Field Investigators: ADE Detectives
Transcript of Video Presentation
for the Audio-visual Self-learning Modules on Conducting Field Inspections of Postmarketing Adverse Event Reporting Compliance

This transcript is to be used for purposes of training FDA ORA Field Investigators in their task of postmarketing surveillance of adverse drug events reporting compliance.

The Presentation Participants

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Opening Remarks by Janet Woodcock, M.D., Director
Center for Drug Evaluation and Research

[**Janet Woodcock, Center Director**]

Every time someone uses a prescription medicine, they use it on trust:
Trust that the doctor prescribed it correctly ... trust that the pharmacist filled the prescription correctly ... and, most important, trust that it will help them - not hurt them. Our job at the Food and Drug Administration, and your job as an investigator, is to safeguard that public trust.

Manufacturers of prescription drugs are required by federal regulations to submit adverse drug reaction reports to the FDA. As field investigators, it's your task to inspect manufacturers and ensure that they file the reports required by law. Once a product is approved, your inspections are one of the primary means for assuring industry compliance. That's why your job is so critical to the FDA's mission.

In the following presentation, you'll learn more about the FDA's role, your role, and how you can work more effectively with your headquarters team.

Safeguarding the public from adverse drug effects is a demanding task.

Working together, we can make a difference.

Field Investigators: ADE Detectives

Section 1: Introduction to the Team & Their Roles

[**Narrator**]

You're an investigator! A scientific investigator in the Food and Drug Administration's continuing program to safeguard the public from unforeseen adverse drug effects.

It's a challenging mission. As an Investigator in the FDA's Postmarketing Adverse Drug Experience Inspectional Program, you're on the front lines … performing investigations, meeting with company representatives and reporting the facts.

This presentation is designed to help you locate all the information, guidance and support you need to get the job done efficiently and effectively.

Your role as a Scientific Investigator is critical to the success of FDA's program. Here's Dr. Peter Honig, Director of the Office of Postmarketing Drug Risk Assessment, "OPDRA," to describe the agency's mission and why your role is so important.

[**Peter Honig, Office of Postmarketing Drug Risk Assessment**]

You are the eyes and ears of the agency. You carry a great responsibility because you represent the Agency, and you interact with regulated industry. Your work allows us to make decisions on the interpretation of a large number of adverse event reports. Your role is highly visible and increasingly important.

The public expects FDA to "promote and protect public health by assuring that safe and effective drugs are available to Americans." You are a key to our success. It is truly a mission that can make a life-and-death difference for people.

Because of your work, we've been able to secure more accurate and complete labeling for certain drug products and to remove drugs that can be harmful from the market when the risks of using the drugs outweigh their benefits.

The postmarketing safety evaluations are largely based on the adverse drug reaction reports we receive. And the majority of the reports we receive are from manufacturers. That's why we're dependent on our field investigators to ensure that the manufacturer is forwarding information in accordance with the regulations.

The Office of Postmarketing Drug Risk Assessment was created to "provide pharmacovigilance resources to the Center for Drug Evaluation and Research to ensure the safety of marketed drugs." The Center's inspectional program is important, because it's a vital tool for monitoring drug safety. We rely on your inspections to assure that industry is complying with the postmarketing safety reporting regulations by promptly, completely and honestly reporting adverse drug reactions to the Agency.

To carry out our mission, we've created a team … a network that includes:

- Field Investigations
- Office of Postmarketing Drug Risk Assessment
- Office of Compliance
- Regulatory Policy Staff
- Office of Chief Counsel

[**Narrator**]

Dr. Honig described the Postmarketing Drug Risk Assessment Office's objectives; now let's hear from each member of the team…

[**Nancy Haggard, Office of Compliance**]

The Division of Prescription Drug Compliance and Surveillance ensures that postmarketing safety reporting regulations are being followed. We provide guidance to the field investigators on surveillance and compliance activities related to ADE inspections.

We issue and monitor all field assignments, review recommendations from the district compliance offices, and determine the appropriate regulatory actions to take.

It's our job … and yours as investigators … to safeguard the public from possible serious and unexpected adverse drug reactions.

[**Audrey Thomas, Office of Regulatory Policy**]

The Regulatory Policy Staff provides interpretation of the safety reporting regulations for human drug products. When necessary, our office revises these regulations. This process involves soliciting and considering comments from the public on proposed changes before the changes are incorporated into the regulations.

The safety reporting regulations apply to all prescription drugs and those over-the-counter drugs with approved applications, such as drugs that are switched from prescription to over-the-counter.

