

RULE ANALYSIS

Introduction: THE AMENDMENTS ARE SUBMITTED TO THE BOARD FOR CONSIDERATION AS AN ADOPTED RULE

Short Title: Sterile Compounding

Rule Numbers: §291.133

Statutory Authority: Texas Pharmacy Act, Chapter 551-569, Occupations Code:

- (1) Section 551.002 specifies that the purpose of the Act is to protect the public through the effective control and regulation of the practice of pharmacy; and
- (2) Section 554.051 gives the Board the authority to adopt rules for the proper administration and enforcement of the Act.

Purpose: The amendments, if adopted, update the rules with regard to USP <797>.

The Board reviewed and voted to propose the amendments during the May 3, 2016, meeting. The proposed amendments were published in the June 24, 2016, issue of the *Texas Register* at 41 TexReg 4611.

1 **SUBCHAPTER G. SERVICES PROVIDED BY PHARMACIES**

2 **22 TAC §291.133**

3 The Texas State Board of Pharmacy proposes amendments to §291.133 concerning Pharmacies
4 Compounding Sterile Preparations. The amendments, if adopted, update the rules with regard to
5 USP <797>.

6 Gay Dodson, R.Ph., Executive Director/Secretary, has determined that, for the first five-year
7 period the rule is in effect, there will be no fiscal implications for state or local government as a
8 result of enforcing or administering the rule.

9 Ms. Dodson has determined that, for each year of the first five-year period the rule will be in
10 effect, the public benefit anticipated as a result of enforcing the amendments will ensure
11 pharmacies engaged in sterile compounding are doing so in accordance with USP <797>. There
12 is no fiscal impact for individuals, small or large businesses, or to other entities which are
13 required to comply with this section.

14 Written comments on the amendments may be submitted to Allison Vordenbaumen Benz, R.Ph.,
15 M.S., Director of Professional Services, Texas State Board of Pharmacy, 333 Guadalupe Street,
16 Suite 3-600, Austin, Texas 78701, FAX (512) 305-6778. Comments must be received by 5:00
17 p.m., August 1, 2016.

18 The amendments are proposed under §551.002 and §554.051 of the Texas Pharmacy Act
19 (Chapters 551 - 569, Texas Occupations Code). The Board interprets §551.002 as authorizing the
20 agency to protect the public through the effective control and regulation of the practice of
21 pharmacy. The Board interprets §554.051(a) as authorizing the agency to adopt rules for the
22 proper administration and enforcement of the Act.

23 The statutes affected by these amendments: Texas Pharmacy Act, Chapters 551 - 569, Texas
24 Occupations Code.

25 ***§291.133. Pharmacies Compounding Sterile Preparations.***

26 (a) - (b) (No change.)

27 (c) Personnel.

28 (1) - (3) (No change.)

29 (4) Evaluation and testing requirements.

30 (A) All pharmacy personnel preparing sterile preparations shall be trained conscientiously and
31 skillfully by expert personnel through multimedia instructional sources and professional
32 publications in the theoretical principles and practical skills of aseptic manipulations, garbing
33 procedures, aseptic work practices, achieving and maintaining ISO Class 5 environmental

34 conditions, and cleaning and disinfection procedures before beginning to prepare compounded
35 sterile preparations.

36 (B) All pharmacy personnel preparing sterile preparations shall perform didactic review and pass
37 written and media-fill testing of aseptic manipulative skills initially followed by:

38 (i) every 12 months for low- and medium-risk level compounding; and

39 (ii) every six months for high-risk level compounding.

40 (C) Pharmacy personnel who fail written tests or whose media-fill test vials result in gross
41 microbial colonization shall:

42 (i) be immediately re-instructed and re-evaluated by expert compounding personnel to ensure
43 correction of all aseptic practice deficiencies; and

44 (ii) not be allowed to compound sterile preparations for patient use until passing results are
45 achieved.

46 (D) The didactic and experiential training shall include instruction, experience, and demonstrated
47 proficiency in the following areas:

48 (i) aseptic technique;

49 (ii) critical area contamination factors;

50 (iii) environmental monitoring;

51 (iv) structure and engineering controls related to facilities;

52 (v) equipment and supplies;

53 (vi) sterile preparation calculations and terminology;

54 (vii) sterile preparation compounding documentation;

55 (viii) quality assurance procedures;

56 (ix) aseptic preparation procedures including proper gowning and gloving technique;

57 (x) handling of hazardous drugs, if applicable;

58 (xi) cleaning procedures; and

59 (xii) general conduct in the clean room.

