

Meeting Notice

Missouri Board of Pharmacy Sterile Compounding Sub-Committee Conference Call

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

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

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

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

Please see attached tentative agenda for this meeting.

TENTATIVE AGENDA
May 3, 2016 5:30 p.m.

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

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

1 | **20 CSR 2220-2.200 Sterile ~~Pharmaceuticals~~ Compounding**

2 | *PURPOSE: This rule establishes standards for the preparation, labeling, ~~and~~ distribution and*
3 | *dispensing of ~~sterile pharmaceuticals~~ compounded sterile preparations by licensed pharmacies,*
4 | *pursuant to a physician's order or prescription.*

5 | (1) Definitions.

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

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

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

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

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

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

25 | ~~(G) Clean room: A room —~~

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

27 | ~~2. That is constructed and used in a manner to minimize the introduction, generation, and~~
28 | ~~retention of particles inside the room; and~~
29 |

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

32 ~~(H) Clean zone: Dedicated space —~~

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

34 ~~2. That is constructed and used in a manner that minimizes the introduction, generation, and~~
35 ~~retention of particles inside the zone; and~~

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

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

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

43 ~~(F) Compounding: For the purposes of this regulation, compounding is defined as in 20 CSR~~
44 ~~2220-2.400(1). Compounded sterile medications may include, but are not limited to, injectables,~~
45 ~~parenteral nutrition solutions, irrigation solutions, inhalation solutions, intravenous solutions and~~
46 ~~ophthalmic preparations.~~

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

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

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

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

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

68 | ~~(M)~~(L) Critical surface: Any surface that comes into contact with previously sterilized
69 | ~~product~~preparations or containers.

70 | (M) CSP: Compounded sterile preparation.

71 | ~~(N)~~(N) Cytotoxic drugs: A pharmaceutical product that has the capability of direct toxic action
72 | on living tissue that can result in severe leukopenia and thrombocytopenia, depression of the
73 | immune system and the alteration of a host's inflammatory response system.

74 | ~~(O)~~(O) Emergency dispensing: Is a situation where a Risk Level 3 ~~product~~preparation is
75 | necessary for immediate administration of the ~~product~~preparation and no alternative product is
76 | available and the prescriber is informed that the ~~product~~preparation is being dispensed prior to
77 | appropriate testing. Documentation of the dispensing of the ~~product~~preparation, the prescriber's
78 | approval for dispensing prior to the receipt of test results and the need for the emergency must
79 | appear within the prescription record. A separate authorization from the prescriber is required
80 | for each emergency dispensing.

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

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

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

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

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

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

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

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

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

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

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

119 (Z) RABS: Restricted access barrier system (RABS): A primary engineering control that is
120 comprised of a closed system made up of four (4) solid walls, an air-handling system, and

121 transfer and interaction devices. The walls are constructed so as to provide surfaces that are
122 cleanable with coving between wall junctures. The air-handling system provides HEPA filtration
123 of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports.
124 Transfers are designed to minimize the entry of contamination. Manipulations can take place
125 through either glove ports or half suits. Examples of a RABS may include, but is not limited to, a
126 CAI or CACI.

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

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

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

132 ~~(X)~~(CC) Sterilization: A validated process used to render a ~~product~~preparation free of viable
133 organisms.

134 ~~(Y)~~(DD) Temperatures:

135 1. Frozen means temperatures between twenty below zero and ten degrees Celsius (20 and
136 10°C) (four below zero and fourteen degrees Fahrenheit (4 and 14°F)).

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

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

148 (EE) USP: The United States Pharmacopeia and the National Formulary (USP-NF) as
149 adopted and published by the United States Pharmacopeial Convention, effective May 2013.
150 Copies of the USP-NF are published by, and available from, USP, 12601 Twinbrook Parkway,
151 Rockville, MD 20852-1790 or online at <http://www.usp.org/>. The USP-NF is incorporated

152 [herein by reference. This rule does not include any later amendments or additions to the USP-](#)
153 [NF.](#)

154 ~~(Z)~~(FF) Validation: Documented evidence providing a high degree of assurance that specific
155 processes will consistently produce a [productpreparation](#) meeting predetermined specifications
156 and quality attributes.

157 ~~(AA)~~(GG) Definitions of sterile compounded [productpreparations](#) by risk level:

158 1. Risk Level 1: Applies to compounded sterile [productpreparations](#) that exhibit
159 characteristics A., B., ~~and~~ C., stated below. All Risk Level 1 [productpreparations](#) shall be
160 prepared with sterile equipment, sterile ingredients and solutions and sterile contact surfaces for
161 the final [productpreparation](#). Risk Level 1 includes the following:

162 A. [ProductPreparations](#):

163 (I) Stored at ~~room temperature~~[controlled room temperature](#) and ~~completely administered~~
164 ~~within~~ [assigned a beyond-use date of](#) forty-eight (48) hours ~~after preparation~~ [or less](#); or

165 (II) Stored under refrigeration ~~for~~ [and assigned a beyond-use date of](#) seven (7) days or
166 less ~~before complete administration to a patient over a period not to exceed forty eight (48)~~
167 ~~hours~~; or

