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BUSINESS, CONSUMER SERVICES AND HOUSING AGENCY
DEPARTMENT OF CONSUMER AFFAIRS
GOVERNOR EDMUND G. BROWN JR.

To: Board Members

Subject: Agenda Item VIII: DISCUSSION AND POSSIBLE ACTION: to Provide Comments on Recent US Food and Drug Administration Draft Guidance Documents

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The FDA recently released five guidance documents on various aspects of sterile compounding by pharmacies and the production of medication by outsourcing facilities. Each of these guidance documents has been agendized so the board may discuss and take action on any of them. The comments are due in about 70 days (90 days from the date they were initially released).

This time frame would permit the board to direct staff to develop comments and have the board president approve and sign them, or the board can ask that the draft comments be returned to the full board in April to review them at our next board meeting. Again, providing no comments may be the board's decision as well.

Additionally, in mid-March, the board's executive officer will attend a 50-state meeting convened by the FDA to discuss these guidance documents, and the continued development of the federal outsourcing facility licensing provisions and sterile compounding by pharmacies. Also, as discussed earlier in this meeting, the board has agreed to sponsor legislation to license outsourcing facilities doing business in California. The executive officer has been asked to speak on this decision at this FDA meeting.

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a. Draft Guidance: For Entities Considering Whether to Register As Outsourcing Facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act

Attachment 1

This guidance states that entities registered with the FDA as outsourcing facilities will be regulated as outsourcing facilities according to current good manufacturing practice requirements (CGMP) for all products they produce or compound. (Federal law allows outsourcing facilities to be sterile compounding pharmacies as well.) These facilities will be inspected by the FDA on a risk-based schedule. There are approximately 59 FDA registered outsourcing facilities in the US.

The outsourcing guidance states (page 4) that if a facility does not intend to compound all drugs under CGMPs, then the facility should not be registered as an outsourcing facility. Additionally,

The facility:

- Must be engaged in the production of compounding sterile human drugs.
- Does Not repackage drugs (except as discussed in other guidance documents)
- Does Not produce biologic drugs
- Does Not produce animal drugs

The guidance concludes that a facility should not register as an outsourcing facility if the only activities it performs are repackaging, compounding non-sterile or animal drugs, or mixing, diluting or repackaging biological products.

Regardless of whether the board submits comments on this guidance document, these statements may be of value to the board in developing parameters for its legislation to regulate outsourcing facilities.

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b. Draft Guidance for Industry: Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities

Attachment 2

From Page 3 of this guidance:

> "When a drug product is prepackaged, its characteristics may change in ways that have not been evaluated during the FDA approval process and that could affect the safety and efficacy of the drug product. Improper repackaging of drug products can cause serious adverse events. Of particular concern is repackaging of sterile drug products which are susceptible to contamination and degradation For example, failure to properly manipulate sterile drug products under appropriate aseptic conditions could introduce contaminants that could cause serious patient injury or death. Repackaging practices that conflict with approved product labeling could result in drug product degradation and adverse events associated with impurities in the product or lack of efficacy because the active ingredient has deteriorated."

Drugs that are repackaged are not regulated by the FDA under provisions dealing with pharmacy or outsourcing facilities. The guidance states that the FDA does not intend to take action for certain violations of federal requirements for entities that repackage drugs, provided:

1. The facility is licensed by a state as a pharmacy or holds an outsourcing facility license
2. If the repackaging occurs in a pharmacy or federal institution only: 1. after receipt of a patient-specific prescription or written chart order, or 2. Repackaged in advance of receipt of a patient-specific order based on prior demand for a previous, consecutive 14-day period AND history for prior 14-day periods.
3. The repackaging is done by or under the supervision of a licensed pharmacist

4. For single dose vials, the repackaging does not conflict with drug product labeling
5. For single dose vials repackaged into multiple units, the product is repackage in a way that does not conflict with drug product labeling
6. The repackaged drug product conforms to specific beyond use dating (BUD)
7. Provides different requirements for BUD for an outsourcing facility, and requires CGPMs for the repackaging processes. Additionally the guidance provides labeling requirements for the repackaged product.
8. The repackaged product is not sold or transferred by an entity other than the one that repackaged the product.
9. The repackaged drug product is distributed only in states in which the facility repackaging the product meets all applicable state requirements.
10. Addresses guidance for repacking drugs on the FDA's drug shortage list.

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c. Draft Guidance for Industry: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (BLA)

Attachment 3

The background section of this guidance document provides an overview of biological products, their characteristics and their regulation by the FDA. The guidance generally excludes compounding or outsourcing preparation of biologic products. Instead, such a company must possess an approved biologics license application (BLA) for the biologic.

However, the guidance notes that biologics sometimes must be mixed, diluted or repackaged in ways not addressed by the BLA and the guidance notes that the FDA will not take action against a state-licensed pharmacy, federal institution or outsourcing facility that conforms to mix, dilute or repackage a biologic under the conditions specific in the guidance. This includes:

- A biological product that is mixed, diluted or repackaged in a pharmacy or federal facility (but NOT an outsourcing facility) 1. after receipt of a patient-specific prescription or written chart order, or 2. is mixed, diluted or repackaged in anticipation of need based on prior demand, but not dispensed until ordered for a patient.
- The biologic must be mixed, diluted or repackaged by or under the direct supervision of a pharmacist.'
- Specifics about beyond use dating (BUD) for the mixed, diluted or repackaged biologic.

The guidance also specifies a BUD for an outsourcing facility that mixes or dilutes a biologic, and a separate process for a BUD for an outsourcing facility that repackages a biologic.

The guidance provides labeling instructions for biologic products mixed, diluted or repackaged by a pharmacy, federal institution or outsourcing facility.

The guidance also establishes criteria for the creation of prescription sets of allergic extracts under which the FDA will not take action against a pharmacy, federal institution, outsourcing facility or physician.

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d. Draft Guidance for Industry: Adverse Event Reporting for Outsourcing Facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act

Attachment 4

This guidance provides that outsourcing facilities are required to report adverse drug events to the FDA within 15 days. Specifically, all serious, unexpected adverse drug experiences associated with the use of their compounded prescription drug products, and "strongly recommends" that outsourcing facilities report all serious adverse drug experiences generally.

The guidance lists four elements for the investigation to include: the patient, the reporter, the suspect drug, the serious adverse event. It then describes the specific details about each element to include in the report.

Regarding the board's outsourcing facility legislative proposal: the 15 day reporting report for adverse events is longer than the 12 hour requirement in existing California law for compounding pharmacies to report to the board any drug recalled.

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e. Draft Memorandum of Understanding Between a State and the U.S. Food and Drug Administration Addressing Certain Distributions of Compounded Human Drug Products

Attachment 5

From Page 1:

"This Memorandum of Understanding (MOU) establishes an agreement between the State of [insert State] and the U.S. Food and Drug Administration (FDA) regarding the distribution of inordinate amounts of compounded human drug products interstate and the appropriate investigation by the State of [insert State] of complaints relating to compounded human drug products distributed outside the state. This is the MOU provided for by section 503A(b)(3)(B)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C 353a), and does not apply to drugs that are compounded by registered outsourcing facilities."

The MOU exempts the compounded products of pharmacies under specific circumstances from:

- Complying with CGMPs
- Labeling with adequate directions for use
- Possessing FDA prior approval of the drug product

provided the state has entered into the MOU.

If the state has entered into the MOU, then the MOU:

- Requires the home state to investigate issues arising from the interstate distribution of compounded drugs by a pharmacy and to identify the root cause of the problem, and take response to the action

- Requires the state to review compounding records during the inspections of compounding pharmacies to ensure the compounding pharmacy has not distributed an inordinate amount of compounded drug product interstate.

- Defines an inordinate amount as not more than 30 percent of the total number of compounded and non-compounded drug products distributed or dispensed (both in-state and interstate).

At some point in the future, once finalized, the board will need to determine whether it wishes to enter into such an agreement with the FDA.

Attachment 1

For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Sara Rothman (CDER) at 301-796-3110.

