

Meeting Notice

Missouri Board of Pharmacy Sterile Compounding Sub-Committee Conference Call

**April 19, 2016 4:00 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 4:00 p.m. on April 19, 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
April 19, 2016 4:00 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*
3 | *~~distribution~~dispensing of ~~sterile pharmaceuticals~~ compounded sterile preparations by licensed*
4 | *pharmacies, 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 area where the primary engineering control is physically
26 | located.

27 | (F) CETA Certification Guide for Sterile Compounding Facilities: The Controlled
28 | Environment Testing Association Certification Guide for Sterile Compounding Facilities (2008),
29 | which is incorporated herein by reference. Copies of the Certification Guide for Sterile
30 | Compounding Facilities (2008) are published by, and available from, Controlled Environment

31 [Testing Association, 1500 Sunday Drive, Suite 102, Raleigh, NC 27607 or online](#)
32 [at http://www.cetainternational.org/](http://www.cetainternational.org/). [This rule does not include any later amendments or](#)
33 [additions to the Certification Guide.](#)

34
35 (G) Clean room: A room— [\(Should be buffer area\)](#)

36 1. In which the concentration of airborne particles is controlled [to meet ISO air](#)
37 [classifications](#);

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

40 3. In which other relevant variables (e.g., temperature, humidity, and pressure) are controlled
41 as [necessary](#).

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

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

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

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

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

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

53 [\(I\) Compounding Aseptic Containment Isolator \(CACI\): A RABS that is designed for](#)
54 [compounding sterile hazardous drugs and designed to provide worker protection from exposure](#)
55 [to undesirable levels of airborne drugs throughout the compounding and material transfer](#)
56 [processes and to provide an aseptic environment for CSPs.](#)

57 [\(J\) Compounding Aseptic Isolator \(CAI\): A RABS specifically designed for compounding](#)
58 [sterile non-hazardous pharmaceutical ingredients or CSPs and designed to maintain an aseptic](#)
59 [compounding environment within the isolator throughout the compounding and material transfer](#)
60 [processes.](#)

Comment [GK1]: Someone suggested changing "clean room" to "clean area." Our notes are unclear on whether this was the consensus.

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

66 ~~(K)~~(L) Critical area: Any area in the controlled area where ~~products~~ preparations or containers
67 are exposed to the environment.

68 ~~(L)~~(M) Critical site: ~~An opening providing a direct pathway between a sterile product and the~~
69 ~~environment or any surface coming into contact with the product or environment.~~ Any surface,
70 pathway or opening (e.g., vial septa, injection ports, beakers, needle hubs) that provides a direct
71 pathway between a compounded sterile preparation or other ingredient used to compound a
72 sterile preparation and the air, environment or moisture or that poses a risk of touch
73 contamination.

74 ~~(M)~~(N) Critical surface: Any surface that comes into contact with previously sterilized
75 ~~product~~preparations or containers.

76 (O) CSP: Compounded sterile preparation.

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

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

87 ~~(P)~~(R) High-Efficiency Particulate Air (HEPA) filter: A filter composed of pleats of filter
88 medium separated by rigid sheets of corrugated paper or aluminum foil that direct the flow of air
89 forced through the filter in a uniform parallel flow. HEPA filters remove ninety-nine point
90 ninety-seven percent (99.97%) of all particles three-tenths (0.3) microns or larger. When HEPA
91 filters are used as a component of a horizontal- or vertical-laminar-airflow workbench, an

92 | environment can be created consistent with standards for ~~a Class 100 clean room~~ an ISO 5
93 | environment.

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

96 | (T) ISO Class 7 (or the “buffer area”): An area with less than 352,000 particles (0.5 µm and
97 | larger in size) per cubic meter.

98 | (U) ISO Class 8 (or the “ante-area”): An area with less than 3,520,000 particles (0.5 µm and
99 | larger in size) per cubic meter.

