Compounding Certain Beta-Lactam Products in Shortage Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Immediately in Effect Guidance for Industry

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Comments may be submitted at any time for Agency consideration. Submit electronic comments to *https://www.regulations.gov*. Submit written comments to the Dockets Management Staff (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*.

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

November 2022
Compounding

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Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes the Food and Drug Administration's (FDA or the Agency) regulatory and enforcement priorities regarding preparation of beta-lactam oral antibiotic suspension products that appear on FDA's drug shortage list by a licensed pharmacist in a State-licensed pharmacy or Federal facility. There is currently an acute shortage of amoxicillin oral antibiotic powder for suspension. Amoxicillin oral antibiotic powder for suspension products currently appear on FDA's drug shortage list. Amoxicillin is widely used for the treatment of bacterial upper and lower respiratory infections in the pediatric population, among other uses. As a result of this shortage, there is an urgent need to increase the supply of these beta-lactam oral suspension products. FDA has received a number of reports related to increased demand for amoxicillin oral antibiotic suspension products in particular. FDA has also received requests for clarification about preparation of compounded versions of those products from FDA-approved tablets and capsules.

This guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately because of the public health need for amoxicillin oral antibiotic suspension products, but it remains subject to comment in accordance with the Agency's good guidance practices.

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

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

II. BACKGROUND

Compounded drug products are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality. Section 503A of the FD&C Act (21 U.S.C. 353a) provides that a drug product compounded by a licensed pharmacist in a State-licensed pharmacy or a Federal facility or by a licensed physician can qualify for exemptions from requirements under three other sections of the FD&C Act: adequate directions for use (section 502(f)(1) (21 U.S.C. 352(f)(1)), new drug approval requirements (section 505 (21 U.S.C. 355)), and current good manufacturing practice (CGMP) requirements (section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B))) if all of the conditions in section 503A are met.

One of the conditions in section 503A of the FD&C Act is that each drug product must be compounded for an identified individual patient based on the receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient.[2] If an FDA-approved drug product is on FDA's drug shortage list, it may be compounded by an outsourcing facility in accordance with section 503B of the FD&C Act or by a licensed pharmacist in a State-licensed pharmacy or Federal facility in accordance with section 503A of the FD&C Act.[3]

Under the FD&C Act, a drug is adulterated if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health (section 501(a)(2)(A) of the FD&C Act (21 U.S.C. 351(a)(2)(A)) (insanitary conditions provision). Section 503A of the FD&C Act does not provide an exemption from the insanitary conditions provision.[4] Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious adverse events, including death. Processing of beta-lactam drugs without complete and

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[2] See section 503A(a) of the FD&C Act. See also FDA's guidance for industry *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (December 2016). We update guidances periodically. For the most recent version of the guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] The provision in section 503A of the FD&C Act that applies to compounding a drug product that is essentially a copy of a commercially available drug does not apply to compounding a drug on FDA's drug shortage list because FDA does not consider products on FDA's drug shortage list to be commercially available. See section 503A(b)(1)(D) of the FD&C Act, and FDA's guidance for industry *Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (January 2018).

[4] *Insanitary conditions* are conditions that could cause a drug to become contaminated with filth or rendered injurious to health. The drug itself need not actually be contaminated. A drug that is actually contaminated with any filthy, putrid, or decomposed substance is deemed to be adulterated under section 501(a)(1) of the FD&C Act (21 U.S.C. 351(a)(1)).

comprehensive separation[5] from non-beta-lactam products is an example of an insanitary condition that FDA has observed.[6]

In addition to penicillin, all beta-lactam drugs can be sensitizing agents; therefore, cross-contamination between any beta-lactam drug and other drugs could initiate the same types of drug-induced life-threatening allergic reactions that penicillins can trigger. Therefore, any handling of any beta-lactam drugs should be done in a manner to prevent cross-contamination with non-beta-lactam drugs, thereby reducing the potential for drug-induced, life-threatening allergic reactions.

The current shortage of amoxicillin oral antibiotic powder for suspension products and increased demand for beta-lactam oral antibiotic suspension products could lead to potentially serious or life-threatening situations in particular in the pediatric population, especially during the upcoming fall and winter months when the incidence of upper and lower respiratory infections is expected to peak. Therefore, based on risk management principles, in order to address access concerns while also minimizing the potential for cross-contamination and the resulting hypersensitivity or allergic reactions, FDA intends to prioritize its regulatory and enforcement actions regarding the preparation of beta-lactam oral antibiotic suspension products that appear on FDA's drug shortage list by compounders under section 503A as described below.

