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

**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 2018
Compounding and Related Documents**

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Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION AND SCOPE

This guidance sets forth FDA's policy regarding the mixing,² diluting, and repackaging³ of certain types of biological products that have been licensed under section 351 of the Public Health Service Act (PHS Act) when such activities are not within the scope of the product's approved biologics license application (BLA) as described in the approved labeling for the product. This guidance describes the conditions under which FDA does not intend to take action for violations of section 351 of the PHS Act and section 502(f)(1), section 582, and, where specified, section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 352(f)(1), 21 U.S.C. 360eee-1, and 21 U.S.C. 351(a)(2)(B), respectively), when a state-licensed pharmacy, a federal facility, or an outsourcing facility⁴ dilutes, mixes, or repackages certain biological products outside the scope of an approved BLA.

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 FDA Office of Regulatory Affairs.

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 manipulating 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 (21 U.S.C. 353b(d)(4)). See guidance for industry *Guidance for Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (August 2015), available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434171.pdf>.

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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This guidance **does not** address the following:⁵

- Biological products not subject to licensure under section 351 of the PHS Act (i.e., biological products for which a marketing application could properly be submitted under section 505 of the FD&C Act (21 U.S.C. 355) (see section 7002(e) of the Affordable Care Act)).⁶
- Radioactive biological products. It is the Agency’s understanding that pharmacists do not manipulate radioactive biological products outside the scope of the product’s approved labeling.
- Mixing, diluting, or repackaging biological products (other than allergenic extracts) by entities that are not state-licensed pharmacies, federal facilities, or outsourcing facilities (e.g., repackers registered with FDA under section 510 of the FD&C Act (21 U.S.C. 360)); and preparation of allergenic extracts by entities that are not state-licensed pharmacies, federal facilities, outsourcing facilities, or physicians.
- Removing a biological product from the original container at the point of care (e.g., patient’s bedside) for immediate administration to a single patient after receipt of a valid patient-specific prescription or order for that patient (e.g., drawing up a syringe to administer directly to the patient). FDA does not consider this to be “repackaging” for purposes of this guidance.
- Diluting or mixing a biological product at the point of care for immediate administration to a single patient after receipt of a valid patient-specific prescription or order for that patient (e.g., diluting or mixing into a syringe to administer directly to the patient).
- Mixing, diluting, or repackaging a licensed biological product when the product is being mixed, diluted, or repackaged in accordance with the approved BLA as described in the approved labeling for the product. FDA considers this to be an approved manipulation of the product.
- Mixing, diluting, or repackaging of blood and blood components for transfusion,⁷ vaccines, cell therapy products, or gene therapy products. This guidance does not alter FDA’s existing approach to regulating the collection and processing of blood and blood components for transfusion. In addition, FDA intends to consider regulatory action if licensed vaccines, cell therapy products, and gene therapy products are subject to additional manufacturing, including mixing, diluting, or repackaging, in ways not

⁵ FDA is considering the applicability of the policies described in this guidance to hospitals and health systems and intends to address these issues in separate guidance.

⁶ The repackaging of biological products approved under section 505 of the FD&C Act is addressed in a separate guidance for industry, *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities* (January 2017), available at <https://www.fda.gov/downloads/Drugs/Guidances/UCM434174.pdf>.

⁷ This guidance does apply to licensed, plasma-derived biological 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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specified in the product's approved BLA as described in the approved labeling for the product.

- Investigational new drugs being studied under an investigational new drug application. This guidance does not alter FDA's existing approach to regulating investigational new drugs.

As stated above, this guidance does not address the mixing, diluting, or repackaging of a biological product for which a marketing application could properly be submitted under section 505 of the FD&C Act (see section 7002(e) of the Affordable Care Act). Accordingly, in this guidance, the term *biological product* does not include products for which a marketing application can be or has been submitted under section 505 of the FD&C Act.

Section II of this guidance provides background on biological products and the legal framework for FDA's regulation of these products and explains that sections 503A and 503B of the FD&C Act (21 U.S.C. 353a and 21 U.S.C. 353b, respectively) do not provide exemptions for mixing, diluting, or repackaging of biological products. Section III describes FDA's policy on mixing, diluting, or repackaging of certain licensed biological products that is not within the scope of the product's approved BLA as described in the approved labeling for the product.