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

February 2015
Procedural

For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

Additional copies are available from:
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U.S. Department of Health and Human Services
Food and Drug Administration
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February 2015
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For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance[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

This guidance is intended for entities considering whether to register with the Food and Drug Administration (FDA or Agency) as an outsourcing facility under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[2]

FDA has received questions about whether entities engaged in various types of activities (e.g., a facility that is compounding only non-sterile drugs or only repackaging biological products) should register as an outsourcing facility. Because entities that register as outsourcing facilities in fiscal year (FY) 2015 (beginning October 1, 2014) must pay a registration fee and FDA has determined that fees paid pursuant to sections 503B and 744K of the FD&C Act will not be refunded, FDA is issuing this guidance to answer some of these questions and to provide potential registrants additional information about the regulatory impact of registering as an outsourcing facility.

Separate FDA guidance documents contain details on the process for registering as an outsourcing facility[3] and explain how outsourcing facilities should report the products they compound to FDA.[4]

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[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), the Center for Veterinary Medicine (CVM), and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration.

[2] A new section 503B was added to the FD&C Act by the Drug Quality and Security Act (DQSA). See Pub. L. No.113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

[3] See draft guidance for industry *Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

All FDA guidances are available on the FDA guidance Webpage at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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

The Drug Quality and Security Act, signed into law on November 27, 2013, creates a new section 503B of the FD&C Act. Section 503B(d)(4) defines an outsourcing facility as

> a facility at one geographic location or address that— (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section.

Section 503B(d)(4) further states that an outsourcing facility is not required to be a licensed pharmacy and may or may not obtain prescriptions for identified individual patients.[5] Section 503B(d)(5) defines *sterile drug* as a "drug that is intended for parenteral administration, an ophthalmic or oral inhalation drug in aqueous format, or a drug that is required to be sterile under Federal or State law."

A human drug product compounded by or under the direct supervision of a licensed pharmacist in a registered outsourcing facility can *qualify for exemptions* from the drug approval requirements in section 505 of the FD&C Act (21 U.S.C. 355), the requirement to be labeled with adequate directions for use in section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)), and the track and trace requirements in section 582 of the FD&C Act (21 U.S.C. 360eee-1). However to qualify, each of the following conditions must be met.

1. The outsourcing facility must be in compliance with the registration and reporting requirements of section 503B(b). This includes submitting twice yearly reports regarding the drugs compounded by the outsourcing facility and submitting adverse event reports in accordance with section 503B(b)(5).[6,7]

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[4] See draft guidance for industry *Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

[5] Although an outsourcing facility may send prescription drugs to healthcare facilities without obtaining prescriptions for identified individual patients, drugs produced by outsourcing facilities remain subject to the requirements in section 503(b) of the FD&C Act. Therefore, an outsourcing facility cannot dispense a prescription drug to a patient without a prescription.

[6] See section 301(ccc)(3) of the FD&C Act, which makes it a prohibited act for an entity that is registered in accordance with section 503B(b) to fail to report drugs or adverse events as required.

[7] See sections 503B(a)(1) and (b).

2. If the outsourcing facility compounds drugs using one or more bulk drug substances, the bulk drug substances must meet certain requirements.[8]
3. If the outsourcing facility compounds using ingredients other than bulk drug substances, those ingredients must meet certain requirements.[9]
4. The outsourcing facility must not compound drugs that appear on a list published by FDA of drugs that have been withdrawn or removed from the market because the drugs or components of such drugs have been found to be unsafe or not effective.[10,11]
5. The outsourcing facility must not compound drugs that are essentially a copy of one or more approved drugs.[12]
6. The outsourcing facility must not compound drugs that appear on a list published by FDA of drugs that present demonstrable difficulties for compounding.[13]
7. If the outsourcing facility compounds from a drug that is the subject of a risk evaluation and mitigation strategy (REMS) approved with elements to assure safe use pursuant to section 505-1, or from a bulk drug substance that is a component of such drug, the outsourcing facility must demonstrate to FDA before beginning to compound that it will use controls comparable to the controls applicable under the REMS.[14]
8. The outsourcing facility's compounded drugs will not be sold or transferred by an entity other than that outsourcing facility.[15]
9. The outsourcing facility has paid all applicable establishment and reinspection fees owed under section 744(k).[16,17]
10. The outsourcing facility must include on the labels and labeling of its compounded drug products the information required under section 503B(a)(10).[18]

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[8] See section 503B(a)(2).

[9] See section 503B(a)(3).

[10] See section 503B(a)(4).

[11] The list of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (the withdrawn-or-removed list) can be found at 21 CFR 216.24. On July 2, 2014, FDA published a proposed rule that would update that list (Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed from the Market for Reasons of Safety or Effectiveness, 79 FR 37,687). In the preamble to the proposed rule, FDA explained that FDA is proposing to revise and update the withdrawn-or-removed list at 21 CFR 216.24 for purposes of both sections 503A and 503B. Until the final rule revising and updating the withdrawn-or-removed list is published, drugs included on the existing list at 21 CFR 216.24 may not be compounded under section 503B.

[12] See section 503B(a)(5).

[13] See section 503B(a)(6).

[14] See section 503B(a)(7).

[15] See section 503B(a)(8).

[16] See section 503B(a)(9).

[17] See also sections 744J and 744K of the FD&C Act, and guidance for industry Fees for Human Drug Compounding Outsourcing Facilities Under Sections 503B and 744K of the FD&C Act.

[18] See section 503B(a)(10).

11. The outsourcing facility must compound all drugs in accordance with section 503B.[19]

Because drugs compounded by outsourcing facilities are not exempt from section 501(a)(2)(B) of the FD&C Act, outsourcing facilities are subject to current good manufacturing practice (CGMP) requirements, among other requirements under the FD&C Act.[20,21] In addition, outsourcing facilities will be inspected by FDA on a risk-based schedule.[22]

III. GUIDANCE

If you register a facility as an outsourcing facility, you are indicating your intent for the facility's compounded drugs to be regulated under section 503B of the FD&C Act. Under section 503B(a)(11), a compounded drug can only qualify for the exemptions from sections 502(f)(1), 505, and 582 of the FD&C Act if ***all*** of the facility's compounded drugs are compounded in accordance with section 503B. As stated above, drugs compounded in accordance with section 503B are not exempt from CGMP requirements, and outsourcing facilities will be inspected by FDA on a risk-based schedule.

If you do not intend to compound ***all*** drugs at your facility in accordance with section 503B and comply with CGMP requirements, you should not register as an outsourcing facility under section 503B.[23] In addition, entities considering registering as outsourcing facilities should consider the following:

- To meet the definition of an *outsourcing facility*, the facility must be engaged in the compounding[24] of sterile human drugs.[25]
- The definition of *compounding* in section 503B(d)(1) does not include repackaging.
- For purposes of section 503B, a drug, including a sterile drug, does not include a biological product subject to licensure under section 351 of the Public Health Service Act (PHS Act), or an animal drug subject to approval under section 512 of the FD&C Act.[26]

[19] See section 503B(a)(11).

[20] FDA has issued a draft guidance for industry *Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act.* Once finalized, that guidance will represent the Agency's thinking on this topic.

[21] See section 503B(a).

[22] See section 503B(b)(4).

[23] If an entity is not registered as an outsourcing facility under section 503B, its drugs could qualify for the exemptions from sections 505, 502(f)(1), and 501(a)(2)(B) of the FD&C Act, if they meet all of the conditions of section 503A. Otherwise, the drugs would be subject to all of the requirements in the FD&C Act applicable to drugs made by conventional manufacturers.

[24] Section 503B(d)(1) defines the term *compounding*, for purposes of that section, to include the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug.

[25] See section 503B(d)(4).

[26] In addition, for purposes of section 503A of the FD&C Act, the term *drug* does not include a biological product subject to licensure under section 351 of the PHS Act.

Therefore, you should ***not*** register a facility as an outsourcing facility if the ***only*** activities conducted at the facility are repackaging, compounding non-sterile or animal drugs, or mixing, diluting, or repackaging biological products subject to licensure under section 351 of the PHS Act because ***none of the products produced at the facility would qualify for the exemptions provided in section 503B***.

