

Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact Sara Rothman (CDER) at 301-796-3110 or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-8010.

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

**January 2017
Compounding and Related Documents
Revision 1**

Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application Guidance for Industry

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Center for Biologics Evaluation and Research

Food and Drug Administration

10903 New Hampshire Ave., Building 71, Room 3128

Silver Spring, MD 20993

Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov

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1 **Guidance for Industry¹**
2 **Mixing, Diluting, or Repackaging Biological Products Outside the**
3 **Scope of an Approved Biologics License Application**
4

5
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
7 Administration (FDA) on this topic. It does not create any rights for or on any person and is not binding
8 on FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
9 the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff
10 responsible for this guidance.
11

12
13 **I. INTRODUCTION AND SCOPE**
14

15 This guidance sets forth FDA's policy regarding the mixing,² diluting, and repackaging³ of
16 certain types of biological products that have been licensed under section 351 of the Public
17 Health Service Act (PHS Act) when such activities are not within the scope of the product's
18 approved biologics license application (BLA) as described in the approved labeling for the
19 product. This guidance describes the conditions under which FDA does not intend to take action
20 for violations of section 351 of the PHS Act and section 502(f)(1), section 582, and where
21 specified, section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when
22 a state-licensed pharmacy, a Federal facility, or an outsourcing facility⁴ dilutes, mixes or
23 repackages certain biological products outside the scope of an approved BLA.
24

25 This guidance **does not address** the following:

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

² For purposes of this guidance, mixing means combining an FDA-licensed biological product with one or more ingredients.

³ For purposes of this guidance, repackaging means taking a licensed biological product from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product. As used in this guidance, the terms mixing, diluting, and repackaging describe distinct sets of activities with respect to a biological product.

⁴ *Outsourcing facility* refers to a facility that meets the definition of an outsourcing facility under section 503B(d)(4) of the FD&C Act. See FDA's guidance, "*Guidance for Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act.*"

All FDA guidances are available on the Agency's guidance website at <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>. FDA updates guidances regularly. To ensure that you have the most recent version, please check this web page.

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- 26 • Biological products not subject to licensure under section 351 of the PHS Act (i.e.,
27 biological products for which a marketing application could properly be submitted under
28 section 505 of the FD&C Act (see section 7002(e) of the Affordable Care Act)).⁵
29 • Radioactive biological products. It is the Agency’s understanding that pharmacists do
30 not manipulate radioactive biological products outside the scope of the product’s
31 approved labeling.
32 • Mixing, diluting, or repackaging biological products (other than allergenic extracts) by
33 entities that are not state-licensed pharmacies, Federal facilities, or outsourcing facilities
34 (e.g., repackers registered with FDA under section 510 of the FD&C Act); and
35 preparation of allergenic extracts by entities that are not state-licensed pharmacies,
36 Federal facilities, outsourcing facilities, or physicians (see additional information in
37 section III.A. of this draft guidance document).
38 • Removing a biological product from the original container at the point of care (e.g.,
39 patient’s bedside) for immediate administration to a single patient after receipt of a valid
40 patient-specific prescription or order for that patient (e.g., drawing up a syringe to
41 administer directly to the patient). FDA does not consider this to be “repackaging,” for
42 purposes of this guidance document.
43 • Diluting or mixing a biological product at the point of care for immediate administration
44 to a single patient after receipt of a valid patient-specific prescription or order for that
45 patient (e.g., diluting or mixing into a syringe to administer directly to the patient).
46 • Mixing, diluting, or repackaging a licensed biological product when the product is being
47 mixed, diluted, or repackaged in accordance with the approved BLA as described in the
48 approved labeling for the product. FDA considers this to be an approved manipulation of
49 the product.
50 • Mixing, diluting, or repackaging of blood and blood components for transfusion,⁶
51 vaccines, cell therapy products, or gene therapy products. The guidance does not alter
52 FDA’s existing approach to regulating the collection and processing of blood and blood
53 components for transfusion. In addition, FDA intends to consider regulatory action if
54 licensed vaccines, cell therapy products, and gene therapy products are subject to
55 additional manufacturing, including mixing, diluting, or repackaging, in ways not
56 specified in the product’s approved BLA as described in the approved labeling for the
57 product.
58 • Investigational new drugs being studied under an investigational new drug application.
59 This guidance does not alter FDA’s existing approach to regulating investigational new
60 drugs.

61
62 As stated above, this guidance does not address the mixing, diluting, or repackaging of a
63 biological product for which a marketing application could properly be submitted under section
64 505 of the FD&C Act (see section 7002(e) of the Affordable Care Act). Accordingly, the term

⁵ The repackaging of biological products approved under section 505 of the FD&C Act is addressed in a separate guidance, “*Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities.*”

⁶ This guidance does apply to licensed biological products that are plasma derived products, including recombinant and transgenic versions of plasma derivatives that are mixed, diluted, or repackaged outside the scope of an approved BLA.

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65 “*biological product*” as used in this guidance does not include products for which a marketing
66 application can be or has been submitted under section 505 of the FD&C Act.

67
68 Section II of this guidance provides background on biological products and the legal framework
69 for FDA’s regulation of these products, and explains that sections 503A and 503B of the FD&C
70 Act do not provide exemptions for mixing, diluting, or repackaging of biological products.
71 Section III describes FDA’s policy on mixing, diluting, or repackaging of certain licensed
72 biological products that is not within the scope of the product’s approved BLA as described in
73 the approved labeling for the product.

74
75 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
76 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
77 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
78 the word *should* in Agency guidances means that something is suggested or recommended, but
79 not required.

80 81 **II. BACKGROUND**

82 83 **A. Biological Products**

84
85 The term “biological product” is defined in section 351(i)(1) of the PHS Act to mean:

86
87 a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or
88 derivative, allergenic product, protein (except any chemically synthesized
89 polypeptide), or analogous product, or arsphenamine or derivative of
90 arsphenamine (or any other trivalent organic arsenic compound), applicable to
91 the prevention, treatment, or cure of a disease or condition of human beings.

