Field Investigators: ADE Detectives Supplemental Handbook

of the Audio-visual Self-learning Modules on Conducting Field Inspections of Postmarketing Adverse Event Reporting Compliance

This handbook is to be used for purposes of training Field Investigators in their task of postmarketing surveillance of adverse drug events reporting compliance. The instructional design was prepared by Dr. Sakti P. Mukherjee at the Office of Training and Communications, Division of Training & Development, the Center for Drug Evaluation and Research (CDER), FDA. Questions about the content should be directed to the Division of Compliance Risk Management and Surveillance (HFD-332), CDER Office of Compliance.

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Field Investigators: ADE Detectives

An Overview

The Food and Drug Administration (FDA) approves drugs for marketing after careful evaluation of all aspects of experimental and clinical research data on their safety and efficacy as therapeutic agents; yet, some unforeseen adverse health experiences associated with their use in certain individuals or different populations may be identified only after large-scale marketing of these products. To support the use of medicines to their maximum health benefits while minimizing the risk of suffering or injury to the consumer, the Office of Drug Safety (ODS)[1] of the FDA's Center for Drug Evaluation and Research (CDER) monitors reports of adverse drug experiences received from drug manufacturers, health care professionals, and the general public. This awesome and challenging task is shared by a joint team from CDER and the Office of Regulatory Affairs (ORA). The team includes CDER personnel from the Office of Drug Safety, the MedWatch Office, the Office of Compliance, the Regulatory Policy Staff, the Office of the Chief Counsel, and ORA personnel from the Investigation and Compliance Branches. ORA Field Investigators play a key role in the process by collecting information concerning industry's procedures and actual performance of postmarketing safety reporting and documenting performance that does not follow FDA regulations or guidances.

The FDA's MedWatch program, initiated in the 1990's, promotes the public's awareness about drug safety and risks, and facilitates the voluntary reporting of serious adverse events and product problems by the health care community. Voluntary reporting by the health care personnel or the consumers is done on the FDA form 3500 or conveyed directly by phone or email to MedWatch. Pharmaceutical companies are mandated by regulation to collect and evaluate adverse drug experience data and submit safety reports to the FDA. Sponsors, drug manufacturers, packers, and distributors must report adverse event data using the FDA form 3500A or CIOMS 1 form, or submit data electronically[2].

The Field Investigators are on the frontlines of FDA's efforts to protect public health and safety, and need to be aware of the relevant regulations binding the firms they investigate. To ascertain a firm's compliance with FDA postmarketing adverse drug experience reporting requirements, it is important to review the firm's written procedures for data collection, assessment, processing, and submission to FDA, and the firm's performance of those procedures. Investigation may require checking the firm's written procedures, data processing records, and source and submitted documents related to adverse events. Procedures for data collection, data entry, evaluation and reporting to FDA should be assessed. This includes personal interviews with some key members of their staff. It is

[1] The Office of Prescription Drug Risk Assessment (OPDRA) is now known as the Office of Drug Safety (ODS). ODS is a part of the Office of Pharmacoepidemiology and Statistical Science (OPaSS)

[2] Electronic submission of reports from applicants is now permitted. Draft guidance for Industry on Providing Regulatory Submission in Electronic Format-Postmarketing Expedited Safety Reports was published in the Federal Register on May 4, 2001.

important to remember that a firm must evaluate all ADE's associated with the use of an FDA-approved drug, even if the drug is not marketed in the United States, to determine if a report is required to be submitted. A firm's obligation covers their contractual agreements with firms such as clerical or professional service subcontractors, as well as with agreements with other pharmaceutical firms, such as foreign affiliates or domestic marketing partners.

These audio-visual self-learning modules present a comprehensive perspective on the FDA regulations about the firms' obligations, the possible penalties for their default, and guidance on how firms and products are selected using risk management criteria for investigation by field and headquarters personnel, what to investigate and report, and the resources of necessary information and support at the FDA. Armed with this knowledge, the Field Investigators will be able to fulfill the critical responsibility of monitoring the performance of surveillance, evaluation, and transmission of information to the agency on adverse experiences associated with use of drugs. These audits will help the Agency determine the risk-benefit profiles of the drugs and take appropriate precautions to safeguard public health.