In addition, by registering as an outsourcing facility, an entity is electing to have its compounded drugs regulated under section 503B of the FD&C Act, not section 503A. Drugs compounded at an outsourcing facility are not eligible for the exemptions provided in section 503A, even if the conditions in that section are met with respect to the particular drug.

FDA is issuing separate draft guidances on (1) mixing, diluting, and repackaging biological products outside the scope of an approved biologics license application and (2) repackaging certain human drug products by pharmacies and outsourcing facilities. These guidance documents will describe FDA's compliance policies with respect to biological products that are mixed, diluted, or repackaged outside the scope of an approved biologics license application (BLA) and repackaged human drugs.

If a facility compounds sterile human drugs and otherwise meets the definition of an outsourcing facility, any non-sterile human drugs compounded by the facility would also be eligible for the exemptions from sections 505, 502(f)(1), and 582 if the drugs are compounded in accordance with the provisions of section 503B. However, if a facility that meets the definition of an outsourcing facility repackages certain human drugs, or mixes, dilutes, or repackages biological products outside the scope of an approved BLA, FDA does not intend to take action against those products for violations of certain provisions of the FD&C Act or the PHS Act, if applicable, provided those products satisfy the conditions described in the two guidances on biological products and repackaging, referenced above.

Attachment 2

Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Gail Bormel, CDER Office of Unapproved Drugs and Labeling Compliance (OUDLC), at 301-796-3110.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance/OUDLC

February 2015
Compliance

Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance/OUDLC

February 2015
Compliance

Contains Nonbinding Recommendations

Draft — Not for Implementation

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Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities[1]
Guidance for Industry[2]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA'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 the Food and Drug Administration's ("FDA" or "the Agency") policy regarding repackaging by state-licensed pharmacies, Federal facilities, and facilities that register with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act). This guidance describes the conditions under which FDA does not intend to take action for violations of sections 505, 502(f)(1), and where specified, section 501(a)(2)(B) of the Act, when a state-licensed pharmacy, a Federal facility, or an outsourcing facility repackages human prescription drug products.

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

- Biological products that are subject to licensure under section 351 of the Public Health Service (PHS) Act. The repackaging of biological products subject to licensure under section 351 is addressed in a separate draft guidance document.[3]

[1] "Outsourcing facility" refers to a facility that meets the definition of an outsourcing facility under section 503B(d)(4) of the Federal Food, Drug, and Cosmetic Act.

[2] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER) and in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

[3] FDA has issued a draft guidance, titled *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application.* Once finalized, that guidance will represent FDA's thinking on this topic.

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.

- Repackaging drug products for use in animals. FDA will consider addressing this issue in a separate guidance document.
- Repackaging by entities that are not state-licensed pharmacies, Federal facilities, or outsourcing facilities. See additional information in section III.A. of this draft guidance document.
- Removing a drug 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 an individual patient-specific prescription, a licensed pharmacy removing from one container the quantity of solid oral dosage form drug products necessary to fill the prescription and placing it in a smaller container to dispense directly to its customer.

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. Repackaging, Generally

FDA regards repackaging as the act of taking a finished drug 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 drug. Repackaging also includes the act of placing the contents of multiple containers (e.g., vials) of the same finished drug product into one container, as long as the container does not include other ingredients. If a drug is manipulated in any other way, including if the drug is reconstituted, diluted, mixed, or combined with another ingredient, that act is not considered repackaging.

Repackaging is performed by a range of entities, including facilities that specialize in repackaging drug products, and pharmacies, including pharmacies in hospitals and health systems. FDA is aware that repackaging is done for a variety of reasons including: to meet the needs of specific groups of patients (e.g., pediatric patients or ophthalmic patients who require smaller doses of approved sterile drug products that may not be available commercially); to reduce medication errors associated with drawing up a dose from a vial at the point of patient care; to reduce the availability of drug products of abuse when controlled substances are left over in a vial after a dose is drawn out; to provide a particular sized container to fit into a particular device to administer the drug (such as a particular pain medication pump); for convenience for the practitioner administering an injection to a patient; and in some cases to reduce cost. Some repackagers repackage both sterile and non-sterile drug products. For example, tablets and capsules are repackaged from large containers into smaller containers or blister packs, and creams and lotions are sometimes purchased in bulk and repackaged into smaller tubes or containers.

As part of the drug application review and approval process, FDA evaluates the container closure system and the packaging into which the drug will be placed, as well as the conditions under which the drug will be packaged. The container closure system and packaging can affect the quality of the drug product when it is on the market. In particular, during the approval process FDA reviews whether the container closure system and the packaging are appropriate for maintaining the stability of the drug product through its expiration date, as long as the container and package are not breached, and the drug is stored according to the conditions specified in the application. For drug products required to be sterile, FDA also considers whether the container closure system and packaging are adequate to ensure that the drug product will remain sterile until its expiration date, as long as the container closure is not breached and the drug product is stored appropriately.

When a drug product is repackaged, its characteristics may change in ways that have not been evaluated during the FDA approval process and that could affect the safety and efficacy of the drug product. Improper repackaging of drug products can cause serious adverse events. Of particular concern is repackaging of sterile drug products, which are susceptible to contamination and degradation. For example, failure to properly manipulate sterile drug products under appropriate aseptic conditions could introduce contaminants that could cause serious patient injury or death. Repackaging practices that conflict with approved product labeling could result in drug product degradation and adverse events associated with impurities in the product or lack of efficacy because the active ingredient has deteriorated.

B. Regulatory Framework for Repackaging

Repackaged drug products are generally not exempt from any of the provisions of the FD&C Act related to the production of drugs. For example, repackaged drug products are generally subject to the premarket approval, misbranding, and adulteration provisions of the FD&C Act, including section 505 (concerning new drug applications),[4] section 502(f)(1) (concerning labeling with adequate directions for use), and section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP)).

Drugs that are repackaged are not subject to sections 503A and 503B of the FD&C Act.[5] Therefore, drug products repackaged by state-licensed pharmacies, Federal facilities, or outsourcing facilities are not eligible for the exemptions provided under those sections. In this

[4] But see U.S. v. Kaybel, 430 F.2d 1346 (3d Cir. 1970) (holding that repackaging of approved Enovid (estrogen) tablets from large bottles into small bottles did not require pre-approval under section 505 of the FD&C Act).

[5] Section 503A of the FD&C Act exempts compounded drug products from sections 505, 502(f)(1), and 501(a)(2)(B) of the FD&C Act provided certain conditions are met, including that the drug product 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), 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. Drug products compounded in outsourcing facilities are not exempt from the CGMP requirements of section 501(a)(2)(B).

guidance, FDA describes the conditions under which it does not intend to take action regarding violations of certain requirements of the FD&C Act, in the context of drug repackaging.

C. Hospital and Health System[6] 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 are, or have recently been, listed on FDA's drug shortage list[7] 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 final guidance that clarifies the policy of the Food and Drug Administration regarding hospital pharmacies repackaging and safely transferring repackaged drugs to other hospitals within the same health system during a drug shortage."[8] These issues are addressed and clarified by this guidance and the guidance on *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application*. Therefore, when these guidances become final, section 506F of the FD&C Act will no longer apply.

III. POLICY

A. General Policy

As discussed above, repackaged drug products are generally subject to the adulteration, misbranding, and approval provisions of the FD&C Act.[9] FDA does not intend to take action for violations of sections 505 and 502(f)(1) if a state-licensed pharmacy, a Federal facility, or an

[6] 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.

[7] 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)).

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

[9] As described in section II.B., repackaged drug products are generally not exempt from any of the provisions of the FD&C Act related to the production of drugs. Therefore, drug products that do not meet the conditions in this guidance, including drug products repackaged by entities that are not state-licensed pharmacies, Federal facilities, or outsourcing facilities, generally must comply with requirements in the FD&C Act and FDA regulations applicable to drug products including, but not limited to, CGMP and new drug approval requirements.

outsourcing facility repackages drug products in accordance with the conditions described below, and any applicable requirements.[10] In addition, FDA does not intend to take action for violations of section 501(a)(2)(B) of the FD&C Act if the drug product is repackaged by a state-licensed pharmacy or a Federal facility in accordance with the conditions described below, and any applicable requirements.

