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

TABLE OF CONTENTS

Guidance for Industry[1]

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.

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, 10]

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).[11]

---

[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.

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

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

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.[12] Violations relating to this provision are subject to regulatory and enforcement action.

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

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

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

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

[12] 21 U.S.C. 331(ccc)(3).

> 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. For example, if current labeling for a compounded drug product does not list any adverse drug experiences, all adverse drug experiences associated with the compounded drug product would be considered "unexpected."

The regulation requires 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 .[13] In addition, all serious, unexpected adverse drug experiences that are the subject of these reports 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.[14]

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

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.[16] 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.[17]

---

[13] See 21 CFR 310.305(c)(1)(i).

[14] See 21 CFR 310.305(c)(2).

[15] See 21 CFR 310.305(e).

[16] See 21 CFR 310.305(f).

[17] See 21 CFR 310.305(g).

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).

adverse event, or drug involved). 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.[21]

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.[22]

C. Description of the Four Data Elements

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 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.[23]

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:

---

[21] Id.

[22] Id.

[23] See 21 CFR 310.305(e).

- 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 *reporter field* with a statement such as "Requested Anonymity."

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

3. Suspect Drug Product

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 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 should include information on all suspect drug products of which the outsourcing facility is aware.

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. The outsourcing facility should also list any other known 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).

The outsourcing facility should include the information described in this guidance on suspect drug products and concomitant medications of which it is aware after exercising due diligence. For example, although an outsourcing facility should exercise due diligence to determine any concomitant medical products, FDA only expects that it report information about concomitant products that it is able to obtain from the reporter. Furthermore, as noted previously, the report or information submitted by an outsourcing facility pursuant to section 310.305 (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.[24] When investigating the adverse event, FDA considers how the drug was administered, the patient's medical history, and any other relevant information.

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.[25]

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.

C. Attachments

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.[26]

In addition, as part of the adverse event report, we encourage, as appropriate, attachment of the following, if available: (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.

D. How to Report Adverse Events

[24] See 21 CFR 310.305(g).

[25] See 21 CFR 310.305(b).

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

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

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

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

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.[29] FDA may also review whether the outsourcing facility has developed and implemented written processes for the surveillance, receipt, evaluation, and reporting of adverse events for the drug products it compounds as described in 21 CFR 310.305(a) and 211.198.[30]

---

[27] The FDA SRP Web page is available at http://www.safetyreporting.hhs.gov.

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

[29] See section 21 CFR 310.305(f)(3).

[30] 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.

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 adverse event report.