60 (E) The aseptic technique of each person compounding or responsible for the direct supervision
61 of personnel compounding sterile preparations shall be observed and evaluated by expert
62 personnel as satisfactory through written and practical tests, and challenge testing, and such
63 evaluation documented. Compounding personnel shall not evaluate their own aseptic technique
64 or results of their own media-fill challenge testing.

65 (F) Media-fill tests must be conducted at each pharmacy where an individual compounds low or
66 medium risk sterile preparations. If pharmacies are under common ownership and control, the
67 media-fill testing may be conducted at only one of the pharmacies provided each of the
68 pharmacies are operated under equivalent policies and procedures and the testing is conducted
69 under the most challenging or stressful conditions. In addition, each pharmacy must maintain
70 documentation of the media-fill test. No preparation intended for patient use shall be
71 compounded by an individual until the on-site media-fill tests indicate that the individual can
72 competently perform aseptic procedures, except that a pharmacist may temporarily compound
73 sterile preparations and supervise pharmacy technicians compounding sterile preparations
74 without media-fill tests provided the pharmacist completes the on-site media-fill tests within
75 seven days of commencing work at the pharmacy.

76 (G) Media-fill must be conducted at each pharmacy where an individual compounds high risk
77 sterile preparations. No preparation intended for patient use shall be compounded by an
78 individual until the on-site media-fill tests indicate that the individual can competently perform
79 aseptic procedures, except that a pharmacist may temporarily compound sterile preparations and
80 supervise pharmacy technicians compounding sterile preparations without media-fill tests
81 provided the pharmacist completes the on-site media-fill tests within seven days of commencing
82 work at the pharmacy.

83 (H) [~~G~~] Media-fill tests procedures for assessing the preparation of specific types of sterile
84 preparations shall be representative of the most challenging or stressful conditions encountered
85 by the pharmacy personnel being evaluated and, if applicable, for sterilizing high-risk level
86 compounded sterile preparations.

87 (I) [~~H~~] Media-fill challenge tests simulating high-risk level compounding shall be used to
88 verify the capability of the compounding environment and process to produce a sterile
89 preparation.

90 (J) [~~I~~] Commercially available sterile fluid culture media, such as Soybean-Casein Digest
91 Medium shall be able to promote exponential colonization of bacteria that are most likely to be
92 transmitted to compounding sterile preparations from the compounding personnel and
93 environment. Media-filled vials are generally incubated at 20 to 25 degrees Celsius or at 30 to 35
94 degrees Celsius for a minimum of 14 days. If two temperatures are used for incubation of media-
95 filled samples, then these filled containers should be incubated for at least 7 days at each
96 temperature. Failure is indicated by visible turbidity in the medium on or before 14 days.

97 (K) [~~J~~] The pharmacist-in-charge shall ensure continuing competency of pharmacy personnel
98 through in-service education, training, and media-fill tests to supplement initial training.
99 Personnel competency shall be evaluated:

- 100 (i) during orientation and training prior to the regular performance of those tasks;
- 101 (ii) whenever the quality assurance program yields an unacceptable result;
- 102 (iii) whenever unacceptable techniques are observed; and
- 103 (iv) at least on an annual basis for low- and medium-risk level compounding, and every six
104 months for high-risk level compounding.
- 105 (L) [~~(K)~~] The pharmacist-in-charge shall ensure that proper hand hygiene and garbing practices
106 of compounding personnel are evaluated prior to compounding, supervising, or verifying sterile
107 preparations intended for patient use and whenever an aseptic media fill is performed.
- 108 (i) Sampling of compounding personnel glove fingertips shall be performed for all risk level
109 compounding.
- 110 (ii) All compounding personnel shall demonstrate competency in proper hand hygiene and
111 garbing procedures and in aseptic work practices (e.g., disinfection of component surfaces,
112 routine disinfection of gloved hands).
- 113 (iii) Sterile contact agar plates shall be used to sample the gloved fingertips of compounding
114 personnel after garbing in order to assess garbing competency and after completing the media-fill
115 preparation (without applying sterile 70% IPA).
- 116 (iv) The visual observation shall be documented and maintained to provide a permanent record
117 and long-term assessment of personnel competency.
- 118 (v) All compounding personnel shall successfully complete an initial competency evaluation and
119 gloved fingertip/thumb sampling procedure no less than three times before initially being
120 allowed to compound sterile preparations for patient use. Immediately after the compounding
121 personnel completes the hand hygiene and garbing procedure (i.e., after donning of sterile gloves
122 and before any disinfecting with sterile 70% IPA), the evaluator will collect a gloved fingertip
123 and thumb sample from both hands of the compounding personnel onto agar plates or media test
124 paddles by having the individual lightly touching each fingertip onto the agar. The test plates or
125 test paddles will be incubated for the appropriate incubation period and at the appropriate
126 temperature. Results of the initial gloved fingertip evaluations shall indicate zero colony-forming
127 units (0 CFU) growth on the agar plates or media test paddles, or the test shall be considered a
128 failure. In the event of a failed gloved fingertip test, the evaluation shall be repeated until the
129 individual can successfully don sterile gloves and pass the gloved fingertip evaluation, defined as
130 zero CFUs growth. No preparation intended for patient use shall be compounded by an
131 individual until the results of the initial gloved fingertip evaluation indicate that the individual
132 can competently perform aseptic procedures except that a pharmacist may temporarily supervise
133 pharmacy technicians compounding sterile preparations while waiting for the results of the
134 evaluation for no more than three days.