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

106 | (V) Multiple-Dose Container: A multiple-unit container for articles or compounded sterile
107 | preparations that contains more than one dose of medication.

108 | ~~(R)(W)~~ Parenteral: A sterile preparation of drugs for injection through one (1) or more layers
109 | of skin.

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

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

117 | ~~(S)(Z)~~ Process validation or simulation: Microbiological simulation of an aseptic process with
118 | growth medium processed in a manner similar to the processing of the ~~product~~ preparation and
119 | with the same container or closure system.

120 | ~~(F)(AA)~~ Quality assurance: For purposes of these regulations, quality assurance is the set of
121 | activities used to ensure that the processes used in the preparation of sterile drug
122 | ~~product~~ preparations lead to ~~product~~ preparations that meet predetermined standards of quality.

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

127 (CC) RABS: Restricted access barrier system (RABS): A primary engineering control that is
128 comprised of a closed system made up of four (4) solid walls, an air-handling system, and
129 transfer and interaction devices. The walls are constructed so as to provide surfaces that are
130 cleanable with coving between wall junctures. The air-handling system provides HEPA filtration
131 of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports.
132 Transfers are designed to minimize the entry of contamination. Manipulations can take place
133 through either glove ports or half suits. Examples of a RABS may include, but is not limited to, a
134 CAI or CACI.

135 ~~(V)~~(DD) Repackaging: The subdivision or transfer of a compounded ~~product~~preparation from
136 one container or device to a different container or device.

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

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

140 ~~(X)~~(GG) Sterilization: A validated process used to render a ~~product~~preparation free of viable
141 organisms.

142 ~~(Y)~~(HH) Temperatures:

143 1. Frozen means temperatures between twenty below zero and ten degrees Celsius (20 and
144 10°C) (four below zero and fourteen degrees Fahrenheit (4 and 14° F)).

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

147 3. Controlled Rroom temperatures ~~means room temperatures between fifteen and thirty~~
148 ~~degrees Celsius (15 and 30°C) (fifty nine and eighty six degrees Fahrenheit (59 and 86°F)).~~a
149 temperature maintained thermostatically that encompasses the usual and customary working
150 environment of 20° to 25° Celsius (68° to 78° F) and that results in a mean kinetic temperature
151 calculated to be not more than 25° Celsius. Excursions between 15° and 30° Celsius (59° to 86°
152 F) as commonly experienced in pharmacies and other facilities shall be deemed
153 compliant. Provided the mean kinetic temperature remains in the allowed range, transient spikes

154 up to 40°Celsius are permitted as long as they do not exceed 24 hours. Spikes above 40°Celsius
155 are permitted if allowed by the manufacturer.

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

161 ~~(Z)~~(JJ) Validation: Documented evidence providing a high degree of assurance that specific
162 processes will consistently produce a productpreparation meeting predetermined specifications
163 and quality attributes.

164 ~~(AA)~~(KK) Definitions of sterile compounded productpreparations by risk level:

165 1. Risk Level 1: Applies to compounded sterile productpreparations that exhibit
166 characteristics A., B., ~~and~~or C., stated below. All Risk Level 1 productpreparations shall be
167 prepared with sterile equipment, sterile ingredients and solutions and sterile contact surfaces for
168 the final productpreparation. Risk Level 1 includes the following:

169 A. ProductPreparations:

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

172 (II) Stored under refrigeration ~~for~~ and assigned a beyond-use date of seven (7) days or
173 ~~less-before complete administration to a patient over a period not to exceed forty eight (48)~~
174 ~~hours~~; or

175 (III)~~Stored F~~frozen ~~for~~ and assigned a beyond-use date of thirty (30) days or less ~~before~~
176 ~~complete administration to a patient over a period not to exceed forty eight (48) hours.~~

177 B. Unpreserved sterile productpreparations prepared for administration to one (1) patient or
178 batch-prepared productpreparations containing suitable preservatives prepared for administration
179 to more than one (1) patient.