92
93 Biological products can be complex chains or combinations of sugars, amino acids, or nucleic
94 acids, or living entities such as cells and cellular therapies. Biological products include
95 therapeutic proteins, monoclonal antibodies, allergenic extracts, blood and blood derivatives, cell
96 therapy products, gene therapy products, preventive vaccines, and therapeutic vaccines.
97 Generally, biological products have a complex set of structural features (e.g., amino acid
98 sequence, glycosylation, folding) essential to their intended effect, and are very sensitive to
99 changes to their manufacturing process, including, but not limited to, any manipulation outside
100 of their approved container-closure systems. In addition, many biological products are
101 particularly sensitive to storage and handling conditions and can break down or aggregate if
102 exposed to heat and/or light, if dropped, or if shaken during storage and handling. Accordingly,
103 diluting or mixing a biological product with other components, or repackaging a biological
104 product by removing it from its approved container-closure system and transferring it to another
105 container-closure system, is, in the absence of manufacturing controls, highly likely to affect the
106 safety and/or effectiveness of the biological product. Biological products are also particularly
107 susceptible to microbial proliferation in a short period of time if contaminated.

108
109 Nevertheless, certain licensed biological products are sometimes mixed or diluted in a way not
110 described in the approved labeling for the product to meet the needs of a specific patient. For
111 example, for some biological products there is no licensed pediatric strength and/or dosage form,

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112 so the product is diluted for use in pediatric patients. In addition, there may be certain
113 circumstances where a person would repackage a licensed biological product by removing it
114 from its original container and placing it into a different container(s), in a manner that is not
115 within the scope of the approved BLA as described in the approved labeling for the product.
116 Like other drugs, biological products are sometimes repackaged for various reasons including for
117 pediatric or ophthalmic use. For example, a pediatric dialysis unit may repackage a larger
118 quantity of a product into smaller aliquots so that the optimal dose may be administered to each
119 pediatric dialysis patient being treated at that particular time.

120
121 Repackaging a drug or biological product could change its characteristics in ways that have not
122 been evaluated during the approval process and that could affect the safety and effectiveness of
123 the product. Improper repackaging of drugs and biological products can cause serious adverse
124 events. Of particular concern is the repackaging of sterile drugs, which are susceptible to
125 contamination and degradation. For example, failure to properly repackage a sterile drug (such
126 as a biological product) under appropriate aseptic conditions could introduce contaminants that
127 could cause serious patient injury or death. Repackaging practices that conflict with approved
128 product labeling have led to product degradation resulting in adverse events associated with
129 impurities in the product or lack of efficacy because the active ingredient has deteriorated. These
130 risks are often even more acute for biological products due to their complex composition and
131 sensitivity to variations in storage and handling conditions.

132
133 Cell and gene therapy products often contain viable cells or intact/active viral vectors. The
134 manufacturing process for these products is complex and includes multiple controls to assure the
135 safety, purity, and potency of the product. Many cell therapy products are cryopreserved, and
136 the procedures for thawing and handling in preparation for administration described in the
137 approved labeling must be followed to maintain the safety and effectiveness of the product. In
138 addition, because these products are frequently implanted or administered intravenously and are
139 not typically amenable to terminal sterilization, their microbiological safety is dependent largely
140 on facility design, aseptic technique, and manufacturing protocols that are best controlled by
141 robust quality systems.

142
143 Vaccines are manufactured using biological systems and supplied by manufacturers in single
144 dose or multi-dose presentations. Unlike most other drugs and biological products, vaccines are
145 administered to healthy individuals, including infants, to prevent disease. Vaccines may contain
146 live attenuated organisms, inactivated organisms, or components of bacteria or viruses such as
147 polysaccharides, inactivated toxins, or purified proteins. The manufacturing process for vaccines
148 is complex and includes multiple controls to assure safety and effectiveness. Each single dose of
149 a vaccine is formulated to deliver the correct quantity of active ingredient(s) to the recipient.

150
151 The policies in this guidance do not cover cell therapy products, gene therapy products, and
152 vaccines, because of the particularly sensitive nature of these products as described above.

153
154 The policies in this guidance also do not cover or alter FDA's existing approach to regulating the
155 collection and processing of blood and blood components for transfusion. These activities are
156 currently conducted in FDA licensed or registered blood collection establishments and in
157 hospital-based transfusion services regulated in part by the Centers for Medicare and Medicaid

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158 Services under the Clinical Laboratory Improvement Amendments of 1988. In all instances, the
159 collection and processing of blood and blood components for transfusion is already subject to
160 current good manufacturing practice (CGMP) requirements under the existing statutory and
161 regulatory framework for blood and blood components and will not be subject to the policies
162 described here.

163

B. Legal Framework for FDA’s Regulation of Biological Products

164

165
166 Section 351(a)(1) of the PHS Act prohibits the introduction into interstate commerce of any
167 biological product unless “a biologics license...is in effect for the biological product.” For FDA
168 to approve a BLA, the BLA must contain data to demonstrate that the biological product is safe,
169 pure, and potent and that the facility in which the biological product will be manufactured,
170 processed, packed, or held meets standards designed to ensure that the biological product
171 continues to be safe, pure, and potent. Because manufacturing controls are so important to
172 ensuring the safety and effectiveness of biological products, FDA licensing of a biological
173 product is based, in part, on an extensive review of chemistry and manufacturing controls data
174 submitted by the applicant. This includes a thorough evaluation of the raw materials, drug
175 substance, and drug product to ensure consistency in manufacturing and continued safety and
176 effectiveness. In addition, other data are submitted and reviewed (e.g., stability and
177 compatibility testing results) to establish the storage and handling conditions appropriate to
178 ensure the safety, purity, and potency of the biological product.

179

180 A biological product that is mixed, diluted, or repackaged outside the scope of an approved BLA
181 is an *unlicensed biological product* under section 351 of the PHS Act. For example, if a licensed
182 biological product is diluted or mixed with components other than those described in the
183 approved labeling for the product, or if it is removed from its original container-closure system
184 and placed in a new container-closure system that is not described in the approved labeling for
185 the product, these additional manufacturing steps would create a new, unlicensed biological
186 product. To be legally marketed, the new biological product would have to be licensed on the
187 basis of an approved BLA that includes, among other things, chemistry and manufacturing
188 controls data.