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

1. The drug that is being repackaged is a prescription drug product approved under section 505 of the FD&C Act, except as provided in section III.B of this guidance regarding repackaging unapproved drug products that appear on FDA's drug shortage list under section 506E.

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

3. If the drug product is repackaged in a state-licensed pharmacy or a Federal facility (but not an outsourcing facility), it is repackaged and distributed[11] 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 health care setting, unless it is 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 amount of drug product that the state-licensed pharmacy or the Federal facility repackaged pursuant to patient-specific prescriptions or written orders in a previous, consecutive 14-day period, and based on a history of receipt of prescriptions or written orders over a consecutive 14-day period for such repackaged drug products.

4. The drug product is repackaged by or under the direct supervision of a licensed pharmacist.

5. Except as provided below for a single-dose vial, the drug product is repackaged in a way that does not conflict with approved drug product labeling.[12]

   For a single-dose vial that is repackaged into multiple units, the drug product is repackaged in a way that does not conflict with the approved labeling, except for the

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

[11] Distribution means that the repackaged drug product has left the facility in which it was repackaged.

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

statements designating the product as a single dose or single use product, and related language (e.g., discard remaining contents).[13]

6. The repackaged drug product is assigned a beyond-use-date (BUD)[14] as described below:

   a. **FDA-approved drug product with a specified in-use time**: If the drug product being repackaged is an FDA-approved drug product that specifies in the labeling a time within which the opened product is to be used (an "in-use" time), the repackaged drug product is assigned a BUD (1) that is established in accordance with the in-use time on the drug product being repackaged; or (2) that is the expiration date on the drug product being repackaged, whichever is shorter.[15]

   b. **FDA-approved drug product without an in-use time or unapproved drug product**: If the drug product being repackaged is an FDA-approved drug product whose labeling does not specify an in-use time, or if it is an unapproved drug product on the FDA drug shortage list (which does not have an in-use time reviewed by FDA as part of the drug approval process), the repackaged drug product is assigned a BUD (1) that is established in accordance with the time described in (i) or (ii) below, as applicable, or (2) that is the expiration date on the drug product being repackaged, whichever is shorter.[16]

      i. **Sterile Drug Products:** The repackaged drug product is assigned a BUD no longer than the following, even if the time until the expiration date on the drug product being repackaged is longer:

         1. If repackaged in a state-licensed pharmacy or Federal facility, the repackaged drug product is assigned a BUD that is[17]:

[13] This condition would not be satisfied if a drug product repackaged from a single-dose vial is repackaged in a way that conflicts with other language in the approved labeling (e.g., regarding storage conditions).

[14] Unless otherwise indicated, the BUD timeframes in this condition begin from the time in which the container of the original drug product to be repackaged is punctured or otherwise opened.

[15] For example, if an approved drug product that includes a 3-day in-use time and an expiration date of January 15, 2015 on the label is repackaged on January 1, 2015, the applicable BUD for the repackaged drug product would be January 4, 2015, because the labeled in-use time of 3 days is shorter than the time until the labeled expiration date of the drug product (14 days). If the drug product is repackaged on January 14, 2015, the applicable BUD for the repackaged drug product would be January 15, 2015, because the time until the labeled expiration date of the approved drug product is 1 day, which is shorter than the labeled 3-day in-use time.

[16] In other words, if the FDA-approved drug product does not have an in-use time, or the drug product being repackaged is an unapproved drug product, the times in (i) and (ii) are the default BUDs, unless the expiration date on the drug product being repackaged is shorter, in which case the BUD would be the same as the expiration date.

[17] These BUDs are consistent with the BUDs established by USP Chapter <797> for "medium-risk" compounded sterile preparations. Although USP <797> addresses *compounded* sterile preparations, many of the same principles for conditions and practices to assure sterility and stability of compounded drug products, such as the requirement to maintain a sterile environment, engage in appropriate sterile processing techniques, and put appropriate BUDs on the product, also apply to repackaged sterile drug products to help ensure their quality is not compromised during

- ≤ 30 hours if stored at USP controlled room temperature;
- ≤ 9 days if stored in a refrigerator; or
- ≤ 45 days if stored in a solid frozen state between -25°C and -10°C

2. **If repackaged in an outsourcing facility,** the outsourcing facility conducts a sterility test in accordance with CGMP requirements[18] (e.g., using the sterility test described in USP Chapter <71>) and receives passing results before release, and the repackaged drug product is assigned a BUD that is[19]:

- Not more than 14 days beyond completion of the sterility test or 28 days from the time of repackaging, whichever is shorter, if stored at USP controlled room temperature or in a refrigerator; or
- Not more than 45 days beyond completion of the sterility test or 59 days from the time of repackaging, whichever is shorter, if stored in a solid frozen state between -25°C and -10°C[20]

ii. **Non-sterile Drug Products:** The BUD for the repackaged drug product is no longer than the expiration date on the original drug product being repackaged.

7. Except with regard to BUDs, which are addressed in condition 6, above:
   a. If the drug product is repackaged in a state-licensed pharmacy or a Federal facility:
      i. If it is a non-sterile drug product, it is repackaged in accordance with USP Chapter <795>; or

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and after the repackaging operation. The BUDs for medium-risk compounded preparations in USP <797> are appropriate for sterile drug products that do not include an "in-use" time and are repackaged by a state-licensed pharmacy or Federal facility because the two activities present comparable risks.

[18] See 21 CFR part 211.

[19] These longer BUDs reflect 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. FDA has issued a draft guidance entitled, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* ("Interim CGMP Guidance"). (See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf) The Interim CGMP Guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated. The BUDs set forth for sterile drug products repackaged by outsourcing facilities in this condition are consistent with the BUDs listed in the Interim CGMP Guidance that are applicable to sterile drug products compounded at outsourcing facilities.

[20] The 28-day and 59-day timeframes provide for the 14 days it takes to receive results from the sterility test conducted under USP Chapter <71>.

ii. If it is sterile drug product, it is repackaged in accordance with USP Chapter <797>, e.g., a sterile drug product is repackaged in an area with air quality that meets or exceeds ISO Class 5 standards (see USP Chapter <797>, Table 1).

b. If the drug product is repackaged in an outsourcing facility, repackaging is conducted in accordance with CGMP requirements.

8. The drug product that is being repackaged does not appear on a list of drug products that have been withdrawn or removed from the market because they have been found to be unsafe or ineffective. For purposes of this provision, repackagers should refer to the list of drug products in 21 CFR 216.24, developed for use with sections 503A and 503B.

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

10. The repackaged drug product is distributed only in states in which the facility repackaging the drug product meets all applicable state requirements.

11. If the drug product is repackaged by an outsourcing facility:

    a. The label on the immediate container (primary packaging, e.g., the syringe) of the repackaged product includes the following:
        i. The statement "This drug product was repackaged by [name of outsourcing facility]"
        ii. The address and phone number of the outsourcing facility that repackaged the drug product
        iii. The established name of the original, approved drug product that was repackaged
        iv. The lot or batch number of the repackaged drug product
        v. The dosage form and strength of the repackaged drug product
        vi. A statement of either the quantity or volume of the repackaged drug product, whichever is appropriate
        vii. The date the drug product was repackaged
        viii. The BUD of the repackaged drug product
        ix. Storage and handling instructions for the repackaged drug product
        x. The National Drug Code (NDC) number of the repackaged drug product, if available[21]
        xi. The statement "Not for resale," and, if the drug product is distributed by an outsourcing facility other than pursuant to a

[21] The NDC number of the original approved drug product should not be placed on the repackaged drug product.

prescription for an individual identified patient, the statement "Office Use Only"

xii. If included on the label of the FDA-approved drug product from which the drug product is being 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 11.b.i.

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 repackaged products are distributed) includes:
    i. The active and inactive ingredients, if the immediate drug product label is too small to include this information
    ii. Directions for use, including, as appropriate, dosage and administration, and the following information to facilitate adverse event reporting: www.fda.gov/medwatch and 1-800-FDA-1088.

c. Each repackaged drug product is also accompanied by a copy of the prescribing information that accompanied the original drug product that was repackaged.

d. The drug 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, and providing 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 form and route of administration; the package description; the number of individual units produced; and the NDC number of the final product, if assigned.[22]

e. The outsourcing facility reports serious adverse events to FDA that may be associated with its repackaged drug products.