Section I: Introduction to the Team and Their Roles

Field Investigators Are ADE Detectives

This section discusses the critical role of Postmarketing Drug Risk Assessment in CDER's mission to promote and protect public health by making available safe and effective drugs. The network for carrying out this responsibility includes the ODS, the MedWatch Office, the Office of Compliance, the Regulatory Policy Staff, the Office of the Chief Counsel, and the Field Investigators. Each group participates in a team that surveys adverse drug event reports, monitors compliance with regulations and adherence with guidance, and determines the appropriate course of regulatory action.

Learning Objectives:

After completing this section of the videotape, you should be able to:

1. Explain the goal and mission of the FDA in postmarketing surveillance related to public health safety.

2. Describe the administrative network at CDER for postmarketing pharmacovigilance.

3. Describe the roles of the Office of Drug Safety (ODS), the MedWatch Office, the Office of Compliance, Regulatory Policy Staff, the Office of the Chief Counsel, and the Field Investigators.

Section II: The Regulations

It is important for the Investigators to be familiar with the regulations that enable the Agency to effectively conduct its missions. This section discusses the regulations that govern the activities of firms associated with products under FDA/CDER's responsibility, and the range of the Agency's concerns that you as a Field Investigator must be aware of and effectively address. In the context of this discussion, you will be acquainted with the content of the sections of the Title 21 Code of Federal Regulations that apply to postmarket adverse event reporting. These regulations specify who must report, what must be reported, when a report must be submitted, and what records must be maintained. You will also become familiar with the classification of the adverse event reports as an unexpected adverse drug experience, or a serious event, and will be able to distinguish adverse drug experiences and drug quality problems.

On March 14, 2003, a Proposed Rule on Safety Reporting Requirement for Human Drug and Biological Products was published in the Federal Register. The final rule has not been published as of December 2004, but it is anticipated that this major revision to the safety reporting requirements will significantly impact the processing of adverse drug event reporting.

Learning Objectives:

At the completion of this section of the videotape, you should be able to:

1. Describe the postmarketing safety reporting regulations for marketed human drug products, contained in various sections of the Title 21 Code of Federal Regulations.

2. Define adverse drug experiences as serious, life-threatening, or unexpected events.

3. Distinguish between adverse drug experiences and drug quality problems.

Section III: Compliance Program Guidance

This section offers an in-depth look into the types of guidance for conducting inspections that are available from CDER's Compliance Program. With more than 700 pharmaceutical firms with approved applications, the FDA is responsible for conducting an increasing number of inspections. Therefore, field Investigators should have a clear idea about who has a regulatory responsibility for postmarketing adverse event reporting, which firms can be inspected and how the companies and products are chosen to be inspected. Instruction is provided about the documents an investigator may request from the company under investigation. Further, you will become familiar with the various forms used for reporting adverse drug events by industry, health care providers and consumers.

Learning Objectives:

At the completion of this section of the videotape, you should be able to:

1. Identify the several broad industry categories that are covered by FDA's regulations.
2. Differentiate between the types of inspections.
3. Determine the criteria to base the selection of companies or particular products.
4. Utilize the available FDA resources found in the Compliance Guidance Program to support you in performing an inspection.
5. Describe the documents you may want to request from a company under investigation.

Section IV: How to Conduct an Inspection

By this time, you are familiar with the role of the Field Investigators, the team support for postmarketing drug risk assessment in FDA, the agency's regulations for adverse drug events reporting by the pharmaceutical industry, and the Compliance Program at CDER to guide the inspections and information collection from the firms, health care professionals, and consumers. You have also become acquainted with the basis of selecting firms and products for inspection, and the documents an Investigator would need to examine. It is time to discuss some practical aspects of conducting an inspection. In this section you will hear from an FDA Investigator interviewing a drug company representative and illustrating the steps involved in conducting a field inspection of a company.

Learning Objectives:

At the conclusion of this section of the videotape, you should be able to:

1. Identify potential problem areas for inspectional coverage.

2. Develop methods to assess performance in problem areas and select the appropriate contact person at the company for gathering necessary information during an inspection.

3. Determine the deficiencies in the ADE reporting system at a firm being inspected.

4. Recommend appropriate FDA action in the event of noncompliance by a firm.

Section V: Tips

You have learned by this time that a Field Investigator's work is central to FDA's efforts in making critical risk management decisions. An ADE investigation is an involved process: it includes a variety of responsibilities, from becoming familiar with the federal regulations regarding adverse drug events reporting, to scrutinizing and detecting faulty reporting systems and overt noncompliance. In this section, additional tips are offered that will help you in performing an inspection.

