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

Guidance for Industry

DRAFT GUIDANCE

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

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Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application Guidance for Industry[1]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or the Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION AND SCOPE

This guidance sets forth FDA's policy regarding the mixing,[2] diluting, and repackaging[3] 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.[4] This guidance describes the conditions under which FDA does not intend to take action for violations of sections 351 of the PHS Act and sections 502(f)(1) and where specified, section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when a state-licensed pharmacy, a Federal facility, or an outsourcing facility[5] dilutes, mixes or repackages certain biological products without obtaining 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 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. Not covered by this guidance is diluting or mixing a biological product at the point of care for immediate administration to a single patient after receipt of a patient specific prescription or order for that patient (e.g., diluting or mixing into a syringe to administer directly to the patient).

[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] This guidance does not apply to blood and blood components for transfusion, vaccines, cell therapy products, and gene therapy products

[5] *"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 draft guidance, *"Guidance for Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act."*

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

- 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 (see section 7002(e) of the Affordable Care Act)). The repackaging of biological products not subject to licensure under section 351 is addressed in a separate draft guidance document. [6]
- Products intended for use in animals. FDA will consider addressing this issue in a separate guidance document.
- Mixing, diluting, or repackaging biological products (other than allergenic extracts) by entities that are not state-licensed pharmacies, Federal facilities, or outsourcing facilities; and preparation of allergenic extracts by entities that are not state-licensed pharmacies, Federal facilities, outsourcing facilities, or physicians (See additional information in section III.A. of this draft guidance document).
- Removing a biological product from the original container at the point of care for immediate administration to a single patient after receipt of a 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 document.
- Upon receipt of a patient-specific prescription, a licensed pharmacy removing from one container the quantity of solid oral dosage form biological products necessary to fill the prescription and placing it in a smaller container to dispense directly to its customer.
- 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 (see footnote 4). The guidance does not alter FDA's existing approach to regulating the collection and processing of blood and blood components. 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 specified in the product's approved BLA as described in the approved labeling for the product.

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, the term

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[6] The repackaging of biological products approved under section 505 is addressed in a separate draft Guidance, "*Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities.*"

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

"biological product" as used in this guidance 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 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.

FDA's guidance documents, including this guidance, 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 to mean:

> 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 acids, 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, and 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 storage and handling conditions and can break down or aggregate if exposed to heat and/or light, if dropped, or if shaken during storage and handling. Accordingly, 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, in the absence of manufacturing controls, highly likely to affect the safety and/or effectiveness of the biological product.

Nevertheless, certain licensed biological products may need to be mixed or diluted in a way not described in the approved labeling for the product to meet the needs of a specific patient. For example, for some biological products there is no licensed pediatric strength and/or dosage form, so the product must be diluted for use in pediatric patients. In addition, there may be certain

circumstances where a person would repackage a licensed biological product by removing it from its original container and placing it into a different container(s), 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 drug 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 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 purity or potency of the product and its safety and effectiveness. 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. In addition, 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 dose 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 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 active ingredient(s) to the recipient.

The policies in this guidance do not cover cell therapy products, gene therapy products, and vaccines. Because of the particularly sensitive nature of these products as described above, these categories of products must be prepared, and if applicable to that product's use, repackaged, under an approved BLA, in accordance with section 351 of the PHS Act.

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 and Medicaid Services under the Clinical Laboratory Improvement Amendments of 1988. In all instances, blood collection and processing is already subject to current good manufacturing practices (CGMP) 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 ensure that the biological product continues to be safe, pure, and potent. 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

Section 503A of the FD&C Act exempts compounded drugs from sections 505 (concerning new drug approval of human drugs products), 502(f)(1) (concerning labeling of drug products with adequate directions for use), and 501(a)(2)(B) of the FD&C Act (concerning CGMP) 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 as an outsourcing facility with FDA. 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.

D. Hospital and Health System[8] Repackaging of Drugs In Shortage For Use in the Health System (Section 506F of the FD&C Act)

The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law in July, 2012, added section 506F to the FD&C Act. This section exempts certain hospitals within a health system from registration requirements in section 510 of the Act provided certain conditions are met, including that the drugs (including biological products) are, or have recently been, listed on FDA's drug shortage list[9] and are repackaged for the health system. Section 506F of the FD&C Act defines "repackaging," for purposes of that section only, as "divid[ing] the volume of a drug into smaller amounts in order to—(A) extend the supply of a drug in response to the placement of the drug on a drug shortage list under section 506E; and (B) facilitate access to the drug by hospitals within the same health system."

