
Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act Guidance for Industry

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**January 2020
Pharmaceutical Quality/Manufacturing Standards (CGMP)**

Revision 2

Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act

Guidance for Industry

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1 **Current Good Manufacturing Practice—Guidance for Human Drug**
2 **Compounding Outsourcing Facilities**
3 **Under Section 503B of the FD&C Act**
4 **Guidance for Industry¹**
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6
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
12

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16 **I. INTRODUCTION**
17

18 This guidance describes FDA’s policies regarding compliance with current good manufacturing
19 practice (CGMP) requirements for facilities that compound human drugs and register with FDA
20 as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act
21 (FD&C Act). Under section 501(a)(2)(B) of the FD&C Act, a drug is deemed to be adulterated if
22 it is not produced in accordance with CGMP. FDA’s regulations regarding CGMP requirements
23 for the preparation of drug products have been established in 21 CFR parts 210 and 211.² FDA
24 intends to promulgate more specific CGMP regulations for outsourcing facilities. Until these
25 final regulations are promulgated, outsourcing facilities are subject to the CGMP requirements in
26 parts 210 and 211. This guidance provides for conditions under which FDA generally does not
27 intend to take regulatory action against an outsourcing facility regarding certain CGMP
28 requirements in parts 210 and 211 during this interim period. This guidance applies to drugs
29 compounded in accordance with section 503B. In addition, this guidance generally applies to
30 drugs that outsourcing facilities repackage and biological products that outsourcing facilities
31 mix, dilute, or repackage in accordance with relevant guidance for outsourcing facilities.³
32

33 This guidance reflects FDA’s intent to recognize the differences between outsourcing facilities
34 and conventional drug manufacturers, while maintaining the minimum standards necessary to

¹ This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research and in cooperation with the Office of Regulatory Affairs at the Food and Drug Administration.

² Positron emission tomography (PET) drug products are subject to CGMP regulations at 21 CFR part 212 and are not covered by this guidance.

³ See guidances for industry *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities* and *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* (Biologics guidance). To the extent that the policies in the Biologics guidance differ from this guidance (e.g., conditions concerning assigning a beyond-use date to repackaged biological products based on stability testing), the policies described in the Biologics guidance apply. FDA updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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35 protect patients from the risks of contaminated or otherwise substandard compounded drug
36 products.

37
38 This guidance revises the draft guidance *Current Good Manufacturing Practice—Interim*
39 *Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the*
40 *FD&C Act* issued in July 2014. Revision 1 was developed to (1) include considerations for non-
41 sterile compounded drug products; (2) differentiate between requirements applicable to sterile
42 compounded drug products and non-sterile compounded drug products where appropriate; (3)
43 include changes regarding stability testing, including the assignment of a beyond-use date (BUD)
44 as an expiration date, and release testing requirements; and (4) address reserve samples and
45 provide guidance on “in-use times.” Revision 2 refines a description of antimicrobial
46 effectiveness testing in section III.K. and clarifies that section C of appendix B does not apply to
47 non-sterile unpreserved aqueous drug products.

48
49 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
50 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
51 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
52 the word *should* in Agency guidances means that something is suggested or recommended, but
53 not required.

54
55

56 **II. BACKGROUND**

57

58 The Drug Quality and Security Act added a new section 503B to the FD&C Act.⁴ Under section
59 503B(b), a compounder can register as an outsourcing facility with FDA. Drug products
60 compounded in an outsourcing facility can qualify for exemptions from the FDA approval
61 requirements in section 505 of the FD&C Act,⁵ the requirement to label drug products with
62 adequate directions for use under section 502(f)(1) of the FD&C Act,⁶ and the drug supply chain
63 security requirements in section 582 of the FD&C Act,⁷ if the conditions in section 503B are
64 met. Outsourcing facilities are inspected by FDA according to a risk-based schedule and must
65 comply with other provisions of the FD&C Act, including CGMP requirements under section
66 501(a)(2)(B) (see section 503B).

67

68 Under section 501(a)(2)(B), a drug is deemed to be adulterated if:

69

70 [T]he methods used in, or the facilities or controls used for, its manufacture, processing, packing,
71 or holding do not conform to or are not operated or administered in conformity with current good
72 manufacturing practice to assure that such drug meets the requirements of this [Act] as to safety
73 and has the identity and strength, and meets the quality and purity characteristics, which it
74 purports or is represented to possess

75

⁴ See Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587–588 (2013).

⁵ 21 U.S.C. 355.

⁶ 21 U.S.C. 352(f)(1).

⁷ 21 U.S.C. 360eee-1.

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76 Further, section 501 of the FD&C Act, as amended by the Food and Drug Administration Safety
77 and Innovation Act,⁸ states:

78
79 For purposes of paragraph (a)(2)(B), the term “current good manufacturing practice” includes the
80 implementation of oversight and controls over the manufacture of drugs to ensure quality, including
81 managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of
82 drugs, and finished drug products.

83
84 CGMP requirements for finished drug products, except PET drug products, are established in 21
85 CFR parts 210 and 211. The primary focus of this guidance is on those aspects of part 211 that
86 relate to sterility assurance of sterile drug products and the safety of both sterile and non-sterile
87 compounded drug products more generally, including with respect to strength (e.g., subpotency,
88 superpotency), and labeling or drug product mix-ups, because these aspects of outsourcing
89 facility operations pose the highest risk to patient safety if not conducted properly.

90
91 The recommendations in this guidance are consistent with the principles of good manufacturing
92 practice, which hold that quality is best assured by implementing appropriate controls throughout
93 the manufacturing process, with end-product testing providing additional assurance. This
94 guidance also provides a risk-based approach to CGMP requirements. Accordingly, this
95 guidance focuses on control of raw materials, facility design and maintenance, production
96 techniques and controls, and personnel practices as the most critical aspects of ensuring quality
97 for all drug products. Other CGMP requirements, such as testing samples of the finished drug
98 product before batch release and the collection of reserve samples, provide additional assurance
99 of drug quality and are described with respect to higher risk outsourcing facility operations. For
100 example, the guidance distinguishes, where applicable, between higher risk compounding
101 activities (e.g., higher volume of production for a drug product, sterile production, manual
102 manipulations) and lower risk compounding activities (e.g., lower volume of production, non-
103 sterile production, use of automated equipment).

104
105 Depending on the level of risk, the guidance describes certain conditions under which FDA
106 generally does not intend to take regulatory action against an outsourcing facility regarding
107 specific CGMP requirements.

III. CGMP FOR OUTSOURCING FACILITIES

A. Quality Assurance Activities

113
114 Quality assurance activities are needed to ensure that procedures are followed and a quality drug
115 product is produced (see, e.g., §§ 211.22, 211.180, 211.192, 211.198). Part 211 (see, e.g.,
116 § 211.22) requires that drug producers establish a quality control unit to oversee various aspects
117 of production, including strength as well as sterility assurance activities for sterile products and
118 microbiological quality for non-sterile products.

119

⁸ Pub. L. No. 112-114, 126 Stat. 993 (2012).

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120 The quality control unit should be independent; that is, the quality control unit should not take on
121 the responsibilities of other units of the outsourcing facility's organization, such as those handled
122 by production personnel, in order to preserve the integrity of the quality control unit's functions.
123 FDA has found that quality control units that are independent from other operations are more
124 likely to be able to fulfill their required functions.⁹ FDA recommends the staffing level be
125 adequate to perform all quality assurance functions at a level commensurate with the scale of the
126 compounding operation, including number and volume of drug products compounded.

127
128 Procedures describing the role and responsibilities of the quality control unit must be established
129 and followed (§ 211.22(d)). The following aspects of quality assurance and quality control are
130 critical to ensuring the quality of compounded sterile and non-sterile drug products at
131 outsourcing facilities.

132
133 The quality control unit is responsible for ensuring that each batch of finished drug product is
134 sampled and tested to ensure that it meets appropriate specifications for release (see
135 §§ 211.22(a), 211.165(d)). For sterile products, procedures should be established and followed to
136 ensure that for each batch intended to be released without completed sterility testing (see section
137 I and Appendix A), the results of the sterility testing, once available, are reviewed and added to
138 the batch record (see § 211.188).

139
140 The quality control unit must periodically (at least annually) review records of compounding
141 operations to evaluate the quality standards for each drug product to determine the need for
142 changes in specifications or control procedures (§ 211.180(e)). As part of this review, the quality
143 control unit should identify trends and evaluate quality indicators such as (where required by
144 part 211):

- 145
146 • Results of environmental monitoring.
- 147
148 • Results of personnel monitoring.
- 149
150 • Where water is used as a component in the drug product, results of water system testing
151 for water that is purified/processed on-site, or if water is purchased as an incoming
152 component, testing results from the supplier or results of testing conducted by the
153 outsourcing facility.
- 154
155 • Results of finished drug product testing.
- 156
157 • All media fills/process simulations performed since the last review.
- 158
159 • Periodic scrutiny of operations to ensure adherence to procedures and proper aseptic
160 technique.

⁹ FDA inspection information indicates that most outsourcing facilities maintain personnel in a quality control unit that is fully separate from compounding operations. However, FDA recognizes that there may be an extraordinary circumstance in which an individual in the quality control unit may need to participate in another operation. In such circumstances, that person is still accountable for implementing all of the controls and reviewing compounding operations to ensure that facility, process, and product quality standards have been met. See § 211.22.

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- Complaints, discrepancies, failures, and yield variation.

The quality control unit is responsible for discrepancy and failure investigations and the development and oversight of effective corrective actions, which also include changes necessary to prevent recurrence, regarding the following (see, e.g., §§ 211.192, 211.180(e)):

- Results of tests and examinations, regardless of batch disposition, if applicable to evaluate the quality of components, containers, closures, in-process materials, and finished product. Examples of such tests and examinations include but are not limited to sterility testing, endotoxin levels, content assay, impurity assay, particulate matter, reconstitution time, content uniformity, preservative content testing, microbial enumeration, tests for specified microorganisms, and, weight, volume, or counts.
- Unexpected results (e.g., potential defects) or trends.
- Failures that occur during validation or revalidation. These could include process validation, sterilization, or depyrogenation processes, including media fill/process simulation failures, as applicable.
- Stability failures, including failures of quality that are determined to have causes other than degradation of the drug product.
- Environmental and personnel monitoring results that exceed alert or action limits.
- Process deviations or equipment malfunctions that involve critical equipment, such as sterilizers, lyophilizers, pellet machines, capsule machines, mixers, and homogenizers.
- Complaints that indicate possible drug product contamination or other potential risks to patients (e.g., hazy or cloudy drug product, foreign matter/particulates in injectable drug products, cracked or leaky containers, change in color or appearance, particles falling out of oral solutions).

B. Facility Design

Part 211 sets out the requirements applicable to the design of facilities used in the manufacture, processing, packing, or holding of a drug product (see, e.g., § 211.42). The design of a facility should consider the products produced and must provide the necessary level of control to prevent mix-ups and contamination (§ 211.42).

The production areas in which components, drug products, in-process materials, equipment, and containers or closures are prepared, held, or transferred must be designed to minimize the level of contaminants so as to prevent objectionable microorganisms in non-sterile drug products (see § 211.113(a)) and prevent microbiological contamination of drug products purporting to be sterile (see § 211.113(b)). Processing and controlled areas must be clean and sanitary (§ 211.56).

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207 Additional Considerations for Sterile Drug Products

208

209 Outsourcing facilities should meet the following elements:

210

- 211 • Sterile drugs should be produced only in ISO 5 or better air quality as determined under
212 dynamic conditions (see Table 1 for International Organization for Standardization (ISO)
213 cleanroom classification standards).

214

215 **Table 1. ISO Classification of Particulate Matter in Room Air***

ISO Class Name	Particles/m ³
3	35.2
4	352
5	3,520
6	35,200
7	352,000
8	3,520,000

*Limits are in particles of 0.5 µm and larger per cubic meter (current ISO) measured under dynamic conditions. Adapted from ISO 14644-1:2015, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration.

216

- 217 • The facility should be designed and operated with cascading air quality (e.g., by proper
218 air classification and air pressurization) to protect the ISO 5 zone (or critical area¹⁰). The
219 facility layout, room separation, and process flow must be designed to prevent the influx
220 of contamination from adjacent areas and rooms of lower air quality and to avoid any
221 disruption of HEPA unidirectional flow (§ 211.42).

222

- 223 • The air cleanliness classification of the area surrounding the ISO 5 zone immediately
224 adjacent to the aseptic processing line should, at a minimum, meet ISO 7 standards under
225 dynamic conditions.

226

- 227 • If an isolator¹¹ is used, the surrounding area should, at a minimum, meet ISO 8 standards
228 under dynamic conditions.

229

- 230 • If a restricted access barrier¹² is used (e.g., a glove box), the surrounding area should, at a
231 minimum, meet ISO 7 standards under dynamic conditions.

232

- 233 • Terminally sterilized drugs should be produced in ISO 8 or better air quality as
234 determined under dynamic conditions.

¹⁰ A *critical area* is an area designed to maintain sterility of sterile materials. See guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*.

¹¹ An *isolator* is a decontaminated unit supplied with ISO 5 or higher air quality that provides uncompromised, continuous isolation of its interior from the external environment. For further information, see also guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*.

¹² See guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*.