In addition to the material presented in the videotape, the Division of Compliance Risk Management and Surveillance would like to add the following requests:

- Use Turbo EIR to record EIR inspectional findings and 483 deficiencies.
- Contact the CDER Office of Compliance CSO issuing the assignment for assistance in determining how to best capture findings on the FDA 483 and EIR.
- Items discussed with the firm, such as deficient performance covered by guidance, should be documented in the EIR narrative in the section entitled "Discussion with Management".
- If you have OAI findings, send a draft warning or untitled letter with 483, EIR, and exhibits to the attention of the CSO who issued the assignment (or to team leader Jay Schmid if this was a district-initiated ADE inspection).
- Forward a copy of all corrective action plans (CAPs) or other responses submitted by inspected firms to the attention of the CDER CSO who issued the assignment (or team leader Jay Schmid if this was a district initiated ADE inspection). It is acceptable for firms to submit a copy of their CAP directly to the CSO. Notify the CSO if you are notified by firms that they intent to submit a copy to them, or if the firm will not be able to submit a CAP by their original commitment date.

Learning Objectives:

At the conclusion of this section of the videotape, you should be able to:

1. Communicate with firms about their responsibilities to report adverse events associated with the use of a drug.

2. Provide the firm with the basic elements of reporting an adverse drug experiences to the agency.

3. Identify general locations within a firm where ADE information may be maintained, and identify errors in reporting and deficiencies in reporting performance.

4. Identify, in general, the type of persons within a firm who may be involved in collecting and reporting ADE reports data.

5. Assess the quality and accuracy of the data furnished by a firm.

6. Recognize the impact that a firm's noncompliance has on FDA's ability to make timely analyses of drug safety.

7. Discuss with firms identified deficiencies in their reporting system.

8. Recommend appropriate regulatory actions where long-term or deliberate non-compliance by a firm would impact public health.

Self-evaluation Post Test

Direction: For each of the following questions, select the correct answer.
Some questions may have more than one correct answer.

1. The primary function of the Division of Compliance Risk Management and Surveillance at FDA CDER is:
    a. Dissemination of drug information to the public
    b. Enforce postmarketing reporting requirements
    c. Evaluation of drug safety
    d. Evaluation of drug efficacy
    e. Scientific evaluation of adverse drug effects

2. Which is NOT a reason that inspections are conducted:
    a. Approved drugs may be used by many types of patients not included in the clinical trials
    b. The safety and efficacy of drug products are not evaluated prior to approval
    c. Rare adverse events are often not seen before a drug's use in a large population
    d. Serious reactions may occur following a drug's market release

3. The FDA pharmacovigilance team working to ensure the safety of marketed drug products does NOT usually include:
    a. Division of Freedom of Information
    b. ORA Field Investigators
    c. Office of Compliance
    d. Office of General Counsel
    e. Office of Drug Safety

4. The primary goal of the ADE reporting program is:
    a. Assuring identified drug risks are managed appropriately
    b. Assuring adverse event data is available to FDA safety evaluators
    c. Assuring labeling of prescribing information is complete and up-to-date
    d. Checking whether all patients are complying with the prescriber's instructions
    e. Providing the data on which to base decisions for certain drug's availability

5. Which of the following adverse health experiences is considered a reportable adverse drug event by CDER:
    a. An event occurring after withdrawal of the drug
    b. Due to an overdose, whether accidental or intentional
    c. During the normal use of the drug
    d. From off-label use of drugs
    e. From any failure of expected pharmacological action
    f. All of the above

6. Adverse drug experiences may cause which of the following health effects:
    a. Birth defect
    b. Death
    c. Significant incapacity or disability
    d. Extending hospital stay
    e. Skin rash that resolves without treatment
    f. Headache, nausea, or dizziness
    g. All of the above

7. Which of the following do not require periodic reporting of adverse events by drug companies:
    a. Approved New Drug Application
    b. Approved Abbreviated New Drug Applications
    c. Products not marketed or approved in the United States
    d. Prescription drugs that are not required to be approved by FDA

8. Firms that do not comply with the CDER ADE reporting regulations may face the following regulatory actions, EXCEPT:
    a. Issuance of injunction
    b. Prosecution
    c. Revocation of drug marketing approval
    d. Revocation of the firm's business license
    e. Product seizure

9. A US distributor of a prescription product not requiring FDA approval is obligated by regulations to:
    a. Maintain complete records for ten years of all adverse event data they receive, but not report to FDA
    b. Collect, evaluate, and submit information on adverse events from all sources
    c. Forward adverse event information to all sponsors of products with the same active ingredient.