III. DISCUSSION

For a licensed pharmacist in a State-licensed pharmacy or Federal facility that has not registered as an outsourcing facility and that compounds beta-lactam oral antibiotic suspension products that appear on FDA's drug shortage list, the Agency intends to prioritize its regulatory and enforcement actions with respect to the insanitary conditions provision to focus on the potential for harm to the public health, taking into consideration the public health need for beta-lactam oral antibiotic suspension products at this time.

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[5] Complete and comprehensive separation refers to a cross-contamination prevention strategy that consists of: (1) the complete physical separation of beta-lactam production area(s) (including separate air handling system(s)) from production areas for other drugs; and (2) additional design and procedural controls for facilities, equipment, material, and personnel that are necessary to support and maintain the integrity of the physical separation (e.g., dedicated equipment; utilities management (waste flow, including the potential for beta-lactam production exhaust to contaminate an adjacent building air intake, vacuum systems); people/material/equipment flow; personnel gowning; decontamination; monitoring containment; testing; compliance with procedures; investigations). Although separate buildings could ensure separation of beta-lactam operations from non-beta-lactam operations, it is feasible for one building to contain a dedicated area for beta-lactam production that is completely isolated and sealed off from the rest of the building. For example, separate entries and exits to the beta-lactam segment of the building would be necessary to ensure comprehensive separation. In the limited cases in which this design concept could be considered, a risk assessment should demonstrate that the design provides as much protection against cross-contamination as is achieved by producing in a separate building.

[6] See FDA's guidance for industry on *Insanitary Conditions at Compounding Facilities*. The guidance explains that "processing of beta-lactams" does not refer to mixing, reconstituting, or other such acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling, at the immediate point of dispensing for administration to the intended patient.

As noted above, FDA's insanitary conditions guidance describes the processing of beta-lactams without complete and comprehensive separation from non-beta-lactam products as an example of an insanitary condition the Agency has observed. However, during the time that beta-lactam antibiotic powder for oral suspension products are on the FDA shortage list (or for such shorter time as FDA may announce by updating or withdrawing this guidance based on evolving needs and circumstances), based on the Agency's current understanding of the potential for risk of contamination, compounders under section 503A of the FD&C Act that prepare beta lactam oral antibiotic suspension products that appear on FDA's shortage list without complete and comprehensive separation from non-beta-lactam products should take at least the following minimum steps to mitigate the potential risk of cross-contamination and reduce risk to patients. FDA generally intends to prioritize its regulatory and enforcement actions if the following steps are not all followed when preparing beta-lactam oral antibiotic suspension products that appear on FDA's shortage list without complete and comprehensive separation from non-beta-lactam products:

1. Use of FDA-approved beta-lactam tablets and capsules instead of bulk drug substances to compound the beta-lactam oral antibiotic suspension product;
2. Temporal segregation of the compounding of these oral suspensions from non-beta-lactam products;
3. Use of dedicated or disposable equipment, utensils, and personal protective equipment (e.g., gowns, gloves);
4. Segregation and storage in a separate area of any equipment, utensils, and personal protective equipment used in the compounding of these oral suspensions (e.g., glassware, mortar and pestle) from equipment, utensils, and personal protective equipment not used in beta-lactam compounding;
5. Trituration of the FDA-approved product after wetting it with a quantity of the suspension vehicle sufficient to eliminate formation of product dust;
6. Use of proper cleaning procedures after completing compounding, including use of peroxide or bleach solutions to deactivate the beta-lactam ring of any drug residue on surfaces. The use of strong oxidizers should be followed by neutralizers and volatile cleaning agents (e.g., purified water, isopropanol) to minimize damage to these surfaces;
7. Containment and remediation of spills;
8. The beyond-use-date assigned to the compounded oral suspension does not exceed the beyond-use-date of the related reconstituted FDA-approved beta-lactam antibiotic powder for oral suspension product that is on FDA's drug shortage list, as found on the approved labeling; and
9. Storage conditions used for the compounded oral suspension are consistent with those for the related reconstituted FDA-approved beta-lactam antibiotic powder for oral suspension product that is on FDA's drug shortage list, as found on the approved labeling.

Health care providers may also consider FDA-approved alternatives to the product in shortage.

FDA also recommends monitoring for reports of allergic reactions, including anaphylactic shock, that might be related to unintentional beta-lactam exposure from the use of non-beta-lactam drugs. If such reports are confirmed, the pharmacy should take appropriate action, which may include notifying patients and medical providers. If there are reports of anaphylactic shock or

allergic reactions related to unintentional exposure, the pharmacy should stop compounding beta-lactam products.

FDA encourages consumers, patients, and health care professionals to report adverse events or quality problems experienced with the use of compounded drugs to FDA's MedWatch Adverse Event Reporting program:

- Complete and submit the report online at MedWatch: The FDA Safety Information and Adverse Event Reporting Program; or
- Download and complete the form, then submit it via fax at 1-800-FDA-0178.