180 C. ProductPreparations prepared by closed-system aseptic transfer of sterile, nonpyrogenic,
181 finished pharmaceuticals (e.g., from vials or ampules) obtained from licensed manufacturers into
182 sterile final containers obtained from licensed manufacturers.

183 2. Risk Level 2: Sterile productpreparations exhibit characteristic A., B., or C., stated below.
184 All Risk Level 2 productpreparations shall be prepared with sterile equipment, sterile ingredients

185 | and solutions and sterile contact surfaces for the final ~~product~~preparation and with closed-system
186 | transfer methods. Risk Level 2 includes the following:

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

193 | B. Batch-prepared ~~product~~preparations without preservatives that are intended for use by
194 | more than one (1) patient.

195 | C. ~~Product~~Preparations compounded by complex or numerous manipulations of sterile
196 | ingredients obtained from licensed manufacturers in a sterile container or reservoir obtained from
197 | a licensed manufacturer by using closed-system aseptic transfer (e.g., automated compounder).

198 | 3. Risk Level 3: Sterile ~~product~~preparations exhibit either characteristic A. or B.:

199 | A. ~~Product~~Preparations compounded from nonsterile ingredients or compounded with
200 | nonsterile components, containers or equipment before terminal sterilization.

201 | B. ~~Product~~Preparations prepared by combining multiple ingredients (sterile or nonsterile)
202 | by using an open-system transfer or open reservoir before terminal sterilization.

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

204 | (A) A manual, outlining policies and procedures encompassing all aspects of Risk Level 1, 2
205 | and 3 ~~product~~preparations, shall be available for inspection at the pharmacy. The manual shall be
206 | reviewed on an annual basis. The pharmacy shall have current reference materials related to
207 | sterile ~~product~~preparations.

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

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

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

242 (3) Personnel Education, Training and Evaluation.

243 (A) Risk Level 1: All pharmacy personnel preparing sterile ~~product~~preparations must receive
244 suitable didactic and experiential training in aseptic technique and procedures and shall be
245 skilled and trained to accurately and competently perform the duties assigned. Training must be
246 completed and documented prior to initial compounding and every twelve (12) months
247 thereafter. Additional training must be conducted if the level of sterile activity conducted by the
248 individual changes or there is a change in compounding methods. To ensure competency,
249 personnel must successfully pass an Aseptic Technique Skill Assessment that complies with
250 section (9) of this rule.

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

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

- 256 1. Aseptic processing;
- 257 2. Quality assurance of environmental, component, and end-~~product~~preparation testing;
- 258 3. Sterilization; and
- 259 4. Selection and use of containers, equipment, and closures.

260 (4) Storage and Handling in the Pharmacy.

261 (A) Risk Level 1 and 2: Solutions, drugs, supplies and compounding equipment must be stored
262 ~~according to manufacturer or USP requirements~~ and maintained in a manner that will maintain
263 the chemical and microbiological stability of CSPs. Refrigeration ~~and~~, freezer and, if applicable,
264 incubator temperatures shall be documented daily. Other storage areas shall be inspected
265 regularly to ensure that temperature and lighting meet requirements. Drugs and supplies shall be
266 shelved above the floor. Removal of ~~products~~drugs and supplies from boxes shall be done
267 outside controlled areas. Removal of used supplies from the controlled area shall be done at least
268 daily. ProductPreparation recall procedures must comply with section (24) of this rule and must
269 permit retrieving affected ~~product~~preparations from specific involved patients.

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

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

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

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

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

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

301 (5) Facilities and Equipment.

302 (A) Risk Level 1: Risk Level 1 preparations must be prepared in a PEC located in a controlled
303 area that meets the requirements of this rule. A sink with hot and cold water must be near, but
304 not in, the controlled area. The controlled area and inside equipment must be cleaned and
305 disinfected as provided in section (19) of this rule. Computer entry, order processing, label
306 generation, and record keeping shall be performed outside the critical area. Primary engineering
307 controls shall meet the requirements of section (7) of this rule; prefilters must be visually
308 inspected on a regularly scheduled basis and replaced according to manufacturer's specifications.
309 Pumps utilized in the compounding process shall be recalibrated and documented according to
310 manufacturer procedures.