168 (III) ~~Stored F~~[rozen](#) ~~for~~ [and assigned a beyond-use date of](#) thirty (30) days or less ~~before~~
169 ~~complete administration to a patient over a period not to exceed forty eight (48) hours.~~

170 B. Unpreserved sterile [productpreparations](#) prepared for administration to one (1) patient or
171 batch-prepared [productpreparations](#) containing suitable preservatives prepared for administration
172 to more than one (1) patient [with an assigned beyond-use date that does not exceed the beyond-](#)
173 [use date allowed for under section \(1\)\(GG\)1.A. of this rule.](#)

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

178 2. Risk Level 2: Sterile [productpreparations](#) exhibit characteristic A., B., or C., stated below.
179 All Risk Level 2 [productpreparations](#) shall be prepared with sterile equipment, sterile ingredients
180 and solutions and sterile contact surfaces for the final [productpreparation](#) and with closed-system
181 transfer methods. Risk Level 2 includes the following:

182 | A. ~~Products stored beyond seven (7) days under refrigeration, stored beyond thirty (30)~~
183 | ~~days frozen or administered beyond forty eight (48) hours after preparation and storage at room~~
184 | ~~temperature.~~ Preparations stored under refrigeration and assigned a beyond-use date greater than
185 | seven (7) days or preparations stored frozen and assigned a beyond-use date greater than thirty
186 | (30) days or preparations stored at controlled room temperature and assigned a beyond-use date
187 | greater than forty-eight hours.

188 | B. Batch-prepared productpreparations without preservatives that are intended for use by
189 | more than one (1) patient.

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

193 | 3. Risk Level 3: Sterile productpreparations exhibit either characteristic A. or B.:

194 | A. ProductPreparations compounded from nonsterile ingredients or compounded with
195 | nonsterile components, containers or equipment before terminal sterilization.

196 | B. ProductPreparations prepared by combining multiple ingredients (sterile or nonsterile)
197 | by using an open-system transfer or open reservoir before terminal sterilization.

198 | (2) Policy and Procedure Manual/Reference Manuals.

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

203 | (3) Personnel Education, Training and Evaluation.

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

211 | (B) Risk Level 2: In addition to Risk Level 1 requirements, personnel training must includes
212 | assessment of competency in all Risk Level 2 procedures via process simulation.

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

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

220 | (4) Storage and Handling in the Pharmacy.

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

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

235 | ~~(5) Facilities and Equipment.~~

236 | ~~(A) Risk Level 1: The controlled area shall be separated from other operations. The controlled~~
237 | ~~area must be clean and well lit. A sink with hot and cold water must be near, but not in, the~~
238 | ~~controlled area. The controlled area and inside equipment must be cleaned and disinfected~~
239 | ~~regularly. Sterile products must be prepared in at least a Class 100 environment (the critical~~
240 | ~~area). Computer entry, order processing, label generation, and record keeping shall be performed~~

241 ~~outside the critical area. The critical area must be disinfected prior to use. A workbench shall be~~
242 ~~recertified every six (6) months and when it is moved; prefilters must be visually inspected on a~~
243 ~~regularly scheduled basis and replaced according to manufacturer's specifications. Pumps~~
244 ~~utilized in the compounding process shall be recalibrated and documented according to~~
245 ~~manufacturer procedures.~~

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

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

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

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

271 utilized in the compounding process shall be recalibrated and documented according to
272 manufacturer procedures.

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

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

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

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

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

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

298 (F) Pressure Differential: If the controlled area is equipped with a device to monitor pressure
299 differential, pressure differential results must be recorded and documented each day that the
300 pharmacy is open for pharmacy activities. Alternatively, a continuous monitoring system may

301 be used to record pressure differential results if the system maintains ongoing documentation of
302 pressure recordings or maintains pressure alerts that are reviewed daily.

303

304 (6) Primary Engineering Controls (PECs):

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

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

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

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

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

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

323

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

327 (A) Controlled areas must be clean and well-lit and shall be free of infestation by insects,
328 rodents and other vermin. Trash shall be disposed of in a timely and sanitary manner and at least
329 daily. Tacky mats or similar articles shall be prohibited in the controlled area or any ISO
330 classified environment.

331 (B) Traffic flow in or around the controlled area shall be minimized and controlled. Food
332 items, chewing gum, eating, drinking and smoking are prohibited in the area;

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

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

341 ~~(6) Apparel.~~

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

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

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

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

Comment [GK1]: The suggestion was strongly made that the rule require sterile gloves for all sterile compounding.

359 (B) Risk Level 2 and Risk Level 3: In addition to Risk Level 1 requirements, shoe covers and
360 sterile gloves must be worn while compounding and cleaning, including, over RABS gloves. All
361 personnel in the controlled or buffer area must garb as required by this section.
362

363 ~~(7)(9)~~ Aseptic Technique and ~~Product~~ Preparation. Appropriate quality control methods shall be
364 maintained over compounding methods at all times to ensure proper aseptic technique.

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

385 (B) Risk Level 2: In addition to Risk Level 1 requirements, a file containing the formula,
386 components, procedures, sample label, and final evaluation shall be made for each
387 ~~product~~ preparation ~~batch~~. A separate work sheet and lot number for each batch shall be
388 completed. When combining multiple sterile ~~product~~ preparations, a second verification of

389 calculations shall take place. The pharmacist shall verify data entered into any automatic
390 compounder before processing and check the end ~~product~~preparation for accuracy.

