

Guidance for Industry

Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

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

[MONTH] 2015

Compounding and Related Documents

Guidance for Industry

Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Additional copies are available from:

*Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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

**[MONTH] 2015
Compounding and Related Documents**

Contains Nonbinding Recommendations

Draft — Not for Implementation

70
71
72
73

TABLE OF CONTENTS

74 **I. INTRODUCTION.....1**

75 **II. BACKGROUND.....1**

76 A. STATUTORY AND REGULATORY FRAMEWORK.....1

77 B. SECTION 310.305.....3

78 **III. ADVERSE EVENT REPORTING BY OUTSOURCING FACILITIES.....4**

79 A. WHAT TO REPORT.....4

80 B. THRESHOLD FOR REPORTING.....4

81 C. HOW TO REPORT ADVERSE EVENTS.....8

82 D. INSPECTION OF ADVERSE EVENT REPORTING.....8

83 E. RECORDKEEPING.....9

84

Guidance for Industry¹

Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

This guidance represents the current thinking of the Food and Drug Administration (FDA or the Agency) on this topic. It does not create 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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

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

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.

II. BACKGROUND

A. Statutory and Regulatory Framework

On November 27, 2013, the Drug Quality and Security Act (DQSA) was signed into law. Title I of the DQSA contains important provisions related to the oversight of human drug compounding.³ The DQSA added section 503B to the FD&C Act. Under section 503B(b), a

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).

³ See text of Compounding Quality Act at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm376732.htm>.

Contains Nonbinding Recommendations

8
123 compounder can register as an *outsourcing facility* with FDA.⁴ Under section 503B(b)(5), an
124 outsourcing facility must submit adverse event reports to FDA “in accordance with the content
125 and format requirements established through guidance or regulation under section 310.305 of
126 title 21, Code of Federal Regulations (or any successor regulations).”⁵
127

128 Section 310.305 requires, among other things, that manufacturers, packers, and distributors of
129 marketed prescription drug products that are not the subject of an approved new drug application
130 or an abbreviated new drug application establish and maintain records and make reports to FDA
131 of all serious, unexpected adverse drug experiences⁶ associated with the use of their prescription
132 drug products. For purposes of reporting adverse drug experiences, the term *prescription drug*
133 *products* includes any compounded drug product subject to the prescription requirements in
134 section 503(b)(1) of the FD&C Act. The adverse event reporting requirements apply to
135 prescription drug products regardless of whether the outsourcing facility distributes them
136 pursuant to prescriptions.⁷
137

138 In addition, on June 10, 2014, FDA issued a final rule requiring, among other things, that
139 postmarketing safety reports required under 21 CFR 310.305, 314.80, 314.98, and 600.80 be
140 submitted to FDA in an electronic format the Agency can process, review, and archive. The final
141 rule also adds 21 CFR 329.100 to address electronic submission of safety reports required by
142 section 760 of the FD&C Act regarding serious adverse event reporting for nonprescription
143 drugs.⁸ These requirements are effective as of June 10, 2015.^{9, 10}
144

145 Under section 503B, outsourcing facilities are required to submit adverse event reports to FDA,
146 in accordance with content and format requirements established through guidance or regulation
147 under 21 CFR 310.305 (or any successor regulations).¹¹
148

9 ⁴ 21 U.S.C. 353b(b).

10 ⁵ *Id.* at 353b(b)(5).

11 ⁶ This guidance uses the terms *adverse drug experience* and *adverse event* interchangeably.

12 ⁷ Section 503B(d)(4)(C) of the FD&C Act provides that outsourcing facilities may or may not obtain prescriptions
13 for identified individual patients. Although outsourcing facilities may send prescription drugs to healthcare facilities
14 without obtaining prescriptions for identified individual patients, drugs produced by outsourcing facilities remain
15 subject to the requirements in section 503(b) of the FD&C Act. Therefore, an outsourcing facility cannot dispense a
16 prescription drug to a patient without a prescription.