311 (B) Risk Level 2: In addition to all Risk Level 1 requirements, Risk Level 2 preparations must
312 be prepared in a PEC located in a buffer area or prepared in a RABS located within a controlled
313 area. Access to the controlled area must be limited to those who are in appropriate garb.

314 Automated compounding devices must be calibrated and verified as to accuracy, according to
315 manufacturer procedures. Risk Level 2 preparations shall at a minimum remain a Risk Level 2
316 for the life of the preparation.

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

322 (D) All PECs and ISO classified areas shall be certified to ensure compliance with
323 requirements of this rule prior to beginning sterile compounding activities and every six (6)
324 months thereafter. Certification/recertification shall be conducted in accordance with the CETA
325 Certification Guide for Sterile Compounding Facilities using recognized and appropriate
326 certification and testing equipment. The pharmacy shall maintain an attestation or statement
327 from the certifier verifying that certification/recertification was performed in compliance with
328 the required CETA certification guidelines.

329 1. The PEC and ISO classified areas must be recertified when: (1) any changes occur
330 that may affect airflow or environmental conditions or (2) the PEC or room is relocated or
331 altered or (3) major service to the PEC or ISO Class area is performed.
332 Certification/recertification results shall be reviewed by a pharmacist once received.
333 Deficiencies or failures shall be investigated and corrected prior to further compounding.

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

337 (E) Automated compounding devices shall be tested for content, volume and weight accuracy
338 prior to both initial and daily use. Test results shall be reviewed by a pharmacist to ensure
339 compliance. The identity of the reviewing pharmacist and the review date shall be documented
340 in the pharmacy's records.

341

342 (6) Primary Engineering Controls (PECs):

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

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

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

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

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

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

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

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

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

371 (C) Nonessential objects that shed particles shall not be brought into the controlled area,
372 including, but not limited to, pencils, cardboard cartons, paper towels, and cotton items (e.g.,
373 gauze pads). Furniture, carts, supplies and equipment shall be removed from shipping

374 cartons/containers and properly cleaned and disinfected with sterile alcohol before entering any
375 ISO classified area. No shipping or other external cartons may be taken into the controlled area
376 or an ISO classified area.

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

379 ~~(6)~~(8) ~~Apparel~~ Garbing and Hand Hygiene. Individuals engaged in, or assisting with, CSPs shall
380 be trained and demonstrate competence in proper personal garbing, gloving and hand hygiene.
381 Competence must be documented and assessed through direct visual observation as part of the
382 aseptic technique skill assessment required by this rule.

Comment [GK2]: Staff asked clarification on the garbing requirements for a RABS.

383 (A) Risk Level 1: Low-particulate and non-shedding gowns, hair covers, gloves, face masks
384 and beard covers must be worn during compounding. All head and facial hair must be covered.
385 During sterile preparation, gloves shall be disinfected frequently with a suitable agent and
386 changed when integrity is compromised. All personnel entering the controlled area must be
387 garbed as required by this section.

Comment [GK3]: Do we need to address re-use of garbing?

388 (B) Risk Level 2 and Risk Level 3: ~~In the controlled area, personnel wear low particulate,~~
389 ~~clean clothing covers. Head and facial hair is covered. Gloves, gowns, and masks are required. In~~
390 ~~addition to Risk Level 1 requirements, shoe covers and sterile gloves must be worn while~~
391 ~~compounding, including, over RABS gloves. During sterile preparation gloves shall be rinsed~~
392 ~~frequently with a suitable agent and changed when integrity is compromised. All personnel~~
393 entering the controlled or buffer area must garb as required by this section.