135 (vi) Re-evaluation of all compounding personnel shall occur at least annually for compounding
136 personnel who compound low and medium risk level preparations and every six months for
137 compounding personnel who compound high risk level preparations. Results of gloved fingertip
138 tests conducted immediately after compounding personnel complete a compounding procedure
139 shall indicate no more than 3 CFUs growth, or the test shall be considered a failure, in which
140 case, the evaluation shall be repeated until an acceptable test can be achieved (i.e., the results
141 indicated no more than 3 CFUs growth).

142 (M) [~~(L)~~] The pharmacist-in-charge shall ensure surface sampling shall be conducted in all ISO
143 classified areas on a periodic basis. Sampling shall be accomplished using contact plates at the
144 conclusion of compounding. The sample area shall be gently touched with the agar surface by
145 rolling the plate across the surface to be sampled.

146 (5) (No change.)

147 (d) Operational Standards.

148 (1) - (6) (No change.)

149 (7) Primary engineering control device. The pharmacy shall prepare sterile preparations in a
150 primary engineering control device (PEC), such as a laminar air flow hood, biological safety
151 cabinet, compounding aseptic isolator (CAI), or compounding aseptic containment isolator
152 (CACI) which is capable of maintaining at least ISO Class 5 conditions for 0.5 micrometer
153 particles while compounding sterile preparations.

154 (A) Laminar air flow hood. If the pharmacy is using a laminar air flow hood as its PEC, the
155 laminar air flow hood shall:

156 (i) be located in the buffer area and placed in the buffer area in a manner as to avoid conditions
157 that could adversely affect its operation such as strong air currents from opened doors, personnel
158 traffic, or air streams from the heating, ventilating and air condition system;

159 (ii) be certified by a qualified independent contractor according to the appropriate Controlled
160 Environment Testing Association (CETA) standard (CAG-003-2006) for operational efficiency
161 at least every six months and whenever the device or room is relocated or altered or major
162 service to the facility is performed;

163 (iii) have pre-filters inspected periodically and replaced as needed, in accordance with written
164 policies and procedures and the manufacturer's specification, and the inspection and/or
165 replacement date documented; and

166 (iv) be located in a buffer area that has a minimum differential positive pressure of 0.02 to 0.05
167 inches water column. A buffer area that is not physically separated from the ante-area shall
168 employ the principle of displacement airflow as defined in Chapter 797, Pharmaceutical
169 Compounding--Sterile Preparations, of the USP/NF, with limited access to personnel.

170 (B) Biological safety cabinet.

171 (i) If the pharmacy is using a biological safety cabinet as its PEC for the preparation of
172 hazardous sterile compounded preparations, the biological safety cabinet shall be a Class II or III
173 vertical flow biological safety cabinet located in an ISO Class 7 area that is physically separated
174 from other preparation areas. The area for preparation of sterile chemotherapeutic preparations
175 shall:

176 (I) have not less than 0.01 inches water column negative pressure to the adjacent positive
177 pressure ISO Class 7 or better ante-area; and

178 (II) have a pressure indicator that can be readily monitored for correct room pressurization.

179 (ii) Pharmacies that prepare a low volume of hazardous drugs, are not required to comply with
180 the provisions of clause (i) of this subparagraph if the pharmacy uses a device that provides two
181 tiers of containment (e.g., closed-system vial transfer device within a BSC [~~or CACI that is~~
182 ~~located in a non-negative pressure room~~]).