B. Repackaging Drugs on FDA's Drug Shortage List

This guidance addresses repackaging of prescription drug products, including drug products on FDA's drug shortage list, by a state-licensed pharmacy, Federal facility, or outsourcing facility, including within a hospital or health system. This guidance also specifically addresses the repackaging of single-dose vials, a practice that is sometimes used to extend the supply of a drug

[22] 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 current thinking on that topic. Although that guidance addresses reporting of compounded human drug products, outsourcing facilities should follow the same procedure to electronically report the drug products they repackaged.

product that is on the FDA drug shortage list. In addition, the first condition described in section III.A.1 of this guidance provides that the drug product being repackaged is a prescription drug product approved by FDA under section 505 of the FD&C Act. However, with respect to an unapproved drug product that appears on FDA's drug shortage list, FDA also does not intend to take action for violations of sections 505, 502(f)(1), and, as specified above, section 501(a)(2)(B), provided that the state-licensed pharmacy, the Federal facility, or the outsourcing facility (including within a hospital or health system) meets all of the conditions of this guidance, and the repackaged drug product is distributed during any period in which the drug product is listed on the drug shortage list under section 506E of the FD&C Act or during the 30 days following such period. As stated above, this guidance and the guidance on *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* clarify the Agency's policy regarding hospital pharmacies repackaging and safely transferring repackaged drug products to other hospitals within the same health system during a drug shortage. Therefore, when these guidances become final, section 506F of the FD&C Act will no longer apply.

Attachment 3

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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Leah Christl (CDER) at 301-796-0869 or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-7800.

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)

February 2015
Compliance

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

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
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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

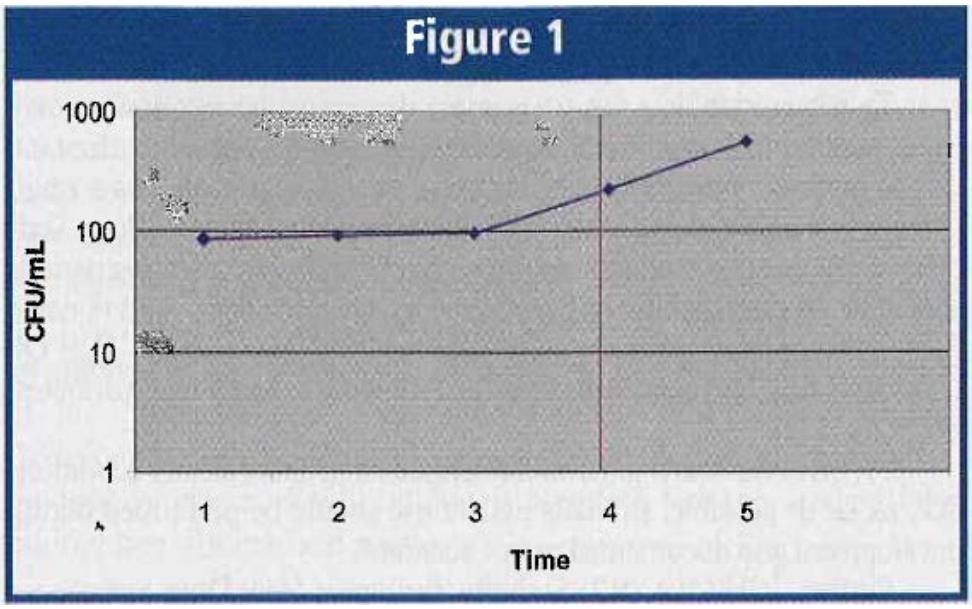
[27] USP51/NF26. United States Pharmacopeial Convention, 2008.
[28] See, Mahl, M.C., et al. Nitrogen Fixation by Members of the Tribe *Klebsielleae*, *J. Bacteriol.*, 1965, 89(6): 1482; Maki, D., et al., Infection Control in Intravenous Therapy, *Annals of Internal Medicine*, 1973, 79: 867.

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.

Figure 1



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.

Attachment 4

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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact H. Joy Sharp at 301-796-3647 or Joy.Sharp@fda.hhs.gov.

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

February 2015
Drug Safety

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

Guidance for Industry

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

February 2015
Drug Safety

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

This guidance is intended for firms that have registered with the Food and Drug Administration (FDA) under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as human drug compounding outsourcing facilities (outsourcing facilities). Under section 503B(b)(5) of the FD&C Act, an outsourcing facility must submit adverse event reports to FDA "in accordance with the content and format requirements established through guidance or regulation under section 310.305 of title 21, Code of Federal Regulations (or any successor regulations)."[2] This guidance explains FDA's current thinking on adverse event reporting for outsourcing facilities.

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. Statutory and Regulatory Framework

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

[2] 21 U.S.C. 353b(b)(5).

On November 27, 2013, the Drug Quality and Security Act (DQSA) was signed into law. Title I of the DQSA contains important provisions related to the oversight of human drug compounding.[3] The DQSA added section 503B to the FD&C Act. Under section 503B(b), a compounder can register as an *outsourcing facility* with FDA.[4] Under section 503B(b)(5), an outsourcing facility must submit adverse event reports to FDA "in accordance with the content and format requirements established through guidance or regulation under section 310.305 of title 21, Code of Federal Regulations (or any successor regulations)."[5]

Section 310.305 requires, among other things, that manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved new drug application or an abbreviated new drug application establish and maintain records and make reports to FDA of all serious, unexpected adverse drug experiences[6] associated with the use of their prescription drug products. For purposes of reporting adverse drug experiences, the term *prescription drug products* includes any compounded drug product subject to the prescription requirements in section 503(b)(1) of the FD&C Act. The adverse event reporting requirements apply to prescription drug products regardless of whether the outsourcing facility distributes them pursuant to prescriptions.[7]

In addition, on June 10, 2014, FDA issued a final rule requiring, among other things, that postmarketing safety reports required under 21 CFR 310.305, 314.80, 314.98, and 600.80 be submitted to FDA in an electronic format the Agency can process, review, and archive. The final rule also adds 21 CFR 329.100 to address electronic submission of safety reports required by section 760 of the FD&C Act regarding serious adverse event reporting for nonprescription drugs.[8] These requirements are effective as of June 10, 2015.[9]

Under section 503B, outsourcing facilities are required to submit adverse event reports to FDA, in accordance with content and format requirements established through guidance or regulation under 21 CFR 310.305 (or any successor regulations).

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[3] See text of Compounding Quality Act at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm376732.htm.

[4] 21 U.S.C. 353b(b).

[5] Id. at 353b(b)(5).

[6] This guidance uses the terms *adverse drug experience* and *adverse event* interchangeably.

[7] Section 503B(d)(4)(C) of the FD&C Act provides that outsourcing facilities may or may not obtain prescriptions for identified individual patients. Although outsourcing facilities may send prescription drugs to healthcare facilities without obtaining prescriptions for identified individual patients, drugs produced by outsourcing facilities remain subject to the requirements in section 503(b) of the FD&C Act. Therefore, an outsourcing facility cannot dispense a prescription drug to a patient without a prescription.

[8] 21 U.S.C. 379aa.

[9] See 79 FR 33072. FDA intends to issue guidance reflecting the requirements of the final rule before they become effective.

Failure to report adverse events by an entity that is registered in accordance with section 503B(b) is a prohibited act under section 301(ccc)(3) of the FD&C Act.[10] Violations relating to this provision are subject to regulatory and enforcement action.

B. Section 310.305

Section 310.305(b) defines a *serious adverse drug experience* to mean:

> Any adverse drug experience occurring at any dose that results in any of the following outcomes:
>
> - Death,
> - A life-threatening adverse drug experience,
> - Inpatient hospitalization or prolongation of existing hospitalization,
> - A persistent or significant disability/incapacity, or
> - A congenital anomaly/birth defect
>
> Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include
>
> - allergic bronchospasm requiring intensive treatment in an emergency room or at home,
> - blood dyscrasias or convulsions that do not result in inpatient hospitalization, or
> - the development of drug dependency or drug abuse.