189

C. Sections 503A and 503B of the FD&C Act Do Not Exempt Biological Products from the Premarket Approval Requirements of the PHS Act or from Provisions of the FD&C Act

190

191
192
193
194 Section 503A of the FD&C Act exempts compounded drugs from sections 505 (concerning new
195 drug approval of human drugs products), 502(f)(1) (concerning labeling of drug products with
196 adequate directions for use), and 501(a)(2)(B) (concerning CGMP) of the FD&C Act provided
197 that certain conditions are met, including that the drug is compounded pursuant to a prescription
198 for an individually-identified patient from a licensed practitioner.

199

200 The Drug Quality and Security Act added a new section 503B to the FD&C Act. Under section
201 503B(b) of the FD&C Act, a compounder can register as an outsourcing facility with FDA.

202 Drug products compounded under the direct supervision of a licensed pharmacist in an
203 outsourcing facility can qualify for exemptions from the FDA approval requirements in section

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204 505 of the FD&C Act and the requirement to label drug products with adequate directions for use
205 under section 502(f)(1) of the FD&C Act if the conditions in section 503B are met. Drugs
206 compounded in outsourcing facilities are not exempt from the CGMP requirements of section
207 501(a)(2)(B).
208

209 Although sections 503A and 503B provide an exemption for certain compounded drugs from the
210 requirement to obtain premarket approval under section 505 of the FD&C Act, they do not
211 provide an exemption from the requirement to obtain premarket approval under section 351 of
212 the PHS Act. Manufacturers of biological products must obtain an approved license under
213 section 351(a) or (k) of the PHS Act. Thus, for purposes of sections 503A and 503B, a *drug*
214 does not include any biological product that is subject to licensure under section 351 of the PHS
215 Act. Accordingly, such biological products are not eligible for the exemptions for compounded
216 drugs under sections 503A and 503B of the FD&C Act. In other words, the FD&C Act does not
217 provide a legal pathway for marketing biological products that have been prepared outside the
218 scope of an approved BLA.
219

220 III. POLICY

221
222 Because biological products are sometimes mixed, diluted, or repackaged in ways not addressed
223 in labeling approved for the product under section 351 of the PHS Act, but do not qualify for the
224 exemptions in sections 503A or 503B of the FD&C Act, FDA has developed this guidance to
225 explain the conditions under which FDA does not intend to take action when certain biological
226 products are mixed, diluted, or repackaged in a manner not described in their approved labeling.
227

228 A. General Conditions

229
230 This guidance addresses the mixing, diluting, or repackaging of a licensed biological product, not
231 a biological product licensed for further manufacturing use only, or a bulk drug substance. The
232 policies expressed in this guidance do not extend to any person or entity that mixes, dilutes, or
233 repackages a biological product from any other starting material. For example, a licensed
234 biological product mixed with a bulk drug substance would not be subject to the policies in this
235 guidance. Consistent with section 351 of the PHS Act, an entity seeking to mix, dilute, or
236 repackage a biological product licensed for further manufacturing use only, or a bulk drug
237 substance, or to mix a licensed biological product with a bulk drug substance, must first submit a
238 BLA and obtain a license for the product.
239

240 Furthermore, the policies expressed in this guidance apply only to the mixing, diluting, or
241 repackaging of certain licensed biological products, in accordance with the conditions specified
242 in section III of this guidance. Except as described in section III, the Agency intends to consider
243 regulatory action if a licensed biological product is subject to additional manufacturing,
244 including mixing, diluting, or repackaging, outside of the conditions specified in the approved
245 labeling for the licensed product.
246

247 As described in section II.B, a biological product that is mixed, diluted, or repackaged outside
248 the scope of an approved BLA is an unlicensed biological product under section 351 of the PHS
249 Act. To be legally marketed, the new biological product would have to be the subject of an

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250 approved BLA and be made in accordance with all other requirements applicable to biological
251 products, including CGMP requirements.

252

B. Mixing, Diluting, or Repackaging Licensed Biological Products⁷

254

255 FDA does not intend to take action for violations of section 351 of the PHS Act or sections
256 502(f)(1) or 582 of the FD&C Act if a state-licensed pharmacy, a Federal facility, or an
257 outsourcing facility mixes, dilutes, or repackages a biological product in accordance with the
258 conditions described below, and any applicable requirements.⁸ In addition, FDA does not intend
259 to take action for violations of section 501(a)(2)(B) of the FD&C Act when a state-licensed
260 pharmacy or a Federal facility mixes, dilutes, or repackages a biological product in accordance
261 with the conditions described below, and any applicable requirements.⁹

262

263 The conditions referred to in the preceding paragraph are as follows:

264

265 1. The biological product that is mixed, diluted, or repackaged is an FDA-licensed biological
266 product, not a biological product licensed for further manufacturing use only or a bulk drug
267 substance. In addition, a licensed biological product is not combined with a biological
268 product licensed for further manufacturing use only, or with a bulk drug substance.

269

270 2. The biological product is mixed, diluted, or repackaged in a State-licensed pharmacy, a
271 Federal facility, or an outsourcing facility.

272

273 3. The biological product is mixed, diluted, or repackaged by or under the direct supervision of
274 a licensed pharmacist.

275

276 4. If the biological product is mixed, diluted, or repackaged in a State-licensed pharmacy or a
277 Federal facility, it is distributed¹⁰ only after the receipt of a valid prescription for an
278 identified, individual patient (including a written order or notation in a patient's chart in a
279 health care setting) directly from the prescribing practitioner or patient. This condition does
280 not apply to biological products mixed, diluted, or repacked in an outsourcing facility.¹¹

⁷ Section III.B does not apply to allergenic extracts. For FDA's policy concerning the preparation of prescription sets for subcutaneous immunotherapy, refer to section III.C of this guidance.

⁸ Applicable requirements include, for example, the requirement that manufacturers not adulterate a biological product by preparing, packing, or holding the drug under insanitary conditions. See section 501(a)(2)(A) of the FD&C Act.

⁹ For purposes of the applicability of the conditions in this guidance document, references to a State-licensed pharmacy or Federal facility do not include a facility that is registered as an outsourcing facility under section 503B of the FD&C Act.

¹⁰ *Distributed* means that the mixed, diluted, or repackaged biological product has left the facility in which it was mixed, diluted, or repackaged.