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

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

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

407 ~~(8) Process Validation.~~

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

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

416 ~~(C) Risk Level 3: In addition to all Risk Level 1 and 2 requirements, written policies shall be~~
417 ~~maintained to validate all processes, procedures, components, equipment and techniques.~~

418

419 (10) Aseptic Technique Skill Assessment. Individuals engaged in sterile compounding must
420 take and successfully pass an aseptic technique skill assessment to verify aseptic competency.
421 The assessment must include a direct visual observation of the individual's aseptic competency
422 during a process simulation that represents the most challenging or stressful conditions
423 encountered or performed by the person being evaluated. The assessment must include media
424 fill testing for all risk levels.

425 (A) The required visual observation shall assess:

- 426 1. Proper aseptic technique, manipulations and work practices, including, but not
427 limited to, avoiding touch contamination, proper use of first air and if
428 applicable, sterilizing high risk CSPs;
- 429 2. Cleaning and disinfection;
- 430 3. Hand hygiene, gloving and garbing;
- 431 4. Identifying, weighing, and measuring of ingredients;
- 432 5. Maintaining and achieving sterility in ISO Class 5 areas and within primary
433 engineering controls, and;
- 434 6. Labeling and inspecting CSPs for quality.

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

441 (C) Frequency: The required Aseptic Technique Skill Assessment must be conducted
442 prior to initial compounding and every twelve (12) months thereafter for Risk Levels 1 and 2
443 compounding and every (6) months thereafter for Risk Level 3 compounding. Additionally, an
444 Aseptic Technique Skill Assessment must be conducted whenever the quality assurance program
445 yields an unacceptable result or whenever unacceptable techniques are observed.

446 (D) Individuals who fail written tests; visual observation of hand hygiene, garbing, and
447 aseptic technique; or media-fill tests must undergo immediate requalification through additional
448 training by competent compounding personnel. Individuals who fail visual observation of hand
449 hygiene, garbing, and aseptic technique; or media-fill tests must pass three successive
450 reevaluations in the deficient area before they can resume compounding of sterile preparations.

451 ~~(9)~~(11) Record Keeping.

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

453 1. Training and competency evaluation of pharmacy personnel involved in sterile ~~product~~
454 ~~preparation~~compounding, including, the dates and results of the required aseptic technique
455 training, aseptic technique skill assessment and media-fill testing;

456 2. Refrigerator, ~~and~~-freezer and, if applicable, incubator temperature logs;

457 3. Certification ~~of workbenches~~ dates and results for any PEC or ISO classified area;

458 4. Copies of any manufacturer ~~standards~~manuals that are relied upon to maintain compliance
459 with this rule;~~and~~

460 5. Other facility quality control logs as appropriate including all maintenance, cleaning, and
461 calibration records; and

462 6. If applicable, pressure recordings including documentation of the review of continuous
463 monitoring system results as required by section (5)(F).

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

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

468 1. Preparation work sheet;

469 2. Sterilization records;

470 3. Quarantine records, if applicable;

471 4. End-~~product~~preparation evaluation and testing records as required in section ~~(12)~~(14); and

472 5. Ingredient validation records as required in section ~~(12)~~(14).

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

477 ~~(10)~~(12) Labeling.

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

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

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

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

488 ~~(11)~~(13) Beyond-Use Dating.

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

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

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

502 ~~(12)~~(14) End-ProductPreparation Evaluation.

503 (A) Risk Level 1: The final productpreparation must be inspected for clarity, container leaks,
504 integrity, and appropriate solution cloudiness or phase separation, ~~particulates in solution,~~
505 ~~appropriate~~ solution color, and solution volume. The pharmacist must verify that the
506 productpreparation was compounded accurately as to the ingredients, quantities, containers, and

507 | reservoirs. Background light or other means for the visual inspection of productpreparations for
508 | any particulate and/or foreign matter must be used as part of the inspection process.

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

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

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

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

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

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

531 | B. All weighings, volumetric measurements, and additions of ingredients were carried out
532 | properly;

533 | C. The compounding or control records include documentation that the fill volumes of all
534 | units available for release were checked and were correct; and

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

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

541 ~~(13) Handling Sterile Products Outside the Pharmacy.~~ (15) Storage, Handling and Transport.

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

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

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

553
554 (16) Point-of-Care Assembled Systems. Assembly of point-of-care assembled systems shall be
555 considered Risk Level 1 compounding. Point-of-care assembled systems shall be assigned a
556 beyond-use date which may exceed the beyond-use-date authorized for Risk Level 1 preparations
557 provided the date is assigned in accordance with the manufacturer's recommendations or
558 labeling.

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

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

566

567 (17) General Cleaning and Disinfection Requirements. Except as otherwise provided herein,
568 cleaning and disinfection of controlled and buffer areas, supplies and equipment shall be
569 performed and conducted in accordance with USP Chapter 797 timeframes and procedures.
570 Controlled areas that do not meet ISO air classifications shall be cleaned and disinfected as
571 required by USP Chapter 797 for segregated compounding areas. If compounding is done less
572 frequently than the cleaning and disinfection timeframes specified in USP Chapter 797, cleaning
573 and disinfection must occur before each compounding session begins.