Section 310.305(b) defines an *unexpected adverse drug experience* as any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. The term *unexpected*, as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling), rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

The regulations require reporting of each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible, but in no case later than 15 calendar days of initial receipt of the information along with a copy of the drug product's current labeling.[11] In addition, all serious, unexpected adverse drug experiences that are the subject of these reports

[10] 21 U.S.C. 331(ccc)(3).

[11] See 21 CFR 310.305(c)(1)(i).

shall be promptly investigated and a follow-up report must be submitted within 15 calendar days of receipt of new information or as requested by FDA.[12]

FDA's regulations also state that information on the names and addresses of individual patients should ***not*** be included.[13] A unique code number should therefore be assigned instead for each individual patient and placed in section A1 of Form FDA 3500A (Patient Identifier).

The regulations require that firms maintain certain records relating to adverse drug experiences required to be reported under section 310.305 for 10 years and provide FDA access to them.[14] The regulations also provide a disclaimer that the report or information submitted (and any release by FDA of that report or information) does not necessarily reflect a conclusion that the report or information constitutes an admission that the drug caused or contributed to an adverse effect.[15]

III. Adverse Event Reporting by Outsourcing Facilities

A. What to Report

Outsourcing facilities must report all serious, unexpected adverse drug experiences associated with the use of their compounded prescription drug products.

In addition, FDA strongly recommends that outsourcing facilities report ***all*** serious adverse drug experiences associated with their compounded prescription drug products. We believe reporting ***all*** serious adverse events would provide important information about potential product quality issues or public health risks associated with drug products compounded by outsourcing facilities.

B. Threshold for Reporting

As noted above, outsourcing facilities must submit to FDA reports of all serious, unexpected adverse events associated with their compounded prescription drugs.[16]

When considering any adverse drug experience for submission to FDA in a report, after receiving information about the adverse drug experience, an outsourcing facility should actively investigate the following four data elements, which are described in greater detail later in this section:

1. An identifiable patient

[12] See 21 CFR 310.305(c)(2).

[13] See 21 CFR 310.305(e).

[14] See 21 CFR 310.305(f).

[15] See 21 CFR 310.305(g).

[16] See 21 CFR 310.305(c).

2. An identifiable reporter
3. A suspect drug
4. A serious adverse event

Although an outsourcing facility should actively seek to obtain each of these four data elements, the facility must submit the report as a *15-day "Alert report"* to FDA as soon as possible, but no later than 15 calendar days after first receiving information about the adverse event.[17] **Reports should be submitted as long as the outsourcing facility has information on at least the suspect drug and the adverse event.**

The outsourcing facility must also promptly investigate adverse events that are the subject of a 15-day "Alert report".[18] If the outsourcing facility was not able to include all four of the data elements in its initial report, it should exercise due diligence to obtain information about any of the remaining elements. Additionally, the outsourcing facility should report new information it obtains regarding data elements listed in its initial report when the information could assist FDA in investigating an adverse event. If additional information is not obtainable, the outsourcing facility should maintain records of the steps that were taken to attempt to seek the additional information.[19]

An outsourcing facility must submit a follow-up report within 15 calendar days of receipt of new information about the adverse event, or as requested by FDA.[20]

1. Identifiable Patient

To have an identifiable patient, there should be enough information to indicate the existence of a specific patient. One or more of the following would qualify a patient as identifiable:

- Age or age category (e.g., adolescent, adult, elderly)
- Gender
- Initials
- Date of birth
- Name
- Patient identification number

A report stating that "an elderly woman had anaphylaxis" or "a young man experienced anaphylaxis" would be sufficient. If a report refers to groups of unknown size, such as "some" or "a few" college students had anaphylaxis, the outsourcing facility should follow up to find out

[17] See 21 CFR 310.305(c)(1)(i).

[18] See 21 CFR 310.305(c)(2).

[19] Id.

[20] Id.

how many students were involved and submit a separate report to FDA for each student, because each is considered to be an identifiable patient. The outsourcing facility should distinguish each identifiable patient so that it is clear that each report is not a duplicate report of a single adverse event.

Patients should not be identified by name or address when reporting to FDA. Instead, the outsourcing facility should assign a unique code number for each patient.[21]

2. Identifiable Reporter

A reporter is a person who initially notifies the outsourcing facility about an adverse event. An initial reporter can be a patient, consumer, family member, doctor, pharmacist, other health care professional, or other individual. The outsourcing facility should obtain, if possible, sufficient information to indicate that the reporter is an identifiable person who purports to have knowledge about the patient, adverse event, and drug involved. One or more of the following would qualify a reporter as identifiable:

- A personal identifier (e.g., name)
- A professional identifier (e.g., doctor, nurse, pharmacist)
- Contact information (e.g., e-mail address, phone number)

When possible, the outsourcing facility should attempt to obtain the initial reporter's contact information so that the outsourcing facility and/or FDA can conduct follow-up investigations. If an identifiable reporter provides contact information, but requests that the outsourcing facility not forward this information to FDA, the outsourcing facility can submit a report to FDA without specifically identifying the reporter by filling out the *initial reporter identity fields* on Form FDA 3500A with a statement such as "Requested Anonymity."

If an adverse event is reported anonymously to an outsourcing facility, the outsourcing facility should note when submitting the report to FDA that the initial reporter is anonymous (section E1 of the Form FDA 3500A).

3. Suspect Drug

A *suspect drug product* is one that the initial reporter suspected was associated with the adverse event.

For reporting purposes, an adverse event report should describe the known product attributes (e.g., active ingredient(s), dosage form, strength, color, lot number). If an adverse event involves multiple suspect drug products that are compounded by the same outsourcing facility, the outsourcing facility should submit only one report that notes the drug product considered most

[21] See 21 CFR 310.305(e).

suspect by the reporter. If the reporter views each drug product as equally suspect, the outsourcing facility should submit only one report that lists all of the drug products as suspect. In all cases, including those where not all of the drug products were made by the outsourcing facility, the report would include information on all suspect drug products.

4. Serious Adverse Event

As described above, outsourcing facilities must report an unexpected adverse event to FDA that results in one or more of the following patient outcomes:

- Death,
- A life-threatening adverse drug experience,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant disability or incapacity, or
- A congenital anomaly or birth defect.[22]

Inpatient hospitalization includes initial admission to the hospital on an inpatient basis (even if released the same day).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience if, when based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

The outsourcing facility must report the adverse event to FDA if it is serious and unexpected. For reporting purposes, an adverse event should be described in terms of signs (including abnormal laboratory findings, if appropriate), symptoms, or disease diagnosis (including any colloquial descriptions obtained), if available.

As part of the adverse event report, we encourage, as appropriate, attachment of the following: (1) hospital discharge summaries, (2) autopsy reports/death certificates, (3) relevant laboratory data, and (4) other critical clinical data. In the case of a death, outsourcing facilities should also provide any available information on the event(s) that led to the death.

C. How to Report Adverse Events

Outsourcing facilities must report adverse events using Form FDA 3500A or an alternate method in accordance with 21 CFR 310.305(d) and should submit the report to FDA as described here. FDA is currently modifying its process to specifically identify reports from outsourcing facilities and drug products compounded by outsourcing facilities. Until those actions are completed, FDA will not be able to effectively accept adverse event reports from outsourcing facilities

[22] See 21 CFR 310.305(b).

through the electronic system, but FDA will issue additional guidance when the electronic interface is ready to accept these reports.

