

Adverse Event Reporting for 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DRAFT GUIDANCE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
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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TABLE OF CONTENTS

I. INTRODUCTION	1
II. BACKGROUND	1
A. STATUTORY AND REGULATORY FRAMEWORK	1
B. SECTION 310.305	3
III. ADVERSE EVENT REPORTING BY OUTSOURCING FACILITIES	4
A. WHAT TO REPORT	4
B. THRESHOLD FOR REPORTING	4
1. <i>Identifiable Patient</i>	5
2. <i>Identifiable Reporter</i>	6
3. <i>Suspect Drug</i>	6
4. <i>Serious Adverse Event</i>	7
C. HOW TO REPORT ADVERSE EVENTS	7
1. <i>Obtaining Form FDA 3500A</i>	8
2. <i>How to Submit Adverse Event Reports</i>	8
3. <i>What Should Be Included</i>	8
D. INSPECTION OF ADVERSE EVENT REPORTING	9
E. RECORDKEEPING	10

1 **Adverse Event Reporting for Outsourcing Facilities**
2 **Under Section 503B of the Federal Food, Drug, and Cosmetic Act**
3 **Guidance for Industry¹**
4
5
6

7
8 This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s or the
9 Agency’s) current thinking on this topic. It does not create or confer any rights for or on any person and
10 does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies
11 the requirements of the applicable statutes and regulations. If you want to discuss an alternative
12 approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the
13 appropriate FDA staff, call the appropriate number listed on the title page of this guidance.
14

15
16
17
18 **I. INTRODUCTION**
19

20 This guidance is intended for firms that have registered with the Food and Drug Administration
21 (FDA) under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as human
22 drug compounding outsourcing facilities (outsourcing facilities). Under section 503B(b)(5) of
23 the FD&C Act, an outsourcing facility must submit adverse event reports to FDA “in accordance
24 with the content and format requirements established through guidance or regulation under
25 section 310.305 of title 21, Code of Federal Regulations (or any successor regulations).”² This
26 guidance explains FDA’s current thinking on adverse event reporting for outsourcing facilities.
27

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

34 **II. BACKGROUND**
35

36 **A. Statutory and Regulatory Framework**
37

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).

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

45
46 Section 310.305 requires, among other things, that manufacturers, packers, and distributors of
47 marketed prescription drug products that are not the subject of an approved new drug application
48 or an abbreviated new drug application establish and maintain records and make reports to FDA
49 of all serious, unexpected adverse drug experiences⁶ associated with the use of their prescription
50 drug products. For purposes of reporting adverse drug experiences, the term *prescription drug*
51 *products* includes any compounded drug product subject to the prescription requirements in
52 section 503(b)(1) of the FD&C Act. The adverse event reporting requirements apply to
53 prescription drug products regardless of whether the outsourcing facility distributes them
54 pursuant to prescriptions.⁷

55
56 In addition, on June 10, 2014, FDA issued a final rule requiring, among other things, that
57 postmarketing safety reports required under 21 CFR 310.305, 314.80, 314.98, and 600.80 be
58 submitted to FDA in an electronic format the Agency can process, review, and archive. The final
59 rule also adds 21 CFR 329.100 to address electronic submission of safety reports required by
60 section 760 of the FD&C Act regarding serious adverse event reporting for nonprescription
61 drugs.⁸ These requirements are effective as of June 10, 2015.⁹

62
63 Under section 503B, outsourcing facilities are required to submit adverse event reports to FDA,
64 in accordance with content and format requirements established through guidance or regulation
65 under 21 CFR 310.305 (or any successor regulations).

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.

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66
67 Failure to report adverse events by an entity that is registered in accordance with section 503B(b)
68 is a prohibited act under section 301(ccc)(3) of the FD&C Act.¹⁰ Violations relating to this
69 provision are subject to regulatory and enforcement action.