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

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

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

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

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

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

595 ~~(14)~~(18) Cytotoxic Drugs.

596 (A) The following additional requirements are necessary for those licensed pharmacies that
597 prepare cytotoxic drugs to insure the protection of the personnel involved:

598 1. Cytotoxic drugs shall be compounded in a vertical flow, Class II biological safety cabinet
599 | or ~~an isolator~~ a CACI. If used for other ~~product~~preparations, the cabinet must be thoroughly
600 cleaned;

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

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

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

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

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

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

620 ~~(16)~~(19) In addition to the requirements outlined in this rule, all standards and requirements as
621 outlined in 20 CSR 2220-2.400 must be maintained. Pharmacies that are registered with the Food
622 and Drug Administration (FDA) are exempt from the distribution restrictions in 20 CSR 2220-
623 2.400(12) for compounded sterile pharmaceuticals distributed with FDA's knowledge and
624 enforcement discretion. This exemption applies only to a twenty-four (24)-hour course of
625 therapy which is needed:

626 (A) To treat an emergency situation; or

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

631
632 (20) Remedial Investigations: A remedial investigation shall be required if: (1) any sampling or
633 testing required by this rule demonstrates a colony forming unit (CFU) count that exceeds USP
634 Chapter 797 recommended action levels for the type of sampling/testing or (2) if a highly
635 pathogenic microorganism is detected in any preparation or ISO classified area (e.g., Gram-
636 negative rods, coagulase positive staphylococcus, molds, fungus or yeasts).

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

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

645
646 (21) Recalls. A recall must be initiated when a CSP is deemed to be misbranded, adulterated or
647 non-sterile or if end-preparation testing results are out of specification. The pharmacy shall
648 notify the prescriber of the nature of the recall, the problem(s) identified and any recommended
649 actions to ensure public health and safety. In cases where the CSP has the potential to harm the
650 patient, the same notification shall be provided to all patients that received the recalled CSP(s).
651 Any recall initiated by a pharmacy shall be reported, in writing, to the board within three (3)
652 business days.

653
654 *AUTHORITY: sections 338.140, 338.240, and 338.280, RSMo 2000 and section 338.010, RSMo*
655 *Supp. 2007.* This rule originally filed as 4 CSR 220-2.200. Original rule filed May 4, 1992,*
656 *effective Feb. 26, 1993. Amended: Filed Oct. 28, 1994, effective May 28, 1995. Rescinded and*
657 *readopted: Filed Dec. 3, 2002, effective July 30, 2003. Moved to 20 CSR 2220-2.200, effective*
658 *Aug. 28, 2006. Amended: Filed Feb. 6, 2008, effective Aug. 30, 2008.*

659 *Original authority: 338.010, RSMo 1939, amended 1951, 1989, 1990, 2007; 338.140, RSMo
660 1939, amended 1981, 1989, 1997; 338.240, RSMo 1951; and 338.280, RSMo 1951, amended
661 1971, 1981.
662
663

1 | **20 CSR 2220-2.200 Sterile ~~Pharmaceuticals~~ Compounding**

2 | *PURPOSE: This rule establishes standards for the preparation, labeling, ~~and~~ distribution and*
3 | *dispensing of ~~sterile pharmaceuticals~~ compounded sterile preparations by licensed pharmacies,*
4 | *pursuant to a physician's order or prescription.*

5 | (1) Definitions.

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

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

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

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

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

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

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

29 | ~~(G) Clean room: A room—~~
30 | ~~1. In which the concentration of airborne particles is controlled;~~

31 ~~2. That is constructed and used in a manner to minimize the introduction, generation, and~~
32 ~~retention of particles inside the room; and~~

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

35 ~~(H) Clean zone: Dedicated space —~~

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

37 ~~2. That is constructed and used in a manner that minimizes the introduction, generation, and~~
38 ~~retention of particles inside the zone; and~~

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

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

42 ~~(F)~~ (E) Compounding: For the purposes of this regulation, compounding is defined as in 20 CSR
43 2220-2.400(1). Compounded sterile medications may include, but are not limited to, injectables,
44 parenteral nutrition solutions, irrigation solutions, inhalation solutions, intravenous solutions and
45 ophthalmic preparations.

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

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

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

59 ~~(J)~~ (J) Critical area: Any area in the controlled area where ~~products~~ preparations or containers
60 are exposed to the environment.

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

- a. Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that must or are required to be sterile when they are administered to patients, including, but not limited to the following dosage forms: bronchial and inhaled nasal preparations intended for deposition in the lung, baths and soaks for live organs and tissues, epidural and intrathecal solutions, bladder/wound solutions, injectables, implantable devices and dosage forms, inhalation solutions, intravenous solutions, irrigation solutions, ophthalmic preparations, parenteral nutrition solutions, and repackaged sterile preparations. Nasal sprays and irrigations intended for deposit in the nasal passages may be prepared as nonsterile compounds;
- b. An FDA approved manufactured sterile product that is either prepared according to the manufacturers' approved labeling/recommendations or prepared differently than published in such labeling; and
- c. Assembling point-of-care activated systems.