Section 506F of the FD&C Act has a termination clause that states "This section [506F] shall not apply on or after the date on which the Secretary issues a final guidance that clarifies the policy of the Food and Drug Administration regarding hospital pharmacies repackaging and safely transferring repackaged drugs [including drugs that are licensed biological products] to other hospitals within the same health system during a drug shortage." [10] These issues are addressed and clarified by this guidance, and the guidance on *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities*. Therefore, when these guidances become final, section 506F of the FD&C Act will no longer apply.

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[8] For purposes of this guidance, the term *"health system"* refers to a collection of hospitals that are owned and operated by the same entity and that share access to databases with drug order information for their patients.

[9] See section 506F(b) (providing that the exemption may be available if, among other factors, the drug is repackaged (1) during any period in which the drug is listed on the drug shortage list under section 506E; or (2) during the 60-day period following any period described in paragraph (1)).

[10] See section 506F(d) of the FD&C Act.

III. POLICY

Because biological products sometimes need to be 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. Consistent with section 351 of the PHS Act, a manufacturer seeking to mix, dilute, or repackage a biological product licensed for further manufacturing use only, or a bulk drug substance, must first submit a BLA and obtain a license for the product.

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 sections III.B and III.C of this guidance. Except as described in sections III.B and III.C, the agency will consider regulatory action if a licensed biological product is subject to additional manufacturing, including mixing, diluting, or repackaging, outside of the conditions specified in the approved labeling for the licensed product.

As described in section 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 licensed on the basis of an approved BLA, have labeling with adequate directions for use, and be made in accordance with biological product standards and CGMP requirements. Therefore, biological products that do not meet the conditions in this guidance, including 1) biological products that are mixed, diluted, or repackaged by entities that are not state-licensed pharmacies, Federal facilities, or outsourcing facilities or 2) prescription sets of allergenic extracts that are not prepared by state-licensed pharmacies, Federal facilities, outsourcing facilities, or licensed physicians, must comply with requirements in the PHS Act, FD&C Act, and FDA regulations applicable to biological products manufactured by "conventional" manufacturers, including, but not limited to, biological product license requirements, and compliance with applicable standards and CGMP requirements.

B. Mixing, Diluting, or Repackaging Licensed Biological Products

FDA does not intend to take action for violations of sections 351 of the PHS Act or 502(f)(1) of the FD&C Act if a state-licensed pharmacy, a Federal facility, or an outsourcing facility[11] mixes, dilutes, or repackages a biological product in accordance with the conditions described below, and any applicable requirements.[12] 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. Outsourcing facilities remain subject to applicable CGMP requirements.

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

1. The biological product that is mixed, diluted, or repackaged is an FDA-licensed biological product, not a biological product licensed for further manufacturing use only or a bulk drug substance.

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

3. If the biological product is mixed, diluted, or repackaged in a state-licensed pharmacy or a Federal facility (but not an outsourcing facility), it is mixed, diluted, or repackaged after (a) the receipt of a valid prescription for an identified, individual patient directly from the prescribing practitioner, patient, or patient's agent; or (b) a written order in a patient's chart in a healthcare setting,[13] unless it is mixed, diluted, or repackaged (but not distributed) in advance of receipt of such a prescription or a written order in a patient's chart in a quantity that does not exceed the expected demand for the biological product within the beyond use date (BUD) on the product, based on a history of receipt of prescriptions or orders for such a biological product for that time period.

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

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[11] As we discuss in section II of this guidance, biological products licensed under section 351 of the PHS Act are not eligible for the statutory exemptions offered by sections 503A or 503B of the FD&C Act, and if a facility registers as an outsourcing facility but only mixes, dilutes, or repackages such biological products, none of the products made at the facility will be eligible for the exemptions under section 503B. However, this guidance describes the conditions under which FDA does not intend to take action for violations of section 351 of the PHS Act and sections 501(a)(2)(B) and 502(f)(1) of the FD&C Act if such biological products are mixed, diluted, or repackaged at a state-licensed pharmacy, a Federal facility, or an outsourcing facility that compounds drug products in accordance with section 503B.

[12] 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.

[13] 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.

5. Except as provided below for a single dose vial, the biological product is mixed, diluted, or repackaged 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 into multiple units, 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]

6. 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 BUD that is not longer than the applicable BUD[16] below:

   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
      - is not longer than 4 hours, or is equal to the time within which the opened product is to be used as specified in the approved labeling, whichever is shorter; [17] or

      - is up to 24 hours if microbial challenge studies performed on the formulation of the diluted, mixed, or repackaged biological product in the type of container in which it will be packaged demonstrate that microbial growth will not progress to an unacceptable level within the period of the BUD. (See Appendix 1 for a description of microbial challenge study design.)

   b. If the biological product is mixed or diluted by an outsourcing facility, it is given a BUD that

[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).