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235
236 The ISO 5 zone or critical area must be qualified (i.e., shown to meet the specifications; see
237 §§ 211.42, 211.113(b)). Qualification should include at least the following studies and tests,
238 which must be documented as having been conducted (see § 211.113(b)), including the particular
239 conditions under which the studies and tests were conducted:¹³

- 240
- 241 • Airflow studies (e.g., an in-situ smoke study) should be conducted under simulated
242 operational conditions to evaluate airflow patterns because of the risk for contamination
243 of exposed product in the critical area. These studies should be conducted at the critical
244 area to demonstrate unidirectional flow and sweeping action over and away from the
245 product under dynamic conditions and should be repeated when any changes are made to
246 the critical area that might affect airflow.¹⁴ Because proper control of airflow is necessary
247 to prevent contamination, any indication of poor air control (e.g., non-unidirectional,
248 turbulent) must be corrected before use (see §§ 211.42, 211.113(b)).
 - 249
 - 250 • HEPA periodic testing/recertification should be performed at least twice a year to ensure
251 that appropriate airflow and quality are maintained. These tests should include integrity
252 testing of the HEPA filters, particle counts, and air velocity checks.
 - 253
 - 254 • Velocities of unidirectional air should be measured 6 inches from the HEPA filter face
255 and at a defined distance close to the work surface in the ISO 5 area.
 - 256
 - 257 • If any portable ISO 5 units are moved from one location to another, requalification of the
258 unit should be performed before resuming sterile compounding.
 - 259

C. Control Systems and Procedures for Maintaining Suitable Facilities

260
261
262 To prevent contamination or mix-ups during the course of operations, § 211.42 requires separate
263 or defined areas or other similar control systems for a facility's operations.¹⁵ Section 211.56
264 requires that procedures be established and followed that assign responsibility for sanitation and
265 describe in detail the cleaning schedules, methods, equipment, and materials to be used in
266 cleaning buildings and facilities.

267
268 For multiuse facilities and nondedicated equipment, changeover and cleaning procedures for
269 equipment and utensils must be established and followed to prevent contamination, including
270 cross-contamination between products (see §§ 211.42, 211.67).

271
272 Procedures for cleaning and disinfecting must also be established (see §§ 211.42, 211.56,
273 211.67). Equipment surfaces that come in contact with drug products, containers, or closures
274 must be cleaned at appropriate intervals to prevent contamination (see § 211.67). The suitability

¹³ In addition to documenting these tests and studies, the CGMP regulations generally require that other key activities be documented (see part 211, subpart J: Records and Reports).

¹⁴ Additional information may be found in NSF/ANSI 49—2014 Biosafety Cabinetry: Design, Construction, Performance, and Field Certification.

¹⁵ For example, this would be especially critical when using powders because powder particles can become airborne and contaminate other areas unless airflow is designed to contain such particles.

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275 and efficacy of the cleaning agents and cleaning methods should be evaluated, and the cleaning
276 agent's compatibility with applicable work surfaces should be assessed. Published literature and
277 supplier certificates of analysis (COAs) can be relied on when initially determining the
278 effectiveness of agents used to clean and disinfect, as necessary, the facility and equipment
279 surfaces, provided that the supplier's cleaning procedures are followed. The expiration dates of
280 cleaning and disinfection agents should be closely monitored and expired solutions should be
281 discarded.

282
283 For non-sterile drug production, water used as a final rinsing agent for any equipment or utensils
284 that come in direct contact with the drug product should meet the requirements for Purified
285 Water, USP, or higher quality standards.¹⁶

286
287 If powder drugs are handled, procedures must be established and followed to appropriately
288 manage cross-contamination risk (see § 211.100). This is particularly important if the powder is
289 cytotoxic or highly sensitizing. FDA recommends the physical segregation of areas in which
290 powder drugs are exposed to the environment. For penicillin products, a separate facility is
291 required (see § 211.42(d)). However, FDA has clarified that separate buildings may not be
292 necessary, provided that the manufacturing operation involving penicillin is isolated (i.e.,
293 completely and comprehensively separated) from the areas in which non-penicillin products are
294 manufactured.¹⁷ For non-penicillin beta-lactam products, FDA recommends complete and
295 comprehensive separation from other products.¹⁸ Additionally, appropriate controls related to
296 movement of equipment, product, and personnel should be established to prevent cross-
297 contamination of non-beta-lactam products.

298
299 In general, processes and procedures at an outsourcing facility should minimize contamination
300 risks posed by, for example, the number and complexity of manipulations, number of
301 simultaneous operations and workstations, and staging of materials used in the process.

Additional Considerations for Sterile Drug Products

304
305 HEPA filters should be qualified to provide appropriate air quality and be periodically
306 maintained and tested to ensure intended air quality. Discolored, dirty, or damaged HEPA filters
307 should be repaired or replaced.

308
309 Temperature and humidity must be maintained in cleanroom areas; such controls are critical to
310 reduce microbiological growth (see § 211.46). A specification for humidity should be established
311 considering that higher humidity supports microbial growth, while too little humidity can cause
312 problems with static electricity (which may be particularly problematic when working with
313 powders) and may lead to increased particulates. Cleanroom temperature and humidity
314 specifications should be maintained solely through the facility's central heating, ventilation, and

¹⁶ See FDA's *Guide to Inspections of High Purity Water Systems* at <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/high-purity-water-system-793>.

¹⁷ Preamble to the final rule, "Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding." 43 FR 45014, at 45038 (September 29, 1978).

¹⁸ See guidance for industry *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination*.

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315 air conditioning (HVAC); peripheral devices such as stand-alone (de-)humidifiers and air
316 conditioners should not be used because they generate airborne particles, are water sources, and
317 may harbor microorganisms. As a scientific matter, a system for environmental monitoring must
318 include the establishment of pressure differential limits (see § 211.42), and control systems
319 should include built-in alarms to detect excursions. An adequate control system includes
320 monitoring for pressure differentials, humidity, and temperature during production and taking
321 prompt action to correct adverse conditions, which are necessary activities to prevent
322 contamination during aseptic processing (see §§ 211.42, 211.46, 211.58). If a problematic
323 condition cannot be immediately corrected, production should stop until it has been corrected.
324 Regardless of whether production is stopped or allowed to continue, the impact of any
325 excursions on product that is already in process should be evaluated. Among other requirements
326 in § 211.192, any unexplained discrepancy must be investigated, the results of which must be
327 documented.

328
329 Monitoring procedures should require documentation and investigation of any instances in which
330 there is a loss of positive pressure in the cleanroom during actual production and documentation
331 of the batches affected and the corrective action taken. These checks should be conducted
332 regularly on a schedule that considers the environment, such as use of an isolator versus a less
333 protected process, and the results should be recorded in logs and evaluated against prespecified
334 alert and action limits at each check.

335
336 In addition to the requirements in §§ 211.42 and 211.56, FDA recommends that outsourcing
337 facilities ensure that air vents and airflow are not obstructed—by large equipment, for example—
338 in such a way that could potentially compromise aseptic operations. Equipment that is not
339 needed for the specific cleanroom operations conducted should not be stored in the cleanroom.

340
341 Procedures for cleaning and disinfecting ISO 5 areas/units should include detailed instructions
342 for consistently and properly cleaning and disinfecting surfaces that are difficult to access. A
343 system for cleaning and disinfecting all critical areas to produce aseptic conditions includes
344 sporicidal and other sterile disinfectants and lint-free sterile wipes (see § 211.42). Procedures
345 must describe the methods and schedule for cleaning (see §§ 211.42, 211.56, 211.67, 211.182)
346 and should include the use of sporicidal disinfectants in the ISO 5 area and other classified areas
347 on a regular basis.

348
349 Water used as a cleaning or rinsing agent for any equipment or utensils that will not be
350 subsequently disinfected or sterilized and depyrogenated must be sterile (see § 211.113(b)).
351 Purified Water, USP, is considered acceptable for use with equipment or utensils that will be
352 sterilized and depyrogenated.

353
354 Based on the results of environmental monitoring (see section D below), the disinfection
355 program must be revised if there are indications that the frequency of disinfection or the methods
356 or type of disinfectant(s) used are inadequate to ensure appropriately clean surfaces (see
357 §§ 211.42, 211.56, 211.67, 211.113). Conducting disinfectant effectiveness testing may be useful
358 in guiding revision of the disinfection program in such cases.

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360 Critical equipment surfaces that come in contact with sterile drug products, containers, and
361 closures must be sterilized at appropriate intervals (see § 211.67); disinfection alone is not
362 sufficient (see section E below). Single-use disposable equipment and supplies that are purchased
363 presterilized and depyrogenated and are discarded after one use need not be resterilized.

D. Environmental and Personnel Monitoring

364
365
366
367 The frequency and methods of environmental and personnel control and monitoring should be
368 commensurate with the risk to product quality. For example, for non-sterile drugs, aqueous-
369 based drugs present the highest microbiological risk to patients. Consequently, water system and
370 environmental monitoring for aqueous non-sterile drug production should be performed more
371 frequently than for non-aqueous non-sterile drugs. During aqueous non-sterile drug production,
372 temperature and humidity should be monitored daily and air (viable¹⁹ and nonviable particles)
373 and surfaces (viable particles) should be monitored periodically (e.g., at least quarterly). Aseptic
374 sterile drug production environments should be monitored at least daily during production. Also,
375 monitoring of product residue may be necessary to ensure that the cleaning program is effective
376 or containment is maintained, with an increased frequency of monitoring and sensitivity of
377 methods when contamination poses a higher risk, such as when producing cytotoxic or highly
378 sensitizing materials.

Additional Considerations for Sterile Drug Products

380
381
382 21 CFR 211.42(c)(10)(iv) requires establishing a system for monitoring environmental
383 conditions in aseptic processing areas, and §§ 211.113(b) and 211.28(a) require personnel
384 sanitation practices and gowning to be both acceptable and qualified for the operations they
385 perform. For example, gowning procedures should ensure that there is no exposed skin on
386 personnel involved in any production activities in, or that can directly affect, the ISO 5 area.²⁰
387 Procedures for monitoring the environment and personnel for the presence of viable particles and
388 nonviable particles should be established and followed as described here.

389
390 Operations and appropriate written procedures designed to prevent microbial contamination
391 include a well-defined and documented program for environmental monitoring that evaluates the
392 potential routes of microbial contamination of the human drug that could arise from the air,
393 surfaces, process, operation, and personnel practices (see §§ 211.42(c)(10)(iv), 211.100,
394 211.113(b)). The program should contain an appropriate detection component(s) to verify state
395 of control of the environment. However, environmental monitoring equipment should not
396 interfere with aseptic operations (e.g., instruments should not interfere with validated and
397 appropriate airflow patterns). In particular, the program should:

- 398
399
400
401
- Cover all production shifts and include monitoring during normal production conditions.
 - Include at least daily monitoring of the ISO 5 zone during operations.

¹⁹ A *viable particle* consists of, or supports, one or more live microorganisms (see ISO 14644-6:2007, Cleanrooms and associated controlled environments—Part 6: Vocabulary).

²⁰ See guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* for further recommendations regarding gowning.

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- 402
- 403
- Establish alert and action limits and appropriate responses when excursions occur.
- 404
- Describe the use of sampling (e.g., contact plates, swabs, active air samplers), alert and action limits and responses, and testing methods (e.g., media, plate exposure times, incubation times and temperatures) that are designed to detect environmental contaminants, including changes in microflora type and amount, and the scientific justification for the testing methods selected.
- 405
- 406
- 407
- 408
- 409
- 410
- Be supported by a scientific justification for sampling locations, based on risk, and sampling methods, which may be based on risk and peer-reviewed literature.
- 411
- 412
- 413
- Investigate results that exceed established limits or demonstrate adverse trends; determine product impact; and execute appropriate actions.
- 414
- 415
- 416

417 Personnel monitoring should:

- 418
- Include a routine program for daily/shift monitoring of operators' gloves and an appropriate schedule for monitoring other critical sites of the gown (e.g., gown sleeves for hood work) during or immediately after completion of aseptic operations. Monitoring should take place before planned disinfection so that actual operating conditions are being assessed.
- 419
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- 423
- Establish and justify limits that are based on the criticality of the operation relative to the contamination risk to the product.
- 424
- 425
- 426
- 427
- Call for an investigation of results that exceed the established levels or demonstrate an adverse trend, a determination of the impact on the sterility assurance of finished products intended to be sterile, and the development and execution of appropriate corrective actions.
- 428
- 429
- 430
- 431
- 432

433 If microbiological media used in performing tests, including environmental and personnel
434 monitoring, are not purchased from a qualified supplier,²¹ the outsourcing facility or contract
435 laboratory's procedures should establish the validity of each medium, including its growth
436 potential. The quality control unit of an outsourcing facility that opts to rely on a contract
437 laboratory for any of the duties described in this section of the guidance must ensure the

²¹ A supplier could be qualified by following the recommendations for component supplier qualification in section III.G.1. of this guidance. Specifically, the outsourcing facility should have a quality agreement with each supplier and make the quality agreement available for review upon request by FDA. Each quality agreement should include, at a minimum: a description of the testing performed before a lot is released and shipped to the outsourcing facility and the specific quantitative (or qualitative, if applicable) results of a representative lot that would be provided on each COA; examples of testing records (such as growth promotion) that the supplier generates in performing release testing before shipping each lot to the outsourcing facility; a description of packaging, labeling, tamper-evident seals, and other features used to ensure package integrity while the purchased media is in distribution; and a commitment that the supplier will notify the outsourcing facility if there is identification of a problem with the quality of the media already shipped to the outsourcing facility.

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438 existence, appropriateness, and implementation of contract laboratory procedures (see §§ 200.10,
439 211.22, 211.160).

440

E. Equipment

442

443 Several provisions of part 211 address controls over the equipment used to compound (see
444 §§ 211.63, 211.65, 211.67, 211.68).

445

446 Equipment (mechanical, electronic, or automated) must be qualified as capable of performing its
447 intended functions or operations before first use, and procedures for routine calibration and
448 maintenance must be established and followed (see § 211.68). Equipment surfaces that come in
449 contact with components, in-process materials, or drugs must not be reactive, additive, or
450 absorptive so as to alter the quality of the drug (see § 211.65). Equipment needs to be designed
451 and located to facilitate operations, cleaning, and maintenance, and equipment may require
452 sanitization or sterilization to prevent contamination (see §§ 211.63, 211.67).