¹¹ Note, however, that drugs produced by outsourcing facilities, including drugs that are also biological products, remain subject to the requirements in section 503(b) of the FD&C Act. Therefore, a prescription drug, including a biological product, cannot be dispensed to a patient without a prescription.

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- 281
282 5. Except as provided below, the biological product is mixed, diluted, or repackaged, and stored
283 and shipped in a way that does not conflict with the approved labeling for the licensed
284 biological product.¹²
285
286 ○ For a biological product packaged in a single-dose vial that is mixed, diluted, or
287 repackaged, the biological product is mixed, diluted, or repackaged in a way that does
288 not conflict with the approved labeling, except for the statements designating the
289 product as a single-dose or single-use product, and related language (e.g., discard
290 remaining contents).¹³
291
292 ○ For a biological product repackaged by an outsourcing facility that assigns a beyond-
293 use-date (BUD) to the product in accordance with Appendix A of this guidance, the
294 biological product is repackaged in a way that does not conflict with the approved
295 labeling, except for the statements regarding the product’s labeled in-use time (and
296 any statements designating the product as a single-dose or single-use product, as
297 described immediately above).
298
299 6. The container into which the biological product is mixed, diluted, or repackaged is suitable
300 for storage of the biological product through its BUD.¹⁴
301
302 7. If the labeling for the licensed biological product includes storage and/or handling
303 instructions (e.g., protect from light, do not freeze, keep at specified storage temperature), the
304 labeling for the biological product that is mixed, diluted, or repackaged specifies the same
305 storage conditions.
306
307 8. If the biological product is mixed, diluted, or repackaged in a State-licensed pharmacy or
308 Federal facility, the duration of time from beginning (i.e., when the original biological
309 product to be repackaged or to be used for mixing or diluting is punctured or otherwise
310 opened) to end of mixing, diluting, or repackaging is no more than four hours.
311

¹² For example, if the approved labeling for the licensed biological product contains instructions for handling or storage of the product, the mixing, diluting, or repackaging is done in accordance with those instructions. Otherwise, it would be considered to be in conflict with the approved labeling for the licensed biological product.

¹³ For example, Avastin (bevacizumab) is packaged in a single-dose vial. This condition could be satisfied even if Avastin is repackaged into multiple single dose syringes despite the fact that the label of the approved product states, “Single-use vial...Discard unused portion.” However, this condition would not be satisfied if Avastin is mixed, diluted, or repackaged in a manner that conflicts with other language in the approved labeling (e.g., regarding the appropriate diluent and storage conditions).

¹⁴ For example, for State-licensed pharmacies and Federal facilities, information provided by the container’s manufacturer could indicate that the container is suitable for biological products mixed, diluted, or repackaged in accordance with this condition. For outsourcing facilities, CGMP requirements address container suitability and drug stability.

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- 312 9. As described in section II of this guidance, biological products are very susceptible to
313 product quality concerns when mixed, diluted, or repackaged. For example, because
314 biological products provide a rich media for microbial growth, they are particularly
315 susceptible to microbial proliferation over time, if contaminated. Therefore, the mixed,
316 diluted, or repackaged biological product is given a BUD¹⁵ that is not longer than the
317 applicable BUD specified below. The BUD timeframes in this condition begin from the time
318 in which the container of the original biological product to be repackaged or to be used for
319 mixing or diluting is punctured or otherwise opened.
320
- 321 a. If the biological product is mixed, diluted, or repackaged by a State-licensed
322 pharmacy or a Federal facility, it is given a BUD that
323
- 324 - does not exceed the time within which the opened product is to be used as
325 specified in the approved labeling of the licensed biological product for any
326 manipulation (“in-use time”) or the expiration date of the biological product being
327 mixed, diluted, or repackaged, whichever is shorter;¹⁶ or
 - 328 - if the approved labeling does not specify an in-use time and the product is
329 refrigerated, is not longer than 24 hours, or the expiration date of the biological
330 product being mixed, diluted, or repackaged, whichever is shorter.
- 331 b. Regarding outsourcing facilities:
332
- 333 i. If the biological product is mixed or diluted, it is given a BUD that
334
- 335 - does not exceed the in-use time specified in the approved labeling of
336 the biological product or the expiration date of the biological product
337 being mixed or diluted, whichever is shorter; or
 - 338 - if the approved labeling does not specify an in-use time and the
339 product is refrigerated, is not longer than 24 hours, or the expiration
340 date of the biological product being mixed or diluted, whichever is
341 shorter.

¹⁵ The BUD is the date beyond which a biological product should not be used.

¹⁶ For example, the approved labeling for Avastin states that “diluted Avastin solutions may be stored at 2-8°C (36-46°F) for up to 8 hours. Store in the original carton until time of use.” Therefore, assigning a BUD to repackaged Avastin of 8 hours, provided that the repackaged Avastin is stored at 2-8°C, would be consistent with conditions 5 and 9. Although the approved labeling refers to diluted Avastin, FDA believes that this BUD is also appropriate for repackaged Avastin because of the potential for time-related product quality problems at a longer BUD. For example, FDA is concerned about the potential for microbial proliferation if Avastin is inadvertently contaminated while being repackaged, particularly because condition 9.a applies to facilities that likely do not comply with CGMP requirements. Furthermore, the approved labeling for Avastin states, “store in the original carton until time of use,” which means that it should be stored in the original carton until it is opened and diluted. At a longer BUD, the Avastin could interact with the container into which it is repackaged, which may result in degradation.