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

II. BACKGROUND

A. Biological Products

The term "biological product" is defined in section 351(i)(1) of the PHS Act as

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

Biological products can be complex chains or combinations of sugars, amino or nucleic acids, or living entities such as cells and cellular therapies. Biological products include therapeutic proteins, monoclonal antibodies, allergenic extracts, blood and blood derivatives, cell therapy products, gene therapy products, preventive vaccines, and therapeutic vaccines. Generally, biological products have a complex set of structural features (e.g., amino acid sequence, glycosylation, folding) essential to their intended effect and are very sensitive to changes to their manufacturing process, including but not limited to any manipulation outside of their approved container-closure systems. In addition, many biological products are particularly sensitive to

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storage and handling conditions and can break down or aggregate if exposed to heat or light, if dropped, or if shaken during storage and handling. Accordingly, in the absence of manufacturing controls, diluting or mixing a biological product with other components or repackaging a biological product by removing it from its approved container-closure system and transferring it to another container-closure system is highly likely to affect the safety or effectiveness of the biological product. Biological products are also particularly susceptible to microbial proliferation in a short period of time if contaminated.

Nevertheless, to meet the needs of a specific patient, certain licensed biological products are sometimes mixed or diluted in a way not described in the product's approved labeling. For example, some biological products have no licensed pediatric strength or dosage form, so the product is diluted for use in pediatric patients. There also may be certain circumstances where a person would repackage a licensed biological product by removing it from its original container and placing it into different containers in a manner that is not within the scope of the approved BLA as described in the approved labeling for the product. Like other drugs, biological products are sometimes repackaged for various reasons, including for pediatric or ophthalmic use. For example, a pediatric dialysis unit may repackage a larger quantity of a product into smaller aliquots so that the optimal dose may be administered to each pediatric dialysis patient being treated at that particular time.

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

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

Vaccines are manufactured using biological systems and supplied by manufacturers in single- or multi-dose presentations. Unlike most other drugs and biological products, vaccines are administered to healthy individuals, including infants, to prevent disease. Vaccines may contain live attenuated organisms, inactivated organisms, or components of bacteria or viruses such as polysaccharides, inactivated toxins, or purified proteins. The manufacturing process for vaccines

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is complex and includes multiple controls to assure safety and effectiveness. Each single dose of a vaccine is formulated to deliver the correct quantity of an active ingredient to the recipient.

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

The policies in this guidance also do not cover or alter FDA's existing approach to regulating the collection and processing of blood and blood components for transfusion. These activities are currently conducted in FDA-licensed or -registered blood collection establishments and in hospital-based transfusion services regulated in part by the Centers for Medicare & Medicaid Services under the Clinical Laboratory Improvement Amendments of 1988. In all instances, the collection and processing of blood and blood components for transfusion is already subject to current good manufacturing practice (CGMP) requirements under the existing statutory and regulatory framework for blood and blood components and will not be subject to the policies described here.

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

Section 351(a)(1) of the PHS Act prohibits the introduction into interstate commerce of any biological product unless "a biologics license . . . is in effect for the biological product." For FDA to approve a BLA, the BLA must contain data to demonstrate that the biological product is safe, pure, and potent and that the facility in which the biological product will be manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent (see section 351(a)(2)(C) of the PHS Act). Because manufacturing controls are so important to ensuring the safety and effectiveness of biological products, FDA licensing of a biological product is based in part on an extensive review of chemistry and manufacturing controls data submitted by the applicant. This includes a thorough evaluation of the raw materials, drug substance, and drug product to ensure consistency in manufacturing and continued safety and effectiveness. In addition, other data are submitted and reviewed (e.g., stability and compatibility testing results) to establish the storage and handling conditions appropriate to ensure the safety, purity, and potency of the biological product.

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

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

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

The Drug Quality and Security Act added a new section 503B to the FD&C Act. Under section 503B(b) of the FD&C Act, a compounder can register with FDA as an outsourcing facility. Drug products compounded under the direct supervision of a licensed pharmacist in an outsourcing facility can qualify for exemptions from the FDA approval requirements in section 505 of the FD&C Act and the requirement to label drug products with adequate directions for use under section 502(f)(1) of the FD&C Act if the conditions in section 503B are met. Drugs compounded in outsourcing facilities are not exempt from the CGMP requirements of section 501(a)(2)(B).