453

454 Outsourcing facilities may choose to use single-use disposable equipment (e.g., transfer tubing
455 and temporary holding vessels), which reduces the need for cleaning between different batches
456 and the potential for contamination (see § 211.67). Single-use disposable equipment should be
457 inspected for damage or contamination following use. The suitability of single-use disposable
458 equipment for its use in processing may be determined by the use of a valid COA from the
459 supplier in lieu of testing or examination by the outsourcing facility (see §§ 211.65, 211.113). In
460 addition, the integrity of the packaging of the single-use disposable equipment should be verified
461 upon receipt before use.

462

Additional Considerations for Sterile Drug Products

464

465 Equipment that comes into contact with the drug product must be evaluated to ensure adequacy
466 for intended use, including to ensure sterility and cleanliness at time of use (see §§ 211.65,
467 211.67(a)). For sterility and endotoxin limits, a valid COA may be used in lieu of testing by the
468 outsourcing facility for single-use disposable equipment (see §§ 211.65, 211.113).

469

470 If the outsourcing facility does not use presterilized and depyrogenated single-use disposable
471 equipment (e.g., filters, transfer tubing, temporary holding vessels), the equipment must be
472 sterilized and depyrogenated before use through processes that have been validated²² (see
473 §§ 211.65, 211.67(a) and (b), 211.100, 211.113).

474

F. Containers and Closures

476

477 Controls for the containers and closures in which the compounded drug product is packaged are
478 critical to ensuring the quality of compounded drug products and are expected to be implemented
479 by outsourcing facilities (see §§ 211.80, 211.82, 211.84, 211.87, 211.94, 211.113).

²² A process has been validated if it has been demonstrated and documented to consistently achieve the desired result when performed under defined conditions.

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480
481 Scientifically sound and appropriate criteria²³ for containers and closures must be established to
482 ensure that drug product containers and closures used for compounded drug products are suitable
483 for each particular drug product for which they will be used (see § 211.160(b)). As part of the
484 selection process, testing of the drug product container-closure system under the proposed
485 storage conditions for the finished product must be performed to verify its ability to meet
486 established quality specifications of the finished drug product over the expiry period (see §§
487 211.94, 211.166). Testing must be performed again if the manufacturer's specification of the
488 container or closure is changed (see §§ 211.94, 211.166). Appropriate procedures must be
489 established for testing or verifying the testing, as applicable, of the containers and closures
490 before use to determine whether they meet the criteria for use; the tests and results must be
491 documented (see §§ 211.84(d)(3), 211.184). Each lot of containers and closures must be
492 examined to verify identity and tested to ensure conformity with appropriate specifications
493 before use (see § 211.84(d)).

494
495 Containers and closures must be handled and stored to protect them from risk of contamination
496 and must be examined and cleaned to prevent introduction of contamination (see §§ 211.80,
497 211.82, 211.84, 211.94).

498
499 If containers or closures are stored for long periods in the absence of a supplier's expiration date
500 or established in-use period, or if they are exposed to air, heat, or other conditions that might
501 adversely affect the drug product container or closure, the containers and closures must be
502 retested or re-examined for integrity and fitness for use before they are used (see § 211.87).

Additional Considerations for Sterile Drug Products

503
504
505
506 Containers and closures that come into contact with the drug product must be evaluated to ensure
507 adequacy for intended use, including to ensure sterility and cleanliness at time of use (see
508 §§ 211.80, 211.84(d)(6)).

509
510 FDA generally does not intend to take regulatory action against an outsourcing facility regarding
511 the identification or testing of each lot of containers and closures if (1) for a finished drug
512 product intended to be sterile, the supplier certifies and labels the material as ready-to-use,
513 sterile, and nonpyrogenic; (2) the supplier's packaging integrity is verified upon receipt before
514 use; and (3) the valid COA provided by the supplier is reviewed to verify that the product is
515 represented to meet the required specifications established by the outsourcing facility, including
516 sterility and depyrogenation. Any container or closure not meeting acceptance requirements must
517 be rejected or not used until rendered suitable for use (see §§ 211.84(d) and (e)).

518
519 If the outsourcing facility does not use presterilized and depyrogenated containers and closures
520 (e.g., vials, syringes), the containers and closures must be sterilized and depyrogenated before
521 first use through processes that have been validated (see § 211.94(c)).

522

²³ For sterile drug products, see guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* for recommended test methods and criteria.

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523 Procedures for storage, if appropriate, of sterilized containers or closures must be established in a
524 manner to prevent contamination and to maintain sterility (see §§ 211.80(a) and (b)). For
525 example, safeguards must be in place to ensure that containers and closures are not contaminated
526 when held for use in areas where other materials are received, unpacked, and stored.

527
528 Containers or closures that are purchased as sterile must not be used after the supplier's
529 expiration date without testing or examination to verify that container or closure integrity has
530 been maintained (see § 211.87). Once the presterilized primary package has been breached, it
531 should remain under the hood or in the ISO 5 area until the containers or closures are used.
532 Where appropriate, any containers or closures removed from the ISO 5 area may be used for
533 sterile production after resterilization using a validated process (which must also establish that
534 the integrity of the container or closure is maintained) or used for drug products that do not
535 require a sterilized container or closure (§§ 211.84, 211.87, 211.94).

G. Components

536
537
538 Controls over the source and quality of components are required (§§ 211.82, 211.84, 211.87,
539 211.113). When producing sterile drug products, one aspect of such controls is the
540 consideration of whether the incoming components are non-sterile. The following controls are
541 considered critical to ensuring the quality of compounded drug products and are expected to
542 be implemented by outsourcing facilities.
543

544
545 Scientifically sound and appropriate specifications must be established for the components used
546 in each drug product (see § 211.160(b)). Scientifically sound and appropriate specifications
547 include those that address the attributes necessary to ensure the quality of the finished drug
548 product and are appropriate for the intended use of the drug product, including the route of
549 administration, as specified in the directions for use. A specification should generally conform to
550 the model described in the ICH guidance for industry *Q6A Specifications: Test Procedures and*
551 *Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*. A
552 specification should minimally include those tests described in ICH Q6A's section 3.2,
553 "Universal Tests/Criteria." Other dosage form-specific attributes may also be considered (see
554 ICH Q6A section 3.3, "Specific Tests/Criteria"). Attributes can include identity, strength, purity,
555 particle size, sterility, bacterial endotoxin level, content uniformity, microbial enumeration, tests
556 for specified microorganisms, or other characteristics that could affect the quality of the final
557 drug product.

558
559 To be eligible for the exemptions provided in section 503B of the FD&C Act, each bulk drug
560 substance used in compounding must be "accompanied by a valid certificate of analysis" (section
561 503B(a)(2)(D)). FDA interprets this provision to mean that *each lot* of a bulk drug substance is
562 accompanied by a valid COA.²⁴ FDA recommends that the COA conform to the model described
563 in ICH Q6A.²⁵ In addition, to be eligible for the exemptions provided in section 503B of the

²⁴ Under certain conditions, a valid COA may be relied upon to minimize testing of incoming components (see § 211.84).

²⁵ The COA should be in English or should be translated into English to facilitate use by the outsourcing facility and review by FDA on inspection if needed.

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564 FD&C Act, the bulk drug substance must be manufactured by an establishment that is registered
565 under section 510 of the FD&C Act (section 503B(a)(2)(C) of the FD&C Act).

566
567 Each shipment of each lot of components must be tested to verify identity and evaluated for
568 conformity with appropriate specifications before use (see § 211.84). Components should not be
569 used beyond the supplier's labeled expiration (or re-test) date. If the component does not have an
570 expiration date, the supplier should provide the date or testing should be conducted to establish
571 an expiration date.

572
573 Components that are not approved finished drug products (both active pharmaceutical
574 ingredients (APIs) and inactive ingredients) must be tested to verify identity and evaluated for
575 conformity with appropriate specifications and, if necessary and depending on intended use,
576 tested for endotoxin level and bioburden before use in compounding (see § 211.84). As described
577 in § 211.84(d)(2), in lieu of testing each shipment of each ingredient, a supplier's COA can be
578 accepted and evaluated to determine whether the lot can be used, provided that the following
579 conditions are met (see also Figure 1 below):

- 580
- 581 • The reliability of the supplier's analyses has been established at appropriate intervals and
582 through appropriate steps to:
583
 - 584 ○ Confirm the supplier's test results for those tests relevant to the specifications
585 established for the compounded drug product.
 - 586 ○ Confirm that the ingredient meets the applicable United States Pharmacopeia (USP)
587 or National Formulary (NF) monograph, if one exists.²⁶

589
590 Such steps may include, but are not limited to, confirmatory testing and remote audit of
591 the supplier's procedures.

592
593 FDA recommends that these steps be carried out no less frequently than annually for
594 APIs and every 2 years for other components.

- 595
- 596 • At least one specific identity test has been conducted before use to confirm that the
597 component is the one specified in the purchase order.

598
599 In addition, as required by § 211.82(a):

- 600
- 601 • Each container or grouping of containers of components must be examined to verify
602 appropriate labeling regarding contents.
 - 603
 - 604 • The shipment's package integrity must be verified upon receipt before use.
- 605

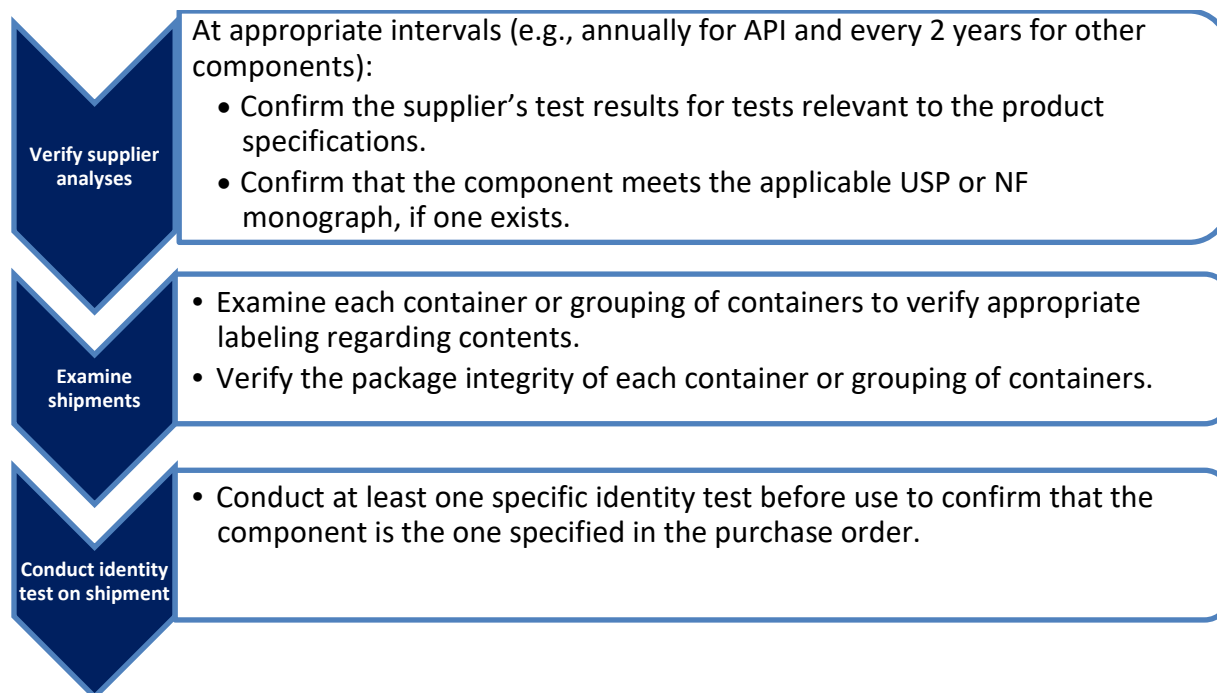
²⁶ Components, both bulk drug substances and other ingredients, used in compounding must comply with the standards of the applicable USP or NF monograph, if such monograph exists, to qualify for the exemptions provided in section 503B of the FD&C Act (see sections 503B(a)(2)(B) and (a)(3)).

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Figure 1. Using a Supplier's COA in Lieu of Testing*



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610
611

* See §§ 211.84(d)(2) and 211.82(a).

612 Acceptance of incoming lots of non-sterile components (including water) for use in sterile drug
613 products must include microbial and endotoxin testing and meet limits appropriate for the drug
614 product's intended use (see § 211.84(d)(6)). FDA generally does not intend to take regulatory
615 action against an outsourcing facility regarding the absence of such testing for water if it is
616 purchased and certified as sterile and nonpyrogenic and if it is accompanied by a valid COA;
617 however, the type of water purchased must be appropriate for its intended use (e.g., Sterile Water
618 for Injection, USP) (§ 211.84). The quality of water produced on-site and used as an ingredient
619 or processing aid must be tested regularly, using validated methods, at point of use to verify
620 acceptable microbial quality, chemical quality, and endotoxin limits (§§ 211.84, 211.160).
621 Acceptance criteria should be in agreement with those specified in the respective USP
622 monograph and be appropriate for the intended use of the product.

623

624 Any component not meeting acceptance requirements must be rejected (see § 211.84(e)).

625

626 Components must be retested or re-examined for identity, strength, quality, and purity after
627 storage for long periods or after exposure to air, heat, or other conditions that might adversely
628 affect the component (see § 211.87). However, additional testing is unnecessary if each lot of
629 components is stored under the supplier's labeled storage conditions, used within the established
630 (i.e., as labeled, as provided by the supplier, or as determined by the outsourcing facility) retest
631 or expiration date, and protected from contamination when portions of the lot are removed (see §
632 211.187).