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- 342 ii. If the biological product is repackaged by an outsourcing facility that does not
343 perform the testing described in Appendix A for that product, it is given a
344 BUD that¹⁷
- 345 - does not exceed the in-use time specified in the approved labeling of
346 the biological product or the expiration date of the biological product
347 being repackaged, whichever is shorter; or
 - 348 - if the approved labeling does not specify an in-use time and the
349 product is refrigerated, is not longer than 24 hours or the expiration
350 date of the biological product being repackaged, whichever is shorter.
- 351 iii. If the biological product is repackaged by an outsourcing facility that
352 performs the testing described in Appendix A for that product, the BUD is
353 assigned based on a stability program conducted in accordance with Appendix
354 A for each container closure system to be used, does not exceed the expiration
355 date of the biological product being repackaged, and the outsourcing facility
356 maintains records of the testing performed in accordance with Appendix A.
357
- 358 10. The biological product is mixed, diluted, or repackaged in accordance with the following:
359
- 360 a. If the biological product is mixed, diluted, or repackaged in a State-licensed pharmacy or
361 a Federal facility, it is done in accordance with the United States Pharmacopeia (USP)
362 Chapter <797>¹⁸, except the BUD is as specified in condition 9.
363
 - 364 b. If the biological product is mixed, diluted, or repackaged in an outsourcing facility, it is
365 done in accordance with CGMP requirements, except the BUD is as specified in
366 condition 9.¹⁹
367
- 368 For purposes of condition 10.b, FDA intends to apply the policies described in the
369 guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug
370 Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*, except for
371 the following:
372

¹⁷ See condition 5, which states that the biological product is mixed, diluted, or repackaged in a way that does not conflict with the approved labeling for the licensed biological product. This means, for example, that the repackaged biological product is stored in accordance with labeled storage conditions, including temperature.

¹⁸ For purposes of this condition, reference to the USP Chapter <797> means USP 39-NF 34 (2016). USP has proposed revisions to USP Chapter <797> that would affect biological products. Once USP has considered the public comments that it received and finalized the revised Chapter <797>, FDA intends to evaluate whether the reference in condition 10.a should be revised.

¹⁹ FDA does not intend to take action against an outsourcing facility for assigning a BUD to be used as an expiration date in lieu of conducting stability studies required under 21 CFR part 211 if the BUD is assigned in accordance with condition 9.b or 9.c.

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- 373 ○ For FDA’s policies concerning expiration dating/BUDs and stability testing for
374 biological products mixed, diluted, or repackaged by outsourcing facilities, see
375 condition 9 and Appendix A of this guidance.
376
- 377 ○ For FDA’s policies concerning release testing requirements for biological products
378 mixed, diluted, or repackaged by outsourcing facilities, see Appendix B of this
379 guidance. Appendix B describes the circumstances under which FDA does not
380 intend to take action against outsourcing facilities for failing to conduct batch
381 release testing of mixed, diluted, or repackaged biological products required under
382 21 CFR part 211.
383
- 384 11. The biological product is not sold or transferred by an entity other than the entity that mixed,
385 diluted, or repackaged the biological product. For purposes of this condition, a sale or
386 transfer does not include administration of a biological product in a health care setting.
387
- 388 12. The mixed, diluted, or repackaged biological product is distributed only in states in which the
389 facility mixing, diluting, or repackaging the biological product meets all applicable state
390 requirements.
391
- 392 13. If the biological product is mixed, diluted, or repackaged by an outsourcing facility:
393
- 394 a. The label on the immediate container (primary packaging, e.g., the syringe) of the
395 mixed, diluted, or repackaged biological product includes the following:
- 396 i. The statement “This biological product was mixed/diluted by [name of
397 outsourcing facility],” or “This biological product was repackaged by [name
398 of outsourcing facility],” whichever statement is appropriate
399 ii. The address and phone number of the outsourcing facility that mixed, diluted,
400 or repackaged the biological product
401 iii. The proper name of the licensed biological product that was mixed, diluted, or
402 repackaged
403 iv. The lot or batch number assigned by the outsourcing facility for the mixed,
404 diluted, or repackaged biological product
405 v. The dosage form and strength of the mixed, diluted, or repackaged biological
406 product
407 vi. A statement of either the quantity or the volume of the mixed, diluted, or
408 repackaged biological product, whichever is appropriate
409 vii. The date the biological product was mixed, diluted, or repackaged
410 viii. The BUD of the mixed, diluted, or repackaged biological product
411 ix. Storage and handling instructions for the mixed, diluted, or repackaged
412 biological product
413 x. The National Drug Code (NDC) number of the mixed, diluted, or repackaged
414 biological product, if available²⁰

²⁰ The NDC number of the original licensed biological product should not be placed on the mixed, diluted, or repackaged biological product.

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- 415 xi. The statement “Not for resale,” and, if the biological product is distributed by
416 an outsourcing facility other than pursuant to a prescription for an individual
417 identified patient, the statement “Office Use Only”
- 418 xii. If included on the label of the FDA-licensed biological product from which
419 the biological product is being mixed, diluted, or repackaged, a list of the
420 active and inactive ingredients in the FDA-licensed biological product, unless
421 such information is included on the label for the container from which the
422 individual units of the mixed, diluted, or repackaged biological product are
423 removed, as described below in 13.b.i; and if the biological product is mixed
424 or diluted, a list of any ingredients that appear in the mixed or diluted product
425 in addition to those ingredients that are on the label of the original FDA-
426 licensed biological product.
- 427
- 428 b. The label on the container from which the individual units are removed for
429 administration (secondary packaging, e.g., the bag, box, or other package in which the
430 mixed, diluted, or repackaged biological products are distributed) includes:
- 431 i. The active and inactive ingredients included on the label of the original FDA-
432 licensed biological product, if the immediate product label is too small to
433 include this information
- 434 ii. Directions for use, including, as appropriate, dosage and administration
- 435 iii. The following information to facilitate adverse event reporting:
436 www.fda.gov/medwatch and 1-800-FDA-1088.
- 437
- 438 c. The mixed, diluted, or repackaged biological product is included on a report
439 submitted to FDA each June and December identifying the drug products made by the
440 outsourcing facility during the previous 6-month period, including: the active
441 ingredient; the source of the active ingredient; NDC number of the source ingredient,
442 if available; strength of the active ingredient per unit; the dosage form and route of
443 administration; the package description; the number of individual units mixed,
444 diluted, or repackaged²¹; and the NDC number of the mixed, diluted, or repackaged
445 biological product, if assigned.²²
- 446
- 447 d. The outsourcing facility reports serious adverse events to FDA that are associated
448 with its mixed, diluted, or repackaged biological products.²³

²¹ Currently, FDA’s electronic drug reporting system is not configured to accept additional information that is specific to biological products, such as license number. In the future, FDA intends to modify the system to accept this information.