[16] 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 ("opened product").

[17] The 4 hour BUD timeframe in this guidance is consistent with the labeling of many licensed biological products, which require the disposal of any product not used within 4 hours after the product has been reconstituted or the container has been entered. Where another timeframe is provided in the labeling, it is based on data generated under specific conditions by the product's manufacturer and submitted with the BLA. Such data are not available for products mixed, diluted, or repackaged outside the scope of a BLA, as described in this guidance.

- is not longer than 4 hours, or is equal to the time within which the opened product is to be used as specified on the approved labeling, whichever is shorter; or

- is up to 24 hours if microbial challenge studies performed on the formulation of the mixed or diluted biological product in the type of container in which it will be packaged demonstrate that microbial growth will not progress to an unacceptable level within the period of the BUD. (See Appendix 1 for a description of microbial challenge study design.)

c. If the biological product is repackaged by an outsourcing facility, it is given a BUD that
   - is not longer than 4 hours, or is equal to the time within which the opened product is to be used as specified on the approved labeling, whichever is shorter; or

   - is up to 24 hours if microbial challenge studies performed on the formulation of the repackaged biological product in the type of container in which it will be packaged demonstrate that microbial growth will not progress to an unacceptable level within the period of the BUD. (See Appendix 1 for a description of microbial challenge study design); or

   - does not exceed 5 days or the expiration date of the biological product being repackaged, whichever is shorter, provided that the outsourcing facility conducts adequate compatibility studies on the container-closure system (e.g., the syringe) of the repackaged biological product to demonstrate compatibility and ensure product integrity. (*See* Title 21, section 211.94 of the Code of Federal Regulations for regulations on drug product containers and closures). [18]

7. 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>, except the BUD is as specified in condition 6; 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 6.

8. 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.

[18] This longer BUD reflects that outsourcing facilities must comply with CGMP requirements and are subject to FDA inspections on a risk-based schedule. Conditions maintained to comply with CGMP requirements provide greater assurance of the quality of manufacturing operations and the products that are produced at the facility. This longer BUD is not provided for mixed or diluted biological products because these activities are more likely to alter the characteristics of the biological product in ways that could harm patients, even if performed under CGMP conditions. To provide a sufficient basis for FDA to conclude that a longer BUD on a mixed or diluted product was justified, an outsourcing facility would need to submit a BLA that included data on the impacts of diluting or mixing the specific product.

9. The mixed, diluted, or repackaged biological product is distributed only in states in which the facility mixing, diluting, or repackaging the biological product meets any applicable state requirements.

10. If the biological product is mixed, diluted, or repackaged by an outsourcing facility:

    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 product was repackaged by [name of outsourcing facility]", whichever statement 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 original 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 of the mixed, diluted, or repackaged biological product, if available[19]
        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"
        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, unless such information is included on the label for the container from which the individual units are removed, as described below in 10.b.i; and if the biological product is mixed or diluted, the label of the mixed or diluted product includes any ingredients that appear in the mixed or diluted product in addition to those ingredients that are on 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:

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

412 i. The active and inactive ingredients, if the immediate product label is too small
413 to include this information
414 ii. Directions for use, including, as appropriate, dosage and administration, and
415 the following information to facilitate adverse event reporting:
416 www.fda.gov/medwatch and 1-800-FDA-1088.
417
418 c. Each mixed, diluted, or repackaged biological product is also accompanied by a copy
419 of the prescribing information that accompanied the original FDA-licensed biological
420 product that was mixed, diluted, or repackaged.
421
422 d. The mixed, diluted, or repackaged biological product is included on a report
423 submitted to FDA each June and December identifying the drug products made by the
424 outsourcing facility during the previous 6-month period, including: a notation that this
425 is a mixed, diluted, or repackaged biological product; the active ingredient; the source
426 of the active ingredient; NDC number of the source ingredient, if available; strength
427 of the active ingredient per unit; the dosage form and route of administration; the
428 package description; the number of individual units mixed, diluted, or repackaged[20];
429 and the NDC number of the final product, if assigned.[21]
430
431 e. The outsourcing facility reports serious adverse events to FDA that may be associated
432 with its mixed, diluted, or repackaged biological products.
433
434 **C. Licensed Allergenic Extracts**
435
436 FDA recognizes that there are circumstances in which licensed allergenic extracts would be
437 mixed and diluted to provide subcutaneous immunotherapy to an individual patient, even though
438 these allergenic extract combinations are not specified in the approved BLAs for the licensed
439 biological products. Such combinations are commonly referred to as prescription sets.[22] For the
440 purpose of this guidance a *prescription set* is defined as a vial or set of vials of premixed licensed
441 standardized and non-standardized allergenic extracts for subcutaneous immunotherapy diluted
442 with an appropriate diluent prepared according to instructions from a prescription or order by a
443 licensed physician for an individual patient.