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1. Regulatory Policy Regarding Component Supplier Qualification Testing

FDA generally does not intend to take regulatory action against an outsourcing facility regarding additional testing to confirm the supplier's COA under § 211.84(d)(2) if the outsourcing facility enters into a quality agreement with each supplier of each component, makes the quality agreement available for review upon request by FDA, and each quality agreement includes, at a minimum:

- A description of the testing performed before a component lot is released and shipped to the outsourcing facility and the specific quantitative (or qualitative, if applicable) results of a representative lot that would be provided on each COA.
- Examples of testing records, such as chromatograms and spectrograms, that the component supplier generates in performing release testing before shipping each lot of the component to the outsourcing facility.
- A description of packaging, labeling, tamper-evident seals, and other features used to ensure package integrity while the purchased component is in distribution.
- A commitment that the component supplier will notify the outsourcing facility if any testing performed to generate the release COA is significantly modified (e.g., change in principle of operation for a test method).
- A commitment that the component supplier will notify the outsourcing facility under specified circumstances, including but not limited to a change in specifications or identification of a problem with the quality of a component already shipped to the outsourcing facility.
- A commitment that the supplier, if not the original component manufacturer, ensures the component's pedigree to the outsourcing facility, including:
 - A description of the supplier's qualification and audit requirements for each manufacturer from which the supplier purchases components.
 - A description of the supply chain authentication controls that the supplier has implemented to verify that before receipt, each component is transported through known and pre-established channels.

2. Regulatory Policy Regarding Testing for Finished Product To Be Used as a Source Material for Processing

FDA generally does not intend to take regulatory action against an outsourcing facility regarding the identification or testing of each lot of a product under § 211.84 that is to be used as a source

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677 material and is an approved human finished drug product if all of the following conditions are
678 met:

- 679 • The product was purchased directly from a manufacturer registered and listed with FDA
680 under section 510 of the FD&C Act and has not been repacked or otherwise altered since
681 initial manufacture, or the product was purchased from a distributor that certifies that it
682 has not been repacked or otherwise altered since initial manufacture.
- 683 • The label of each lot of the product has been examined to verify that the product meets
684 required specifications before use.
- 685 • No portion of the lot has been subject to a recall for reasons that would make it unsuitable
686 for use.
- 687 • The shipment's package integrity has been verified upon receipt before use.

H. Production and Process Controls

693 Production and process controls are required when producing any drug product (see, e.g.,
694 §§ 211.22, 211.25, 211.28, 211.100, 211.111, 211.113, 211.188, 211.192).

695 Written procedures for production and process controls must be designed and followed to ensure
696 the consistent production of a drug that meets the applicable standards of identity, strength,
697 quality, and purity (see § 211.100). These controls are intended to ensure consistent yields;
698 batches failing to meet the theoretical yield must be investigated (see §§ 211.186, 211.192). The
699 degree of batch-by-batch control over product attributes or process parameters should be
700 commensurate with the risk of those attributes and parameters to the process and product. These
701 procedures should ensure documentation that all key process parameters are controlled and that
702 any deviations from the procedures are justified.

703 Before use in production, equipment, components, containers, and closures should be visually
704 examined for indications of damage, degradation, or contamination.

705 Batch records must provide complete documentation of the production of each batch of a drug
706 product (see § 211.188).²⁷ The actual batch output (yield) must be compared to the projected
707 (calculated) output for each drug product (see § 211.103). If the actual output is different than
708 expected after accounting for sampling and known process loss, this finding should be
709 considered an indicator of a potential problem with production and must be investigated
710 (§ 211.192). An acceptance level for actual output should be established that ensures batch-to-
711 batch consistency. Failure to meet the acceptance criteria and production standards must be
712 investigated before making the batch disposition decision and may require that the batch be
713 rejected (see §§ 211.165, 211.192).

²⁷ For aseptic operations that occur in a hood, a contemporaneous recording to the batch record is one that occurs as soon as possible after completion of that unit operation.

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720 Additional Considerations for Sterile Drug Products

721

722 1. *General Production and Process Controls*

723

724 If a drug product intended to be sterile is not terminally sterilized, there must be a validated
725 sterilization step such as sterile filtration (see § 211.113(b)), and it is critical that the sterilization
726 step occur as close to filling into the final product container as is feasible.

727

728 The microbiological content (bioburden) of articles and components that are subsequently
729 sterilized should be controlled. If materials are stored or held during processing (e.g., before
730 sterilization, after sterilization, before container fill), storage or holding times must be
731 established (see §§ 211.110(c), 211.111). Production phase hold times for a drug product should
732 be limited, verified by testing, and based on an understanding of the associated risk of increased
733 bioburden and endotoxin. Hold time assessments can be performed as part of the process for
734 validating sterility assurance (see §§ 211.111, 211.113(b), 211.160). In addition, in-process
735 materials such as bulk stock solutions must be stored in equipment that is protective and does not
736 affect the quality of the drug beyond its established specifications (see §§ 211.65, 211.113(b)).

737

738 2. *Drug Product Sterilization*

739

740 a. Terminal sterilization

741

742 For sterile drug products that are terminally sterilized, at least a 10^{-6} sterility assurance level
743 should be demonstrated in validation studies during process development using an appropriate
744 sterilization load monitor, such as biological indicators and thermocouples.²⁸ Validation studies
745 should be performed for each load size (container closure and number of vials) intended for
746 sterilization. For terminally sterilized drug products that are not subjected to an overkill terminal
747 sterilization cycle, presterilization bioburden limits should be established (i.e., determining the
748 number of microorganisms that can be reliably killed) and measured before sterilization. The
749 selected sterilization method should both sterilize and maintain the strength, purity, quality, and
750 package integrity of the sterile product.²⁹

751

752 b. Aseptic processing

753

754 If a drug product intended to be sterile is not terminally sterilized, the finished drug product
755 should be sterilized immediately before filling into the final product container. This is typically
756 done by filtration; however, other validated sterilization methods may be used. If a finished drug

²⁸ See guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*. For products such as pellets or powders, validation studies should be conducted using a biological indicator placed inside the product (i.e., inside the powder or pellets in their marketed containers) and spaced throughout the load to verify that the sterilization cycle results in sterility of the entire batch. Pellets should be placed in a defined and specified pattern in the sterilization chamber to demonstrate that appropriate lethality is delivered to each unit of the batch. Refer to ISO 11137-1:2006, Sterilization of health care products—Radiation—Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices; and ISO 11137-2:2013, Sterilization of health care products—Radiation—Part 2: Establishing the sterilization dose. See PDA Technical Report No.1 (Parenteral Drug Association 2007).

²⁹ See also USP General Chapters <1211> *Sterility Assurance* and <1229> *Sterilization of Compendial Articles*.

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757 product cannot be filtered (e.g., certain suspensions), components should be sterilized (e.g.,
758 filter) at the last possible step (e.g., before forming the suspension). Manipulations following the
759 component sterilization step must use aseptic practices to maintain sterility (see § 211.113).

760
761 Introductory training on microbiology, aseptic technique, cleanroom behavior, gowning, and
762 procedures covering aseptic manufacturing area operations must be established and conducted
763 before an individual is permitted to enter the aseptic manufacturing area or conduct operations in
764 a laminar flow hood (see § 211.25(a)). Once introductory training outside of the aseptic
765 manufacturing area is completed, further training based on department-specific requirements and
766 individual job descriptions should be conducted. Individuals would be considered qualified to
767 conduct aseptic operations after passing at least three successful, successive media fill
768 simulations based on a scientifically sound protocol designed to verify the adequacy of their
769 technique and behavior. Production simulations should be conducted in the same area where
770 production occurs.

771
772 Techniques intended to maintain sterility of items and surfaces should include the following:
773

- 774 • Sterile materials should be handled only with sterile instruments.
- 775
776 • After initial gowning, sterile gloves should be regularly sanitized (e.g., using sterile 70
777 percent isopropyl alcohol) during production or, when needed, changed.
- 778
779 • Sterile and non-shedding gowning components should be used. Gowning components
780 should be stored such that their sterility is not compromised.
- 781
782 • Torn or defective gowns should be changed immediately.
- 783
784 • Sterile products, the product-contacting surfaces of containers or closures, or other
785 critical surfaces should not directly touch any part of the gown or gloves.
- 786
787 • Personnel should move slowly and deliberately within the cleanroom or hood.
- 788
789 • Personnel should keep their bodies and objects out of the path of unidirectional flow
790 above open containers and products being filled.

791
792 Procedures for aseptic processing should address the following considerations:
793

- 794 • The design of equipment used in aseptic processing should limit the number and
795 complexity of aseptic manipulations and should be suitable for its intended use.
- 796
797 • Personnel, material, and process flow should be optimized to prevent unnecessary
798 activities that could increase the potential for introducing contaminants to exposed
799 product, containers or closures, or the surrounding environment.
- 800
801 • In-process material, including intermediates such as stock solutions, should be placed in
802 containers or closures that protect the material from the cleanroom environment.

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- 803 Containers or closures holding sterile in-process material should not be breached in an
804 environment less than ISO 5.
805
- 806 • Products should be transferred under appropriate cleanroom conditions. For example,
807 transfer, loading, and unloading of aseptically filled product to and from the lyophilizer
808 should occur only in classified areas that provide ISO 5 or better protection to the
809 partially sealed containers.
810
 - 811 • All aseptic manipulations, including processing of sterile materials, filling, and closing
812 (e.g., placement and sealing of stoppers on vials), should be performed under
813 unidirectional flow that is ISO 5 or better.
814
 - 815 • Appropriate steps to prepare equipment for sterilization should be established, such as
816 cleaning and use of wrapping that ensures protection while still allowing penetration of
817 the sterilizing agent.
818
 - 819 • The validation of sterilization operations for equipment associated with aseptic
820 processing (e.g., holding vessels, filling equipment, lyophilizer) and periodic verification
821 activities and results must be documented (see § 211.113(b)).
822
 - 823 • For sterile drug products that are filter-sterilized, prefiltration bioburden limits should be
824 established and measured before sterile filtration, unless all components consist of FDA-
825 approved sterile drug products and/or components purchased and certified to be sterile
826 and nonpyrogenic. A sterile pharmaceutical sterilizing-grade filter appropriate for the
827 drug product (e.g., chemically compatible) should be used. The filter must be compliant
828 with § 211.72 and filter integrity testing should be conducted after each filtration or
829 production run.
830

831 For aseptic processing of sterile drug products (i.e., not subjected to terminal sterilization), the
832 process for ensuring sterility must be validated (§ 211.113(b)), for example by conducting media
833 fills simulating the production process. Validation should be performed semi-annually. Media fill
834 studies should closely simulate aseptic manufacturing operations incorporating, as appropriate,
835 worst-case activities and conditions that are challenging to aseptic operations. The media fill
836 program should address applicable issues such as the following:

- 837
- 838 • Factors associated with the longest permitted run of the aseptic processing operation that
839 can pose contamination risk (e.g., operator fatigue, quality of processing environment).
840
- 841 • Representative number, type, and complexity of normal interventions that occur with
842 each run, as well as nonroutine interventions and events (e.g., maintenance, stoppages,
843 equipment adjustments). (The maximum number of expected interventions should be
844 included to simulate worst-case conditions.³⁰)

³⁰ When the possibility of contamination is higher based on the process design (e.g., manually intensive filling lines), a larger number of units, generally at or approaching the full production batch size, should be used. In contrast, a process conducted in an isolator can have a low risk of contamination because of the lack of direct human intervention and can be simulated with a lower number of units as a proportion of the overall operation.

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- 845
- 846
- Lyophilization, when applicable.
- 847
- Aseptic assembly of equipment (e.g., at start-up, during processing).
- 848
- Number of personnel and their activities. (The maximum expected number of personnel should be included to simulate worst-case conditions.)
- 849
- 850
- Representative number of aseptic additions (e.g., filling containers and closures as well as sterile ingredients) or transfers.
- 851
- 852
- Shift changes, breaks, and gown changes (when applicable).
- 853
- Type of aseptic equipment disconnections/connections.
- 854
- Aseptic sample collections.
- 855
- Operational configurations in the ISO 5 zone and line speeds (when applicable).
- 856
- Weight checks.
- 857
- Container-closure systems (e.g., size, type, compatibility with equipment).
- 858
- Specific provisions in written procedures related to aseptic processing (e.g., conditions beyond which discarding of exposed materials in the ISO 5 area or line clearance is mandated).
- 859
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I. Release Testing

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873

874 Sections 211.165 and 211.167 require that finished drug products be tested to determine whether

875 they meet final product specifications before their release for distribution. Section 211.22

876 establishes that the quality control unit is responsible for ensuring that the finished drug product

877 is not released until this testing is conducted and the results confirm that the finished drug

878 product meets specifications. Procedures for final release testing should be established and

879 followed as outlined here.

880

881 Appropriate specifications must be established for each drug product (see § 211.160(b)).

882 Specifications must address those attributes necessary to ensure the quality of the finished drug

883 product and must include, at a minimum (§§ 211.160(b), 211.165, 211.167):

884

- Identity and strength of the API.³¹
- 885

³¹ If the API is known (from literature or other scientific information) to have the potential to form genotoxic degradants as discussed in ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk*, the presence of the impurity or impurities should be evaluated as part of the assay or, if the assay method is not sufficiently sensitive, using a different test.