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

III. POLICY

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

A. General Conditions

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

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

As described in section II.B, a biological product that is mixed, diluted, or repackaged outside the scope of an approved BLA is an unlicensed biological product under section 351 of the PHS Act. To be legally marketed, the new biological product would have to be the subject of an approved BLA and made in accordance with all other requirements applicable to biological products, including CGMP requirements.

B. Mixing, Diluting, or Repackaging Licensed Biological Products⁸

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 state-licensed pharmacy, a federal facility, or an outsourcing facility mixes, dilutes, or repackages a biological product in accordance with the conditions described below, and any applicable requirements.⁹ In addition, FDA does not intend to take action for violations of section 501(a)(2)(B) of the FD&C Act when a state-licensed pharmacy or a Federal facility mixes, dilutes, or repackages a biological product in accordance with the conditions described below, and any applicable requirements.¹⁰

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

1. The FDA-licensed biological product is a biological product that is mixed, diluted, or repackaged, not a biological product licensed for further manufacturing use only or a bulk drug substance. Additionally, a licensed biological product is not combined with a biological product licensed for further manufacturing use only or with a bulk drug substance. Any materials used in mixing or diluting are sterile, pharmaceutical grade,¹¹ and otherwise appropriate for such use.

⁸ 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.

⁹ 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.

¹⁰ 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.

¹¹ For purposes of this guidance, *pharmaceutical grade* refers to materials that are suitable for administration in humans.

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2. The biological product is mixed, diluted, or repackaged in a state-licensed pharmacy, a federal facility, or an outsourcing facility.
3. The biological product is mixed, diluted, or repackaged by or under the direct supervision of a licensed pharmacist.
4. If the biological product is mixed, diluted, or repackaged in a state-licensed pharmacy or a federal facility, it is distributed¹² only after the receipt of a valid prescription for an individually identified patient (including a written order or notation in a patient's chart in a health care setting) directly from the prescribing practitioner or patient. This condition does not apply to biological products mixed, diluted, or repacked in an outsourcing facility.¹³
5. Except as provided below, the biological product is mixed, diluted, or repackaged, then stored and shipped in a way that does not conflict with the approved labeling for the licensed biological product.¹⁴
 - For a biological product packaged in a single-dose vial that is mixed, diluted, or repackaged, the biological product is mixed, diluted, or repackaged in a way that does not conflict with the approved labeling, except for the statements designating the product as a single-dose or single-use product, and related language (e.g., discard remaining contents).¹⁵
 - For a biological product repackaged by an outsourcing facility that assigns a beyond use date (BUD) to the product in accordance with Appendix A of this guidance, the biological product is repackaged in a way that does not conflict with the approved labeling, except for the statements regarding the product's labeled in-use time (and any statements designating the product as a single-dose or single-use product, as described immediately above).

¹² *Distributed* means that the mixed, diluted, or repackaged biological product has left the facility in which it was mixed, diluted, or repackaged.

¹³ Note, however, that drugs produced by outsourcing facilities, including drugs that are also biological products, remain subject to the requirements in section 503B of the FD&C Act. Therefore, a prescription drug, including a biological product, cannot be dispensed to a patient without a prescription.

¹⁴ 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.

¹⁵ 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).

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6. The container-closure system¹⁶ (e.g., syringe) into which the mixed, diluted, or repackaged biological product is placed is suitable for storage of the biological product through its BUD¹⁷ and the primary packaging is sterile.
7. If the labeling for the licensed biological product includes storage or handling instructions (e.g., protect from light, do not freeze, keep at specified storage temperature), the labeling for the biological product that is mixed, diluted, or repackaged specifies the same storage conditions.¹⁸
8. If the biological product is mixed, diluted, or repackaged in a state-licensed pharmacy or federal facility, the duration of time from beginning (i.e., when the original biological product to be repackaged or to be used for mixing or diluting is punctured or otherwise opened) to end of mixing, diluting, or repackaging is no more than four hours.
9. As described in section II of this guidance, biological products are very susceptible to product quality concerns when mixed, diluted, or repackaged. For example, because biological products provide a rich media for microbial growth, they are particularly susceptible to microbial proliferation over time if contaminated. Therefore, the mixed, diluted, or repackaged biological product is given a BUD¹⁹ that is not longer than the applicable BUD specified below. The BUD timeframes in this condition begin from the time in which the container of the original biological product to be repackaged or to be used for mixing or diluting is punctured or otherwise opened.
 - a. If the biological product is mixed, diluted, or repackaged by a state-licensed pharmacy or a federal facility, it is given a BUD that:
 - does not exceed the time frame within which the opened product is to be used as specified in the approved labeling of the licensed biological product for any manipulation (“in-use time”) or the expiration date of the biological product being mixed, diluted, or repackaged, whichever is shorter;²⁰ or