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

398 ~~(7)~~(9) Aseptic Technique and ~~Product~~ Preparation. Appropriate quality control methods shall be
399 maintained over compounding methods at all times to ensure proper aseptic technique.

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

420 (B) Risk Level 2: In addition to Risk Level 1 requirements, a file containing the formula,
421 components, procedures, sample label, and final evaluation shall be made for each
422 ~~product~~preparation batch. A separate work sheet and lot number for each batch shall be
423 completed. When combining multiple sterile ~~product~~preparations, a second verification of
424 calculations shall take place. The pharmacist shall verify data entered into any automatic
425 compounder before processing and check the end ~~product~~preparation for accuracy.

426 (C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, nonsterile components must
427 meet compendial standards ~~if available, as~~ or must be verified by a pharmacist and a certificate
428 of analysis. Batch preparation files shall also include comparisons of actual with anticipated
429 yields, sterilization methods, and quarantine specifications. Presterilized containers shall be used
430 when feasible. Final containers must be sterile and capable of maintaining ~~product~~preparation

431 integrity throughout the shelf life. Sterilization methods must be based on properties of the
432 ~~product~~ preparation and must be conducted in a method recognized for the preparation by USP.

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

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

442 ~~(8) Process Validation.~~

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

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

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

453 (10) Aseptic Technique Skill Assessment. Individuals engaged in sterile compounding must
454 take and successfully pass an aseptic technique skill assessment to verify aseptic competency.
455 The assessment must include a direct visual observation of the individual's aseptic competency
456 during a process simulation that represents the most challenging or stressful conditions
457 encountered or performed by the person being evaluated. The assessment must also include both
458 glove fingertip sampling and media-fill testing.

459 (A) The required visual observation shall assess:

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

469 (B) Media-Fill Testing. Pharmacies shall establish and follow policies and procedures for
470 conducting media-fill testing to assess the quality of aseptic skills/techniques. Media-fill testing
471 shall comply with USP Chapter 797's recommended procedures and methods. Media-fill testing
472 must be conducted using the most challenging or stressful conditions or compounding actually
473 encountered or performed by the person being evaluated using the same container or closure. A
474 minimum of three media-fill tests must be completed during initial media-fill testing.

475 (C) Glove-Fingertip Sampling. Initial and ongoing fingertip sampling must be completed
476 for Risk Level 2 & 3. Sampling shall be completed in accordance with USP Chapter 797
477 procedures and methods. Ongoing sampling must be conducted after each required media-fill
478 test.

479 (D) Frequency: The required assessment shall be conducted prior to initial compounding
480 and every twelve (12) months thereafter for Risk Levels 1 and 2 compounding and every (6)
481 months thereafter for Risk Level 3 compounding. Additionally, an aseptic technique skill
482 assessment must be conducted whenever the quality assurance program yields an unacceptable
483 result, or whenever unacceptable techniques are observed.

484 (E) If an individual fails to demonstrate competency or if microbial growth is detected, the
485 required didactic and experiential aseptic technique training must be repeated and the aseptic
486 technique skill assessment conducted again that includes media fill testing of a minimum of three
487 media-fill tests. Staff must pass the required aseptic technique skill assessment prior to
488 beginning or continuing any further **compounding**.

489 ~~(9)~~(11) Record Keeping.

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

Comment [GK4]: This standard is stricter than 797. 797 says:

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

491 1. Training and competency evaluation of pharmacy personnel involved in sterile ~~product~~
492 ~~preparation~~ compounding, including, the dates and results of the required aseptic technique
493 training, aseptic technique skill assessment, glove fingertip sampling and media-fill testing;
494 2. Refrigerator ~~and~~ freezer and, if applicable, incubator temperature logs;
495 3. Certification ~~of workbenches~~ dates and results for any PEC or ISO classified area;
496 4. Copies of any manufacturer ~~standards~~ manuals that are relied upon to maintain compliance
497 with this rule; ~~and~~
498 5. Other facility quality control logs as appropriate including all maintenance, cleaning, and
499 calibration records; and
500 6. Pressure recordings, if applicable, including documentation of the daily review of
501 continuous monitoring system results required by section (18)(D).
502 (B) Risk Level 2: In addition to Risk Level 1 requirements, records of any end-
503 ~~product~~ preparation testing and batch preparation records must be maintained.
504 (C) Risk Level 3: In addition to Risk Level 1 and 2 requirements, record requirements for Risk
505 Level 3 ~~product~~ preparations must include:
506 1. Preparation work sheet;
507 2. Sterilization records;
508 3. Quarantine records, if applicable;
509 4. End-~~product~~ preparation evaluation and testing records as required in section ~~(12)(14)~~; and
510 5. Ingredient validation records as required in section ~~(12)(14)~~.
511 (D) All records and reports shall be maintained either electronically or physically for two (2)
512 years and shall be readily retrievable; and subject to inspections by the board of pharmacy or its
513 agents. At a minimum, records shall be physically or electronically produced immediately or
514 within two (2) hours of a request from the Board or the Board's authorized designee.
515 ~~(10)(12)~~ Labeling.
516 (A) Risk Level 1: Sterile ~~product~~ preparations ~~dispensed to patients~~ shall be labeled in
517 accordance with section 338.059, RSMo and with the following supplemental information
518 ~~affixed to a permanent label~~:
519 1. Beyond-use date;
520 2. Storage requirements if stored at other than controlled room temperature;
521 3. Any device specific instructions; ~~and~~

522 4. Auxiliary labels, when applicable; and
523 5. A designation indicating the preparation is hazardous, when applicable.
524 ~~(B) Risk Level 2: All requirements for Risk Level 1 must be met.~~
525 ~~(C) Risk Level 3: All requirements for Risk Level 1 must be met.~~
526 ~~(11)~~(13) Beyond-Use Dating.
527 (A) Risk Level 1 and Risk Level 2: All sterile ~~product~~preparations must bear a beyond-use
528 date. Beyond-use dates ~~are~~must be assigned based on current drug stability information and
529 sterility considerations.
530 (B) ~~Risk Level 2: All requirements for Risk Level 1 must be met.~~
531 ~~(C)~~Risk Level 3: In addition to all Risk Level 1 requirements, there must be a reliable method
532 for establishing all expirationbeyond-use dates, ~~including laboratory testing of product stability,~~
533 ~~pyrogenicity, particulate contamination and potency. Expiration dating not specifically~~
534 ~~referenced in the product's approved labeling or not established by product specific instrumental~~
535 ~~analysis, shall be limited to thirty (30) days.~~ Beyond-use dating not specifically referenced in the
536 products approved labeling or not established by product specific instrumental analysis shall be
537 limited to thirty (30) days. ~~There must be a reliable method for establishing all beyond use~~
538 ~~dating.~~ Products maintaining beyond-use dating of greater than thirty (30) days shall have lab
539 testing of product stability and potency.
540 ~~(12)~~(14) End-~~Product~~Preparation Evaluation.
541 (A) Risk Level 1: The final ~~product~~preparation must be inspected for clarity, container leaks,
542 integrity, and appropriate solution cloudiness or phase separation, ~~particulates in solution,~~
543 ~~appropriate~~ solution color, and solution volume. The pharmacist must verify that the
544 ~~product~~preparation was compounded accurately as to the ingredients, quantities, containers, and
545 reservoirs. Background light or other means for the visual inspection of ~~product~~preparations for
546 any particulate and/or foreign matter must be used as part of the inspection process.
547 (B) Risk Level 2: All Risk Level 1 requirements must be met.
548 (C) Risk Level 3: In addition to all Risk Level 1 requirements, the process validation procedure
549 shall be supplemented with a program of end-~~product~~preparation sterility testing according to a
550 formal sampling plan. Samples shall be statistically valid to ensure that batches are sterile. A
551 method for recalling batch ~~product~~preparations shall be established if end-~~product~~preparation

552 testing results are unacceptable. All sterile ~~product~~preparations must be tested for sterility. All
553 parenteral sterile ~~product~~preparations must also be tested for pyrogenicity. ~~Sterile products~~
554 ~~compounded from nonsterile components~~ Risk Level 3 preparations must be quarantined and
555 stored to maintain chemical and microbiological stability pending results of end-
556 ~~product~~preparation testing.