17 ⁸ 21 U.S.C. 379aa.

18 ⁹ See 79 FR 33072.

19 ¹⁰ The effective date for the Electronic Safety Reporting Rule requiring electronic submissions of postmarketing
20 safety reports was June 10, 2015. However, in the *Federal Register* of [INSERT], FDA announced that it is
21 delaying the compliance date for this final rule to September 8, 2015.

22 ¹¹ Certain state boards of pharmacy may also require outsourcing facilities licensed in their states to report adverse
23 events. Outsourcing facilities must comply with any state reporting requirements independent of and in addition to
24 reporting adverse events as described in this guidance.

Contains Nonbinding Recommendations

25

149 Failure to report adverse events by an entity that is registered in accordance with section 503B(b)
150 is a prohibited act under section 301(ccc)(3) of the FD&C Act.¹² Violations relating to this
151 provision are subject to regulatory and enforcement action.

152

153 Adverse event reporting for drug products compounded by outsourcing facilities is a critical
154 mechanism by which FDA identifies signals of potential quality problems that may be associated
155 with a particular drug or drug component, and which may have been caused by substandard
156 conditions or processes at a facility where the drug or its components were made or handled.
157 FDA needs to distinguish such cases from cases of medication error, hospital or clinic procedural
158 problems, or quality issues associated with ingredients such as active pharmaceutical ingredients
159 (APIs) or excipients. For example, several reports of adverse events in patients who received
160 compounded drug products from the same outsourcing facility may be a signal of a quality issue
161 resulting from a deficiency in the outsourcing facility's manufacturing processes. However, if
162 several different outsourcing facilities report adverse events in patients who received drug
163 products that contained the same API, this may suggest a quality problem associated with the
164 API used in the compounded drug product.

165

166 An adverse event may be reported for reasons other than a quality problem. For example, it may
167 be a side effect of taking the drug product, or have resulted from lack of efficacy of the drug
168 product, with the patient's underlying medical condition, or use of a concomitant medication. To
169 address the reported adverse event appropriately, FDA reviews information provided by the
170 outsourcing facilities, such as the description of the circumstances associated with the adverse
171 event such as the source of the drug and its ingredients, concomitant medications that the patient
172 was taking, and relevant information reflected in hospital discharge summaries, autopsy
173 reports/death certificates, relevant laboratory data, and other critical clinical data used to
174 determine the cause of the adverse event .

175

176 When FDA receives adverse event reports from outsourcing facilities, FDA evaluates the reports
177 on a case-by-case basis to determine whether further action is warranted. FDA may contact the
178 outsourcing facility or the reporter to obtain additional information, and if the report signals a
179 potential product quality issue, FDA may initiate an inspection of the outsourcing facility or
180 manufacturer of a component of the compounded drug to further investigate the incident.

181

B. Section 310.305

182

183
184 Section 310.305(b) defines a *serious adverse drug experience* to mean:

185

186 Any adverse drug experience occurring at any dose that results in any of the
187 following outcomes:

188

189

190

191

192

193

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

26

¹² 21 U.S.C. 331(ccc)(3).

Contains Nonbinding Recommendations

27
194 Important medical events that may not result in death, be life-threatening, or
195 require hospitalization may be considered a serious adverse drug experience
196 when, based upon appropriate medical judgment, they may jeopardize the
197 patient or subject and may require medical or surgical intervention to prevent
198 one of the outcomes listed in this definition. Examples of such medical
199 events include
200 • allergic bronchospasm requiring intensive treatment in an emergency
201 room or at home,
202 • blood dyscrasias or convulsions that do not result in inpatient
203 hospitalization, or
204 • the development of drug dependency or drug abuse.
205