[20] 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.

[21] FDA has issued a draft guidance for industry, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* , which prescribes how human drug compounding facilities are to submit drug product reports to FDA. Although this guidance addresses reporting of compounded human drug products, outsourcing facilities should follow the same procedure to electronically report the biological products they mixed, diluted, or repackaged.

[22] Under 21 CFR 610.17, licensed biological products must not be combined with other licensed biological 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.

FDA does not intend to take action for violations of section 351 of the PHS Act or section 502(f)(1) of the FD&C Act if a physician, state-licensed pharmacy, a Federal facility, or outsourcing facility prepares prescription sets of allergenic extracts in accordance with the conditions described below, and any applicable requirements.[23]

In addition, with respect to a prescription set prepared in accordance with the following conditions and any applicable requirements, 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 in accordance with the conditions described below; outsourcing facilities remain subject to applicable CGMP requirements.

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

1. The prescription set is prepared from FDA-licensed allergenic extracts and appropriate diluents.

2. The prescription set is prepared in a in a physician's office, state-licensed pharmacy, a Federal facility, or outsourcing facility.

3. If the prescription sets are prepared in a physician's office, state-licensed pharmacy, or a Federal facility (but not an outsourcing facility), each set is prepared after (a) the receipt of a valid prescription for an identified, individual patient directly from the prescribing practitioner, patient, or patient's agent; or (b) a written order in a patient's chart, unless it is prepared in advance of receipt of such a prescription or a written order in a quantity that does not exceed the expected demand for that prescription set within the BUD for the product, based on a history of receipt of prescriptions or orders for such a prescription set for that time period. If the prescription sets are prepared in an outsourcing facility, those sets are prepared either after, or in anticipation of, receiving valid prescriptions for an identified, individual patient or a written order in a patient's chart.

4. The prescription set is distributed to a physician or to a health system for use within the health system only after the receipt of a valid prescription for an identified, individual patient or a written order in a patient's chart.

5. 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.[24]

6. 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.

[23] See note 12.
[24] See note 15.

7. If the prescription set is prepared in a state-licensed pharmacy or a Federal facility, or in a physician's office, it is prepared in accordance with USP Chapter <797>, except the BUD is as specified in condition 6; 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 6.

8. 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.

9. The prescription set is distributed[25] only in states in which the facility preparing the prescription set meets any applicable state requirements.

10. If the prescription set is prepared by an outsourcing facility:

    a. The label on the immediate container(s) (primary packaging) of the prescription set includes the following:
        i. The patient's name as identified on the prescription
        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 of 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 and the FDA approved package insert for each allergenic extract.

    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 previous 6-month period, including: a notation that this is a biological product; the active ingredient(s); source of the active ingredient(s); NDC number of the source ingredient(s), if available; strength of the active ingredient(s) per unit; the dosage

[25] *Distribution* means that the prepared prescription set has left the facility in which it was prepared.

form and route of administration; the package description; the number of individual units produced; and the NDC number of the final product, if assigned.[26]

e. The outsourcing facility reports serious adverse events to FDA that may be associated with its prescription sets.

[26] FDA has issued a draft guidance for industry, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* , which prescribes how human drug compounding facilities are to submit drug product reports to FDA. Once finalized, that guidance will represent the Agency's thinking on that topic. Although this guidance addresses reporting of compounded human drug products, outsourcing facilities should follow the same procedure to electronically report the prescription sets they prepared.

APPENDIX 1 – MICROBIAL CHALLENGE STUDY DESIGN

The following design recommendations for product growth promotion studies should be followed to extend the BUD to up to 24 hours for a mixed, diluted, or repackaged biological product as referenced in Section II. B.

Microbial challenge studies are designed to demonstrate that the product in question does not support adventitious microbial growth under the proposed storage conditions. Each facility would conduct a microbial challenge study at least once for each mixed, diluted, or repackaged biological product, to demonstrate that the microbial quality of the biological product mixed, diluted, or repackaged by that facility can be ensured. The microbial challenge study should be repeated if the formulation or the container-closure system is changed. The studies should be accurately documented and records maintained for inspection.

