Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 The repackaging of biological products subject to licensure under section 351 is addressed in a separate draft guidance document.[3]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[3] FDA has issued a draft guidance, titled *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application.* Once finalized, that guidance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.