70
71 **B. Section 310.305**

72
73 Section 310.305(b) defines a *serious adverse drug experience* to mean:

74
75 Any adverse drug experience occurring at any dose that results in any of the
76 following outcomes:

- 77 • Death,
- 78 • A life-threatening adverse drug experience,
- 79 • Inpatient hospitalization or prolongation of existing hospitalization,
- 80 • A persistent or significant disability/incapacity, or
- 81 • A congenital anomaly/birth defect

82
83 Important medical events that may not result in death, be life-threatening, or
84 require hospitalization may be considered a serious adverse drug experience
85 when, based upon appropriate medical judgment, they may jeopardize the
86 patient or subject and may require medical or surgical intervention to prevent
87 one of the outcomes listed in this definition. Examples of such medical
88 events include

- 89 • allergic bronchospasm requiring intensive treatment in an emergency
90 room or at home,
- 91 • blood dyscrasias or convulsions that do not result in inpatient
92 hospitalization, or
- 93 • the development of drug dependency or drug abuse.

94
95 Section 310.305(b) defines an *unexpected adverse drug experience* as any adverse drug
96 experience that is not listed in the current labeling for the drug product. This includes events that
97 may be symptomatically and pathophysiologically related to an event listed in the labeling, but
98 differ from the event because of greater severity or specificity. The term *unexpected*, as used in
99 this definition, refers to an adverse drug experience that has not been previously observed (i.e.,
100 included in the labeling), rather than from the perspective of such experience not being
101 anticipated from the pharmacological properties of the pharmaceutical product.

102
103 The regulations require reporting of each adverse drug experience received or otherwise obtained
104 that is both serious and unexpected as soon as possible, but in no case later than 15 calendar days
105 of initial receipt of the information along with a copy of the drug product's current labeling.¹¹ In
106 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).

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

109
110 FDA’s regulations also state that information on the names and addresses of individual patients
111 should **not** be included.¹³ A unique code number should therefore be assigned instead for each
112 individual patient and placed in section A1 of Form FDA 3500A (Patient Identifier).

113
114 The regulations require that firms maintain certain records relating to adverse drug experiences
115 required to be reported under section 310.305 for 10 years and provide FDA access to them.¹⁴

116 The regulations also provide a disclaimer that the report or information submitted (and any
117 release by FDA of that report or information) does not necessarily reflect a conclusion that the
118 report or information constitutes an admission that the drug caused or contributed to an adverse
119 effect.¹⁵

120

121 **III. Adverse Event Reporting by Outsourcing Facilities**

122

123 **A. What to Report**

124

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

127

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

132

133 **B. Threshold for Reporting**

134

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

137

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

142

- 143 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).

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- 144 2. An identifiable reporter
145 3. A suspect drug
146 4. A serious adverse event
147

148 Although an outsourcing facility should actively seek to obtain each of these four data elements,
149 the facility must submit the report as a *15-day “Alert report”* to FDA as soon as possible, but no
150 later than 15 calendar days after first receiving information about the adverse event.¹⁷ **Reports**
151 **should be submitted as long as the outsourcing facility has information on at least the**
152 **suspect drug and the adverse event.**
153

154 The outsourcing facility must also promptly investigate adverse events that are the subject of a
155 15-day “Alert report”.¹⁸ If the outsourcing facility was not able to include all four of the data
156 elements in its initial report, it should exercise due diligence to obtain information about any of
157 the remaining elements. Additionally, the outsourcing facility should report new information it
158 obtains regarding data elements listed in its initial report when the information could assist FDA
159 in investigating an adverse event. If additional information is not obtainable, the outsourcing
160 facility should maintain records of the steps that were taken to attempt to seek the additional
161 information.¹⁹
162

163 An outsourcing facility must submit a follow-up report within 15 calendar days of receipt of new
164 information about the adverse event, or as requested by FDA.²⁰
165

166 1. *Identifiable Patient*
167

168 To have an identifiable patient, there should be enough information to indicate the existence of a
169 specific patient. One or more of the following would qualify a patient as identifiable:
170

- 171 • Age or age category (e.g., adolescent, adult, elderly)
172 • Gender
173 • Initials
174 • Date of birth
175 • Name
176 • Patient identification number
177

178 A report stating that “an elderly woman had anaphylaxis” or “a young man experienced
179 anaphylaxis” would be sufficient. If a report refers to groups of unknown size, such as “some”
180 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.