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

67 ~~(M)(L)~~ Critical surface: Any surface that comes into contact with previously sterilized
68 ~~product~~preparations or containers.

69 (M) CSP: Compounded sterile preparation.

70 ~~(N)(N)~~ Cytotoxic drugs: A pharmaceutical product that has the capability of direct toxic action
71 on living tissue that can result in severe leukopenia and thrombocytopenia, depression of the
72 immune system and the alteration of a host's inflammatory response system.

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

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

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

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

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

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

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

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

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

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

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

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

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

120 (AA) RABS: Restricted access barrier system (RABS): A primary engineering control that is
121 comprised of a closed system made up of four (4) solid walls, an air-handling system, and

122 transfer and interaction devices. The walls are constructed so as to provide surfaces that are
123 cleanable with coving between wall junctures. The air-handling system provides HEPA filtration
124 of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports.
125 Transfers are designed to minimize the entry of contamination. Manipulations can take place
126 through either glove ports or half suits. Examples of a RABS may include, but is not limited to, a
127 CAI or CACI.

128 ~~(V)~~(BB) Repackaging: The subdivision or transfer of a compounded ~~product~~preparation from
129 one container or device to a different container or device.

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

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

133 ~~(X)~~(DD) Sterilization: A validated process used to render a ~~product~~preparation free of viable
134 organisms.

135 ~~(Y)~~(EE) Temperatures:

136 1. Frozen means temperatures between twenty below zero and ten degrees Celsius (20 and
137 10°C) (four below zero and fourteen degrees Fahrenheit (4 and 14°F)).

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

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

149 (FF) USP: The United States Pharmacopeia and the National Formulary (USP-NF) as adopted
150 and published by the United States Pharmacopeial Convention, effective May 2013. Copies of
151 the USP-NF are published by, and available from, USP, 12601 Twinbrook Parkway, Rockville,

152 [MD 20852-1790](http://www.usp.org/) or online at <http://www.usp.org/>. The USP-NF is incorporated herein by
153 [reference. This rule does not include any later amendments or additions to the USP-NF.](#)

154 ~~(Z)~~(GG) Validation: Documented evidence providing a high degree of assurance that specific
155 processes will consistently produce a [productpreparation](#) meeting predetermined specifications
156 and quality attributes.

157 ~~(AA)~~(HH) Definitions of sterile compounded [productpreparations](#) by risk level:

158 1. Risk Level 1: Applies to compounded sterile [productpreparations](#) that exhibit
159 characteristics A., B., ~~and~~ C., stated below. All Risk Level 1 [productpreparations](#) shall be
160 prepared with sterile equipment, sterile ingredients and solutions and sterile contact surfaces for
161 the final [productpreparation](#). Risk Level 1 includes the following:

162 A. [ProductPreparations](#):

163 (I) Stored at ~~room temperature~~[controlled room temperature](#) and ~~completely administered~~
164 ~~within~~ [assigned a beyond-use date of](#) forty-eight (48) hours ~~after preparation or less~~; or

165 (II) Stored under refrigeration ~~for~~ [and assigned a beyond-use date of](#) seven (7) days or
166 less ~~before complete administration to a patient over a period not to exceed forty eight (48)~~
167 ~~hours~~; or

168 (III) ~~Stored F~~[rozen for](#) [and assigned a beyond-use date of](#) thirty (30) days or less ~~before~~
169 ~~complete administration to a patient over a period not to exceed forty eight (48) hours.~~

170 B. Unpreserved sterile [productpreparations](#) prepared for administration to one (1) patient or
171 batch-prepared [productpreparations](#) containing suitable preservatives prepared for administration
172 to more than one (1) patient [with an assigned beyond-use date that does not exceed the beyond-](#)
173 [use date allowed for Risk Level 1 under section \(1\)\(HH\)1.A. of this rule.](#)

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

178 2. Risk Level 2: Sterile [productpreparations](#) exhibit characteristic A., B., or C., stated below.
179 All Risk Level 2 [productpreparations](#) shall be prepared with sterile equipment, sterile ingredients
180 and solutions and sterile contact surfaces for the final [productpreparation](#) and with closed-system
181 transfer methods. Risk Level 2 includes the following:

182 | A. ~~Products stored beyond seven (7) days under refrigeration, stored beyond thirty (30)~~
183 | ~~days frozen or administered beyond forty eight (48) hours after preparation and storage at room~~
184 | ~~temperature.~~ Preparations stored under refrigeration and assigned a beyond-use date greater than
185 | seven (7) days or preparations stored frozen and assigned a beyond-use date greater than thirty
186 | (30) days or preparations stored at controlled room temperature and assigned a beyond-use date
187 | greater than forty-eight hours.

188 | B. Batch-prepared productpreparations without preservatives that are intended for use by
189 | more than one (1) patient.

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

193 | 3. Risk Level 3: Sterile productpreparations exhibit either characteristic A. or B.:

194 | A. ProductPreparations compounded from nonsterile ingredients or compounded with
195 | nonsterile components, containers or equipment before terminal sterilization.

