampling.

[28]

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- 982 A. Compounding areas and segregated compounding areas shall be free of
983 infestation by insects, rodents and other vermin. Trash shall be disposed of in a
984 timely and sanitary manner.
- 985 B. Cleaning and disinfection shall be performed and conducted in accordance with
986 USP Chapter 797 timeframes and procedures, except as otherwise provided
987 herein.
- 988 C. Individuals responsible for cleaning and disinfecting shall be trained in proper
989 cleaning and disinfection procedures and mechanisms prior to performing
990 cleaning/disinfection activities. Training shall include direct visual observation
991 of the individual's cleaning and disinfecting process by qualified staff. The
992 individual shall be annually reassessed for competency through direct visual
993 observation. Documentation of the required training and training dates shall be
994 maintained in the pharmacy's records. Individuals who fail to demonstrate
995 competency shall be reinstructed and successfully reevaluated prior to cleaning
996 or disinfecting the compounding or segregated compounding area.
- 997 D. Cleaning, disinfection and mopping activities shall be performed using approved
998 agents and procedures described in the pharmacy's written policies and
999 procedures. Cleaning and disinfecting agents shall be selected based on
1000 compatibility, effectiveness and the absence of inappropriate or toxic residues.
1001 Manufacturers' directions or published peer-reviewed literature for minimum
1002 contact time shall be followed.
- 1003 E. Primary engineering controls shall be cleaned with a germicidal agent followed
1004 by sterile alcohol. Sterile water for irrigation shall be used to dilute germicidal
1005 agents used inside the PEC that require dilution.
- 1006 F. At a minimum, the DCA shall be cleaned and disinfected prior to
1007 compounding, between batches and whenever contamination is suspected using
1008 sterile alcohol or an equivalent or superior agent which is allowed to dry
1009 immediately prior to compounding.
- 1010 G. ***Segregated Compounding Areas***: Floors and work surfaces within the line of
1011 demarcation shall be cleaned and disinfected daily or immediately prior to
1012 compounding if not used daily. Shelving and storage areas shall be cleaned and
1013 disinfected monthly.
- 1014
- 1015 (30) **Quality Assurance**. Sterile compounding pharmacies shall establish and follow a
1016 written quality assurance program for monitoring and evaluating the quality of
1017 compounding activities.

[29]

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- 1018 A. At a minimum, the quality assurance program shall include procedures for
1019 monitoring and tracking infection rates, adverse drug events, CSP recalls and
1020 complaints from prescribers, patients or other individuals or entities.
1021 B. The quality assurance plan shall delineate the individuals responsible for each
1022 aspect of the quality assurance program either by name or position title.
1023 C. The quality assurance plan shall be maintained at the pharmacy or readily
1024 retrievable upon request. The pharmacist-in-charge shall annually review the
1025 quality assurance program and document the review in the pharmacy's records.
1026

1027 ~~(31) **Recalls.** A recall must be initiated when a CSP is deemed to be misbranded,
1028 adulterated or non sterile or if end preparation testing results are out of specification.
1029 The pharmacy shall notify the prescriber of the nature of the recall, the problem(s)
1030 identified and any recommended actions to ensure public health and safety. In cases
1031 where the CSP has the potential to harm the patient, the same notification shall be
1032 provided to all patients that received the recalled CSP(s).~~

1033 ~~A. Patient and prescriber notifications required by this section shall be made initiated
1034 as soon as reasonably practicable but in no event later than one (1) business day of
1035 the recall. The date and manner of notification shall be documented in the
1036 pharmacy's records.~~

1037 ~~B. If a patient recall notification is unsuccessful, the pharmacy shall mail notification
1038 to the patient within the required one (1) business day timeframe.~~

1039 ~~C. Recalls initiated pursuant to this section shall be reported to the board in writing
1040 within three (3) business days.~~

1041 ~~D. If recall notification cannot be conducted as required herein, the pharmacy may
1042 submit to the Board a written plan to extend the notification period. The request
1043 must include a description of the nature of the recall, the potential number of
1044 patients affected, the reason(s) supporting the extension request and a proposed
1045 timeframe for completing the required notifications.~~

1047 (31) **Recalls.** A recall must be initiated when a CSP is deemed to be misbranded,
1048 adulterated or non-sterile or if end-preparation testing results are out of specification.
1049 The pharmacy shall notify the prescriber of the nature of the recall, the problem(s)
1050 identified and any recommended actions to ensure public health and safety. In cases
1051 where the CSP has the potential to harm the patient, the same notification shall be
1052 provided to all patients that received the recalled CSP(s).

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

Leave manner of notification open but require documentation when notification can't be made.
Only require notification to be "initiated" within 1 day.