²² FDA has issued a guidance for industry, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. This guidance describes how outsourcing facilities submit drug product reports to FDA. Although that guidance addresses reporting of compounded drug products, outsourcing facilities should follow the same procedure to electronically report the biological products they mixed, diluted, or repackaged.

²³ FDA has issued a guidance for industry, *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, which describes how outsourcing facilities submit adverse event reports to FDA and the content and format of the reports that they are required to submit. Although that guidance

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C. Licensed Allergenic Extracts for Subcutaneous Immunotherapy²⁴

FDA recognizes that there are circumstances in which licensed allergenic extracts would be mixed and diluted to provide subcutaneous immunotherapy to an individual patient, even though these allergenic extract combinations are not specified in the approved BLAs for the licensed biological products. Such combinations are commonly referred to as prescription sets.²⁵ For the purpose of this guidance a *prescription set* is defined as a vial or set of vials of premixed licensed standardized and non-standardized allergenic extracts for subcutaneous immunotherapy diluted with an appropriate diluent prepared according to instructions from a valid prescription (including a chart order in a health care setting) by a licensed physician for an individual patient.

FDA does not intend to take action for violations of section 351 of the PHS Act or sections 502(f)(1) or 582 of the FD&C Act if a physician, state-licensed pharmacy, Federal facility, or outsourcing facility prepares prescription sets of allergenic extracts in accordance with the conditions described below, and any applicable requirements.

In addition, FDA does not intend to take action for violations of section 501(a)(2)(B) of the FD&C Act when the prescription set is prepared by a physician, state-licensed pharmacy, or a Federal facility that is not registered with FDA as an outsourcing facility if the prescription set is prepared in accordance with the conditions described below, and any applicable requirements.

The conditions referred to in the preceding two paragraphs are as follows:

1. The prescription set is prepared from FDA-licensed allergenic extracts and appropriate diluents.
3. The prescription set is prepared in a physician’s office, state-licensed pharmacy, Federal facility, or outsourcing facility.
4. Each prescription set is distributed²⁶ only after the receipt of a valid prescription for an identified, individual patient (including a written order or notation in a patient’s chart in a health care setting) directly from the prescribing practitioner or patient.

addresses reporting of adverse events associated with compounded drug products, outsourcing facilities should follow the procedure described in that guidance to electronically report adverse events associated with the biological products they mixed, diluted, or repackaged.

²⁴ Allergenic extracts are subject to FDA’s BLA and investigational new drug application requirements. The policies described in this guidance only apply to allergenic extracts for subcutaneous immunotherapy; they do not apply to allergenic extracts for use in cutaneous diagnostic testing.

²⁵ Under 21 CFR 610.17, licensed biological products must not be combined with other licensed products, either therapeutic, prophylactic or diagnostic, except as covered by a license obtained for the combined product. All mixes of allergenic extracts that are not prescription sets must be the subject of an approved BLA, or have in effect an investigational new drug application.

²⁶ *Distributed* means that the prepared prescription set has left the facility in which it was prepared.

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483 5. The prescription set is prepared in a way that does not conflict with approved labeling of the
484 licensed biological products that are part of the prescription set.²⁷
485
486 6. The BUD for the prescription set is no later than the earliest expiration date of any allergenic
487 extract or any diluent that is part of the prescription set, and the BUD does not exceed one
488 year from the date the prescription set is mixed or diluted.²⁸
489
490 7. The prescription set is prepared in accordance with the following:
491
492 a. If the prescription set is prepared in a State-licensed pharmacy or Federal facility, or
493 in a physician's office, it is prepared in accordance with USP Chapter <797>²⁹,
494 except the BUD is as specified in condition 5.
495
496 b. If the prescription set is prepared in an outsourcing facility, it is prepared in
497 accordance with applicable CGMP requirements, except the BUD is as specified in
498 condition 5.
499
500 For purposes of condition 7.b, FDA intends to apply the policies described in the
501 guidance, *Current Good Manufacturing Practice — Interim Guidance for Human*
502 *Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*,
503 except for the following:
504
505 o For FDA's policies concerning expiration dating/BUDs and stability testing for
506 prescription sets prepared by outsourcing facilities, see condition 5 of this
507 guidance.
508
509 o For FDA's policies concerning release testing requirements for prescription sets
510 prepared by outsourcing facilities, see Appendix B of this guidance. Appendix
511 B describes the circumstances under which FDA does not intend to take action
512 against outsourcing facilities for failing to conduct batch release testing of
513 prescription sets.
514

²⁷ See note 17.

²⁸ FDA does not intend to take action against an outsourcing facility for assigning a BUD to be used as an expiration date in lieu of conducting stability studies required under 21 CFR part 211, if the outsourcing facility assigns a BUD in accordance with this condition.

²⁹ For purposes of this condition, the reference to the USP Chapter <797> means in USP 39-NF 34 (2016). USP has proposed revisions to USP Chapter <797> that would affect biological products. Once USP has evaluated the public comments that it received and finalized the revised Chapter <797>, FDA intends to consider whether condition 7 should refer to the updated chapter, or conditions should be adopted that are different than those included in final Chapter <797>.

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- 515 8. The prepared prescription set is not sold or transferred by an entity other than the entity that
516 prepared the prescription set. For purposes of this condition, a sale or transfer does not
517 include administration of a prescription set in a health care setting.
518
- 519 9. The prescription set is distributed only in states in which the facility preparing the
520 prescription set meets all applicable state requirements.
521
- 522 10. If the prescription set is prepared by an outsourcing facility:
523
- 524 a. The label on the immediate container(s) (primary packaging) of the prescription set
525 includes the following:
 - 526 i. The patient’s name as identified on the prescription or order
 - 527 ii. The statement “This prescription set was prepared by [name of outsourcing
528 facility]”
 - 529 iii. The address and phone number of the outsourcing facility that prepared the
530 prescription set
 - 531 iv. The identity of each allergenic extract in the prescription set, and the quantity
532 of each
 - 533 v. The dilution of each dilution vial
 - 534 vi. The lot or batch number of the prescription set
 - 535 vii. The date the prescription set was prepared
 - 536 viii. The BUD as the expiry date for the prescription set
 - 537 ix. Storage and handling instructions for the prescription set
 - 538 x. The statement “Not for resale”
 - 539
 - 540 b. The label of the container from which the individual units of the prescription set are
541 removed for administration (secondary packaging) includes the following information
542 to facilitate adverse event reporting: www.fda.gov/medwatch and 1-800-FDA-1088.
543
 - 544 c. Each prescription set also is accompanied by instructions for use.
545
 - 546 d. The prescription set is included in a report submitted to FDA each June and
547 December identifying the drug products made by the outsourcing facility during the
548 previous 6-month period, including: the active ingredient(s); source of the active
549 ingredient(s); NDC number of the source ingredient(s), if available; strength of the
550 active ingredient(s) per unit; the dosage form and route of administration; the package
551 description; the number of individual units produced; and the NDC number of the
552 final product, if assigned.³⁰
553

³⁰ FDA has issued a guidance for industry, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. This guidance describes how outsourcing facilities submit drug product reports to FDA. Although that guidance addresses reporting of compounded drug products, outsourcing facilities should follow the same procedure to electronically report the prescription sets that they prepared.

