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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (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*.

For questions regarding this draft document contact H. Joy Sharp at 301-796-3647 or Joy.Sharp@fda.hhs.gov.

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

Additional copies are available from:

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

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

February 2015
Drug Safety

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Draft — Not for Implementation

Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance for Industry[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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or the Agency's) current thinking on this topic.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 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.

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

A. Statutory and Regulatory Framework

[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).

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 compounder can register as an *outsourcing facility* with FDA.[4] Under section 503B(b)(5), 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)."[5]

Section 310.305 requires, among other things, that manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved new drug application or an abbreviated new drug application establish and maintain records and make reports to FDA of all serious, unexpected adverse drug experiences[6] associated with the use of their prescription drug products. For purposes of reporting adverse drug experiences, the term *prescription drug products* includes any compounded drug product subject to the prescription requirements in section 503(b)(1) of the FD&C Act. The adverse event reporting requirements apply to prescription drug products regardless of whether the outsourcing facility distributes them pursuant to prescriptions.[7]

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

Under section 503B, outsourcing facilities are required to submit adverse event reports to FDA, in accordance with content and format requirements established through guidance or regulation 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.

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

B. Section 310.305

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

> Any adverse drug experience occurring at any dose that results in any of the following outcomes:
>
> - 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
>
> Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include
>
> - allergic bronchospasm requiring intensive treatment in an emergency room or at home,
> - blood dyscrasias or convulsions that do not result in inpatient hospitalization, or
> - the development of drug dependency or drug abuse.

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

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

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

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

The regulations require that firms maintain certain records relating to adverse drug experiences required to be reported under section 310.305 for 10 years and provide FDA access to them.[14] The regulations also provide a disclaimer that the report or information submitted (and any release by FDA of that report or information) does not necessarily reflect a conclusion that the report or information constitutes an admission that the drug caused or contributed to an adverse effect.[15]

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, 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.[16]

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

[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).

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.[17] **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".[18] 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. Additionally, the outsourcing facility should report new information it obtains regarding data elements listed in its initial report when the information could assist FDA in investigating an adverse event. If additional information is not obtainable, the outsourcing facility should maintain records of the steps that were taken to attempt to seek the additional information.[19]

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

1. Identifiable Patient

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

- Age or age category (e.g., adolescent, adult, elderly)
- Gender
- Initials
- Date of birth
- Name
- Patient identification number

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

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

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

2. Identifiable Reporter

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

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

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

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

3. Suspect Drug

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

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

[21] See 21 CFR 310.305(e).

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

4. Serious Adverse Event

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

- Death,
- A life-threatening adverse drug experience,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant disability or incapacity, or
- A congenital anomaly or birth defect.[22]

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

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

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

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

C. How to Report Adverse Events

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

[22] See 21 CFR 310.305(b).

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

1. Obtaining Form FDA 3500A

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

- Download and print the Form FDA 3500A and instructions from the Internet at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

- Request a paper copy of Form FDA 3500A and instructions from CDER's Division of Drug Information:

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

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

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

2. How to Submit Adverse Event Reports

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

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

3. What Should Be Included

[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.

Outsourcing facilities must indicate whether the report is a 15-day Alert report or a 15-day Alert report-follow-up [24] and should include the following header on the first page of a cover letter accompanying each Form FDA 3500A:

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

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

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

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

D. Inspection of Adverse Event Reporting

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

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

[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).

reporting of adverse events for the drug products it compounds as described in 21 CFR 310.305(a) and 211.198.[27]

E. Recordkeeping

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