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- 886
- 887
- Purity of the drug product.
- 888
- For drug products purporting to be sterile and/or nonpyrogenic, sterility³² and a limit for bacterial endotoxins.
- 889
- 890
- 891
- Antimicrobial effectiveness for sterile drug products labeled as multiple dose and for aqueous non-sterile drug products labeled as multiple dose.³³ If antimicrobial effectiveness testing was previously performed using the subject formulation and container-closure system, preservative content testing may be used in lieu of a full antimicrobial effectiveness study. Appropriate specifications for aqueous drug products labeled as multiple dose include assurances that the product is adequately self-preserving or contains appropriate preservative content to limit microbial proliferation of microorganisms and assure that the product maintains its quality and purity for each dose.³⁴
- 892
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- 900

901

902 The product must also meet any other specifications included in an applicable USP monograph

903 (see, e.g., section 501(b) of the FD&C Act). In addition, FDA recommends consideration of the

904 following specifications:

- 905
- Color, clarity.
- 906
- pH, if applicable (e.g., for aqueous formulations).
- 907
- For drug products that are not solutions, content uniformity.³⁵
- 908
- For drug products that are non-sterile, microbial testing (i.e., microbial enumeration, tests for specified microorganisms).
- 909
- 910
- 911
- 912
- 913
- 914

³² Sterility testing should be conducted using USP General Chapter <71> *Sterility Tests*. Any other method used for sterility testing should be validated. See, for example, USP General Chapter <1223> *Validation of Alternative Microbiological Methods* or PDA Technical Report No. 33 (see Parenteral Drug Association 2013) for recommended validation methods.

³³ See USP General Chapter <51> *Antimicrobial Effectiveness Testing* for more information.

³⁴ Unsafe injection practices, including the improper use of needles, syringes, and vials for more than one patient, threaten patient safety and have resulted in multiple blood borne bacterial and viral infection outbreaks. Bacterial infections have been transmitted to patients when single-dose containers were used improperly, the contents became contaminated, and these contents were then administered to multiple patients. Therefore it is critical that drug products that are not adequately self-preserving and do not contain appropriate preservative content be labeled as single-dose to prevent such risks to health.

³⁵ For oral solid dosage forms (e.g., tablets and capsules), content should be assessed between dosage units. For nonsolid oral products (e.g., suspensions), the content should be assessed within the container (e.g., from the top and bottom of the container).

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- 915 • For drug products that are solutions purporting to be sterile, a limit for visible particles³⁶
916 and subvisible particles (10µm-100µm).³⁷
917

918 Other appropriate specifications for generally recognized attributes for the dosage form, such as
919 those described in ICH Q6A, should also be considered. For example, the specification for
920 immediate release solid oral dosage forms typically includes disintegration testing, while non-
921 immediate release dosage forms include dissolution testing as a measure of the release rate of
922 drug substance from the drug product (see § 211.167).
923

924 Procedures for release must be established that ensure that each batch of a drug product is not
925 released until the following have been completed (see §§ 211.22, 211.165, 211.167, 211.192):
926

- 927 • An appropriate laboratory determination has been conducted to ensure that each batch of
928 a drug product conforms to specifications.
- 929
- 930 • A review of environmental and personnel monitoring data, if applicable, has been
931 conducted to ensure that manufacturing conditions were acceptable during production of
932 the batch.
- 933
- 934 • Associated laboratory data and documentation have been reviewed by the quality control
935 unit, and they demonstrate that the drug product meets specifications.
- 936
- 937 • A designated qualified individual from the quality control unit has authorized final
938 release.
- 939

940 Under certain conditions described in Appendix A, FDA generally does not intend to take action
941 against an outsourcing facility regarding the release testing requirements described immediately
942 above and in the appendix.
943

Additional Considerations for Sterile Drug Products

944
945

946 Finished product sterility testing provides additional verification of sterility, even for those
947 products compounded from sterile starting materials, because an unexpected event posing a risk
948 to sterility may have occurred but may not have been detected. Appendix A describes the
949 conditions under which FDA generally does not intend to take regulatory action against an
950 outsourcing facility regarding finished product sterility testing based on mitigating factors, such
951 as the use of a validated terminal sterilization method and the use of other approaches to evaluate
952 sterility of the finished product before release.
953

³⁶ Such a limit may be established for any solution by following USP General Chapter <790> *Visible Particulates in Injections*.

³⁷ Applicable only to parenteral preparations. See USP General Chapters <788> *Particulate Matter in Injections* and <789> *Particulate Matter in Ophthalmic Solutions* for additional information.

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954 For finished products purporting to be nonpyrogenic, the product must meet endotoxin limits³⁸
955 before release (§ 211.167). For finished products compounded from starting materials that are
956 sterile and nonpyrogenic, endotoxin testing can be conducted on all starting materials (through
957 testing of the starting materials, or reliance on a statement of the limit met on a valid COA, or
958 where specified in an applicable USP monograph) or through testing of samples of the finished
959 product. The fact that a starting material is labeled nonpyrogenic does not necessarily ensure that
960 the finished product will meet the appropriate endotoxin limit because starting materials,
961 including FDA-approved products, may have been tested against different endotoxin limits,
962 depending on the intended dose and the route of administration.³⁹
963

J. Laboratory Controls

964
965
966 When testing components, in-process materials, and finished drug products, laboratories must
967 use controls to ensure the reliability of the tests (§ 211.160). Each laboratory used to test
968 components, in-process materials, or finished drug products—whether in-house or external to the
969 outsourcing facility—must employ the following critical aspects of laboratory controls to ensure
970 the quality of non-sterile and sterile drug products compounded by the outsourcing facility (see
971 §§ 211.160, 211.194):
972

- 973 • Follow appropriate written procedures for the conduct of each test and document the
974 results.
975
- 976 • Design sampling and testing procedures to ensure that components, in-process materials,
977 and drug products conform to the specifications set for the drug product.
978
- 979 • Use analytical methods and equipment that are suitable for their intended use and are
980 capable of producing valid results. If using a validated or an established compendial test
981 procedure in a specification, the test has been verified and documented to work under the
982 conditions of actual use.
983
- 984 • Keep complete records of all tests performed to ensure compliance with established
985 specifications and standards, including examinations and assays.
986

987 When an outsourcing facility seeks the services of a contract facility to perform all or part of the
988 testing of a drug, the outsourcing facility's quality control unit is responsible for approving and
989 rejecting drugs tested by the contractor. See §§ 200.10(b) and 211.22(a) and guidance for
990 industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*. In addition,
991 FDA recommends that contract facilities performing testing of a drug be ISO 17025 accredited.
992

³⁸ Typically, endotoxin testing is not required for topically administered ophthalmic products. See USP General Chapter <771> *Ophthalmic Products—Quality Tests*.

³⁹ See also guidance for industry *Pyrogens and Endotoxins Testing: Questions and Answers*.

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993 **K. Stability/Expiration Dating for Compounded Drug Products**

994

995 **1. Stability Program and Beyond-Use Dating**

996

997 A stability program must be established to assess the stability characteristics of finished drug
998 products, and the results of stability testing must be used to determine appropriate storage
999 conditions and expiration dates (§ 211.166). Stability testing is used to ensure that a drug product
1000 will retain its quality (e.g., strength) and remain sterile, if applicable, through the labeled
1001 expiration date. A stability program for compounded drug products should use past experiences,
1002 available literature, and fundamental scientific principles to establish the parameters for the
1003 program. An expiration date is established through the conduct of a stability program that
1004 includes testing to assess the product's performance against specifications after aging to the
1005 desired expiration date (§ 211.137); the conditions outlined in ICH guidance for industry
1006 *Q1A(R2) Stability Testing of New Drug Substances and Products* are recommended.

1007

1008 FDA understands that a compounded drug's batch size may be small and the frequency of batch
1009 production may vary considerably. The policies regarding stability testing and expiration dating
1010 in this guidance recognize these potential aspects of compounded drug production while
1011 addressing concerns regarding the quality of these products using a risk-based approach.

1012

1013 FDA generally does not intend to take regulatory action against an outsourcing facility regarding
1014 stability testing requirements if all of the following apply:

1015

1016 • The drug product is compounded solely by combining two or more drug products
1017 approved under section 505 of the FD&C Act.

1018

1019 • The approved drug product labeling of at least one of the components specifies how to
1020 assign an *in-use time*.

1021

1022 • The compounded drug product has been prepared and labeled with an in-use time in
1023 accordance with the approved product labeling.

1024

1025 • The in-use time is used as the expiration date, provided the in-use time does not exceed
1026 the expiration date of any of the approved drug products used to compound the drug. If
1027 two or more approved drug products with in-use times are used in the compounded drug
1028 product, the shortest in-use time is used as the expiration date for the compounded drug
1029 product.

1030

1031 In addition, taking into account the unique aspects of compounding, FDA generally does not
1032 intend to take regulatory action against an outsourcing facility under the conditions described in
1033 the remainder of this section and in Appendix B, such as using a BUD established through
1034 limited stability testing or, for certain lower risk situations, using a default BUD as the expiration

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1035 date, in lieu of establishing an expiration date through the conduct of a full stability program
1036 required under part 211,⁴⁰ if all of the following apply:

- 1037
- 1038 • The compounded drug’s BUD does not exceed appropriately established expiration or
1039 retest-by dates for any of the components used to compound the drug.
1040
 - 1041 • If the drug is compounded from an approved drug product, and the approved product
1042 labeling recommends one type of storage (e.g., refrigeration through the expiry date, such
1043 as 18 months), but also provides for storage at another condition (e.g., stable at room
1044 temperature for a time frame shorter than the expiry date, such as up to 14 days), the
1045 compounded drug product is not labeled with a BUD that is longer than the relevant
1046 storage time frame in the approved product labeling (e.g., the BUD of the compounded
1047 drug does not exceed 14 days for room temperature).
1048

1049 In addition, for repackaged products, FDA generally does not intend to take regulatory action
1050 against an outsourcing facility under the conditions described in the remainder of this section and
1051 in Appendix B, in lieu of establishing an expiration date through the conduct of a full stability
1052 program, if (1) the BUD does not exceed the expiration date of the drug product that is being
1053 repackaged; and (2) if the approved product labeling for the drug product being repackaged
1054 recommends one type of storage (e.g., refrigeration through the expiry date, such as 18 months)
1055 but also provides for storage at another condition (e.g., stable at room temperature for a time
1056 frame shorter than the expiry date, such as up to 14 days), the repackaged product is not labeled
1057 with a BUD that is longer than the relevant storage time frame in the approved product labeling
1058 (e.g., the BUD does not exceed 14 days for room temperature). For more information on
1059 repackaging, see the guidance for industry *Repackaging of Certain Human Drug Products by*
1060 *Pharmacies and Outsourcing Facilities*.
1061

1062 Whether you use an expiration date or BUD to be used as an expiration date according to the
1063 provisions outlined below and in Appendix B, the two studies below are required to be
1064 completed before a batch is released (see §§ 211.166, 211.167). Each study only needs to be
1065 conducted once for each formulation and container-closure system, and a bracketing or matrixing
1066 approach can be considered to minimize the amount of testing. See Appendix B for more
1067 information regarding bracketing approaches.
1068

- 1069 • **Container-closure integrity testing** is conducted on samples aged to or beyond the
1070 desired BUD or expiration date to ensure that sterility is maintained over that time
1071 period.⁴¹
1072

⁴⁰ To meet the conditions under section 503B of the FD&C Act, the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI)).

⁴¹ See USP General Chapter <1207> *Package Integrity Evaluation—Sterile Products* for more information on container-closure integrity testing.

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- 1073 • **Antimicrobial effectiveness testing** for drug products labeled or intended to be multiple
1074 dose is conducted on samples aged to the proposed BUD or expiration date. (Note that
1075 antimicrobial effectiveness testing is container-closure specific.)⁴²
1076

1077 Tables 2 and 3 highlight the conditions under which FDA generally does not intend to take
1078 regulatory action against an outsourcing facility for assigning a BUD to be used as an expiration
1079 date in lieu of conducting full stability studies required under part 211.
1080

1081 a. Non-sterile limited stability testing
1082

1083 For small batches ($\leq 5,000$ units⁴³ in an aggregate batch⁴⁴), FDA generally does not intend to take
1084 regulatory action if the relevant default BUDs provided in Appendix B are used for the
1085 expiration date and the conditions set forth in Appendix B are met. Alternatively, for small
1086 batches, FDA generally does not intend to take regulatory action if limited stability testing is
1087 conducted to support a BUD longer than the relevant default BUDs in accordance with Appendix
1088 B, and that BUD is used as an expiration date in lieu of conducting full stability studies required
1089 under part 211. For larger batches ($> 5,000$ units in an aggregate batch), FDA generally does not
1090 intend to take regulatory action regarding stability testing if the relevant conditions for the
1091 limited stability testing outlined in Appendix B are met. If, at any time during a 6-month
1092 reporting period, the total number of units compounded exceeds the 5,000-unit limit, the
1093 conditions applicable to small batches (i.e., $\leq 5,000$ units) do not apply.
1094

1095 **Table 2. BUDs for Non-Sterile Compounded Drug Products, by Aggregate Batch Size**

Aggregate Batch Size (over 6-month reporting period)	Default BUD (no testing)	BUD Based on Limited Stability Testing
$\leq 5,000$ units	Default BUD, which may be further limited by literature or other scientific information. See Appendix B for the conditions that must be met.	Data-driven stability program. See Appendix B for the conditions that must be met.
$> 5,000$ units	N/A. Default BUDs are not applicable to large aggregate batch sizes.	Data-driven stability program. See Appendix B for the conditions that must be met.

1096

⁴² See USP General Chapter <51> *Antimicrobial Effectiveness Testing* for more information.

⁴³ *Units* are individual tablets or capsules for solid oral dosage forms and suppositories, inserts, or immediate containers (e.g., vial, syringe, IV bag, tube) for other dosage forms.

