

# 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### *DRAFT GUIDANCE*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**

# For Entities Considering Whether to Register As 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  
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***Contains Nonbinding Recommendations***

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*Contains Nonbinding Recommendations*

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1 **For Entities Considering Whether to Register As Outsourcing**  
2 **Facilities Under Section 503B of the Federal Food, Drug, and**  
3 **Cosmetic Act**  
4 **Guidance<sup>1</sup>**  
5

6  
7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or the  
8 Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and  
9 does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies  
10 the requirements of the applicable statutes and regulations. If you want to discuss an alternative  
11 approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the  
12 appropriate FDA staff, call the appropriate number listed on the title page of this guidance.  
13

14  
15 **I. INTRODUCTION**  
16

17 This guidance is intended for entities considering whether to register with the Food and Drug  
18 Administration (FDA or Agency) as an outsourcing facility under section 503B of the Federal  
19 Food, Drug, and Cosmetic Act (FD&C Act).<sup>2</sup>  
20

21 FDA has received questions about whether entities engaged in various types of activities (e.g., a  
22 facility that is compounding only non-sterile drugs or only repackaging biological products)  
23 should register as an outsourcing facility. Because entities that register as outsourcing facilities  
24 in fiscal year (FY) 2015 (beginning October 1, 2014) must pay a registration fee and FDA has  
25 determined that fees paid pursuant to sections 503B and 744K of the FD&C Act will not be  
26 refunded, FDA is issuing this guidance to answer some of these questions and to provide  
27 potential registrants additional information about the regulatory impact of registering as an  
28 outsourcing facility.  
29

30 Separate FDA guidance documents contain details on the process for registering as an  
31 outsourcing facility<sup>3</sup> and explain how outsourcing facilities should report the products they  
32 compound to FDA.<sup>4</sup>

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<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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>.

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33  
34 FDA’s guidance documents, including this guidance, do not establish legally enforceable  
35 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should  
36 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
37 cited. The use of the word *should* in Agency guidances means that something is suggested or  
38 recommended, but not required.

### 39 40 **II. BACKGROUND**

41  
42 The Drug Quality and Security Act, signed into law on November 27, 2013, creates a new  
43 section 503B of the FD&C Act. Section 503B(d)(4) defines an outsourcing facility as

44  
45 a facility at one geographic location or address that— (i) is engaged in the  
46 compounding of sterile drugs; (ii) has elected to register as an outsourcing  
47 facility; and (iii) complies with all of the requirements of this section.

48 Section 503B(d)(4) further states that an outsourcing facility is not required to be a licensed  
49 pharmacy and may or may not obtain prescriptions for identified individual patients.<sup>5</sup> Section  
50 503B(d)(5) defines *sterile drug* as a “drug that is intended for parenteral administration, an  
51 ophthalmic or oral inhalation drug in aqueous format, or a drug that is required to be sterile under  
52 Federal or State law.”

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

- 59 1. The outsourcing facility must be in compliance with the registration and reporting  
60 requirements of section 503B(b). This includes submitting twice yearly reports regarding  
61 the drugs compounded by the outsourcing facility and submitting adverse event reports in  
62 accordance with section 503B(b)(5).<sup>6,7</sup>

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<sup>4</sup> 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*.

<sup>5</sup> 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.

<sup>6</sup> 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.

<sup>7</sup> See sections 503B(a)(1) and (b).

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

---

<sup>8</sup> See section 503B(a)(2).

<sup>9</sup> See section 503B(a)(3).

<sup>10</sup> See section 503B(a)(4).

<sup>11</sup> 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.

<sup>12</sup> See section 503B(a)(5).

<sup>13</sup> See section 503B(a)(6).

<sup>14</sup> See section 503B(a)(7).

<sup>15</sup> See section 503B(a)(8).

<sup>16</sup> See section 503B(a)(9).

<sup>17</sup> 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.

<sup>18</sup> See section 503B(a)(10).

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85 11. The outsourcing facility must compound all drugs in accordance with section 503B.<sup>19</sup>

86

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

### 91 III. GUIDANCE

92 If you register a facility as an outsourcing facility, you are indicating your intent for the facility's  
93 compounded drugs to be regulated under section 503B of the FD&C Act. Under section  
94 503B(a)(11), a compounded drug can only qualify for the exemptions from sections 502(f)(1),  
95 505, and 582 of the FD&C Act if *all* of the facility's compounded drugs are compounded in  
96 accordance with section 503B. As stated above, drugs compounded in accordance with section  
97 503B are not exempt from CGMP requirements, and outsourcing facilities will be inspected by  
98 FDA on a risk-based schedule.

99

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

104

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

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<sup>19</sup> See section 503B(a)(11).

<sup>20</sup> 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.

<sup>21</sup> See section 503B(a).

<sup>22</sup> See section 503B(b)(4).

<sup>23</sup> 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.

<sup>24</sup> 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.

<sup>25</sup> See section 503B(d)(4).

<sup>26</sup> 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.

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

117  
118 In addition, by registering as an outsourcing facility, an entity is electing to have its compounded  
119 drugs regulated under section 503B of the FD&C Act, not section 503A. Drugs compounded at  
120 an outsourcing facility are not eligible for the exemptions provided in section 503A, even if the  
121 conditions in that section are met with respect to the particular drug.

122  
123 FDA is issuing separate draft guidances on (1) mixing, diluting, and repackaging biological  
124 products outside the scope of an approved biologics license application and (2) repackaging  
125 certain human drug products by pharmacies and outsourcing facilities. These guidance  
126 documents will describe FDA's compliance policies with respect to biological products that are  
127 mixed, diluted, or repackaged outside the scope of an approved biologics license application  
128 (BLA) and repackaged human drugs.

129  
130 If a facility compounds sterile human drugs and otherwise meets the definition of an outsourcing  
131 facility, any non-sterile human drugs compounded by the facility would also be eligible for the  
132 exemptions from sections 505, 502(f)(1), and 582 if the drugs are compounded in accordance  
133 with the provisions of section 503B. However, if a facility that meets the definition of an  
134 outsourcing facility repackages certain human drugs, or mixes, dilutes, or repackages biological  
135 products outside the scope of an approved BLA, FDA does not intend to take action against  
136 those products for violations of certain provisions of the FD&C Act or the PHS Act, if  
137 applicable, provided those products satisfy the conditions described in the two guidances on  
138 biological products and repackaging, referenced above.