¹⁶ A *container-closure system* is the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.

¹⁷ 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. CGMP requirements address container suitability and drug stability for outsourcing facilities.

¹⁸ See section IV of this guidance.

¹⁹ The BUD is the date beyond which a biological product should not be used.

²⁰ 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 between 2°C and 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

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- if the approved labeling does not specify an in-use time and the product is refrigerated, the in-use time is not longer than 24 hours, or the expiration date of the biological product being mixed, diluted, or repackaged, whichever is shorter.

b. Regarding outsourcing facilities:

i. If the biological product is mixed or diluted, it is given a BUD that

- does not exceed the in-use time specified in the approved labeling of the biological product or the expiration date of the biological product being mixed or diluted, whichever is shorter; or
- if the approved labeling does not specify an in-use time and the product is refrigerated, the in-use time is not longer than 24 hours, or the expiration date of the biological product being mixed or diluted, whichever is shorter.

ii. If the biological product is repackaged by an outsourcing facility that does not perform the testing described in Appendix A for that product, it is given a BUD that²¹:

- does not exceed the in-use time specified in the approved labeling of the biological product or the expiration date of the biological product being repackaged, whichever is shorter; or
- if the approved labeling does not specify an in-use time and the product is refrigerated, the in-use time is not longer than 24 hours or the expiration date of the biological product being repackaged, whichever is shorter.

iii. If the biological product is repackaged by an outsourcing facility that performs the testing described in Appendix A for that product, the BUD is assigned based on a stability program conducted in accordance with Appendix A for each container closure system to be used, the BUD does not exceed the expiration date of the biological product being repackaged, and the

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 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 in which it is repackaged, which may result in degradation.

²¹ 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.

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outsourcing facility maintains records of the testing performed in accordance with Appendix A.²²

10. The biological product is mixed, diluted, or repackaged in accordance with the following:
- a. If the biological product is mixed, diluted, or repackaged in a state-licensed pharmacy or a federal facility, it is done in accordance with the United States Pharmacopeia (USP) Chapter <797>,²³ except the BUD is as specified in condition 9.
 - b. If the biological product is mixed, diluted, or repackaged in an outsourcing facility, it is done in accordance with CGMP requirements, except the BUD is as specified in condition 9.²⁴

For purposes of condition 10.b, FDA intends to apply the policies described in the guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (July 2014),²⁵ once that guidance is finalized, except for the following:

- See condition 9 and Appendix A of this guidance for FDA’s policies concerning expiration dating or BUDs and stability testing for biological products mixed, diluted, or repackaged by outsourcing facilities.
- See Appendix B of this guidance for FDA’s policies concerning release testing requirements for biological products mixed, diluted, or repackaged by outsourcing facilities. Appendix B describes the circumstances under which FDA does not intend to take action against outsourcing facilities for failing to conduct batch release testing required under 21 CFR part 211 of mixed, diluted, or repackaged biological products.

11. The biological product is not sold or transferred by an entity other than the entity that mixed, diluted, or repackaged the biological product. For purposes of this condition, a sale or transfer does not include administration of a biological product in a health care setting.

²² See section IV of this guidance with respect to the maintenance of testing records.

²³ For purposes of this condition, reference to the USP Chapter <797> means USP 40-NF 35 (2017). 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 to revise the reference in condition 10.a.

²⁴ 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.