The challenge microbes should include the panel provided in USP<51> Antimicrobial Effectiveness Testing.[27] These strains represent the species *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus brasiliensis* (formerly *Aspergillus niger*). It should also incorporate typical skin microflora and nosocomial agents to simulate the types of flora that may contaminate a drug product in a healthcare setting. Finally, the challenge should include strains of the tribe *Klebsielleae*, as they have been shown to proliferate in infusion products.[28]

Individual containers of the mixed, diluted, or repackaged biological product should be inoculated with each challenge organism, with each container receiving one type of organism. The inoculum size should be small but also measurable and repeatable. For example, if a membrane filtration method is used to quantify the number of organisms, an inoculum size of fewer than 100 CFU/mL is appropriate.

Following inoculation of the final product with the challenge organisms, the test units should be stored at the temperature(s) described in the biological product's labeling. Samples should be removed periodically throughout the duration of the study for determination of microbial count for up to 72 hours (3 times the maximum BUD). To support a BUD of 24 hours, each challenge organism should demonstrate no increase from the initial count (where *no increase* is defined as not more than 0.5 log10 unit higher than the initial inoculum at any time point up to 72 hours) and no evidence of growth. As explained in the example below, data from a study of 72 hours' duration should be examined for trending and to establish a maximum storage time of up to 24 hours at a specified temperature.

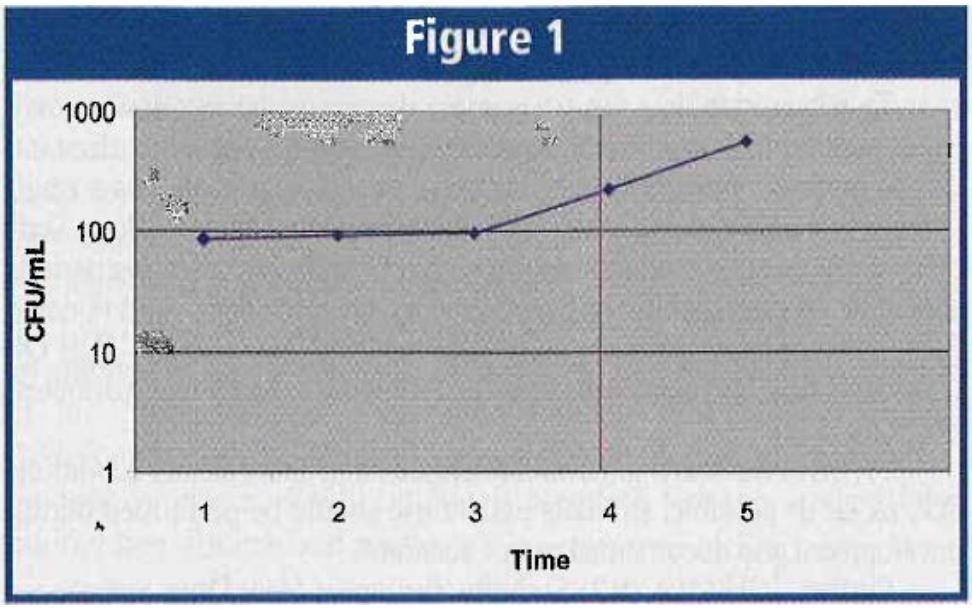
Example: Determination of Microbial Growth

[27] USP51/NF26. United States Pharmacopeial Convention, 2008.
[28] See, Mahl, M.C., et al. Nitrogen Fixation by Members of the Tribe *Klebsielleae*, *J. Bacteriol.*, 1965, 89(6): 1482; Maki, D., et al., Infection Control in Intravenous Therapy, *Annals of Internal Medicine*, 1973, 79: 867.

The following table represents data from a hypothetical microbial challenge experiment where the inoculum is less than 100 CFU/mL, and the requested maximum hold time is equivalent to Time Point 4.

Time	Microbial Count (CFU/mL)	Log of Microbial Count
1	88	1.9
2	95	2
3	98	2
4	220	2.3
5	552	2.7

These data reflect *no increase* from the initial count through Time Point 4. However, as illustrated in Figure 1 below, the semi-logarithmic graph of CFU/mL vs. Time shows clear evidence of growth of the challenge organism at Time Point 4.



Thus, a maximum hold time equivalent to that of Time Point 4 would pose potential risk to the microbiological quality of the hypothetical mixed, diluted, or repackaged biological product, and the acceptable BUD would be set at one-third of Time Point 3. It is also important to note that, if the experiment were concluded at Time Point 4, the ability to predict the trend of the data would be lost. As presented in the graphic, the growth trend appears to signal the start of log-phase growth, which could occur earlier or later with different strains of a given species. Such growth would produce exponential increases in the microbial population that pose significant risk to patients. This concern is the reason for periodic sampling when determining microbial concentration.