[30]

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1053 | A. Patient and prescriber notifications required by this section shall be made [initiated]
1054 | as soon as reasonably practicable. The date and manner of notification shall be
1055 | documented in the pharmacy's records.
1056 | B. Recalls initiated pursuant to this section shall be reported to the board in writing
1057 | within three (3) business days. The request must include a description of the nature
1058 | of the recall, the potential number of patients affected and a designation of when
1059 | the required notifications were or will be made.
1060 |

[31]

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- 1061 |
1062 (32) **Record Keeping.** The pharmacy shall maintain the following records:
1063 A. Aseptic competency training and aseptic technique skill assessment dates and
1064 results;
1065 B. Testing dates and results for glove fingertip sampling, media-fill tests and end-
1066 CSP testing;
1067 C. Environmental sampling dates and results, including, any corrective efforts
1068 taken;
1069 D. Required refrigerator and temperature logs;
1070 E. Cleaning and disinfection records that document compliance with this rule;
1071 F. Equipment calibration dates and results and maintenance reports;
1072 G. Certificates of analysis for compounding ingredients, if applicable;
1073 H. Certification records for PECs and sterile compounding areas;
1074 I. Copies of any manufacturer equipment standards that are relied upon to
1075 maintain compliance with this rule;
1076 J. Batch CSP files;
1077 K. For high risk CSPs, sterilization, quarantine and ingredient validation records;
1078 L. Emergency dispensing records as required by subsection (17), including,
1079 documentation of prescriber authorization and the dates of such authorization;
1080 M. CSP recall records, including, dates, patients affected and any investigation,
1081 corrective actions or recall notifications made; and
1082 N. All other records required by this rule or governing law.
1083 O. Except as otherwise provided herein, records and reports required by this rule
1084 shall be either electronically or physically maintained for two (2) years.
1085 Records shall be readily retrievable and subject to inspection by the Board of
1086 Pharmacy or its agents upon request. At a minimum, records shall be
1087 physically or electronically produced immediately or within two (2) hours of a
1088 request from the Board or the Board's authorized designee.
1089 P. Prescription records shall be maintained in compliance with Missouri law and
1090 the rules of the Board.
1091
1092 (33) **Hazardous Drugs.** Hazardous drugs shall be prepared, stored and compounded in
1093 accordance with the USP-NF. Compounding staff engaged in handling, preparing or
1094 compounding hazardous drugs shall be trained as required by USP-NF and the rules of
1095 the Board. The following additional requirements shall be implemented to insure the
1096 protection of the staff involved:

[32]

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- 1097 A. Hazardous drugs/CSPs shall be stored, handled and prepared under
1098 conditions that protect ~~workers and other~~ staff.
- 1099 B. Appropriate disposal containers shall be available for used needles, syringes,
1100 and if applicable, hazardous waste from the CSP of chemotherapy agents and
1101 infectious waste. Disposal of hazardous waste shall comply with all
1102 applicable local, state and federal requirements;
- 1103 C. Written procedures for handling major and minor spills and generated waste
1104 of hazardous agents must be developed and must be included in the policy
1105 and procedure manual, and;
- 1106 D. Prepared doses of hazardous drugs must be labeled with proper precautions
1107 inside and outside, and shipped in a manner to minimize the risk of
1108 accidental rupture of the primary container.
- 1109
- 1110 (34) **Applicability.** If a conflict between this rule and the applicable provisions of
1111 USP exists, the requirements of this rule shall apply unless otherwise indicated
1112 herein. In the interest of public protection, the use of an alternative technology,
1113 technique, material or procedure not specifically included in this rule or USP
1114 shall only be authorized if an exemption is approved by the Board. The
1115 exemption request must be in writing and must include:
- 1116 (A) A description of the exemption requested and the reasons supporting the
1117 request;
- 1118 (B) Testing or other scientific evidence demonstrating the technology,
1119 technique, material or procedure is equivalent or superior with statistical
1120 significance to those included in this rule or USP. Peer-reviewed
1121 literature shall be insufficient without actual proof of the testing or other
1122 scientific evidence methods and results supporting the request;
- 1123 (C) A detailed statement of any hardship or public harm that will occur if
1124 the exemption is not granted, and;
- 1125 (D) Any other evidence requested by the Board.
- 1126

[33]

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1127 (35) Effective Date. Compliance with this rule shall be required within six (6)
1128 months after this rule becomes effective. Pharmacies that hold a current and active
1129 pharmacy permit on the effective date of this rule shall be granted an additional one (1) year
1130 after such effective date to comply with the provisions of section (7) or (8) of this rule that
1131 require physical or structural changes to the pharmacy to be compliant. The one (1) year
1132 exemption shall not apply to pharmacies that undergo a change of ownership or change of
1133 location.

1134
1135 (36) A pharmacy may submit a written request to the Board for a variance from the
1136 physical or structural requirements of this rule. The Board may revoke or deny a request if
1137 the requested variance would detrimentally impact the health, safety or welfare of patients,
1138 staff or the public or result in an unsterile product, as determined by the Board. If approved,
1139 the Board's written determination shall identify a variance expiration date. The pharmacy
1140 shall inform the Board in writing within thirty (30) days of any change in the conditions
1141 warranting the variance request. Variance requests shall contain:

1142 (A) The section number of the requirement(s) in question;

1143 (B) Specific reasons why compliance with the requirement(s) would impose an
1144 undue hardship on the public or the pharmacy, including an estimate of any additional cost
1145 which might be involved;

1146 (C) An explanation of any extenuating factors which may be relevant;

1147 (D) A complete description of the steps, safeguards or processes that are in place
1148 or will be taken to ensure the sterility of CSPs or to safeguard the health, safety and welfare
1149 of the patient, staff or public if the variance request is granted; and

1150 (E) The length of time the variance is requested.

1151

1152

[34]

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