⁴⁴ For the purposes of this guidance, batch size has been considered by defining *aggregate batch* as the sum of all units produced from any number of batches over the 6-month period for which a drug product report is submitted. For more information about product reports, see the guidance for industry *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

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1097 b. Sterile limited stability testing

1098
1099 For small batches ($\leq 1,000$ units in an aggregate batch), FDA generally does not intend to take
1100 regulatory action if the relevant default BUDs provided in Appendix B are used for the
1101 expiration date and the conditions set forth in Appendix B are met. Alternatively, for small
1102 batches, FDA generally does not intend to take regulatory action if limited stability testing is
1103 conducted to support a BUD longer than the relevant default BUDs in accordance with Appendix
1104 B, and that BUD is used as an expiration date in lieu of conducting full stability studies required
1105 under part 211. For larger batches ($> 1,000$ units in an aggregate batch), FDA generally does not
1106 intend to take regulatory action regarding stability testing if the relevant conditions for the
1107 limited stability testing outlined in Appendix B are met. If, at any time during a 6-month
1108 reporting period, the total number of units compounded exceeds the 1,000-unit limit, the
1109 conditions applicable to small batches (i.e., $\leq 1,000$ units) do not apply.

1110

1111 **Table 3. BUDs for Sterile Compounded Drug Products, by Aggregate Batch Size**

Aggregate Batch Size (over 6-month reporting period)	Default BUD (no testing)	BUD Based on Limited Stability Testing
$\leq 1,000$ units	Default BUD, which may be further limited by literature or other scientific information. See Appendix B for the conditions that must be met.	Data-driven stability program. See Appendix B for the conditions that must be met.
$> 1,000$ units	N/A. Default BUDs are not applicable to large aggregate batch sizes.	Data-driven stability program. See Appendix B for the conditions that must be met.

1112

1113 2. *Establishing an In-Use Time for Sterile Drug Products*

1114

1115 To be eligible for the exemptions under section 503B of the FD&C Act, the container for the
1116 compounded drug product must include directions for use, including, as appropriate, dosage and
1117 administration (section 503B(a)(10)(B) of the FD&C Act). If the compounded drug product
1118 requires additional manipulation before administration (e.g., reconstitution and/or dilution), FDA
1119 interprets the directions for use requirement to include an in-use time because the health care
1120 practitioner who manipulates or administers the drug would need to know how long it is
1121 expected to retain its quality after being manipulated. Furthermore, stability studies (as required
1122 by § 211.166) would be needed to support the stated in-use time. However, FDA generally does
1123 not intend to take regulatory action regarding the requirement to have data to support the stated
1124 in-use time, such as microbial challenge and stability studies, if the sterile product has directions
1125 for use that include an in-use time less than 4 hours at room temperature or less than 24 hours
1126 refrigerated.⁴⁵

1127

⁴⁵ For a description of methods and acceptance criteria for microbial challenge studies, see Metcalfe 2009.

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1128 Under §§ 211.160 and 211.165(b), appropriate laboratory testing of products required to be free
1129 of objectionable microorganisms are required, and laboratory controls must include scientifically
1130 sound and appropriate specifications and test procedures designed to provide assurance that the
1131 product conforms to appropriate standards of identity, strength, quality, and purity. For multiple
1132 dose products, appropriate laboratory tests and specifications include ones for antimicrobial
1133 effectiveness, whether the product contains a preservative or antimicrobial activity is inherent in
1134 the formulation. See USP General Chapter <51> for antimicrobial effectiveness test methods and
1135 acceptance criteria. If the acceptance criteria described in USP General Chapter <51> are met,
1136 labeling up to a 28-day in-use period is considered to be appropriate for multiple-dose products,
1137 subject to the conditions regarding stability testing discussed below.
1138

1139 In addition to microbial challenge studies, the stability of the manipulated product must be
1140 assessed (see § 211.166). FDA generally does not intend to take regulatory action regarding the
1141 requirement to conduct full stability studies to assess the stability of the manipulated product if
1142 the tests conducted as part of the limited stability testing described in Appendix A are conducted
1143 on samples aged to at least 2/3 of the labeled BUD (if longer than the default BUDs outlined in
1144 Appendix B), manipulated (e.g., reconstituted or diluted) as described in labeling, and then held
1145 for the desired in-use time (up to 28 days).
1146

1147 The labeled directions for use⁴⁶ should include instructions to the health care provider or patient
1148 that the time in storage plus the administration phase should not exceed the BUD. Consider, for
1149 example, a sterile powder formulation in a vial that must be reconstituted with Sterile Water for
1150 Injection, USP, before patient administration with a label that includes an in-use-time of within 4
1151 hours at room temperature or within 24 hours if refrigerated. The in-use time begins when the
1152 sterile powder vial is entered and reconstituted with Sterile Water for Injection, USP. The
1153 reconstituted solution should be administered to the patient within 4 hours if the solution is held
1154 at room temperature or within 24 hours if it is stored in the refrigerator.
1155

3. In-Use Time and BUDs for Sterile Drug Products

1156
1157
1158 The outsourcing facility should establish the BUD placed on a compounded drug product's label,
1159 taking into consideration that the BUD is the date/time after which the product is to be discarded.
1160 The labeled directions for use should include instructions to the health care provider or patient
1161 accordingly. If the product does not require any manipulation (e.g., dilution or reconstitution)
1162 before administration, the directions for use should advise that administration to the patient
1163 should be completed before reaching the BUD. For example, if an IV bag containing a
1164 compounded drug product with a BUD of 24 hours is to be infused to the patient over a period of
1165 4 hours, the infusion should begin by 20 hours to ensure that administration will be complete
1166 before reaching the BUD, at which point the compounded drug product should be discarded.
1167

⁴⁶ Section 503B(a)(10)(B) of the FD&C Act provides the following: "The container from which the individual units of the drug are removed for dispensing or for administration . . . shall include . . . directions for use, including, as appropriate, dosage and administration."

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1168 **L. Packaging and Labels**

1169
1170 Packaging of non-sterile and sterile drugs must be appropriate to the product and capable of
1171 ensuring the sterility, if applicable, and integrity of the product until it is administered to a
1172 patient (see §§ 211.94, 211.122). Labels must contain required information, and labeling
1173 operations must include controls to prevent mix-ups; furthermore, procedures must be developed
1174 to ensure these requirements are met (§§ 211.122, 211.125, 211.130, 211.134).

1175
1176 The following aspects of packaging and labeling are critical to ensure the quality of compounded
1177 drug products and must be implemented by outsourcing facilities:

- 1178
- 1179 • The container, closure, and packaging systems provide adequate protection against
1180 foreseeable external factors in storage, shipment, and use that could cause contamination
1181 or deterioration of the finished drug product (e.g., cracked vials, leaks in bags)
1182 (§ 211.94).
 - 1183
 - 1184 • Adequate controls have been established for issuing labels, examining issued labels, and
1185 reconciliation of used labels to prevent mix-ups (§ 211.125).
 - 1186
 - 1187 • There is adequate separation between the labeling and packaging operations of different
1188 products, including ones with different strengths or containers or closures, to prevent
1189 mix-ups (§ 211.130).
 - 1190
 - 1191 • Adequate controls have been established to ensure proper identification of any filled
1192 containers of non-sterile or sterile drug products that will be stored unlabeled for any
1193 period of time (§ 211.130).
 - 1194
 - 1195 • Packaging records include results of examinations of labels used (§ 211.134) and
1196 specimens or copies of all labeling used (§ 211.188).
 - 1197
 - 1198 • The labeled finished drug product has been examined for accuracy before release
1199 (§ 211.134).

1200 **M. Reserve Samples**

1201
1202
1203 An appropriately identified reserve sample that is representative of each lot or batch of drug
1204 product must be retained and stored under conditions consistent with product labeling
1205 (§ 211.170). FDA generally does not intend to take regulatory action against an outsourcing
1206 facility regarding reserve sample requirements if all of the following apply:

- 1207
- 1208 • Once >10,000 units are produced of a given drug product formulation and container-
1209 closure system in a 6-month reporting period, an appropriately identified and
1210 representative reserve sample is collected each time 1,000 units of that specific
1211 formulation and container-closure system is produced for the remainder of the current
1212 reporting period and for the entire subsequent 6-month reporting period.

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- The reserve sample is retained and stored under the labeled storage conditions and in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics (e.g., same material, same headspace for liquids).
 - The reserve sample is held for at least 30 days following the expiration date.
 - The reserve sample consists of at least the quantity of drug product necessary for all tests required at release, except for sterility and pyrogen testing.

N. Complaint Handling

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Outsourcing facilities must have procedures for handling complaints that they receive about their compounded drug products (§ 211.198). Written and oral complaints concerning the quality or purity of a drug product must be reviewed by the quality control unit, which must determine the need to investigate the complaint in accordance with § 211.192 (§ 211.198). If an investigation is needed, in addition to the quality control unit, personnel appropriate to evaluate the complaint should be involved. Complaint handling procedures must include provisions for review to determine whether the complaint represents an adverse event that must be reported to FDA (see § 211.198, section 301(ccc)(3) of the FD&C Act, and the guidance for industry *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*).

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Guidances for Industry

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Guidance for industry *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*

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- 1260 Guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*
1261
- 1262 Guidance for industry *Electronic Drug Product Reporting for Human Drug Compounding*
1263 *Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*
1264
- 1265 Guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical*
1266 *Production*
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- 1268 Guidance for industry *Mixing, Diluting, or Repackaging Biological Products Outside the Scope*
1269 *of an Approved Biologics License Application*
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- 1271 Guidance for industry *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing*
1272 *Cross-Contamination*
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- 1274 Guidance for industry *Pyrogens and Endotoxins Testing: Questions and Answers*
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- 1276 Guidance for industry *Repackaging of Certain Human Drug Products by Pharmacies and*
1277 *Outsourcing Facilities*
1278
- 1279 Guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good*
1280 *Manufacturing Practice*
1281
- 1282 Guidance for industry *Submission Documentation for Sterilization Process Validation in*
1283 *Applications for Human and Veterinary Drug Products*
1284
- 1285 Guidance for industry *Submission of Documentation in Applications for Parametric Release of*
1286 *Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes*
1287
- 1288 **ICH Guidances for Industry**
1289
- 1290 ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic)*
1291 *Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk*
1292
- 1293 ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*
1294
- 1295 ICH guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New*
1296 *Drug Substances and Products*
1297
- 1298 ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for*
1299 *New Drug Substances and New Drug Products: Chemical Substances*
1300
- 1301 **ISO Standards**
1302
- 1303 ISO 11137-1:2006, Sterilization of health care products—Radiation—Part 1: Requirements for
1304 the development, validation and routine control of a sterilization process for medical devices
1305

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1306 ISO 11137-2:2013, Sterilization of health care products—Radiation—Part 2: Establishing the
1307 sterilization dose

1308
1309 ISO 14644-1:2015, Cleanrooms and associated controlled environments—Part 1: Classification
1310 of air cleanliness by particle concentration

1311
1312 ISO 14644-6:2007, Cleanrooms and associated controlled environments—Part 6: Vocabulary

1313
1314

1315 **V. GLOSSARY**

1316

1317 **Action Limit:** An established microbial or airborne particle level that, when exceeded, should
1318 trigger appropriate investigation and corrective action based on the investigation.

1319

1320 **Active Pharmaceutical Ingredient (API):** Any substance that is intended for incorporation into
1321 a finished drug product and is intended to furnish pharmacological activity or other direct effect
1322 in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or
1323 any function of the body. *API* does not include intermediates used in the synthesis of the
1324 substance.

1325

1326 **Aggregate Batch:** The sum of all units produced from any number of batches over the 6-month
1327 period for which a drug product report is submitted.

1328

1329 **Alert Limit:** An established microbial or airborne particle level giving early warning of potential
1330 drift from normal operating conditions and triggering appropriate scrutiny and follow-up to
1331 address the potential problem. Alert limits are always lower than action limits.

1332

1333 **Aseptic:** Free from germs that cause disease; sterile.

1334

1335 **Aseptic Manufacturing Area:** The classified part of a facility that includes the aseptic
1336 processing room and ancillary cleanrooms.

1337

1338 **Aseptic Process:** The process by which a sterile product is packaged in a sterile container in a
1339 manner that maintains sterility.

1340

1341 **Batch:** A specific quantity of a drug or other material that is intended to have uniform character
1342 and quality, within specified limits, and is produced according to a single compounding order
1343 during the same cycle of production.

1344

1345 **Beyond-Use Date (BUD):** A date beyond which a compounded drug product should not be used.
1346 A BUD notifies the user of the period during which a compounded drug product's required
1347 quality characteristics (e.g., sterility, strength, purity, freedom from particulate matter) can be
1348 ensured.

1349

1350 **Bioburden:** The total number of microorganisms associated with a specific item before sterilization.

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1352 **Biological Indicator (BI):** A population of microorganisms inoculated onto a suitable medium
1353 (e.g., solution, container or closure) and placed within appropriate sterilizer load locations to
1354 determine the sterilization cycle efficacy of a physical or chemical process. The challenge
1355 microorganism is selected based on its resistance to the given process. Incoming lot D-value and
1356 microbiological count define the quality of the BI.

1357

1358 **Bulk Drug Substance:** See definition for *active pharmaceutical ingredient*.

1359

1360 **Cleanroom:** A room designed, maintained, and controlled to prevent particle and
1361 microbiological contamination of drug products. Such a room is assigned a classification based
1362 on reproducibly meeting appropriate air cleanliness limits.

1363

1364 **Component:** Any ingredient intended for use in the manufacture of a drug product, including
1365 ingredients that may not appear in the final drug product.

1366

1367 **Critical Area:** An area designed to maintain sterility of sterile materials.

1368

1369 **Critical Surface:** Surfaces that may come into contact with or directly affect a sterilized product
1370 or its containers or closures.

1371

1372 **Depyrogenation:** A process used to destroy or remove pyrogens (e.g., endotoxins).