183 (iii) If the pharmacy is using a biological safety cabinet as its PEC for the preparation of non-
184 hazardous sterile compounded preparations, the biological safety cabinet shall:

185 (I) be located in the buffer area and placed in the buffer area in a manner as to avoid conditions
186 that could adversely affect its operation such as strong air currents from opened doors, personnel
187 traffic, or air streams from the heating, ventilating and air condition system;

188 (II) be certified by a qualified independent contractor according to the International Organization
189 of Standardization (ISO) Classification of Particulate Matter in Room Air (ISO 14644-1) for
190 operational efficiency at least every six months and whenever the device or room is relocated or
191 altered or major service to the facility is performed, in accordance with the manufacturer's
192 specifications and test procedures specified in the Institute of Environmental Sciences and
193 Technology (IEST) document IEST-RP-CC002.3;

194 (III) have pre-filters inspected periodically and replaced as needed, in accordance with written
195 policies and procedures and the manufacturer's specification, and the inspection and/or
196 replacement date documented; and

197 (IV) be located in a buffer area that has a minimum differential positive pressure of 0.02 to 0.05
198 inches water column.

199 (C) Compounding aseptic isolator.

200 (i) If the pharmacy is using a compounding aseptic isolator (CAI) as its PEC, the CAI shall
201 provide unidirectional airflow within the main processing and antechambers, and be placed in an
202 ISO Class 7 buffer area unless the isolator meets all of the following conditions:

- 203 (I) The isolator must provide isolation from the room and maintain ISO Class 5 during dynamic
204 operating conditions including transferring ingredients, components, and devices into and out of
205 the isolator and during preparation of compounded sterile preparations.
- 206 (II) Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site
207 must maintain ISO Class 5 levels during compounding operations.
- 208 (III) The CAI must be validated according to CETA CAG-002-2006 standards.
- 209 (IV) The pharmacy shall maintain documentation from the manufacturer that the isolator meets
210 this standard when located in worse than ISO Class 7 environments.
- 211 (ii) If the isolator meets the requirements in clause (i) of this subparagraph, the CAI may be
212 placed in a non-ISO classified area of the pharmacy; however, the area shall be segregated from
213 other areas of the pharmacy and shall:
- 214 (I) be clean, well lit, and of sufficient size;
- 215 (II) be used only for the compounding of low- and medium-risk, non-hazardous sterile
216 preparations;
- 217 (III) be located in an area of the pharmacy with non-porous and washable floors or floor covering
218 to enable regular disinfection; and
- 219 (IV) be an area in which the CAI is placed in a manner as to avoid conditions that could
220 adversely affect its operation.
- 221 (iii) In addition to the requirements specified in clauses (i) and (ii) of this subparagraph, if the
222 CAI is used in the compounding of high-risk non-hazardous preparations, the CAI shall be
223 placed in an area or room with at least ISO 8 quality air so that high-risk powders weighed in at
224 least ISO-8 air quality conditions, compounding utensils for measuring and other compounding
225 equipment are not exposed to lesser air quality prior to the completion of compounding and
226 packaging of the high-risk preparation.
- 227 (D) Compounding aseptic containment isolator.
- 228 (i) If the pharmacy is using a compounding aseptic containment isolator as its PEC for the
229 preparation of low- and medium-risk hazardous drugs, the CACI shall be located in a separate
230 room away from other areas of the pharmacy and shall:
- 231 (I) provide at least 0.01 inches water column negative pressure compared to the other areas of the
232 pharmacy;
- 233 (II) provide unidirectional airflow within the main processing and antechambers, and be placed
234 in an ISO Class 7 buffer area, unless the CACI meets all of the following conditions.

235 (-a-) The isolator must provide isolation from the room and maintain ISO Class 5 during
236 dynamic operating conditions including transferring ingredients, components, and devices into
237 and out of the isolator and during preparation of compounded sterile preparations.

238 (-b-) Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site
239 must maintain ISO Class 5 levels during compounding operations.

240 (-c-) The CACI must be validated according to CETA CAG-002-2006 standards.

241 (-d-) The pharmacy shall maintain documentation from the manufacturer that the isolator meets
242 this standard when located in worse than ISO Class 7 environments.