²⁵ When final, this guidance will represent FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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12. The mixed, diluted, or repackaged biological product is distributed only in states in which the facility mixing, diluting, or repackaging the biological product meets all applicable state requirements.
13. If the biological product is mixed, diluted, or repackaged by an outsourcing facility:²⁶
 - a. The label on the immediate container (primary packaging, e.g., the syringe) of the mixed, diluted, or repackaged biological product includes the following:
 - i. The statement “This biological product was mixed/diluted by [name of outsourcing facility]” or “This biological product was repackaged by [name of outsourcing facility],” whichever is appropriate
 - ii. The address and phone number of the outsourcing facility that mixed, diluted, or repackaged the biological product
 - iii. The proper name of the licensed biological product that was mixed, diluted, or repackaged
 - iv. The lot or batch number assigned by the outsourcing facility for the mixed, diluted, or repackaged biological product
 - v. The dosage form and strength of the mixed, diluted, or repackaged biological product
 - vi. A statement of either the quantity or the volume of the mixed, diluted, or repackaged biological product, whichever is appropriate
 - vii. The date the biological product was mixed, diluted, or repackaged
 - viii. The BUD of the mixed, diluted, or repackaged biological product
 - ix. Storage and handling instructions for the mixed, diluted, or repackaged biological product
 - x. The National Drug Code (NDC) number for the mixed, diluted, or repackaged biological product, if available²⁷
 - xi. The statement “Not for resale” and, if the biological product is distributed by an outsourcing facility other than pursuant to a prescription for an individual identified patient, the statement “Office Use Only”

²⁶ See section IV of this guidance with respect to sections 13.a.i-x and xii, sections 13.b.i-ii, and section 13.c.

²⁷ The NDC number for the original licensed biological product should not be placed on the mixed, diluted, or repackaged biological product.

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- xii. If included on the label of the FDA-licensed biological product from which the biological product is being mixed, diluted, or repackaged, a list of the active and inactive ingredients in the FDA-licensed biological product, unless such information is included on the label for the container from which the individual units of the mixed, diluted, or repackaged biological product are removed, as described below in 13.b.i; and, if the biological product is mixed or diluted, a list of any ingredients that appear in the mixed or diluted product in addition to those ingredients that are on the label of the original FDA-licensed biological product.
- b. The label on the container from which the individual units are removed for administration (secondary packaging, e.g., the bag, box, or other package in which the mixed, diluted, or repackaged biological products are distributed) includes:
 - i. The active and inactive ingredients included on the label of the original FDA-licensed biological product, if the immediate product label is too small to include this information
 - ii. Directions for use, including dosage and administration, as appropriate
 - iii. The following information to facilitate adverse event reporting:
www.fda.gov/medwatch and 1-800-FDA-1088.
- c. The mixed, diluted, or repackaged biological product is included on a report submitted to FDA each June and December identifying the drug products made by the outsourcing facility during the previous 6-month period, including the active ingredient; the source of the active ingredient; NDC number of the source ingredient, if available; strength of the active ingredient per unit; the dosage form and route of administration; the package description; the number of individual units mixed, diluted, or repackaged;²⁸ and the NDC number of the mixed, diluted, or repackaged biological product, if assigned.²⁹
- d. The outsourcing facility reports serious adverse events to FDA that are associated with its mixed, diluted, or repackaged biological products.³⁰

²⁸ 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.

²⁹ 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* (December 2016), available at <https://www.fda.gov/downloads/drugs/newsevents/ucm424303.pdf>. 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.

³⁰ FDA has issued a guidance for industry, *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (October 2015), available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434188.pdf>,

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C. Licensed Allergenic Extracts for Subcutaneous Immunotherapy³¹

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.³² 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 by a licensed physician for an individual patient according to instructions from a valid prescription (including a chart order in a health care setting).

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 diluents that are sterile, pharmaceutical grade, and otherwise appropriate for such use.
2. The prescription set is prepared in a physician's office, state-licensed pharmacy, federal facility, or outsourcing facility.

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 biological products they mixed, diluted, or repackaged.

³¹ 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.

³² 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.

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3. Each prescription set is distributed³³ 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.
4. The prescription set is prepared in a way that does not conflict with approved labeling of the licensed biological products that are part of the prescription set.³⁴
5. The BUD for the prescription set is no later than the earliest expiration date of any allergenic extract or any diluent that is part of the prescription set, and the BUD does not exceed one year from the date the prescription set is mixed or diluted.³⁵
6. The prescription set is prepared in accordance with the following:
 - a. If the prescription set is prepared in a State-licensed pharmacy or Federal facility, or in a physician's office, it is prepared in accordance with USP Chapter <797>,³⁶ except the BUD is as specified in condition 5.
 - b. If the prescription set is prepared in an outsourcing facility, it is prepared in accordance with applicable CGMP requirements, except the BUD is as specified in condition 5.