1373

1374 **Disinfection:** A process by which surface bioburden is reduced to a safe level or eliminated.

1375

1376 **Endotoxin:** A pyrogenic product (e.g., lipopolysaccharide) present in the bacterial cell wall.
1377 Endotoxins can lead to reactions ranging from fever to death in patients receiving injections.

1378

1379 **Expiration Date:** A date on the drug product label that indicates how long the drug can meet
1380 applicable standards of identity, strength, quality, and purity under labeled storage conditions
1381 before it is used. Expiration dates are determined based on product-specific stability studies
1382 evaluating the specific formulation of a drug product, in the specific container in which it is to be
1383 stored, and under the conditions to which it may be exposed. Temperature, humidity, and light
1384 are some of the factors that can affect whether and how much a drug product degrades over time.

1385

1386 **HEPA Filter:** A high-efficiency particulate air filter with minimum 0.3 μm particle retaining
1387 efficiency of 99.97 percent.

1388

1389 **In-Use Time:** The maximum amount of time that can be allowed to elapse between penetration
1390 of a container-closure system once the drug product has been sterilized, or after a lyophilized
1391 drug product has been reconstituted, and before patient administration.

1392

1393 **Intervention:** An aseptic manipulation or activity that occurs in the critical area.

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- 1395 **Isolator:** A decontaminated unit supplied with ISO 5 or higher air quality that provides
1396 uncompromised, continuous isolation of its interior from the external environment (e.g.,
1397 surrounding cleanroom air and personnel).⁴⁷
1398
- 1399 **Lot:** A batch, or a specific identified portion of a batch, having uniform character and quality
1400 within specified limits; or, in the case of a drug product produced by continuous process, a
1401 specific identified amount produced in a unit of time or quantity in a manner that provides
1402 assurance of its having uniform character and quality within specified limits.
1403
- 1404 **Operator:** Any individual participating in the aseptic processing operation, including line set-up,
1405 filler, or maintenance, or any other personnel associated with aseptic line activities.
1406
- 1407 **Pyrogen:** A substance that induces a febrile reaction in a patient.
1408
- 1409 **Terminal Sterilization:** The application of a lethal agent (e.g., heat) to sealed, finished drug
1410 products for the purpose of achieving a predetermined sterility assurance level (SAL) of usually
1411 less than 10^{-6} (i.e., a probability of a non-sterile unit of greater than one in a million).
1412
- 1413 **Unidirectional Flow:** An airflow moving in a single direction, in a robust and uniform manner,
1414 and at sufficient speed to reproducibly sweep particles away from the critical processing or
1415 testing area.
1416
- 1417 **Viable Particle:** A particle that consists of, or supports, one or more live microorganisms.
1418

⁴⁷ See Appendix 1 in guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*.

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1419 **APPENDIX A. CONDITIONS UNDER WHICH FDA GENERALLY DOES NOT** 1420 **INTEND TO TAKE REGULATORY ACTION REGARDING CERTAIN RELEASE** 1421 **TESTING REQUIREMENTS**

1422
1423 Procedures for release must be established that ensure that each batch of a drug product is not
1424 released until the following have been completed (see §§ 211.22, 211.165, 211.167(a), 211.192):
1425

- 1426 • An appropriate laboratory determination has been conducted to ensure that each batch of
1427 a drug product conforms to specifications.
- 1428
- 1429 • A review of environmental and personnel monitoring data, if applicable, has been
1430 conducted to ensure that manufacturing conditions were acceptable during production of
1431 the batch.
- 1432
- 1433 • Associated laboratory data and documentation have been reviewed by the quality control
1434 unit, and they demonstrate that the drug product meets specifications.
- 1435
- 1436 • A designated qualified individual from the quality control unit has authorized final
1437 release.
- 1438

1439 **A. Non-Sterile Drug Products**

1440
1441 FDA generally does not intend to take regulatory action against an outsourcing facility regarding
1442 these release requirements **under the conditions described in Table A**, which is at the end of
1443 Appendix A. For any given product, consider which conditions in Table A apply. If multiple
1444 conditions apply, choosing the least stringent option for **each** individual batch release test among
1445 the applicable conditions would be consistent with the enforcement policy set forth in this
1446 appendix.

1447
1448 Example 1: All of the following conditions apply:

- 1449
- 1450 • The batch size is >60 units.
- 1451
- 1452 • The water activity is ≤ 0.6 (it is not a solid dosage form).
- 1453
- 1454 • The product is tested for strength by a method that is highly specific (e.g., high
1455 performance liquid chromatography (HPLC)) and uses a reference standard.
- 1456

1457 From Table A, conditions 2b and 3 apply; under those conditions, FDA generally does not intend
1458 to take regulatory action against an outsourcing facility regarding batch release tests for identity,
1459 AET/preservative content, microbial enumeration, or tests for specified microorganisms if the
1460 outsourcing facility assessed strength, content uniformity, pH, appearance, and the other
1461 appropriate specifications for that product.

1462
1463 Example 2: All of the following conditions apply:

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- 1465 • The batch size is 30 units *each month*.
- 1466
- 1467 • The starting material is a bulk drug substance.
- 1468
- 1469 • The product is a solid dosage form.
- 1470
- 1471 • The product is tested for strength by a method that is highly specific (e.g., HPLC) and
- 1472 uses a reference standard.
- 1473

1474 From Table A, conditions 1b and 3 apply for the first batch of 30 units; conditions 2c and 3 apply
1475 for the second batch of 30 units (i.e., when a total of 60 units has been produced); conditions 1b
1476 and 3 apply for the third batch of 30 units; and so on. Under those conditions, FDA generally
1477 does not intend to take regulatory action against an outsourcing facility regarding batch release
1478 testing for identity, content uniformity, pH, AET/preservative content, microbial enumeration,
1479 tests for specified microorganisms, or the other appropriate specifications if the outsourcing
1480 facility assessed strength and appearance for every batch and also assessed content uniformity
1481 and the other appropriate specifications for that product for every other batch.

1482 **B. Sterile Drug Products**

1483 FDA generally does not intend to take regulatory action against an outsourcing facility regarding
1484 these release requirements **as they apply to sterility testing** if sterility testing is *initiated before*
1485 batch release (see also Table D in Appendix B for BUDs for products released without a
1486 completed sterility test) and established procedures specify that if the drug product fails to meet a
1487 criterion for sterility:
1488

- 1489
- 1490
- 1491 • All facilities that received the drug product are notified immediately of the test results
1492 and provided with any appropriate information and recommendations to aid in the
1493 treatment of patients.
- 1494
- 1495 • The notification is documented.
- 1496
- 1497 • FDA is notified in writing within 5 working days.⁴⁸
- 1498

1499 In addition, FDA generally does not intend to take regulatory action against an outsourcing
1500 facility regarding the release requirements for sterility testing **under the conditions described in**
1501 **Table B**, which is at the end of Appendix A. For any given product, consider which conditions in
1502 Table B apply. If multiple conditions apply, choosing the least stringent option for **each**
1503 individual batch release test among the applicable conditions would be consistent with the
1504 enforcement policy set forth in this appendix.

1505

1506 Example 1: All of the following conditions apply:

- 1507
- 1508 • The batch size is 30 units *each month*.

⁴⁸ Reports should be emailed to FDA at OFAAlertReport@fda.hhs.gov.

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- 1509
- 1510
- 1511
- 1512
- 1513
- 1514
- 1515
- 1516
- The product is a solution or total parenteral nutrition (TPN) and the bulk solution but not the finished drug product is tested for identity and strength immediately before filling into the final and prelabeled drug product containers.
 - The product is terminally sterilized using a validated sterilization cycle that uses physical, chemical, or biological indicators.

1517 From Table B, conditions 2, 5, and 6 apply to the first batch of 30 units; conditions 1, 5, and 6
1518 apply to the second batch of 30 units (i.e., when a total of 60 units has been produced); and so
1519 on. Under those conditions, FDA generally does not intend to take regulatory action against an
1520 outsourcing facility regarding batch release testing for identity, strength, sterility, pH, visible
1521 particulates, subvisible particulates (where applicable), or other appropriate specifications,
1522 including USP monograph specifications, if the outsourcing facility conducted testing for
1523 endotoxin, color, and clarity on that product for each batch and also conducted testing on pH,
1524 visible particulates, subvisible particulates (where applicable), and other appropriate
1525 specifications, including USP monograph specifications on every other batch.

1526

1527 Example 2: Both of the following conditions apply:

- 1528
- 1529
- 1530
- 1531
- 1532
- 1533
- 1534
- 1535
- 1536
- The batch size is >60 units.
 - Drug product is a multicomponent injectable drug product (e.g., total parenteral nutrition product, cardioplegia solution) compounded from APIs produced only by FDA-registered manufacturers, the finished product is compounded using automated equipment with validated software, and the equipment is calibrated immediately before and after each personnel shift.

1537 From Table B, conditions 1 and 5 apply; under those conditions, FDA generally does not intend
1538 to take regulatory action against an outsourcing facility regarding batch release testing for
1539 identity and strength if the outsourcing facility conducted testing for sterility, endotoxin, pH,
1540 color, clarity, visible particulates, subvisible particulates (where applicable), and other
1541 appropriate specifications, including USP monograph specifications.

1542

1543 **C. Additional Considerations**

1544

1545 FDA generally does not intend to take regulatory action against an outsourcing facility regarding
1546 the requirement to test the *finished* product before release (see § 211.165, 211.167) if the drug
1547 product is aseptically filled into secured, sterile cartridges or cassettes that are designed to
1548 prevent misuse through a locking mechanism that prevents the outsourcing facility from testing
1549 the finished product, and all testing/examinations are conducted on a sample from the container
1550 that holds the pooled, compounded drug product (e.g., pump reservoir) after all final containers
1551 are filled.⁴⁹

⁴⁹ See Table 2 in USP General Chapter <71> *Sterility Tests* for more information regarding the volume to be sampled.

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- 1552
1553 To reduce the need for the manufacturing of additional units to meet the sterility testing
1554 requirement (see § 211.167) by following the procedures in USP General Chapter <71> *Sterility*
1555 *Tests*, FDA generally does not intend to take action against an outsourcing facility regarding the
1556 number of units tested if:
1557
- 1558 • For batch sizes up to and including 10 units that do not also meet conditions 3 or 6 in
1559 Table B, at least 1 unit is tested; and
1560
 - 1561 • For batch sizes of greater than 10 units and fewer than 40 units, the sterility test is
1562 conducted using a number of containers that equals 10 percent rounded up to the next
1563 whole number.

1564 Table A. Conditions Regarding Batch Release Tests for Non-Sterile Drug Products

Conditions	Batch Release Test								
	○ Test for which FDA generally does not intend to take regulatory action under the conditions listed ● Test expected to be performed, if applicable								
	Identity	Strength	Content Uniformity ^c	pH	Appearance	AET/Preservative Content ^d	Microbial Enumeration (bacteria and fungi) ^e	Tests for Specified Microorganisms ^e	Other Appropriate Specifications ^f
Tests are conducted according to these conditions ...									
1. Batch size <60 units, ^a if omitted tests are performed once 60 units are produced ^b									
1a. Starting from FDA-approved product	○	○	○	○	●	○	○	○	○
1b. Starting from bulk drug substance	●	●	○	○	●	○	○	○	○
2. Batch size ≥60 units <i>or</i> once 60 units are produced ^b and considering the following characterizations of water activity:									
2a. Water activity >0.6	●	●	●	●	●	●	●	●	●
2b. Water activity ≤0.6 (other than solid dosage forms)	●	●	●	●	●	○	○	○	●
2c. Solid dosage forms	●	●	●	○	●	○	○	○	●
... unless conditions 3 or 4 also apply. If so, choosing the least stringent option for each test among applicable conditions would be consistent with the enforcement policy set forth in this appendix.									
3. Product tested for strength by method that is highly specific (e.g., HPLC) and uses a reference standard	○	●	●	●	●	●	●	●	●
4. Compounded drug product is single dilution of FDA-approved drug product, or is made from one or more dilutions of FDA-approved drug product performed per labeling dilution instructions and using automated equipment calibrated immediately before and after production	○	○	●	●	●	●	●	●	●
^a Individual tablets or capsules for solid oral dosage forms and suppositories, inserts, or containers (e.g., vial, syringe, IV bag, tube) for other dosage forms. ^b Omitted tests under these conditions need only be performed one time after a single batch of 60 or more units has been produced or once 60 or more units have been produced in more than 1 batch within a year of the time the first batch is produced, and resets once testing has been performed or at 1 year from the time the first batch is produced if a minimum of 60 units was not produced. For example, if the batch size is consistently 30 units (e.g., tubes) of a particular volume of drug, the omitted tests are conducted on every second batch produced. Or, if the first, second, and third batches in the year include 25, 30, and 10 units respectively, the omitted tests are performed on the third batch because the minimum of 60 units has been met. ^c FDA generally does not intend to take regulatory action if content uniformity testing is not performed on solutions. ^d If the drug product is self-preserving, then either test for the API/excipient that is providing the preserving effect or conduct antimicrobial effectiveness testing (AET). For products with a preservative, conduct preservative content testing. Nonetheless, AET should be performed at least one time on a formulation using the lowest preservative concentration for the subject formulation and container-closure system. ^e See, for example, USP General Chapter <1111>. ^f These include generally recognized attributes for each dosage form such as those described in ICH Q6A or USP monographs or general chapters.									