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

185

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

188

189 2. *Identifiable Reporter*

190

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

197

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

201

202 When possible, the outsourcing facility should attempt to obtain the initial reporter's contact
203 information so that the outsourcing facility and/or FDA can conduct follow-up investigations. If
204 an identifiable reporter provides contact information, but requests that the outsourcing facility
205 not forward this information to FDA, the outsourcing facility can submit a report to FDA without
206 specifically identifying the reporter by filling out the *initial reporter identity fields* on Form FDA
207 3500A with a statement such as "Requested Anonymity."

208

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

212

213 3. *Suspect Drug*

214

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

217

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

²¹ See 21 CFR 310.305(e).

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

226

227 4. *Serious Adverse Event*

228

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

231

- 232 • Death,
- 233 • A life-threatening adverse drug experience,
- 234 • Inpatient hospitalization or prolongation of existing hospitalization,
- 235 • A persistent or significant disability or incapacity, or
- 236 • A congenital anomaly or birth defect.²²

237

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

240

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

245

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

250

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

255

256 **C. How to Report Adverse Events**

257

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

²² See 21 CFR 310.305(b).

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

265

266 1. *Obtaining Form FDA 3500A*

267

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

269

- 270 • Download and print the Form FDA 3500A and instructions from the Internet at
271 <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>
272
- 273 • Request a paper copy of Form FDA 3500A and instructions from CDER’s Division of
274 Drug Information:

275

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

277

278 By phone: 1-800-FDA-1088
279 1-888-INFO-FDA
280 1-888-463-6332 or (301) 796-3400

281

282 By mail: Division of Drug Information
283 10903 New Hampshire Avenue
284 WO51-2201
285 Silver Spring, MD 20993-0002

286

287 2. *How to Submit Adverse Event Reports*

288

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

293

294 Central Document Room
295 Center for Drug Evaluation and Research
296 Food and Drug Administration
297 5901-B Ammendale Rd.
298 Beltsville, MD 20705-1266

299

300 3. *What Should Be Included*

301

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.

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302 Outsourcing facilities must indicate whether the report is a 15-day Alert report or a 15-day Alert
303 report-follow-up²⁴ and should include the following header on the first page of a cover letter
304 accompanying each Form FDA 3500A:

305

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

307

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

315

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

318

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

322

D. Inspection of Adverse Event Reporting

323

324 Under section 503B(b)(4) of the FD&C Act, outsourcing facilities are subject to inspection
325 pursuant to section 704 of the FD&C Act and are not eligible for the exemption under section
326 704(a)(2)(A) of the FD&C Act.

327

328 As part of its inspections of outsourcing facilities, FDA may review adverse event information
329 received by the outsourcing facility.²⁶ FDA may also review whether the outsourcing facility has
330 developed and implemented written processes for the surveillance, receipt, evaluation, and
331

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).

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332 reporting of adverse events for the drug products it compounds as described in 21 CFR
333 310.305(a) and 211.198.²⁷

334

335 **E. Recordkeeping**

336

337 Under section 310.305, all entities subject to the regulation must maintain for 10 years the
338 records of all adverse events required to be reported under this section, including raw data and
339 any correspondence relating to the adverse event, and allow FDA access to review, copy, and
340 verify these records, in accordance with 21 CFR 310.305(f). In addition, the outsourcing facility
341 should maintain records of its efforts to obtain the four data elements discussed in section III.B.
342 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>.