1. Obtaining Form FDA 3500A

Outsourcing facilities can access paper copies of Form FDA 3500A as follows:

- Download and print the Form FDA 3500A and instructions from the Internet at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

- Request a paper copy of Form FDA 3500A and instructions from CDER's Division of Drug Information:

  By e-mail: druginfo@fda.hhs.gov

  By phone: 1-800-FDA-1088
  1-888-INFO-FDA
  1-888-463-6332 or (301) 796-3400

  By mail: Division of Drug Information
  10903 New Hampshire Avenue
  WO51-2201
  Silver Spring, MD 20993-0002

2. How to Submit Adverse Event Reports

Until FDA modifies its adverse event collection database to more effectively accommodate direct electronic submissions from outsourcing facilities, adverse event reports and follow-up reports for compounded drug products should be provided in hard copy.[23] In accordance with section 310.305(c), outsourcing facilities must submit a copy of Form FDA 3500A to:

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

3. What Should Be Included

[23] FDA is currently modifying its database to include fields specifically identifying reports from outsourcing facilities and drug products compounded by outsourcing facilities. As noted above, on June 10, 2014, FDA issued a final rule requiring that, among other things, postmarketing safety reports under 21 CFR 310.305 be submitted to FDA in electronic format (79 FR 33072). This rule is effective as of June 10, 2015.

Outsourcing facilities must indicate whether the report is a 15-day Alert report or a 15-day Alert report-follow-up [24] and should include the following header on the first page of a cover letter accompanying each Form FDA 3500A:

Adverse event report submitted by human drug compounding outsourcing facility (503B)

If the compounded drug product contains multiple components (e.g., excipients, drug substances, finished dosage forms), the outsourcing facility should list each component and its manufacturer, if known, in section C10 of Form FDA 3500A. The outsourcing facility should also list in section C10, in addition to the components of the compounded drug and each component's manufacturer, any other medical product(s) the patient was taking at the time he or she experienced the adverse event and the manufacturer of that product(s) (i.e., any concomitant medical products).

As part of each adverse event report, outsourcing facilities must submit a copy of the current labeling for the compounded drug product that is the subject of the report.[25]

When submitting a follow-up report under 21 CFR 310.305(c)(2), the report should be assigned the same manufacturer report number that appears in section G9 of the initially submitted Form FDA 3500A.

D. Inspection of Adverse Event Reporting

Under section 503B(b)(4) of the FD&C Act, outsourcing facilities are subject to inspection pursuant to section 704 of the FD&C Act and are not eligible for the exemption under section 704(a)(2)(A) of the FD&C Act.

As part of its inspections of outsourcing facilities, FDA may review adverse event information received by the outsourcing facility.[26] FDA may also review whether the outsourcing facility has developed and implemented written processes for the surveillance, receipt, evaluation, and

[24] 21 CFR 310.305(c)(4).

[25] See section 21 CFR 310.305(c)(1)(i).

[26] See section 21 CFR 310.305(f)(3).

reporting of adverse events for the drug products it compounds as described in 21 CFR 310.305(a) and 211.198.[27]

E. Recordkeeping

Under section 310.305, all entities subject to the regulation must maintain for 10 years the records of all adverse events required to be reported under this section, including raw data and any correspondence relating to the adverse event, and allow FDA access to review, copy, and verify these records, in accordance with 21 CFR 310.305(f). In addition, the outsourcing facility should maintain records of its efforts to obtain the four data elements discussed in section III.B. for each individual case report.

[27] Outsourcing facilities are subject to current good manufacturing practice (CGMP) requirements. Pending the development of further regulations, FDA expects outsourcing facilities, among other things, to comply with the CGMP requirements in 21 CFR 211.198, which is a companion to 21 CFR 310.305. This section requires that "[w]ritten procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed," and further requires that these procedures must include "provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with [section] 310.305 … of this chapter." See FDA's guidance for industry, *Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf.

Attachment 5

DRAFT MEMORANDUM OF UNDERSTANDING ADDRESSING CERTAIN DISTRIBUTIONS OF COMPOUNDED HUMAN DRUG PRODUCTS BETWEEN THE STATE OF [insert STATE] AND THE U.S. FOOD AND DRUG ADMINISTRATION

I. PURPOSE

This Memorandum of Understanding (MOU) establishes an agreement between the State of [insert State] and the U.S. Food and Drug Administration (FDA) regarding the distribution of inordinate amounts of compounded human drug products interstate and the appropriate investigation by the State of [insert State] of complaints relating to compounded human drug products distributed outside such State. This is the MOU provided for by section 503A(b)(3)(B)(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 353a), and does not apply to drugs that are compounded by registered outsourcing facilities.

II. BACKGROUND

a. Section 503A of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from three sections of the FD&C Act requiring:

    1. Compliance with current good manufacturing practice (CGMP) (section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B));

    2. Labeling with adequate directions for use (section 502(f)(1) (21 U.S.C. 352(f)(1)); and

    3. FDA approval prior to marketing (section 505 (21 U.S.C. 355)).

b. To qualify for these exemptions, among other things, a compounded human drug product must meet the condition in section 503A(b)(3)(B) of the FD&C Act, under which the drug product is compounded in a State that:

    1. Has entered into an MOU with FDA that addresses the distribution of inordinate amounts[1] of compounded human drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded human drug products distributed outside such State (section 503A(b)(3)(B)(i)); or

[1]The definition of *inordinate amounts* in this MOU is separate and distinct from and should not be used in relation to the term *inordinate amounts* as it is used in section 503A(b)(1)(D) of the FD&C Act (pertaining to compounding a drug product that is essentially a copy a of commercially available drug product).

2. Has not entered into an MOU with FDA and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded human drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician (section 503A(b)(3)(B)(ii)).

c. Section 503A(b)(3) of the FD&C Act directs FDA to develop a standard MOU for use by the States in complying with section 503A(b)(3)(B)(i). The content of this MOU conforms with the standard MOU developed by FDA for this purpose.

III. SUBSTANCE OF AGREEMENT

a. Investigation of Complaints Relating to Compounded Human Drug Products Distributed Outside the State

1. Appropriate agencies of the State of [insert State] will investigate complaints received relating to human drug products compounded by a pharmacist, pharmacy, or physician located in the State of [insert State] and distributed outside the State. Primary responsibility for investigating complaints involving human drug products compounded by a pharmacy or pharmacist will generally lie with the [insert State Board of Pharmacy or other appropriate State agency] and similar responsibility for human drug products compounded by a physician will generally lie with the [insert State Medical Licensing Board or other appropriate State agency], except where State laws otherwise require. The [insert State Board of Pharmacy or other appropriate State agency] and [insert State Medical Licensing Board or other appropriate State agency] will cooperate in investigating any complaints involving overlapping jurisdiction.

2. Complaints relating to compounded human drug products distributed outside the State that will be investigated include reports received by the State concerning adverse drug experiences, or product quality issues that if left uncorrected could lead to potential public health risks or safety concerns. See Appendix A for definitions of *adverse drug experiences* and *product quality issues*.

3. Any investigations performed by the State of [insert State] under this MOU will include, but are not limited to (1) determination of whether there is a potential public health risk or safety concern associated with the compounded human drug product; and (2) confirmation that any risk or safety concern associated with the product is adequately contained (i.e., there is no ongoing risk to the public).

4. Based on findings from an investigation of a complaint about compounded human drug products distributed outside the State, if the complaint is found to be valid, the State of [insert State], in accordance with State law, will take appropriate action to ensure that the relevant compounding pharmacist, pharmacy, or physician determines the root cause of the problem that is the subject of the complaint and undertakes sufficient corrective action to eliminate any identified public health risk relating to the complaint, including the risk that future similar complaints may occur.

5. The State of [insert State] will notify FDA by sending an e-mail to StateMOU@fda.hhs.gov (see section III.c.1 of this MOU) within 72 hours of receiving any complaint relating to a compounded human drug product distributed outside the State involving a public health risk or immediate safety concern, such as a report of a serious adverse drug experience or serious product quality issue. The notification will include the State's initial assessment of the validity of the complaint relating to a compounded human drug product distributed outside the State, as well as a description of any actions the State has taken or plans to take to address such complaints. See Appendix A for definitions of *serious adverse drug experience* and *serious product quality issue*.