243 (ii) If the CACI meets all conditions specified in clause (i) of this subparagraph, the CACI shall
244 not be located in the same room as a CAI, but shall be located in a separate room in the
245 pharmacy, that is not required to maintain ISO classified air. The room in which the CACI is
246 located shall provide a minimum of 0.01 inches water column negative pressure compared with
247 the other areas of the pharmacy and shall meet the following requirements:

248 (I) be clean, well lit, and of sufficient size;

249 (II) be maintained at a temperature of 20 degrees Celsius or cooler and a humidity below 60%;

250 (III) be used only for the compounding of hazardous sterile preparations;

251 (IV) be located in an area of the pharmacy with walls, ceilings, floors, fixtures, shelving,
252 counters, and cabinets that are smooth, impervious, free from cracks and crevices, non-shedding
253 and resistant to damage by disinfectant agents; and

254 (V) have non-porous and washable floors or floor covering to enable regular disinfection.

255 (iii) If the CACI is used in the compounding of high-risk hazardous preparations, the CACI shall
256 be placed in an area or room with at least ISO 8 quality air so that high-risk powders, weighed in
257 at least ISO-8 air quality conditions, are not exposed to lesser air quality prior to the completion
258 of compounding and packaging of the high-risk preparation.

259 (iv) Pharmacies that prepare a low volume of hazardous drugs, are not required to comply with
260 the provisions of clauses (i) and (iii) of this subparagraph if the pharmacy uses a device that
261 provides two tiers of containment (e.g., CACI that is located in a non-negative pressure room).

262 (8) - (13) (No change.)

263 (14) Quality Assurance.

264 (A) Initial Formula Validation. Prior to routine compounding of a sterile preparation, a pharmacy
265 shall conduct an evaluation that shows that the pharmacy is capable of compounding a
266 preparation that is sterile and that contains the stated amount of active ingredient(s).

267 (i) Low risk preparations.

268 (I) Quality assurance practices include, but are not limited to the following:

269 (-a-) Routine disinfection and air quality testing of the direct compounding environment to
270 minimize microbial surface contamination and maintain ISO Class 5 air quality.

271 (-b-) Visual confirmation that compounding personnel are properly donning and wearing
272 appropriate items and types of protective garments and goggles.

273 (-c-) Review of all orders and packages of ingredients to ensure that the correct identity and
274 amounts of ingredients were compounded.

275 (-d-) Visual inspection of compounded sterile preparations, except for sterile
276 radiopharmaceuticals, to ensure the absence of particulate matter in solutions, the absence of
277 leakage from vials and bags, and the accuracy and thoroughness of labeling.

278 (II) Example of a Media-Fill Test Procedure. This, or an equivalent test, is performed at least
279 annually by each person authorized to compound in a low-risk level under conditions that closely
280 simulate the most challenging or stressful conditions encountered during compounding of low-
281 risk level sterile preparations. Once begun, this test is completed without interruption within an
282 ISO Class 5 air quality environment. Three sets of four 5-milliliter aliquots of sterile Soybean-
283 Casein Digest Medium are transferred with the same sterile 10-milliliter syringe and vented
284 needle combination into separate sealed, empty, sterile 30-milliliter clear vials (i.e., four 5-
285 milliliter aliquots into each of three 30-milliliter vials). Sterile adhesive seals are aseptically
286 affixed to the rubber closures on the three filled vials. The vials are incubated within a range of
287 20 - 35 degrees Celsius for a minimum of 14 days. Failure is indicated by visible turbidity in the
288 medium on or before 14 days. The media-fill test must include a positive-control sample.

289 (ii) Medium risk preparations.

290 (I) Quality assurance procedures for medium-risk level compounded sterile preparations include
291 all those for low-risk level compounded sterile preparations, as well as a more challenging
292 media-fill test passed annually, or more frequently.

293 (II) Example of a Media-Fill Test Procedure. This, or an equivalent test, is performed at least
294 annually under conditions that closely simulate the most challenging or stressful conditions
295 encountered during compounding. This test is completed without interruption within an ISO
296 Class 5 air quality environment. Six 100-milliliter aliquots of sterile Soybean-Casein Digest
297 Medium are aseptically transferred by gravity through separate tubing sets into separate
298 evacuated sterile containers. The six containers are then arranged as three pairs, and a sterile 10-
299 milliliter syringe and 18-gauge needle combination is used to exchange two 5-milliliter aliquots
300 of medium from one container to the other container in the pair. For example, after a 5-milliliter
301 aliquot from the first container is added to the second container in the pair, the second container
302 is agitated for 10 seconds, then a 5-milliliter aliquot is removed and returned to the first container
303 in the pair. The first container is then agitated for 10 seconds, and the next 5-milliliter aliquot is

304 transferred from it back to the second container in the pair. Following the two 5-milliliter aliquot
305 exchanges in each pair of containers, a 5-milliliter aliquot of medium from each container is
306 aseptically injected into a sealed, empty, sterile 10-milliliter clear vial, using a sterile 10-
307 milliliter syringe and vented needle. Sterile adhesive seals are aseptically affixed to the rubber
308 closures on the three filled vials. The vials are incubated within a range of 20 - 35 degrees
309 Celsius for a minimum of 14 days. Failure is indicated by visible turbidity in the medium on or
310 before 14 days. The media-fill test must include a positive-control sample.