196 | B. ProductPreparations prepared by combining multiple ingredients (sterile or nonsterile)
197 | by using an open-system transfer or open reservoir before terminal sterilization.

198 | (2) Policy and Procedure Manual/Reference Manuals.

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

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

- 204 | 1. Staff education, training and evaluation and monitoring competency;
- 205 | 2. Maintaining, verifying and testing the accuracy and functioning of compounding
206 | equipment, including, time frames for calibration, testing, equipment monitoring and
207 | both annual and routine maintenance;
- 208 | 3. Certifying primary engineering controls and ISO classified areas;
- 209 | 4. Staff garbing and hand hygiene;
- 210 | 5. Aseptic technique and preparation, including, compounding, labeling and dispensing
211 | CSPs;
- 212 | 6. Aseptic technique skill assessment, including glove-fingertip sampling;

- 213 7. Media-fill testing. Policies and procedures shall address/identify media-fill
214 procedures, media selection, fill volume, incubation requirements, time and
215 temperature requirements, testing documentation, analyzing results, and any
216 corrective action guidelines or procedures;
- 217 8. Beyond-use dating;
- 218 9. End-preparation evaluation, including, approved methods of sterilization;
- 219 10. Storing, transporting and delivering CSPs;
- 220 11. Handling and reporting accidental exposures or spills of hazardous CSPs, including,
221 reporting methods and timeframes;
- 222 12. Measures for preventing cross-contamination when compounding activities require
223 the manipulation of a patient's blood-derived or other biological material (e.g.,
224 radiolabeling a patient's or donor's white blood cells);
- 225 13. Environmental sampling, including, specified time frames and locations;
- 226 14. Reporting and investigating environmental deficiencies;
- 227 15. Cleaning and disinfection. Policies and procedures shall identify authorized
228 cleaning/disinfecting agents and materials, schedules of use and methods of
229 application;
- 230 16. Reporting and investigating any real or suspected adverse event or any real or
231 suspected contaminated, non-sterile or defective final CSP;
- 232 17. Conducting remedial investigations;
- 233 18. Recall procedures which must include procedures for identifying and notifying
234 affected patients, prescribers and regulators when applicable; and
- 235 19. Educating patients and/or caregivers concerning the appropriate storage, use and
236 control of CSPs, when applicable.

237 (3) Personnel Education, Training and Evaluation.

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

245 (B) Risk Level 2: In addition to Risk Level 1 requirements, personnel training must includes
246 assessment of competency in all Risk Level 2 procedures via process simulation.

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

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

254 (4) Storage and Handling in the Pharmacy.

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

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

269 ~~(5) Facilities and Equipment.~~

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

277 ~~regularly scheduled basis and replaced according to manufacturer's specifications. Pumps~~
278 ~~utilized in the compounding process shall be recalibrated and documented according to~~
279 ~~manufacturer procedures.~~

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

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

295 (5) Facilities and Equipment.

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

305 (B) Risk Level 2: In addition to all Risk Level 1 requirements, Risk Level 2 preparations must
306 be prepared in a PEC located in a buffer area or prepared in a RABS located within a controlled

307 area. Risk Level 2 preparations shall at a minimum remain a Risk Level 2 for the life of the
308 preparation.

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

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

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

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

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

335 (F) Pressure Differential: If the controlled area is equipped with a device to monitor pressure
336 differential, pressure differential results must be recorded and documented each day that the
337 pharmacy is open for pharmacy activities. Alternatively, a continuous monitoring system may

338 be used to record pressure differential results if the system maintains ongoing documentation of
339 pressure recordings or maintains pressure alerts that are reviewed daily.

340

341 (6) Primary Engineering Controls (PECs):

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

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

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

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

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

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

360

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

364 (A) Controlled areas must be clean and well-lit and shall be free of infestation by insects,
365 rodents and other vermin. Trash shall be disposed of in a timely and sanitary manner and at least
366 daily. Tacky mats or similar articles shall be prohibited in the controlled area or any ISO
367 classified environment.

368 (B) Traffic flow in or around the controlled area shall be minimized and controlled. Food
369 items, chewing gum, eating, drinking and smoking are prohibited in the area;

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

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

378 ~~(6) Apparel.~~

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

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

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

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

Comment [GK2]: Our notes said that sterile gloves would not be required in the emergency but would be OK in the amended. Is this correct?

398 donned during that same work shift only. All other garb must be discarded and cannot be re-
399 used.

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

402 ~~(7)~~(9) Aseptic Technique and Product Preparation. Appropriate quality control methods shall be
403 maintained over compounding methods at all times to ensure proper aseptic technique.

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

424 (B) Risk Level 2: In addition to Risk Level 1 requirements, a file containing the formula,
425 components, procedures, sample label, and final evaluation shall be made for each
426 ~~product preparation~~batch. A separate work sheet and lot number for each batch shall be
427 completed. When combining multiple sterile ~~product~~preparations, a second verification of

428 calculations shall take place. The pharmacist shall verify data entered into any automatic
429 compounder before processing and check the end ~~product~~preparation for accuracy.