6. The State of [insert State] will maintain records of the complaint, the investigation of the complaint, and any response to or action taken as a result of the complaint, beginning when the State receives notice of the complaint. The State will maintain these records for at least 3 years. The 3-year period begins on the date of final action on a complaint, or the date of a decision that the complaint requires no action.

b. Distribution of Inordinate Amounts of Compounded Human Drug Products Interstate

1. The State of [insert State] will review compounding records during inspections of compounding pharmacies to identify whether the compounding pharmacy, or the compounding pharmacist or physician, is distributing inordinate amounts of compounded human drug products interstate. See Appendix A for the definition of *distribution*.

2. The State of [insert State] will notify FDA by sending an e-mail to StateMOU@fda.hhs.gov (see section III.c.1 of this MOU) within 7 days of identifying a pharmacist, pharmacy, or physician within its jurisdiction that has distributed inordinate amounts of compounded human drug products interstate.

3. The State of [insert State] will take action regarding any pharmacy, pharmacist, or physician that distributes inordinate amounts of

compounded human drug products interstate. State action may include a warning letter, enforcement action, suspension or revocation of a license, or other action consistent with State law. FDA may also take action regarding any pharmacy, pharmacist, or physician that distributes inordinate amounts of compounded human drug products interstate.

4. For purposes of this MOU, a pharmacist, pharmacy, or physician has distributed an inordinate amount of compounded human drug products interstate if the number of units of compounded human drug products distributed interstate during any calendar month is equal to or greater than 30 percent of the number of units of compounded and non-compounded drug products distributed or dispensed both intrastate and interstate by such pharmacist, pharmacy, or physician during that month. Exception: For purposes of this MOU, FDA does not intend to include, in the consideration of inordinate amounts, prescriptions dispensed to a patient (or patient's agent), if the patient (or patient's agent) to whom the drug is dispensed carries the drug across State lines after it has been dispensed to the patient (or patient's agent) at the facility in which the drug was compounded.

c. Submission and Disclosure of Information

1. When submitting information to StateMOU@fda.hhs.gov regarding complaints relating to compounded drug products distributed outside the State or distribution of inordinate amounts of drugs interstate, the following minimum information will be included:

- Name and contact information of the complainant, in the case of a complaint;
- Name and address of the pharmacist/pharmacy/physician that is the subject of the complaint or distribution in inordinate amounts;
- Description of the complaint, or description of the evidence indicating that the pharmacist/pharmacy/physician has distributed inordinate amounts of compounded human drug products interstate, including a description of any compounded drug product that is the subject of the complaint or distribution;
- State's initial assessment of the validity of the complaint relating to a compounded human drug product distributed outside the State; and

- Description and date of any actions the State has taken to address the complaint or the distribution of inordinate amounts of compounded human drug products interstate.

2. The parties to this MOU will share information consistent with applicable statutes and regulations. The parties recognize that a separate agreement under 21 CFR 20.88 or commissioning of officials under 21 CFR 20.84 may be necessary before FDA can share information that is protected from public disclosure. Such an agreement, or commissioning terms, will govern FDA's sharing of the following types of information:

    - confidential commercial information, such as the information that would be protected from public disclosure under Exemption 4 of the Freedom of Information Act (FOIA) (5 U.S.C. 552(b)(4));

    - personal privacy information, such as information that would be protected from public disclosure under Exemption 6 or 7(C) of the FOIA (5 U.S.C. 552(b)(6) and(7)(C)); or

    - information that is otherwise protected from public disclosure by Federal statutes and their implementing regulations (e.g., Trade Secrets Act (18 U.S.C. 1905)), the Privacy Act (5 U.S.C. 552a), other Freedom of Information Act exemptions not mentioned above (5 U.S.C. 552(b)), the FD&C Act (21 U.S.C. 301 et seq.), the Health Insurance Portability and Accountability Act (Public Law 104-191), and FDA's regulations in parts 20 and 21 (21 CFR parts 20 and 21)).

    FDA agrees that information provided to FDA by the State of [insert State] will only be disclosed consistent with applicable federal law and regulations governing the disclosure of such information, including, but not limited to, the FOIA (5 U.S.C. 552(b)), the FD&C Act (21 U.S.C. 301 et seq.), 21 U.S.C. 331(j), 21 U.S.C. 360j(c), the Trade Secrets Act (18 U.S.C. 1905), FDA's regulations in 21 CFR parts 20 and 21, and other pertinent laws and regulations.

IV. ENFORCEMENT AUTHORITIES AND LEGAL STATUS OF AGREEMENT

The parties to this MOU recognize that FDA and the State of [insert State] retain the statutory and regulatory authorities provided by the FD&C Act, other Federal statutes and attendant regulations, and State statutes and regulations. The parties also recognize that this agreement does not restrict FDA or any other Federal agency from taking enforcement action, when appropriate, to ensure compliance with Federal statutes, including the FD&C Act and attendant regulations, or

prevent the State of [insert State] from taking enforcement action, as appropriate, to ensure compliance with applicable State statutes and regulations. This MOU does not create or confer any rights for or on any person. By signing this MOU, the State of [insert State] affirms that it now possesses and will maintain, at the discretion of the State legislature, the legal authority (under State statutes and/or regulations) and the resources necessary to effectively carry out all aspects of this MOU. If State law changes such that the State no longer has the legal authority or resources necessary to effectively carry out all aspects of this MOU, the State will notify FDA.

V. NAME AND ADDRESS OF PARTICIPATING AGENCIES

U.S. Food and Drug Administration
Center of Drug Evaluation and Research
Office of Compliance
Office of Unapproved Drugs and Labeling Compliance
10903 New Hampshire Avenue
Bldg. 51, Suite 5100
Silver Spring, MD 20993-0002
Telephone: (301) 796-3110
E-mail: StateMOU@fda.hhs.gov

[State]
TBD

Upon signing the MOU, each party must designate one or more liaisons to act as points of contact. Each party may designate new liaisons at any time by notifying the other party's liaison(s) in writing. If, at any time, an individual designated as a liaison under this agreement becomes unavailable to fulfill those functions, the parties will name a new liaison within 2 weeks and notify the other party's liaison(s).

VI. PERIOD OF AGREEMENT

a. When accepted by both parties, this MOU will be effective from the date of the last signature and will continue until terminated by either party. It may be terminated in writing by either party, upon a 30-day notice of termination. Notice of termination will be sent to the address listed in section V of this MOU.

b. If the State does not adhere to the provisions of this MOU, including conducting an investigation of complaints related to compounded human drug products distributed outside the State, the MOU may be terminated upon 30-days' notice of termination.

In case of termination, FDA will post a notice of the termination on its Web site and the State will notify all pharmacists, pharmacies, and physicians within the

State of the termination and advise them that as of 30 days from the date of the posting of the termination notice, compounded human drug products may be distributed (or caused to be distributed) out of the State only in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by the licensed pharmacist, licensed pharmacy, or licensed physician (section 503A(b)(3)(B)(ii) of the FD&C Act).

VII. APPROVALS

APPROVED AND ACCEPTED FOR THE U.S. FOOD AND DRUG ADMINISTRATION	APPROVED AND ACCEPTED FOR THE STATE OF [insert State]
By (Type Name)	By (Type Name)
Title	Title
Date	Date

Appendix A. Definition of Terms Used in the MOU

- **Adverse Drug Experience**: Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose, whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action (21 CFR 310.305(b)).

- **Distribution:** *Distribution* means that a compounded human drug product has left the facility in which the drug was compounded. Distribution includes delivery or shipment to a physician's office, hospital, or other health care setting for administration and dispensing to an agent of a patient or to a patient for the patient's own use.

  Note: To qualify for the exemptions under section 503A, a compounder must obtain a prescription for an individually identified patient (section 503A(a) of the FD&C Act). This MOU will not alter this condition.

- **Product Quality Issue**: Information concerning (1) any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or (2) any bacteriological contamination; any significant chemical, physical, or other change or deterioration in the distributed drug product; or any failure of one or more distributed batches of the drug product to meet the applicable specifications (21 CFR 314.81(b)(1)). Contamination in general, including but not limited to mold, fungal, bacterial, or particulate contamination, is a product quality issue.

- **Serious Adverse Drug Experience**: Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 310.305(b)).

- **Serious Product Quality Issue**: Any product quality issue that may have the potential to cause a serious adverse drug experience (e.g., possible contamination, superpotent product).