206 Section 310.305(b) defines an *unexpected adverse drug experience* as any adverse drug
207 experience that is not listed in the current labeling for the drug product. This includes events that
208 may be symptomatically and pathophysiologically related to an event listed in the labeling, but
209 differ from the event because of greater severity or specificity. The term *unexpected*, as used in
210 this definition, refers to an adverse drug experience that has not been previously observed (i.e.,
211 included in the labeling), rather than from the perspective of such experience not being
212 anticipated from the pharmacological properties of the pharmaceutical product. For example, if
213 current labeling for a compounded drug product does not list any adverse drug experiences, all
214 adverse drug experiences associated with the compounded drug product would be considered
215 “unexpected.”
216

217 The regulation requires reporting of each adverse drug experience received or otherwise obtained
218 that is both serious and unexpected as soon as possible, but in no case later than 15 calendar days
219 of initial receipt of the information along with a copy of the drug product’s current labeling
220 .¹³ In addition, all serious, unexpected adverse drug experiences that are the subject of these
221 reports shall be promptly investigated and a follow-up report must be submitted within 15
222 calendar days of receipt of new information or as requested by FDA.¹⁴
223

224 FDA’s regulations also state that information on the names and addresses of individual patients
225 should **not** be included.¹⁵ A unique code number should therefore be assigned instead for each
226 individual patient.
227

228 The regulations require that firms maintain certain records relating to adverse drug experiences
229 required to be reported under section 310.305 for 10 years and provide FDA access to them.¹⁶
230 The regulations also provide a disclaimer that the report or information submitted (and any
231 release by FDA of that report or information) does not necessarily reflect a conclusion that the
232 report or information constitutes an admission that the drug caused or contributed to an adverse
233 effect.¹⁷

28 ¹³ See 21 CFR 310.305(c)(1)(i).

29 ¹⁴ See 21 CFR 310.305(c)(2).

30 ¹⁵ See 21 CFR 310.305(e).

31 ¹⁶ See 21 CFR 310.305(f).

32 ¹⁷ See 21 CFR 310.305(g).

33
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275

34
35
36

III. Adverse Event Reporting by Outsourcing Facilities

A. What to Report

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

In addition, although outsourcing facilities are not required to do so, FDA strongly recommends that outsourcing facilities report ***all*** serious adverse drug experiences associated with their compounded prescription drug products. We believe reporting ***all*** serious adverse events would provide important information about potential product quality issues or public health risks associated with drug products compounded by outsourcing facilities.

B. Threshold for Reporting

As noted above, outsourcing facilities must submit to FDA reports of all serious, unexpected adverse events associated with their compounded prescription drugs.¹⁸

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

1. An identifiable patient
2. An identifiable reporter
3. A suspect drug
4. A serious adverse event

Although an outsourcing facility should actively seek to obtain each of these four data elements, the facility must submit the report as a 15-day “Alert report” to FDA as soon as possible, but no later than 15 calendar days after first receiving information about the adverse event.¹⁹ **Reports should be submitted as long as the outsourcing facility has information on at least the suspect drug and the adverse event.**

The outsourcing facility must also promptly investigate adverse events that are the subject of a 15-day “Alert report.”²⁰ If the outsourcing facility was not able to include all four of the data elements in its initial report, it should exercise due diligence to obtain information about any of the remaining elements and should keep records of its efforts to obtain this and other relevant information (e.g., dates of discussions with the reporter to determine how many patients experienced a particular adverse event or dates of discussions with a healthcare facility to obtain contact information for an identifiable person who purports to have knowledge about the patient,

¹⁸ See 21 CFR 310.305(c).
¹⁹ See 21 CFR 310.305(c)(1)(i).
²⁰ See 21 CFR 310.305(c)(2).