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554 e. The outsourcing facility reports serious adverse events to FDA that are associated
555 with its prescription sets.³¹
556

D. Establishment Registration and Drug Listing

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558 Under section 510(b)(1) of the FD&C Act, between October 1 and December 31 of each year,
559 every person who owns or operates any establishment in any State engaged in the manufacture,
560 preparation, propagation, compounding, or processing of a drug or drugs (including biological
561 products) is required to register with FDA, and under section 510(j) of the FD&C Act, every
562 person who registers with FDA under section 510(b) must list its drugs manufactured, prepared,
563 propagated, compounded, or processed for commercial distribution with the Agency. A drug is
564 misbranded under section 502(o) of the FD&C Act if it was manufactured, prepared, propagated,
565 compounded, or processed in an establishment that is not registered under section 510, or if it
566 was not included on a list required by section 510(j). Pharmacies that mix, dilute, or repackage
567 biological products may qualify for an exemption from registration and thus also not be required
568 to list their drugs with FDA. Specifically, under section 510(g)(1), the registration requirement
569 of section 510 does not apply to:
570

571
572 pharmacies which maintain establishments in conformance with any applicable local laws
573 regulating the practice of pharmacy and medicine and which are regularly engaged in
574 dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to
575 administer such drugs or devices to patients under the care of such practitioners in the
576 course of their professional practice, and which do not manufacture, prepare, propagate,
577 compound, or process drugs or devices for sale other than in the regular course of their
578 business of dispensing or selling drugs or devices at retail.
579

580 **With respect to entities that do not qualify for the exemptions from registration**
581 **under section 510 of the FD&C Act,³² FDA does not intend to take action**
582 **against outsourcing facilities for violations of section 502(o) of the FD&C Act**
583 **for failure to register and list under section 510 biological products that are**
584 **mixed, diluted, or repackaged in accordance with this guidance.³³**

³¹ FDA has issued a guidance for industry, *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, which describes how outsourcing facilities submit adverse event reports to FDA and the content and format of the reports that they are required to submit. Although that guidance addresses reporting of adverse events associated with compounded drug products, outsourcing facilities should follow the procedure described in that guidance to electronically report adverse events associated with the prescription sets they prepared.

³² See also, 21 CFR 207.10.

³³ Outsourcing facilities that mix, dilute, or repackage biological products under this guidance are registered with FDA under section 503B of the FD&C Act and report mixed, diluted, or repackaged biological products to FDA in accordance with condition 13.c in section III.B or, for licensed allergenic extracts for subcutaneous immunotherapy, condition 9.d in section III.C.

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Appendix A – Assigning a BUD for Repackaged Biological Products Based on Stability Testing³⁴

As noted above, outsourcing facilities are subject to CGMP requirements. For example, an outsourcing facility that repackages biological products must have a written stability testing program that includes³⁵:

- Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;
- Storage conditions for samples retained for testing;
- Stability-indicating test methods that are reliable, meaningful, and specific;
- Evaluation of samples of the biological product in the same container closure system as that in which the product is marketed.³⁶
- Testing of biological products for reconstitution at the time of dispensing (as directed in the labeling) as well as after reconstitution.

The initial time point for the tests described below is the time at which the outsourcing facility conducts this testing on the initial source material (i.e., licensed biological product) used for repackaging.

Stability testing is intended to confirm certain quality attributes of a repackaged biological product held under the labeled storage conditions for the duration of the BUD. To assign a BUD for a repackaged biological product beyond 24 hours³⁷ and remain eligible for the policies described in this guidance, the outsourcing facility would conduct a series of tests, described below. Samples evaluated for stability must be representative of the batch from which they were obtained (see 21 CFR 211.160 and 211.166). The data from each time point would be evaluated against specifications that the outsourcing facility established for the repackaged product prior to beginning the stability program. Specifications should be meaningful for the specific product being tested, and the outsourcing facility should have scientific justification for each specification.

After specifications have been established, the outsourcing facility would conduct the testing described below on one lot of a particular biological product in the container into which it will be repackaged to establish the BUD for that product, and then the outsourcing facility would

³⁴ Appendix A applies only to biological products repackaged by outsourcing facilities, and it does not apply to prescription sets of allergenic extracts. BUDs for biological products mixed, diluted, or repackaged by state-licensed pharmacies or Federal facilities that are not outsourcing facilities are addressed in section III.B.9, and BUDs for prescription sets of allergenic extracts are addressed in section III.C.6.

³⁵ See 21 CFR 211.166.

³⁶ For purposes of this guidance, the evaluation of samples of the biological product may be in the same container closure system as that in which the product is distributed.

³⁷ See condition III.B.9 of this guidance. Note that under this condition, the BUD does not exceed the expiration date of the licensed biological product being repackaged, even if the BUD is assigned on the basis of stability testing under this appendix.

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619 conduct these tests on one lot annually and whenever the formulation of the biological product
620 being repackaged or the container into which it is being repackaged may have changed.³⁸ In lieu
621 of performing the testing itself, the outsourcing facility may contract with a testing facility to
622 perform this testing.³⁹

623
624 When establishing the BUD for a repackaged biological product, if the data for any test does not
625 meet the established specifications, the BUD is limited to the time point at which all of the data
626 remained within specifications.⁴⁰ For this reason, FDA recommends testing at one or more
627 interim time points. If the data at the last time point do not confirm the stability of the product at
628 the desired BUD (e.g., some measurements fall outside of the established specifications), but the
629 data at the interim meet the established specifications, assigning a BUD equal to the interim time
630 point would be consistent with the policies in this guidance.

