U.S. FOOD & DRUG ADMINISTRATION

Center of Excellence

Adverse Event Reporting for Outsourcing Facilities

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Objectives

- Understand adverse event reporting requirements applicable to outsourcing facilities
- Describe pertinent adverse event documents FDA may review during the inspection of an outsourcing facility

Adverse Event Reporting for Outsourcing Facilities

- Section 503B(b)(5) of the FD&C Act requires outsourcing facilities to report adverse events to FDA in accordance with the content and format requirements established through guidance or regulation under 21 CFR 310.305 (or any successor regulations).
- Failure of an outsourcing facility to report adverse events is a prohibited act under section 301(ccc)(3) of the FD&C Act

Adverse Event Reporting for Outsourcing Facilities (cont.)

- Outsourcing facilities must electronically report to FDA all **serious *and* unexpected** adverse drug experiences associated with the use of their compounded prescription drug products.

Adverse Event Reporting

Per 21 CFR 310.305

Adverse drug experience is any adverse event associated with the use of a drug in humans, whether or not considered drug related.

Manufacturers, packers and distributors of marketed prescription drug products that are not the subject of an approved new drug or abbreviated new drug application are required to:

- *Establish and maintain records* AND
- *Make reports to FDA of all serious, unexpected adverse drug experiences associated with the use of their drug products*
- *Develop written procedures for surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA*

Serious Adverse Drug Experience

Serious adverse drug experience includes any adverse event associated with the following outcomes:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity, or
- Congenital anomaly/birth defect

See 21 CFR 310.305(b) and https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event

Serious Adverse Drug Experience (cont.)

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

See 21 CFR 310.305(b) and https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event

Unexpected Adverse Event

- An adverse event is ***unexpected*** when it is not listed in the current labeling for the drug product.
- Compounded drug products are not FDA-approved and FDA does not review their labeling prior to marketing.
- FDA strongly recommends that outsourcing facilities report **all** serious adverse drug experiences associated with their compounded prescription drug products.

FDA Adverse Event Reporting Guidance

- FDA has issued a final Guidance, Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
  - Please Note: FDA uses the terms *adverse event* and *adverse drug experience* interchangeably in the guidance

Repackaged Drugs and Biological Products

- Section 503B addresses human drug compounding, and not activities such as repackaging of drugs or mixing, diluting, or repackaging of biological products.
- FDA guidance describes the conditions under which it *does not* intend to take action regarding violations of certain requirements of the FD&C Act and the Public Health Service Act, in the context of drug repackaging, and mixing, diluting, and repackaging of certain types of biological products. One of the conditions is that outsourcing facilities report to FDA serious adverse events associated with these products[2,3]

2. See Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities Guidance
3. See Mixing, Diluting, or Repackaging Biological Products Outside Scope of an Approved Biologics License Application Guidance

FDA Inspection

During an inspection of an Outsourcing Facility, FDA may:

- Determine if the outsourcing facility has received any adverse event reports
- Obtain copies of all adverse event reports received by the outsourcing facility
- Determine if the outsourcing facility submitted adverse events to FDA in accordance with content and format requirements established through guidance or regulation under 21 CFR 310.305
- *Failure to submit an adverse drug event report to FDA within 15 calendar days of receipt by the OF may be documented as an observation on the Form FDA 483*

1. See 21 CFR 310.305(a)

FDA Inspection (cont.)

Additionally, during an inspection, FDA may:

- Review whether the outsourcing facility has adequate written adverse event processes
- Obtain copies of the outsourcing facility's adverse event and complaint Standard Operating Procedures (SOP)

2. See 21 CFR 211.198

Reviewing Your Adverse Event/Complaints SOP

The following slides will describe examples of elements outsourcing facilities have included in written procedures

#1 Definition of Serious, Unexpected Adverse Event

- An adverse event is “serious” when, occurring at any dose, it results in any of the following outcomes:
  - death;
  - a life-threatening adverse event;
  - inpatient hospitalization or prolongation of existing hospitalization;
  - a persistent or significant disability/incapacity; or
  - a congenital anomaly/birth defect
  - Important medical events that, based upon appropriate medical judgment, may jeopardize the patient and may require medical/surgical intervention to prevent one of these outcomes
- An adverse event is “unexpected” when it is not listed in the current labeling for the drug product

1. See 21 CFR 310.305(b)

#2 Timeframe for Submitting Adverse Event Reports to FDA

21 CFR 310.305 requires:

- An adverse event determined to be serious and unexpected to be reported to FDA within 15 calendar days of initial receipt[1]
- The facility to promptly investigate and submit a follow-up report regarding a serious, unexpected adverse event within 15 calendar days of receipt of *new information* or as requested by FDA[2]

1. See 21 CFR 310.305(c)(1)(i)
2. See 21 CFR 310.305(c)(2)

#3 Description of the Four Data Elements

- The four data elements the facility should investigate
  - Identifiable Patient
  - Identifiable Reporter
  - Suspect Drug
  - Serious Adverse Event

#4 How to Electronically Submit Adverse Event Reports to FDA

- There are two options for electronic submission of serious, unexpected adverse event reports to FDA:
  - Safety Reporting Portal (SRP)
  - Electronic Submission Gateway (ESG)[1]

1. See 21 CFR 310.305(e) regarding electronic format for submissions

New SOP Initiative

- FDA has piloted a new initiative in which FDA sent adverse event SOP information request letters to newly registered outsourcing facilities. The initiative:
  - Provides outsourcing facilities with a *voluntary* opportunity to submit to FDA for review their written procedures for reporting adverse events
  - Allows FDA to review the written procedures and provide feedback, as appropriate, to the outsourcing facilities prior to their scheduled inspections

QUESTIONS????

References

- Adverse Event Reporting for Outsourcing Facilities Under Section 503B, Final Guidance
- FDA regulations at 21 CFR 310.305
- FDA Adverse Event Reporting System (FAERS) Electronic Submissions
- Providing Submissions in Electronic Format – Postmarketing Safety Reports