311 (iii) High risk preparations.

312 (I) Procedures for high-risk level compounded sterile preparations include all those for low-risk
313 level compounded sterile preparations. In addition, a media-fill test that represents high-risk level
314 compounding is performed twice a year by each person authorized to compound high-risk level
315 compounded sterile preparations.

316 (II) Example of a Media-Fill Test Procedure Compounded Sterile Preparations Sterilized by
317 Filtration. This test, or an equivalent test, is performed under conditions that closely simulate the
318 most challenging or stressful conditions encountered when compounding high-risk level
319 compounded sterile preparations. Note: Sterility tests for autoclaved compounded sterile
320 preparations are not required unless they are prepared in batches of more than 25 units. This test
321 is completed without interruption in the following sequence:

322 (-a-) Dissolve 3 grams of non-sterile commercially available Soybean-Casein Digest Medium in
323 100 milliliters of non-bacteriostatic water to make a 3% non-sterile solution.

324 (-b-) Draw 25 milliliters of the medium into each of three 30-milliliter sterile syringes. Transfer 5
325 milliliters from each syringe into separate sterile 10-milliliter vials. These vials are the positive
326 controls to generate exponential microbial growth, which is indicated by visible turbidity upon
327 incubation.

328 (-c-) Under aseptic conditions and using aseptic techniques, affix a sterile 0.2-micron porosity
329 filter unit and a 20-gauge needle to each syringe. Inject the next 10 milliliters from each syringe
330 into three separate 10-milliliter sterile vials. Repeat the process for three more vials. Label all
331 vials, affix sterile adhesive seals to the closure of the nine vials, and incubate them at 20 to 35
332 degrees Celsius for a minimum of 14 days. Inspect for microbial growth over 14 days as
333 described in Chapter 797 Pharmaceutical Compounding--Sterile Preparations, of the USP/NF.

334 (III) Filter Integrity Testing. Filters need to undergo testing to evaluate the integrity of filters
335 used to sterilize high-risk preparations, such as Bubble Point Testing or comparable filter
336 integrity testing. Such testing is not a replacement for sterility testing and shall not be interpreted
337 as such. Such test shall be performed after a sterilization procedure on all filters used to sterilize
338 each high-risk preparation or batch preparation and the results documented. The results should be
339 compared with the filter manufacturer's specification for the specific filter used. If a filter fails
340 the integrity test, the preparation or batch must be sterilized again using new unused filters.

341 (B) Finished preparation release checks and tests.

342 (i) All high-risk level compounded sterile preparations that are prepared in groups of more than
343 25 identical individual single-dose packages (such as ampuls, bags, syringes, and vials), or in
344 multiple dose vials for administration to multiple patients, or are exposed longer than 12 hours at
345 2 - 8 degrees Celsius and longer than six hours at warmer than 8 degrees Celsius before they are
346 sterilized shall be tested to ensure they are sterile and do not contain excessive bacterial
347 endotoxins as specified in Chapter 71, Sterility Tests of the USP/NF before being dispensed or
348 administered.

349 (ii) All compounded sterile preparations, except for sterile radiopharmaceuticals, that are
350 intended to be solutions must be visually examined for the presence of particulate matter and not
351 administered or dispensed when such matter is observed.

352 (iii) The prescription drug and medication orders, written compounding procedure, preparation
353 records, and expended materials used to make compounded sterile preparations at all
354 contamination risk levels shall be inspected for accuracy of correct identities and amounts of
355 ingredients, aseptic mixing and sterilization, packaging, labeling, and expected physical
356 appearance before they are dispensed or administered.

357 (iv) Written procedures for checking compounding accuracy shall be followed for every
358 compounded sterile preparation during preparation, in accordance with pharmacy's policies and
359 procedures, and immediately prior to release, including label accuracy and the accuracy of the
360 addition of all drug products or ingredients used to prepare the finished preparation and their
361 volumes or quantities. A pharmacist shall ensure that components used in compounding are
362 accurately weighed, measured, or subdivided as appropriate to conform to the formula being
363 prepared.

364 (C) Environmental Testing.

