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DRAFT GUIDANCE

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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
Procedural

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Contains Nonbinding Recommendations

Draft — Not for Implementation

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Contains Nonbinding Recommendations

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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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or the Agency's) current thinking on this topic.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]

[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]

[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.