Contains Nonbinding Recommendations

37
276 adverse event, or drug involved). Additionally, the outsourcing facility should report new
277 information it obtains regarding data elements listed in its initial report when the information
278 could assist FDA in investigating an adverse event. If additional information is not obtainable,
279 the outsourcing facility should maintain records of the steps that were taken to attempt to seek
280 the additional information.²¹

281
282 An outsourcing facility must submit a follow-up report within 15 calendar days of receipt of new
283 information about the adverse event, or as requested by FDA.²²

284

C. Description of the Four Data Elements

286

1. Identifiable Patient

288

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

291

- 292 • Age or age category (e.g., adolescent, adult, elderly)
- 293 • Gender
- 294 • Initials
- 295 • Date of birth
- 296 • Name
- 297 • Patient identification number

298

299 A report stating that “an elderly woman had anaphylaxis” or “a young man experienced
300 anaphylaxis” would be sufficient. If a report refers to groups of unknown size, such as “some”
301 or “a few” college students had anaphylaxis, the outsourcing facility should follow up to find out
302 how many students were involved and submit a separate report to FDA for each student, because
303 each is considered to be an identifiable patient. The outsourcing facility should distinguish each
304 identifiable patient so that it is clear that each report is not a duplicate report of a single adverse
305 event.

306

307 Patients should not be identified by name or address when reporting to FDA. Instead, the
308 outsourcing facility should assign a unique code number for each patient.²³

309

2. Identifiable Reporter

311

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

38

²¹ Id.

39

²² Id.

40

²³ See 21 CFR 310.305(e).

Contains Nonbinding Recommendations

41

318

- 319 • A personal identifier (e.g., name)
- 320 • A professional identifier (e.g., doctor, nurse, pharmacist)
- 321 • Contact information (e.g., e-mail address, phone number)

322

323 When possible, the outsourcing facility should attempt to obtain the initial reporter's contact
324 information so that the outsourcing facility and/or FDA can conduct follow-up investigations. If
325 an identifiable reporter provides contact information, but requests that the outsourcing facility
326 not forward this information to FDA, the outsourcing facility can submit a report to FDA without
327 specifically identifying the reporter by filling out the *reporter field* with a statement such as
328 "Requested Anonymity."

329

330 If an adverse event is reported anonymously to an outsourcing facility, the outsourcing facility
331 should indicate in the reporter field when submitting the report to FDA that the initial reporter is
332 anonymous.

333

334 3. *Suspect Drug Product*

335

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

338

339 For reporting purposes, an adverse event report should describe the known product attributes
340 (e.g., active ingredient(s), dosage form, strength, color, lot number). If an adverse event involves
341 multiple suspect drug products that are compounded by the same outsourcing facility, the
342 outsourcing facility should submit only one report that notes the drug product considered most
343 suspect by the reporter. If the reporter views each drug product as equally suspect the
344 outsourcing facility should submit only one report that lists all of the drug products as suspect.
345 In all cases, including those where not all of the drug products were made by the outsourcing
346 facility, the report should include information on all suspect drug products of which the
347 outsourcing facility is aware.

348

349 If the compounded drug product contains multiple components (e.g., excipients, drug substances,
350 finished dosage forms), the outsourcing facility should list each component and its manufacturer,
351 if known. The outsourcing facility should also list any other known medical product(s) the
352 patient was taking at the time he or she experienced the adverse event and the manufacturer of
353 that product(s) (i.e., any concomitant medical products).

354

355 The outsourcing facility should include the information described in this guidance on suspect
356 drug products and concomitant medications of which it is aware after exercising due diligence.
357 For example, although an outsourcing facility should exercise due diligence to determine any
358 concomitant medical products, FDA only expects that it report information about concomitant
359 products that it is able to obtain from the reporter. Furthermore, as noted previously, the report
360 or information submitted by an outsourcing facility pursuant to section 310.305 (and any release
361 by FDA of that report or information) does not necessarily reflect a conclusion that the report or

Contains Nonbinding Recommendations

42

362 information constitutes an admission that the drug caused or contributed to an adverse effect.²⁴
363 When investigating the adverse event, FDA considers how the drug was administered, the
364 patient's medical history, and any other relevant information.