365 (i) Viable and nonviable environmental sampling testing. Environmental sampling shall occur, at
366 a minimum, every six months as part of a comprehensive quality management program and
367 under any of the following conditions:

368 (I) as part of the commissioning and certification of new facilities and equipment;

369 (II) following any servicing of facilities and equipment;

370 (III) as part of the re-certification of facilities and equipment;

371 (IV) in response to identified problems with end products or staff technique; or

372 (V) in response to issues with compounded sterile preparations, observed compounding
373 personnel work practices, or patient-related infections (where the compounded sterile preparation
374 is being considered as a potential source of the infection).

375 (ii) Total particle counts. Certification that each ISO classified area (e.g., ISO Class 5, 7, and 8),
376 is within established guidelines shall be performed no less than every six months and whenever

377 the equipment is relocated or the physical structure of the buffer area or ante-area has been
378 altered. All certification records shall be maintained and reviewed to ensure that the controlled
379 environments comply with the proper air cleanliness, room pressures, and air changes per hour.
380 Testing shall be performed by qualified operators using current, state-of-the-art equipment, with
381 results of the following:

382 (I) ISO Class 5 - not more than 3520 particles 0.5 micrometer and larger size per cubic meter of
383 air;

384 (II) ISO Class 7 - not more than 352,000 particles of 0.5 micrometer and larger size per cubic
385 meter of air for any buffer area; and

386 (III) ISO Class 8 - not more than 3,520,000 particles of 0.5 micrometer and larger size per cubic
387 meter of air for any ante-area.

388 (iii) Pressure differential monitoring. A pressure gauge or velocity meter shall be installed to
389 monitor the pressure differential or airflow between the buffer area and the ante-area and
390 between the ante-area and the general environment outside the compounding area. The results
391 shall be reviewed and documented on a log at least every work shift (minimum frequency shall
392 be at least daily) or by a continuous recording device. The pressure between the ISO Class 7 or
393 ISO Class 8 and the general pharmacy area shall not be less than 0.02 inch water column.

394 (iv) Sampling plan. An appropriate environmental sampling plan shall be developed for airborne
395 viable particles based on a risk assessment of compounding activities performed. Selected
396 sampling sites shall include locations within each ISO Class 5 environment and in the ISO Class
397 7 and 8 areas and in the segregated compounding areas at greatest risk of contamination. The
398 plan shall include sample location, method of collection, frequency of sampling, volume of air
399 sampled, and time of day as related to activity in the compounding area and action levels.

400 (v) Viable air sampling. Evaluation of airborne microorganisms using volumetric collection
401 methods in the controlled air environments shall be performed by properly trained individuals for
402 all compounding risk levels. For low-, medium-, and high-risk level compounding, air sampling
403 shall be performed at locations that are prone to contamination during compounding activities
404 and during other activities such as staging, labeling, gowning, and cleaning. Locations shall
405 include zones of air backwash turbulence within the laminar airflow workbench and other areas
406 where air backwash turbulence may enter the compounding area. For low-risk level compounded
407 sterile preparations within 12-hour or less beyond-use-date prepared in a primary engineering
408 control that maintains an ISO Class 5, air sampling shall be performed at locations inside the ISO
409 Class 5 environment and other areas that are in close proximity to the ISO Class 5 environment
410 during the certification of the primary engineering control.

411 (vi) Air sampling frequency and process. Air sampling shall be performed at least every 6
412 months as a part of the re-certification of facilities and equipment. A sufficient volume of air
413 shall be sampled and the manufacturer's guidelines for use of the electronic air sampling
414 equipment followed. At the end of the designated sampling or exposure period for air sampling
415 activities, the microbial growth media plates are recovered and their covers secured and they are

416 inverted and incubated at a temperature and for a time period conducive to multiplication of
417 microorganisms. Sampling data shall be collected and reviewed on a periodic basis as a means of
418 evaluating the overall control of the compounding environment. If an activity consistently shows
419 elevated levels of microbial growth, competent microbiology or infection control personnel shall
420 be consulted. A colony forming unit (cfu) count greater than 1 cfu per cubic meter of air for ISO
421 Class 5, greater than 10 cfu per cubic meter of air for ISA Class 7, and greater than 100 cfu per
422 cubic meter of air for ISO Class 8 or worse should prompt a re-evaluation of the adequacy of
423 personnel work practices, cleaning procedures, operational procedures, and air filtration
424 efficiency within the aseptic compounding location. An investigation into the source of the
425 contamination shall be conducted. The source of the problem shall be eliminated, the affected
426 area cleaned, and resampling performed. Counts of cfu are to be used as an approximate measure
427 of the environmental microbial bioburden. Action levels are determined on the basis of cfu data
428 gathered at each sampling location and trended over time. Regardless of the number of cfu
429 identified in the pharmacy, further corrective actions will be dictated by the identification of
430 microorganisms recovered by an appropriate credentialed laboratory of any microbial bioburden
431 captured as a cfu using an impaction air sampler. Highly pathogenic microorganisms (e.g., gram-
432 negative rods, coagulase positive staphylococcus, molds and yeasts) can be potentially fatal to
433 patient receiving compounded sterile preparations and must be immediately remedied, regardless
434 of colony forming unit count, with the assistance, if needed, of a competent microbiologist,
435 infection control professional, or industrial hygienist.