1566 Table B. Conditions Regarding Batch Release Tests for Sterile Drug Products

Conditions	Batch Release Test									
	Identity	Strength	Sterility	Endotoxin ^c	pH	Color	Clarity	Visible Particulates	Subvisible Particulates	Other Appropriate Specifications ^d
<p>○ Test for which FDA generally does not intend to take regulatory action under the conditions listed</p> <p>● Test expected to be performed</p>										
Tests are conducted according to these conditions ...										
1. Batch size ≥60 units ^a or once 60 units are produced ^b	●	●	●	●	●	●	●	●	●	●
2. Batch size <60 units, if omitted tests are performed once 60 units are produced ^b	○	○	●	●	○	●	●	○	○	○
3. Batch <10 units compounded pursuant to prescription for single patient and label bears BUD per Table D in Appendix B, if omitted tests are performed once 60 units are produced ^b	○	○	○	●	○	●	●	○	○	○
... unless conditions 4, 5, or 6 also apply. If so, choosing the least stringent option for each test among applicable conditions would be consistent with the enforcement policy set forth in this appendix.										
4. Product tested for strength (potency) by method that is highly specific (e.g., HPLC) and uses a reference standard	○	●	●	●	●	●	●	●	●	●
5. For solutions or total parenteral nutrition (TPN) only: - Compounded drug product is single dilution of FDA-approved drug product, or is made from one or more dilutions of FDA-approved drug product performed per labeling dilution instructions and using automated equipment calibrated immediately before and after production - OR - - Bulk solution but not finished drug product is tested for identity and strength immediately before filling into final and pre-labeled drug product containers - OR - - Drug product is multicomponent injectable drug product (e.g., TPN product, cardioplegia solution) compounded from APIs produced only by FDA-registered manufacturers, finished product is compounded using automated equipment with validated software, and equipment is calibrated immediately before and after each personnel shift	○	○	●	●	●	●	●	●	●	●
6. Product is terminally sterilized using validated sterilization cycle that uses physical, chemical, or biological indicators	●	●	○	●	●	●	●	●	●	●
<p>^a Individual tablets or capsules for solid oral dosage forms and suppositories, inserts, or containers (e.g., vial, syringe, IV bag, tube) for other dosage forms.</p> <p>^b Omitted tests under this condition need only be performed one time after a single batch of 60 or more units has been produced or once 60 or more units have been produced in more than 1 batch within a year from the time the first batch is produced, and resets once testing has been performed or at 1 year from the time the first batch is produced if a minimum of 60 units was not produced. For example, if the batch size is consistently 35 units (e.g., vials) of a particular volume of drug, testing is conducted on every second batch produced. Or, if the first, second, and third batches in the year include 25, 20, and 30 units respectively, testing is performed on the third batch because the minimum of 60 units has been met.</p> <p>^c For finished products compounded from starting materials that are sterile and nonpyrogenic, see section I, Release Testing, for more information on endotoxin testing.</p> <p>^d These include generally recognized attributes for each dosage form such as those described in ICH Q6A or USP monographs or general chapters.</p>										

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1568 **APPENDIX B. CONDITIONS UNDER WHICH FDA GENERALLY DOES NOT** 1569 **INTEND TO TAKE REGULATORY ACTION REGARDING STABILITY TESTING** 1570 **AND EXPIRATION DATE REQUIREMENTS**

1571 1572 **A. Default BUD (No Testing) for Non-Sterile Drug Products: Aggregate Batch** 1573 **Size ≤5,000 Units** 1574

1575 FDA generally does not intend to take regulatory action against an outsourcing facility regarding
1576 the requirements for stability studies and expiration dates for non-sterile drug products under
1577 §§ 211.166 and 211.137 if (1) a BUD has been assigned according to Table C; (2) water activity
1578 testing is conducted as described below, if applicable, to determine the type of product for
1579 assigning the BUD; (3) literature or other scientific information, including relevant commercially
1580 available product labeling for a similar drug (e.g., components, dosage form, route of
1581 administration, primary container-closure type), does not indicate that the drug product may not
1582 be physicochemically stable over the time period listed; and (4) the BUD is used as the
1583 expiration date.⁵⁰
1584

1585 The default BUDs in Table C are based on the likelihood of microbial proliferation as
1586 determined by water activity testing. Products with a water activity >0.6 are of greater concern
1587 microbiologically because there is potential for proliferation of microorganisms in the product.
1588 Use of a validated preservative strategy⁵¹ can greatly reduce the likelihood of microbial
1589 proliferation in finished drug products.
1590

1591 Water activity testing is conducted as follows to determine the type of product for assigning the
1592 default BUD:
1593

- 1594 • Solid dosage forms (i.e., tablets and capsules): No water activity testing is necessary.
1595
- 1596 • Products with water activity >0.6: No water activity testing is necessary if the product is
1597 known or assumed to have a high water activity (e.g., liquid oral solution) and the
1598 applicable default BUD for products with water activity >0.6 is used.
1599
- 1600 • Products with suspected low water activity (other than solid dosage forms) (e.g.,
1601 suppository): Water activity testing is conducted once for each non-sterile drug product
1602 formulation according to validated test procedures such as those described in USP
1603 General Chapter <1112>. Depending on the results of the water activity test, the BUD
1604 should be set according to Table C.
1605

⁵⁰ To be eligible for the exemptions provided under section 503B of the FD&C Act, the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI)).

⁵¹ See USP General Chapter <51>.

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1606 **Table C: Default BUDs for Non-Sterile Drug Products With Aggregate Batch Size ≤5,000**
 1607 **Units**

Type of Product	Storage Conditions	
	Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)
Solid dosage forms	180 days	N/A
Water activity >0.6	Preserved: 30 days Unpreserved: Not applicable	Preserved: 30 days Unpreserved: 14 days
Water activity ≤0.6	90 days	N/A

1608
 1609 **B. Default BUD (No Testing) for Sterile Drug Products: Aggregate Batch Size**
 1610 **≤1,000 Units**

1611
 1612 FDA generally does not intend to take regulatory action against an outsourcing facility regarding
 1613 the requirements for stability studies and expiration dates under §§ 211.166 and 211.137 if (1) a
 1614 BUD has been assigned according to the criteria based on processing conditions in Table D; (2)
 1615 literature or other scientific information, including relevant commercially available product
 1616 labeling for a similar drug (e.g., components, dosage form, route of administration, primary
 1617 container-closure type), does not indicate that the drug product may not be physicochemically
 1618 stable over the time period listed; and (3) the BUD is used as the expiration date.⁵²

1619
 1620 **Table D. Default BUDs for Aggregate Batch Size ≤1,000 Units With Given Processing and**
 1621 **Storage Conditions**

Processing Conditions	Contains a Preservative?	Storage Conditions		
		Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)	Freezer (-25° to -10°C)
<ul style="list-style-type: none"> Finished drug product is aseptically processed; and A sterility test has not been completed before release 	No	6 days	9 days	45 days
	Yes	28 days	42 days	45 days
<ul style="list-style-type: none"> Finished drug product is terminally sterilized; A validated sterilization cycle that uses physical, 	No	14 days	28 days	45 days

⁵² To be eligible for the exemptions provided under section 503B of the FD&C Act, the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI)).

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chemical, or biological indicators is employed; and • A sterility test has not been completed before release	Yes	28 days	42 days	45 days
• Finished drug product is aseptically processed or terminally sterilized and has a completed, passing sterility test before release	No	28 days	42 days	45 days
	Yes	42 days	42 days	45 days

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C. Enforcement Policy Regarding the Use of Limited Stability Testing To Assign a BUD

Stability testing is intended to confirm the stability performance of a non-sterile or sterile compounded drug product held under the labeled storage conditions for the duration of the BUD. Procedures established for assessing the stability of drug products compounded by outsourcing facilities must achieve the following (§§ 211.122, 211.160, 211.166):

- Incorporate stability-indicating test methods that are reliable, meaningful, and specific.
- Evaluate samples of the drug product in the same container-closure system and with the same or representative label and adhesive that will be affixed to the container in which the drug product is marketed.
- Evaluate samples for stability that are representative of the batch from which they were obtained and are stored under suitable conditions.
- Incorporate testing to evaluate antimicrobial effectiveness for drug products labeled or intended to be multiple dose. If antimicrobial effectiveness has been previously established for the formulation and container-closure system, a test for preservative content may be used in lieu of a full antimicrobial effectiveness study.

FDA generally does not intend to take regulatory action against an outsourcing facility regarding stability testing and expiration date requirements if the outsourcing facility uses the approach outlined below describing a number of lots and a set of tests—which should be conducted at lot release as part of normal operations—to be performed at the time of the desired BUD. This section C does not apply to non-sterile unpreserved aqueous drug products because of the higher risk of microbiological proliferation.

The following conditions apply:

- Samples are evaluated following aging under the long-term storage conditions (i.e., temperature and humidity) in ICH Q1A(R2).
- The data from each time point are evaluated against the established specifications for the compounded drug product.

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- 1659 • The BUD is not longer than 12 months.
1660
1661 • If the data for any test fall outside of the established specifications, the BUD is restricted
1662 to the last time point at which the data remained within specifications, or the default BUD
1663 (described above) is used.
1664

1665 Because of the possibility that a sample may not meet specifications at the final time point, FDA
1666 strongly recommends the inclusion of testing at at least one interim time point. If the data at the
1667 final time point do not confirm the stability of the product at the desired BUD (e.g., some
1668 measurements fall outside of the established specifications), but the data at the interim time point
1669 are acceptable (i.e., measurements meet the established specifications), a BUD equal to the
1670 interim time point meets the second condition above.
1671

1672 Under this policy, samples from one lot are tested. Each unit subjected to one or more tests that
1673 compromise the integrity of the primary container-closure is only tested at a single time point
1674 (i.e., not at additional time points). If a single unit is to be used for multiple discrete tests to
1675 minimize destructive testing, the unit dosage is subdivided into multiple aliquots that are not held
1676 longer than the time to complete the testing (typically not longer than 48-72 hours) and the
1677 aliquots are placed into appropriate testing containers (e.g., high performance liquid
1678 chromatography vials or sample tubes) that protect the sample from being compromised (e.g.,
1679 from exposure to air, light, evaporation).
1680

1681 *I. Non-sterile*

1682 a. Nondestructive tests
1683
1684

1685 The following test is conducted:
1686

- 1687 • Appearance.
1688

1689 b. Destructive chemical tests
1690

1691 The tests to be conducted include:
1692

- 1693 • pH, if applicable (e.g., for aqueous formulations).
1694 • Assay.⁵³
1695 • Appropriate specifications.
1696

⁵³ See note 31.

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1697 c. Microbiological tests, if water activity >0.6

1698

1699 The tests to be conducted include:

1700

1701 • Antimicrobial effectiveness testing/preservative content testing at expiry.

1702 • Microbial enumeration⁵⁴ (USP General Chapter <61>).

1703 • Test for specified organisms⁵⁵ (USP General Chapter <62>).

1704

1705 2. *Sterile*

1706

1707 a. Nondestructive tests

1708

1709 The following tests are conducted:

1710

1711 • Appearance.

1712 • Color and clarity.

1713 • Visible particulates.

1714

1715 b. Destructive chemical tests

1716

1717 The tests to be conducted include:

1718

1719 • pH, if applicable (e.g., for aqueous formulations).

1720 • Assay.⁵⁶

1721 • Subvisible particles (10µm–100µm).⁵⁷

1722

1723 c. Sterility or container-closure integrity tests

1724

1725 To confirm that sterility is maintained over the proposed BUD, container-closure integrity testing
1726 (such as described in USP General Chapter <1207>) or a sterility test (see USP General Chapter
1727 <71>) is conducted. When performed, container-closure integrity testing is conducted on a
1728 number of units that is suitable for the chosen test method.

1729

D. Bracketing

1730

1731 Use of bracketing in stability studies allows for more streamlined evaluation of drug products for
1732 which there are multiple strengths or volume presentations produced. Bracketing assumes that
1733 the stability of intermediate strengths (or intermediate fill volumes) is adequately represented by
1734

⁵⁴ See, for example, USP General Chapter <1111>.

⁵⁵ Ibid.

⁵⁶ See note 31.

⁵⁷ Applicable only to intrathecal, intravenous, intra-arterial, ophthalmic, intramuscular, sterile otic, and subcutaneous preparations.

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1735 the extremes tested.⁵⁸ For multiple drug products to be eligible for bracketing stability studies,
1736 the candidate formulations should vary only in strength (or concentration) or fill volume.
1737 Although individual excipient amounts may vary, all excipients (in worst-case amounts) should
1738 be in all bracketed formulations. Proportional formulations are not required. The same container-
1739 closure system must be used (§ 211.166). If three or more strengths, concentrations, or volume
1740 presentations exist, intermediate cases for stability studies as follows may reflect an appropriate
1741 use of bracketing:

- 1742
- 1743 • If 3 or 4 drug product strengths, concentrations, or volume presentations are produced,
1744 test the high and low extremes (e.g., if available strengths include 2.0 mg/mL, 3.5
1745 mg/mL, 5.0 mg/mL, and 10.0 mg/mL, test 2.0 mg/mL and 10.0 mg/mL).
 - 1746
 - 1747 • If 5-10 drug product strengths, concentrations, or volume presentations are produced, test
1748 the high and low extremes and 1 intermediate case.
 - 1749
 - 1750 • If more than 10 drug product strengths, concentrations, or volume presentations are
1751 produced, test the high and low extremes and 2 intermediate cases.

1752

1753 It is critical that determination of the extremes be done with care. For example, with respect to
1754 volume fill, the appropriate extremes are not necessarily always the highest and lowest
1755 fluid volume fills. Rather, the head space-to-fluid volume ratio may better represent the
1756 appropriate extreme depending on the container volume used in the various presentations.

1757

1758 Bracketing as described in this section does not apply to microbial testing of sterility, endotoxins,
1759 or bioburden. Bracketing may be appropriate for water activity testing and antimicrobial
1760 effectiveness testing when used in conjunction with a preservative content testing strategy.

⁵⁸ See ICH guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products* for more information on bracketing and matrixing.