For purposes of condition 6.b, FDA intends to apply the policies described in the guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*, once that guidance is finalized, except for the following:

- See condition 5 of this guidance for FDA's policies concerning expiration dating/BUDs for prescription sets prepared by outsourcing facilities.
- See Appendix B of this guidance for FDA's policies concerning release testing requirements for prescription sets prepared by outsourcing facilities. Appendix B describes the circumstances under which FDA does not intend to take action against outsourcing facilities for failing to conduct batch release testing of prescription sets.

³³ *Distributed* means that the prepared prescription set has left the facility in which it was prepared.

³⁴ See note 14.

³⁵ 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, so long as the outsourcing facility assigns a BUD in accordance with this condition.

³⁶ For purposes of this condition, the reference to the USP Chapter <797> means in USP 40-NF 35 (2017). 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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7. The prepared prescription set is not sold or transferred by an entity other than the entity that prepared the prescription set. For purposes of this condition, a sale or transfer does not include administration of a prescription set in a health care setting.
8. The prescription set is distributed only in states in which the facility preparing the prescription set meets all applicable state requirements.
9. If the prescription set is prepared by an outsourcing facility:³⁷
 - a. The label on any immediate containers (primary packaging) of the prescription set includes the following:
 - i. The patient's name as identified on the prescription or order
 - ii. The statement "This prescription set was prepared by [name of outsourcing facility]"
 - iii. The address and phone number of the outsourcing facility that prepared the prescription set
 - iv. The identity of each allergenic extract in the prescription set and the quantity of each
 - v. The dilution of each dilution vial
 - vi. The lot or batch number of the prescription set
 - vii. The date the prescription set was prepared
 - viii. The BUD as the expiry date for the prescription set
 - ix. Storage and handling instructions for the prescription set
 - x. The statement "Not for resale"
 - b. The label of the container from which the individual units of the prescription set are removed for administration (secondary packaging) includes the following information to facilitate adverse event reporting: www.fda.gov/medwatch and 1-800-FDA-1088.
 - c. Each prescription set also is accompanied by instructions for use.
 - d. The prescription set is included in a report submitted to FDA each June and December identifying the drug products made by the outsourcing facility during the

³⁷ With respect to sections 9.a.i-ix; section 9.c; and section 9.d., see section IV of this guidance.

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previous 6-month period, including the active ingredients; source of the active ingredients; NDC number of the source ingredients, if available; strength of the active ingredients per unit; the dosage form and route of administration; the package description; the number of individual units produced; and the NDC number of the final product, if assigned.³⁸

- e. The outsourcing facility reports serious adverse events to FDA that are associated with its prescription sets.³⁹

D. Establishment Registration and Drug Listing

Under section 510(b)(1) of the FD&C Act, between October 1 and December 31 of each year, every person who owns or operates any establishment in any State engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs (including biological products) is required to register with FDA, and under section 510(j) of the FD&C Act, every person who registers with FDA under section 510(b) must list its drugs manufactured, prepared, propagated, compounded, or processed for commercial distribution with the Agency. A drug is misbranded under section 502(o) of the FD&C Act (21 U.S.C. 352(o)) if it was manufactured, prepared, propagated, compounded, or processed in an establishment that is not registered under section 510, or if it was not included on a list required by section 510(j). Pharmacies that mix, dilute, or repackage biological products may qualify for an exemption from registration and therefore also not be required to list their drugs with FDA. Specifically, under section 510(g)(1), the registration requirement of section 510 does not apply to

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

With respect to entities that do not qualify for the exemptions from registration under section 510 of the FD&C Act,⁴⁰ FDA does not intend to take action against outsourcing facilities for

³⁸ 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.

³⁹ 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.

⁴⁰ See also, 21 CFR 207.13.