557 1. Sterility testing: Sampling for the sterility test shall occur promptly upon the completion of
558 preparation. The sterility test, including the sampling scheme, shall be conducted according to
559 one (1) of the USP methods.

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

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

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

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

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

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

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

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

583 ~~(13) Handling Sterile Products Outside the Pharmacy.~~ (15) Storage, Handling and Transport.
584 ~~(A) Risk Level 1: Sterile preparations shall be correctly packaged, transported, stored, dispensed~~
585 ~~and distributed.~~ The pharmacist-in-charge shall assure the environmental control of all sterile
586 compounded ~~product~~preparations shipped. Sterile ~~product~~preparations shall be transported so as
587 to be protected from excesses of temperatures and light within appropriate packaging or delivery
588 containers that maintain necessary storage conditions to preserve the quality and integrity of
589 sterile ~~product~~preparations. The pharmacy shall follow written procedures that specify packing
590 techniques, configuration, and materials for groups of ~~product~~preparations with common storage
591 characteristics and for specific ~~product~~preparations where unique storage conditions are required
592 to retain adequate stability and ~~product~~preparation quality.

593 ~~(B) Risk Level 2: All requirements for Risk Level 1 must be met.~~
594 ~~(C) Risk Level 3: All requirements for Risk Level 1 must be met.~~

595 ~~(14)~~(16) 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~~ 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
616 (17) Point-of-Care Assembled Systems. Assembly of point-of-care assembled systems shall be
617 considered Risk Level 1 compounding. Point-of-care assembled systems shall be assigned a
618 beyond-use date in accordance with the manufacturer’s recommendations or labeling.

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

624 (B) Point of care assembled systems shall be assembled and stored in accordance with
625 the manufacturer’s labeling and recommendations.

626
627 (18) Environmental Sampling/Testing. The pharmacy shall establish and follow proper controls
628 to ensure environmental quality and to prevent environmental contamination. Routine
629 environmental sampling of all ISO classified areas must be conducted to evaluate air quality
630 compliance and microbial bio burden levels. Sampling/testing shall be conducted during
631 dynamic operating conditions in accordance with USP Chapter 797. Samples must be tested for
632 bacteria and fungus and shall comply with the following:

633 A. Surface Sampling: Surface sampling shall be conducted in accordance with USP
634 Chapter 797 using media for the identification of bacteria and fungus. Surface sampling for
635 pharmacies engaged in Risk Level 1 or Risk Level 2 compounding must be performed every
636 thirty (30) days. For Risk Level 3 compounding, surface sampling shall be performed every
637 fourteen (14) days.

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

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

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

653 D. Pressure Differential: If the controlled area is equipped with a device to monitor the
654 pressure differential between the buffer area and the general environment outside the controlled
655 area, the cascading pressure between ISO Class 7 and ISO Class 8 areas and the outside
656 environment shall not be less than 5 pascals (0.02 inch water column). Pressure differential
657 monitoring must be routinely conducted to ensure compliance with this rule. At a minimum,
658 pressure results must be recorded and documented each day that the pharmacy is open for
659 pharmacy activities. Alternatively, a continuous monitoring system may be maintained if the
660 system maintains ongoing documentation of pressure recordings or, if applicable, maintains
661 pressure alerts that are reviewed daily.
662

663 (19) General Cleaning and Disinfection Requirements. Except as otherwise provided herein,
664 cleaning and disinfection of controlled and buffer areas, supplies and equipment shall be
665 performed and conducted in accordance with USP Chapter 797 timeframes and procedures. For
666 purposes of cleaning and disinfection, controlled areas that do not meet ISO air classifications
667 shall be cleaned and disinfected as required by USP Chapter 797 for segregated compounding
668 areas. If compounding is done less frequently than the cleaning and disinfection timeframes
669 specified in USP Chapter 797, cleaning and disinfection must occur before each compounding
670 session begins.