10. If a drug company you are investigating has foreign affiliates, the firm should be able to inform you of all of the following, EXCEPT:
    a. The financial status of the firm's foreign affiliate
    b. The roles of their foreign operations in ADE data collection, processing, and submission.
    c. The data transmission system between the affiliated firms
    d. The confirmation system that verifies ADE data transmission and receipt
    e. The reporting responsibilities of the foreign affiliates

11. During the inspection, you should routinely collect information about which of the following:
    a. The person at the firm who oversees product distribution
    b. The person in charge of New Drug Applications
    c. The person conducting preclinical drug research
    d. The person within the firm with overall responsibility for collecting, evaluating, processing, and submitting adverse event reports

12. If any inaccuracy or omission in reporting is observed or suspected during an investigation, which of the following should be considered:
    a. Whether this is an isolated instance
    b. Whether the lapse was intentional
    c. Whether this inaccurate or incomplete reporting may significantly impact the drug's safety profile
    d. Whether the firm has already identified and corrected the cause
    e. All of the Above
    f. None of the Above

13. All of the following types of data are reportable to FDA as adverse drug events, EXCEPT:
    a. A drug-related adverse experience in a foreign country for a US approved product
    b. An adverse experience suspected from a product not approved by FDA and not marketed in the United States
    c. A publication or study data on a serious, unlabeled adverse drug experience related to the use of an approved drug product
    d. A spontaneously reported drug-related adverse experience occurring in US

14. What is the time limit for an application holder to submit a MedWatch report of a serious and unlabeled drug-related event:
    a. 5 calendar days
    b. 5 working days
    c. 15 calendar days
    d. 30 working days
    e. 90 calendar days

15. If a drug manufacturer, packer, or distributor chooses not to submit directly to FDA, what is the time limit for that firm to submit information about adverse drug events to the applicant:
    a. 3 calendar days
    b. 5 calendar days
    c. 15 calendar days
    d. 30 calendar days
    e. 90 calendar days

16. During an investigation, which of the following action should be focused on:
    a. Conducting the investigation properly, including collecting documents that support any identified deficiencies
    b. Making medical evaluation of the adverse drug events
    c. Recommending labeling or manufacturing changes
    d. The firm's future plans for modified procedures to reflect draft regulation

17. Which of the following would be considered appropriate for a firm to initiate at the conclusion of an inspections that identified deficiencies in Adverse Drug Events (ADE) reporting:
    a. To clearly understand the violations and the ADE requirements
    b. To review the ADE handling procedures in depth
    c. To maintain quality audits
    d. To develop a corrective action plan to correct the deficiencies
    e. All of the above

18. Before submitting a report to the FDA, a firm should have knowledge of all the following facts, EXCEPT:
    a. An identifiable patient
    b. An identifiable reporter
    c. A suspect drug associated with the adverse event
    d. The adverse event or fatal outcome associated with the use of a drug
    e. The identifiable cause of the adverse event

19. Pharmaceutical companies are required to maintain all adverse drug event records and all raw data, including phone logs and complaint files, concerning ADEs for:
    a. One year
    b. Five years
    c. Ten years
    d. Fifteen years

20. Firms that may be selected for inspection include firms:
    a. With previous recalls
    b. With products with limited safety information
    c. With late reporting noted in the Adverse Event Reporting System (AERS)
    d. With a recently approved new molecular entity
    e. Which have recently merged or acquired applications
    f. All of the Above

21. If a firm is receiving, processing and submitting adverse event information according to regulations, it is acceptable for the firm to have written procedures that do not describe their actual reporting processes.
    a. True
    b. False

22. If a firm has an approved application in the U.S. and the drug is marketed overseas, then the firm is required to submit to FDA all foreign events that are serious and unlabeled, and related to the drug.
    a. True
    b. False

For the following questions, choose the letter or letters for the reporting submissions which may use the form:

a. Mandatory reporting from manufacturers
b. Voluntary reporting from health care professionals and consumers
c. Manufacturers reporting foreign adverse drug events

23. MedWatch form 3500 _____

24. MedWatch form 3500A _____

25. Council for International Organization of Medical Science (CIOMS 1) form_____

Answer Sheet

1. b
2. b
3. a
4. b
5. f
6. g
7. c
8. d
9. b
10. a
11. d
12. e
13. b
14. c
15. b
16. a
17. e
18. e
19. c
20. f
21. b
22. a
23. b
24. a,c
25. c