631
632 The stability studies are performed for each container-closure system to be used.

633
634 FDA does not intend to take action against an outsourcing facility for non-compliance with 21
635 CFR 211.166 when it repackages biological products in accordance with the conditions set forth
636 in this guidance provided that it conducts a stability program that includes, at minimum, the
637 following tests. The outsourcing facility conducts these tests at each time point, except where
638 specified:

640 1. Nondestructive Tests

641
642 The tests to be conducted include:

- 643
- 644 • Appearance
 - 645 • Color and clarity
 - 646 • Visible particulates
- 647

648 2. Destructive chemical tests

649
650 The tests to be conducted include:

³⁸ This is intended to assure that the product remains stable under labeled storage conditions for the duration of the BUD in the event of a change in the formulation of the biological product being repackaged or in the container into which it will be repackaged that the outsourcing facility is not aware of.

³⁹ When an outsourcing facility seeks the services of a contract facility to perform all or part of the testing of a biological product, the outsourcing facility's quality control unit is responsible for approving and rejecting biological products tested by the contractor, and the outsourcing facility is responsible for assuring the stability of the repackaged biological product. See 21 CFR 200.10(b) and 211.22(a). See also draft guidance for industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*; when finalized, this guidance will represent FDA's current thinking on this topic. We recommend that the testing facility be ISO 17025 accredited.

⁴⁰ If the outsourcing facility receives failing results, it decreases the BUD to the time point at which all data remained within specifications and notifies its customers who received the product of the failing results and provides an alternate date by which the product should be used or discarded.

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- Subvisible particles. (See e.g., USP Chapter <788> *Particulate Matter in Injections* or USP Chapter <789> *Particulate Matter for Ophthalmic Solutions*, as appropriate for the route of administration. When the repackaged biological product being tested amounts to less than 1 mL, the outsourcing facility may complete this test by pooling a minimum of 10 units of the product and increasing the volume with particle free water in accordance with USP Chapter <788>.)
 - Protein content. (See USP Chapter <1057> *Biotechnology-Derived Articles – Total Protein Assay*).
 - Product-related impurities including, at minimum, protein aggregation, size and charge variants.
 - Potency. (See *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (“ICH Q6B validated assay”) for developing a validated assay or purchasing a kit containing a validated assay. It is the outsourcing facility’s responsibility to select an appropriate kit and to demonstrate that it is using the kit properly and obtaining repeatable data.)

3. Sterility and container closure integrity tests

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- The outsourcing facility conducts a sterility test at the time when the product is repackaged. (See 21 CFR 610.12 and USP Chapter <71> *Sterility Tests*)⁴¹
 - The outsourcing facility conducts either a sterility test or a container closure integrity test (see USP Chapter <1207> *Sterile Product Packaging—Integrity Evaluation*) at additional time points.

4. Shipping

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The outsourcing facility ensures that the biological product remains stable and maintains appropriate package integrity during shipping. For example, the outsourcing facility ensures that the shipping temperature does not deviate from the recommended storage temperature range set forth in the approved product labeling for the licensed biological product.

⁴¹ Sterility testing should be conducted using USP General Chapter <71> *Sterility Tests*. Any other method used for sterility testing should be validated.

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687 **Appendix B –Release Testing for Biological Products Mixed, Diluted, or** 688 **Repackaged by Outsourcing Facilities** 689

690 21 CFR 211.165 and 211.167 require that finished drug products be tested to determine whether
691 they meet final product specifications before their release for distribution. 21 CFR 211.22
692 requires the establishment of a quality control unit, which is responsible for ensuring that the
693 finished drug product is not released until this testing is conducted and the results confirm that
694 the finished drug product meets specifications.
695

- 696 • FDA does not intend to take action against an outsourcing facility for failing to conduct
697 batch⁴² release testing under 21 CFR 211.165 and 211.167 for mixed, diluted, or
698 repackaged biological products that are assigned a BUD that does not exceed the in-use
699 time of the licensed biological product or 24 hours in accordance with condition III.B.9,
700 and that are mixed, diluted, or repackaged in accordance with all of the other conditions
701 of this guidance and any applicable requirements.
702
- 703 • FDA does not intend to take action against an outsourcing facility for failing to conduct
704 batch release testing under 21 CFR 211.165 and 211.167 for biological products that the
705 outsourcing facility repackaged in accordance with the conditions of this guidance, and
706 that are assigned a BUD in accordance with Appendix A, provided that the outsourcing
707 facility conducts the following release tests on each batch of biological products that it
708 has repackaged:
 - 709 • Sterility (the outsourcing facility *initiates* sterility testing before release)
 - 710 • Endotoxin⁴³
 - 711 • Color
 - 712 • Clarity
 - 713 • Visible particulates
 - 714 • Subvisible particulates
715
- 716 • FDA does not intend to take action against an outsourcing facility for failing to conduct
717 batch release testing under 21 CFR 211.165 and 211.167 for prescription sets that the
718 outsourcing facility prepared in accordance with the conditions described in this
719 guidance, provided that the outsourcing facility conducts the following release tests on
720 each prescription set (at minimum, the first vial) that it has prepared, and it receives
721 passing test results prior to distribution:
722

⁴² See definition of “batch” at 21 CFR 210.3(b)(2).

⁴³ For finished products repackaged from starting materials that are sterile and nonpyrogenic, endotoxin testing can be conducted on all starting materials (through testing of the starting materials, reliance on a statement of the limit met on a certificate of analysis, or where specified in an applicable USP monograph) or through testing of samples of the finished product. An outsourcing facility should not rely on the fact that a starting material is labeled nonpyrogenic to ensure that the finished product will meet the appropriate endotoxin limit because starting materials, including FDA-licensed products, may have been tested against different endotoxin limits, depending on the intended dose and the route of administration. See also the guidance for industry *Pyrogens and Endotoxin Testing: Questions and Answers*.

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 - 724
 - 725
 - 726
- Sterility
 - Color
 - Visible particulates