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

674 (B)Individuals shall be trained in proper cleaning and disinfection procedures prior to
675 performing such activities. Training shall include direct visual observation of the
676 individual’s cleaning and disinfecting process by qualified staff. The individual shall be
677 annually reassessed for competency through direct visual observation. Documentation
678 of the required training and training dates shall be maintained in the pharmacy’s records.
679 Individuals who fail to demonstrate competency shall be reeducated and successfully
680 reevaluated prior to any further cleaning or disinfection.

681 (C)Cleaning and disinfection activities shall be performed using approved agents and
682 procedures described in the pharmacy’s written policies and procedures. Manufacturers’
683 directions for minimum contact time shall be followed.

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

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

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

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

697 (16) In addition to the requirements outlined in this rule, all standards and requirements as
698 outlined in 20 CSR 2220-2.400 must be maintained. Pharmacies that are registered with the Food
699 and Drug Administration (FDA) are exempt from the distribution restrictions in 20 CSR 2220-
700 2.400(12) for compounded sterile pharmaceuticals distributed with FDA's knowledge and
701 enforcement discretion. This exemption applies only to a twenty-four (24)-hour course of
702 therapy which is needed:

703 (A) To treat an emergency situation; or

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

708
709 (23) Remedial Investigations: A remedial investigation shall be required if: (1) any sampling or
710 testing required by this rule demonstrates a colony forming unit (CFU) count that exceeds USP
711 Chapter 797 recommended action levels for the type of sampling/testing or (2) any sampling or
712 testing demonstrates the presence of a highly pathogenic microorganism (e.g., Gram-negative
713 rods, coagulase positive staphylococcus, molds, fungus or yeasts).

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

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

Comment [GK5]: The subcommittee didn't reach a consensus on this section or what should be reported. We were asked to research the new Mass. rules on reporting and found this language:

(6) Every pharmacy engaged in sterile compounding and licensed pursuant to M.G.L. c. 112, § 39 shall report within seven business days of identification all errors relating to the preparation of medications in that pharmacy inconsistent with *United States Pharmacopeia General Chapter 797* standards or criteria for factors including but not limited to pyrogenicity, stability, improper composition, mislabeling, or sterility.

(7) Every pharmacy licensed pursuant to M.G.L. c. 112, § 39 shall report within seven business days all abnormal results, including failure of certification as required pursuant to 247 CMR 6.01(5)(c), and identification of environmental contaminants or improper potency in that pharmacy inconsistent with *United States Pharmacopeia General Chapter 797* standards or criteria.

722
723 (24) Recalls. A recall must be initiated when a CSP is deemed to be misbranded, adulterated or
724 non-sterile or if end-preparation testing results are out of specification. The pharmacy shall
725 notify the prescriber of the nature of the recall, the problem(s) identified and any recommended
726 actions to ensure public health and safety. In cases where the CSP has the potential to harm the
727 patient, the same notification shall be provided to all patients that received the recalled CSP(s).
728 Any recall initiated by a pharmacy shall be reported, in writing, to the board within three (3)
729 business days.

730

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

736 **Original authority: 338.010, RSMo 1939, amended 1951, 1989, 1990, 2007; 338.140, RSMo*
737 *1939, amended 1981, 1989, 1997; 338.240, RSMo 1951; and 338.280, RSMo 1951, amended*
738 *1971, 1981.*

739
740