365

366

367 4. *Serious Adverse Event*

368

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

371

- 372 • Death,
- 373 • A life-threatening adverse drug experience,
- 374 • Inpatient hospitalization or prolongation of existing hospitalization,
- 375 • A persistent or significant disability or incapacity, or
- 376 • A congenital anomaly or birth defect.²⁵

377

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

380

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

385

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

390

391 **C. Attachments**

392

393 As part of each adverse event report, outsourcing facilities must submit a copy of the current
394 labeling for the compounded drug product that is the subject of the report.²⁶

395

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

401

402 **D. How to Report Adverse Events**

403

43 ²⁴ See 21 CFR 310.305(g).

44 ²⁵ See 21 CFR 310.305(b).

45 ²⁶ See section 21 CFR 310.305(c)(1)(i).

Contains Nonbinding Recommendations

47

404 FDA provides two options for electronic submission of initial and follow-up adverse event reports to
405 FDA: (1) submission through the Safety Reporting Portal (SRP)²⁷ or (2) submission through the
406 Electronic Submissions Gateway (ESG).²⁸ For a discussion of electronic submission of adverse
407 event reports to FDA, please review the draft guidance, *Guidance for Industry, Providing*
408 *Submissions in Electronic Format – Postmarketing Safety Reports*, available at:
409 [http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/
410 ucm072369.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072369.pdf)

411

412 Before submitting an adverse event report in electronic format to FDA for the first time, whether
413 through the ESG or SRP, you should notify the FAERS Electronic Submission Coordinator of your
414 intent at faersesub@fda.hhs.gov. The FAERS Coordinator will assist you to ensure that all steps have
415 been completed for successful submission of adverse event reports.

416

417 Postmarketing safety reporting often involves submitting a series of reports consisting of the
418 initial individual case safety report (ICSR) and follow-up, along with any associated attachments,
419 over the life cycle of an individual case. To avoid duplicate adverse event reports in the FAERS
420 database, each report should have a unique case identification number, regardless of how it is
421 transmitted to the FDA (i.e., SRP or ESG). See section III.D in the draft guidance, *Guidance for*
422 *Industry, Providing Submissions in Electronic Format – Postmarketing Safety Reports*.

423

424 **D. Inspection of Adverse Event Reporting**

425

426 Under section 503B(b)(4) of the FD&C Act, outsourcing facilities are subject to inspection
427 pursuant to section 704 of the FD&C Act and are not eligible for the exemption under section
428 704(a)(2)(A) of the FD&C Act.

429

430 As part of its inspections of outsourcing facilities, FDA may review adverse event information
431 received by the outsourcing facility.²⁹ FDA may also review whether the outsourcing facility has
432 developed and implemented written processes for the surveillance, receipt, evaluation, and
433 reporting of adverse events for the drug products it compounds as described in 21 CFR
434 310.305(a) and 211.198.³⁰

48 ²⁷ The FDA SRP Web page is available at <http://www.safetyreporting.hhs.gov>.

49

50 ²⁸ The FDA ESG Web page is available at <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm2005551.htm>.

51

52 ²⁹ See section 21 CFR 310.305(f)(3).

53

54 ³⁰ Outsourcing facilities are subject to current good manufacturing practice (CGMP) requirements. Pending the
55 development of further regulations, FDA expects outsourcing facilities, among other things, to comply with the
56 CGMP requirements in 21 CFR 211.198, which is a companion to 21 CFR 310.305. This section requires that
57 “[w]ritten procedures describing the handling of all written and oral complaints regarding a drug product shall be
58 established and followed,” and further requires that these procedures must include “provisions for review to
59 determine whether the complaint represents a serious and unexpected adverse drug experience which is required to
60 be reported to the Food and Drug Administration in accordance with [section] 310.305 ... of this chapter.” See
61 FDA’s guidance for industry, *Current Good Manufacturing Practice—Interim Guidance for Human Drug*
62 *Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*, available at:
63 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf>.

64

Contains Nonbinding Recommendations

65

435

436 **E. Recordkeeping**

437

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