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

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

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

446 ~~(8) Process Validation.~~

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

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

455 ~~(C) Risk Level 3: In addition to all Risk Level 1 and 2 requirements, written policies shall be~~
456 ~~maintained to validate all processes, procedures, components, equipment and techniques.~~

457

458 (10) Aseptic Technique Skill Assessment. Individuals engaged in sterile compounding must
459 take and successfully pass an aseptic technique skill assessment to verify aseptic competency.
460 The assessment must include a direct visual observation of the individual's aseptic competency
461 during a process simulation that represents the most challenging or stressful conditions
462 encountered or performed by the person being evaluated. The assessment must include media
463 fill testing for all risk levels and glove fingertip sampling.

464 (A) The required visual observation shall assess:

- 465 1. Proper aseptic technique, manipulations and work practices, including, but not
466 limited to, avoiding touch contamination, proper use of first air and if
467 applicable, sterilizing high risk CSPs;
- 468 2. Cleaning and disinfection;
- 469 3. Hand hygiene, gloving and garbing;
- 470 4. Identifying, weighing, and measuring of ingredients;
- 471 5. Maintaining and achieving sterility in ISO Class 5 areas and within primary
472 engineering controls, and;
- 473 6. Labeling and inspecting CSPs for quality.

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

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

483 (D) Frequency: The required Aseptic Technique Skill Assessment must be conducted
484 prior to initial compounding and every twelve (12) months thereafter for Risk Levels 1 and 2
485 compounding and every (6) months thereafter for Risk Level 3 compounding. Additionally, an
486 Aseptic Technique Skill Assessment must be conducted whenever the quality assurance program
487 yields an unacceptable result or whenever unacceptable techniques are observed.

488 (E) Individuals who fail written tests; visual observation of hand hygiene, garbing, and
489 aseptic technique; gloved fingertip/thumb sampling; or media-fill tests must undergo immediate
490 requalification through additional training by competent compounding personnel. Individuals
491 who fail visual observation of hand hygiene, garbing, and aseptic technique; gloved
492 fingertip/thumb sampling; or media-fill tests must pass three successive reevaluations in the
493 deficient area before they can resume compounding of sterile preparations.

494 ~~(9)~~(11) Record Keeping.

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

496 1. Training and competency evaluation of pharmacy personnel involved in sterile ~~product~~
497 ~~preparation~~compounding, including, the dates and results of the required aseptic technique
498 training, aseptic technique skill assessment, glove fingertip sampling and media-fill testing;

499 2. Refrigerator, ~~and~~ freezer and, if applicable, incubator temperature logs;

500 3. Certification ~~of workbenches~~ dates and results for any PEC or ISO classified area;

501 4. Copies of any manufacturer ~~standards~~ manuals that are relied upon to maintain compliance
502 with this rule; ~~and~~

503 5. Other facility quality control logs as appropriate including all maintenance, cleaning, and
504 calibration records; and

505 6. If applicable, pressure recordings including documentation of the review of continuous
506 monitoring system results as required by section (5)(F).

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

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

511 1. Preparation work sheet;

512 2. Sterilization records;

513 3. Quarantine records, if applicable;

514 4. End-~~product~~preparation evaluation and testing records as required in section ~~(12)~~(14); and

515 5. Ingredient validation records as required in section ~~(12)~~(14).

516 (D) All records and reports shall be maintained either electronically or physically for two (2)
517 years and shall be readily retrievable; and subject to inspections by the board of pharmacy or its

518 agents. At a minimum, records shall be physically or electronically produced immediately or
519 within two (2) hours of a request from the Board or the Board's authorized designee.

520 ~~(10)~~(12) Labeling.

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

524 1. Beyond-use date;

525 2. Storage requirements if stored at other than controlled room temperature;

526 3. Any device specific instructions; ~~and~~

527 4. Auxiliary labels, when applicable; ~~and~~

528 5. If applicable, a designation indicating the preparation is hazardous.

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

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

531 ~~(11)~~(13) Beyond-Use Dating.

532 (A) Risk Level 1 and Risk Level 2: All sterile ~~product~~preparations must bear a beyond-use date
533 that complies with section of this rule. Beyond-use dates ~~are~~must be assigned based on current
534 drug and microbiological stability information and sterility considerations.

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

536 ~~(C)~~ Risk Level 3: In addition to all Risk Level 1 requirements, there must be a reliable method
537 for establishing all ~~expiration~~beyond-use dates, including laboratory testing of product stability,
538 pyrogenicity, particulate contamination and potency. ~~Expiration dating not specifically~~

539 ~~referenced in the product's approved labeling or not established by product specific instrumental~~
540 ~~analysis, shall be limited to thirty (30) days.~~ Beyond-use dating not specifically referenced in the

541 products approved labeling or not established by product specific instrumental analysis shall be
542 limited ~~to thirty (30) days~~to twenty-four (24) hours if stored at controlled room temperature,

543 three (3) days if stored at cold temperature and forty-five (45) days if stored frozen. ~~There must~~

544 ~~be a reliable method for establishing all beyond use dating. Products maintaining beyond use~~
545 ~~dating~~ Preparations assigned a beyond-use date of greater than thirty (30) days shall have lab
546 testing of productpreparation stability and potency.

547 ~~(12)~~(14) End-ProductPreparation Evaluation.