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violations of section 502(o) of the FD&C Act for failure to register and list under section 510 biological products that are mixed, diluted, or repackaged in accordance with this guidance.⁴¹

IV. PAPERWORK REDUCTION ACT

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). See footnotes 18, 22, 26, and 37. These provisions require review and are not in effect until they display a currently valid OMB control number. The information collection provisions in this guidance have been submitted to OMB for review as required by section 3507(d) of the Paperwork Reduction Act of 1995. FDA will publish a notice in the Federal Register announcing OMB's decision regarding the information collection provisions in this guidance.

⁴¹ 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 Testing⁴²

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 includes:⁴³

- 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 to be marketed by the outsourcing facility; and
- Testing of biological products for reconstitution at the time of dispensing (as directed in the labeling) and 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 beyond 24 hours⁴⁴ for a repackaged biological product 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.

⁴² 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.5.

⁴³ See 21 CFR 211.166.

⁴⁴ 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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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 conduct these tests on one lot annually and whenever the formulation of the biological product being repackaged or the container into which it is being repackaged may have changed.⁴⁵ In lieu of performing the testing itself, the outsourcing facility may contract with a testing facility to perform this testing.⁴⁶

When establishing the BUD for a repackaged biological product, if the data for any test does not meet the established specifications, the BUD is limited to the time point at which all of the data remained within specifications.⁴⁷ For this reason, FDA recommends testing at one or more interim time points. If the data at the last time point do not confirm the stability of the product at the desired BUD (e.g., some measurements fall outside of the established specifications) but the data at the interim meet the established specifications, assigning a BUD equal to the interim time point would be consistent with the policies in this guidance.

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

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

1. Nondestructive Tests⁴⁸

The following tests are conducted to assure consistency with the biological product being repackaged and its approved labeling:

- Appearance
- Color and clarity

⁴⁵ 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.

⁴⁶ 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 guidance for industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*. We recommend that the testing facility be ISO 17025 accredited.

⁴⁷ 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.

⁴⁸ If the container occludes visible determination of appearance, color, particulates, these tests are conducted without the container as part of the destructive tests (e.g., subvisible particulates).

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- Visible particulates

2. Destructive chemical tests

The tests to be conducted include:

- pH
- 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 a minimum, protein aggregation, and variants in the size and charge of the protein⁴⁹
- 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

- 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*.⁵⁰

⁴⁹ In general, these impurities can be characterized by standard biochemical methods, including but not limited to SE-HPLC or SDS PAGE.

⁵⁰ 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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- 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

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 temperature throughout the shipping period does not deviate from the recommended storage temperature range set forth in the approved product labeling for the licensed biological product.

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Appendix B

Release Testing for Biological Products Mixed, Diluted, or Repackaged by Outsourcing Facilities

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

- FDA does not intend to take action against an outsourcing facility for failing to conduct batch⁵¹ release testing under 21 CFR 211.165 and 211.167 for mixed, diluted, or repackaged biological products that are assigned a BUD that does not exceed the in-use time of the licensed biological product or 24 hours (in accordance with condition III.B.9 herein) and that are mixed, diluted, or repackaged in accordance with all of the other conditions of this guidance and any applicable requirements.
- FDA does not intend to take action against an outsourcing facility for failing to conduct batch release testing under 21 CFR 211.165 and 211.167 for biological products that the outsourcing facility repackaged in accordance with the conditions of this guidance and that are assigned a BUD in accordance with Appendix A, provided that the outsourcing facility conducts the following release tests on each batch of biological products that it has repackaged and, except with respect to sterility testing, receives passing results *prior* to distribution:
 - Sterility (the outsourcing facility *initiates* sterility testing before release and notifies customers of any failing results)
 - Endotoxin⁵²
 - Color
 - Clarity
 - Visible particulates
 - Subvisible particulates
- FDA does not intend to take action against an outsourcing facility for failing to conduct batch release testing under 21 CFR 211.165 and 211.167 for prescription sets

⁵¹ See definition of “batch” at 21 CFR 210.3(b)(2).

⁵² 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* (June 2012), available at <https://www.fda.gov/downloads/drugs/guidances/ucm310098.pdf>.

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that the outsourcing facility prepared in accordance with the conditions described in this guidance, provided that the outsourcing facility conducts the following release tests on each prescription set (at minimum, the first vial) that it has prepared, and it receives passing test results prior to distribution:

- Sterility
- Color
- Visible particulates