436 (vii) Compounding accuracy checks. Written procedures for checking compounding accuracy
437 shall be followed for every compounded sterile preparation during preparation and immediately
438 prior to release, including label accuracy and the accuracy of the addition of all drug products or
439 ingredients used to prepare the finished preparation and their volumes or quantities. At each step
440 of the compounding process, the pharmacist shall ensure that components used in compounding
441 are accurately weighed, measured, or subdivided as appropriate to conform to the formula being
442 prepared.

443 (15) (No change.)

444 (e) Records. Any testing, cleaning, procedures, or other activities required in this subsection shall
445 be documented and such documentation shall be maintained by the pharmacy.

446 (1) (No change.)

447 (2) Compounding records.

448 (A) Compounding pursuant to patient specific prescription drug orders or medication orders.
449 Compounding records for all compounded preparations shall be maintained by the pharmacy
450 [~~electronically or manually as part of the prescription drug or medication order, formula record,~~
451 ~~formula book, or compounding log]~~ and shall include:

452 (i) the date and time of preparation;

453 (ii) a complete formula, including methodology and necessary equipment which includes the
454 brand name(s) of the raw materials, or if no brand name, the generic name(s) or official name
455 and name(s) of the manufacturer(s) or distributor of the raw materials and the quantities of each;
456 however, if the sterile preparation is compounded according to the manufacturer's labeling
457 instructions, then documentation of the formula is not required;

458 (iii) written or electronic signature or initials of the pharmacist or pharmacy technician or
459 pharmacy technician trainee performing the compounding;

460 (iv) written or electronic signature or initials of the pharmacist responsible for supervising
461 pharmacy technicians or pharmacy technician trainees and conducting final checks of
462 compounded pharmaceuticals if pharmacy technicians or pharmacy technician trainees perform
463 the compounding function;

464 ~~[(v) the quantity in units of finished preparation or amount of raw materials;]~~

465 (v) [(vi)] the container used and the number of units of finished preparation prepared; and

466 (vi) [(vii)] a reference to the location of the following documentation which may be maintained
467 with other records, such as quality control records:

468 (I) the criteria used to determine the beyond-use date; and

469 (II) documentation of performance of quality control procedures.

470 (B) Compounding records when batch compounding or compounding in anticipation of future
471 prescription drug or medication orders.

472 (i) Master work sheet. A master work sheet shall be developed and approved by a pharmacist for
473 preparations prepared in batch. Once approved, a duplicate of the master work sheet shall be
474 used as the preparation work sheet from which each batch is prepared and on which all
475 documentation for that batch occurs. The master work sheet shall contain at a minimum:

476 (I) the formula;

477 (II) the components;

478 (III) the compounding directions;

479 (IV) a sample label;

480 (V) evaluation and testing requirements;

481 (VI) specific equipment used during preparation; and

482 (VII) storage requirements.

483 (ii) Preparation work sheet. The preparation work sheet for each batch of preparations shall
484 document the following:

485 (I) identity of all solutions and ingredients and their corresponding amounts, concentrations, or
486 volumes;

487 (II) lot number for each component;

488 (III) component manufacturer/distributor or suitable identifying number;

489 (IV) container specifications (e.g., syringe, pump cassette);

490 (V) unique lot or control number assigned to batch;

491 (VI) expiration date of batch-prepared preparations;

492 (VII) date of preparation;

493 (VIII) name, initials, or electronic signature of the person(s) involved in the preparation;

494 (IX) name, initials, or electronic signature of the responsible pharmacist;

495 (X) finished preparation evaluation and testing specifications, if applicable; and

496 (XI) comparison of actual yield to anticipated or theoretical yield, when appropriate.

497 (f) - (g) (No change.)