Comment [GK3]: This language conflicts with (14)(C) below and would lower Missouri's current standard that requires testing of all R3s. Staff recommends keeping the same language as the emergency rule.

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

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

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

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

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

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

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

576 B. All weighings, volumetric measurements, and additions of ingredients were carried out
577 properly;

578 C. The compounding or control records include documentation that the fill volumes of all
579 units available for release were checked and were correct; and

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

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

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

589 ~~(13) Handling Sterile Products Outside the Pharmacy.~~ (15) Storage, Handling and Transport.

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

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

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

601
602 (16) Point-of-Care Assembled Systems. Assembly of point-of-care assembled systems shall be
603 considered Risk Level 1 compounding. Point-of-care assembled systems shall be assigned a
604 beyond-use date which may exceed the beyond-use-date authorized for Risk Level 1 preparations
605 provided the date is assigned in accordance with the manufacturer's recommendations or
606 labeling.

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

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

614
615 (17) General Cleaning and Disinfection Requirements. Except as otherwise provided herein,
616 cleaning and disinfection of controlled and buffer areas, supplies and equipment shall be
617 performed and conducted in accordance with USP Chapter 797 timeframes and procedures.
618 Controlled areas that do not meet ISO air classifications shall be cleaned and disinfected as
619 required by USP Chapter 797 for segregated compounding areas. If compounding is done less
620 frequently than the cleaning and disinfection timeframes specified in USP Chapter 797, cleaning
621 and disinfection must occur before each compounding session begins.

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

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

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

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

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

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

643
644 (18) Environmental Sampling/Testing. The pharmacy shall establish and follow proper controls
645 to ensure environmental quality, prevent environmental contamination and maintain air quality in
646 all ISO classified areas. Sampling/testing shall be conducted during dynamic operating
647 conditions in accordance with USP Chapter 797. Samples must be tested for bacteria and fungus
648 and shall comply with the following:

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

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

- 659 1. As part of the initial certification and recertification of new facilities and equipment;
- 660 2. Whenever the physical structure of the ISO classified has been altered;
- 661 3. In response to identified problems with CSPs or end-preparation testing failure; and
- 662 4. Whenever maintenance, repairs or changes to the PEC or ISO classified area may
663 affect the airflow pattern. The date and type of maintenance, repair or change shall
664 be documented in the pharmacy's records.

665 ~~(14)~~(19) Cytotoxic Drugs.

666 (A) The following additional requirements are necessary for those licensed pharmacies that
667 prepare cytotoxic drugs to insure the protection of the personnel involved:

668 1. Cytotoxic drugs shall be compounded in a vertical flow, Class II biological safety cabinet
669 | or ~~an isolator~~ a CACI. If used for other ~~product~~preparations, the cabinet must be thoroughly
670 cleaned;

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

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

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

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

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

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

690 ~~(16) In addition to the requirements outlined in this rule, all standards and requirements as~~
691 ~~outlined in 20 CSR 2220 2.400 must be maintained. Pharmacies that are registered with the Food~~
692 ~~and Drug Administration (FDA) are exempt from the distribution restrictions in 20 CSR 2220~~
693 ~~2.400(12) for compounded sterile pharmaceuticals distributed with FDA's knowledge and~~
694 ~~enforcement discretion. This exemption applies only to a twenty four (24) hour course of~~
695 ~~therapy which is needed:~~

696 ~~(A) To treat an emergency situation; or~~

697 ~~(B) For an unanticipated procedure for which a time delay would negatively affect a patient~~
698 ~~outcome. In order to continue beyond twenty four (24) hours, the pharmacy must obtain a~~
699 ~~prescription and comply with all record and labeling requirements as defined by law or~~
700 ~~regulation.~~

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

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

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

714
715 (21) Recalls. A recall must be initiated when a CSP is deemed to be misbranded, adulterated or
716 non-sterile or if end-preparation testing results are out of specification. The pharmacy shall
717 notify the prescriber of the nature of the recall, the problem(s) identified and any recommended
718 actions to ensure public health and safety. In cases where the CSP has the potential to harm the
719 patient, the same notification shall be provided to all patients that received the recalled CSP(s).
720 Any recall initiated by a pharmacy shall be reported, in writing, to the board within three (3)
721 business days.

722
723 *AUTHORITY: sections 338.140, 338.240, and 338.280, RSMo 2000 and section 338.010, RSMo*
724 *Supp. 2007.* This rule originally filed as 4 CSR 220-2.200. Original rule filed May 4, 1992,*
725 *effective Feb. 26, 1993. Amended: Filed Oct. 28, 1994, effective May 28, 1995. Rescinded and*
726 *readopted: Filed Dec. 3, 2002, effective July 30, 2003. Moved to 20 CSR 2220-2.200, effective*
727 *Aug. 28, 2006. Amended: Filed Feb. 6, 2008, effective Aug. 30, 2008.*

728 *Original authority: 338.010, RSMo 1939, amended 1951, 1989, 1990, 2007; 338.140, RSMo
729 1939, amended 1981, 1989, 1997; 338.240, RSMo 1951; and 338.280, RSMo 1951, amended
730 1971, 1981.
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