[**Rick Blumberg, Office of Chief Counsel**]

To support the compliance program, the Chief Counsel's Office is dedicated to providing legal counsel to FDA's staff, to evaluate cases for legal sufficiency and to process ADE court cases.

We work closely with the Division of Prescription Drug Compliance and Surveillance, OCI and the Department of Justice to bring cases that will support the ADE program.

[**Christine Cerenzio – Office of Regulatory Affairs Field Investigations**]

Our role as Scientific Investigators is to determine, through on-site visits, if companies are submitting all the required reports of adverse drug reactions. It's our job to assure that the reports are complete, accurate and timely.

When we uncover reports of adverse events that aren't submitted or are incomplete, inaccurate or late, we must document the problem so that appropriate regulatory action can be taken.

You spend long hours reviewing and sorting through documents, reviewing regulations and writing reports. Often, an investigator must be a detective, searching for clues and missing data.

It's a challenging and exciting job. And it's good to know we have a support team behind us.

[**Narrator**]

Now that we've met the team, let's take a closer look at why inspections are conducted and why they're so important.

Our job is to serve as an industry watchdog, performing inspections or investigations that help protect the safety of all citizens.

Once a prescription drug is approved by the FDA as safe and effective, it becomes available to a nationwide patient population. After approval, unforeseen reactions may occur that need to be documented and reported.

The reasons we need to follow-up are clear:

- After approval, drugs are used in many types of patients --including older, sicker, or those taking other medications -- that were not studied during the pre-approval period;
- and rare, serious adverse reactions are often not discovered until many thousands of patients have taken the drug.

[**Honig**]

The FDA is responsible for making sure that the benefit-risk profile of each drug is continuously evaluated throughout its marketing life. The Agency assures that:

- Labeling changes relating to prescribing information are complete and up-to-date, and
- drug risks are quickly and appropriately managed.

We also provide the data on which to base decisions for allowing certain drugs to remain available.

[**Narrator**]

The cornerstone of postmarketing surveillance of the prescription drug industry is to assure that accurate benefit-risk analyses of marketed drugs can be made. The risk part of the analysis depends on prompt, accurate and complete ADE reports.

Now here's a look at the following sections of our presentation:

- We'll cover the regulations that govern our activities;
- the types of guidance available from the Compliance Program;
- information on how to conduct an inspection;
- and we'll end with helpful tips and information for Investigators.

Section 2: The Regulations

[**Narrator**]

The American public trusts that when a health care practitioner prescribes a medication, that drug will provide positive benefits … not cause further harm and suffering.

And that's why the safety reporting requirements are so important. They cover all persons who market over-the-counter drugs with approved applications and prescription drugs, whether or not there is an approved application for the drug. These persons include applicants, manufacturers, packers and own label distributors who are required to review all safety information obtained or otherwise received from all sources, foreign and domestic.

Safety information includes commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/ surveillance studies, reports in the scientific literature, and unpublished scientific articles. Here's Audrey Thomas to elaborate:

[**Thomas**]

The postmarketing safety reporting regulations for marketed human drug products are contained in various sections of Title 21 of the Code of Federal Regulations. These regulations specify who must submit safety reports, what must be reported, when a report must be submitted, and what records must be maintained.

- Section 314.80 applies to human drugs with Approved New Drug applications.
- Section 314.98 applies to human drugs with approved Abbreviated New Drug Applications.
- Section 310.305 applies to prescription drug products for human use that are marketed without approved applications.
- Section 211.198 requires industry to establish, maintain and follow written procedures for handling complaints regarding a company's drug products, including adverse drug experiences. This section also requires industry to review each complaint to determine whether a serious and unexpected adverse drug experience occurred that must be reported.

The full text of these regulations is on your CD-ROM.

Before taking a closer look at the regulations, it's important to understand the differences between a drug quality or labeling problem and an adverse drug experience.

Section 314.81 requires that a field alert report be submitted to FDA when there is a concern about the quality or labeling of the drug. Drug quality problems occur during manufacturing, shipping or storage, and may include contamination, defective components, poor packaging, and questionable stability of the drug.

Sections 310.305 and 314.80 define an adverse drug experience as any adverse event associated with the use of a drug in humans, whether or not it is considered drug related … including:

- An adverse event occurring in the course of the use of a drug product in professional practice;
- or from a drug overdose, whether accidental or intentional;
- or from drug abuse;
- or from drug withdrawal;
- and also including any failure of expected pharmacological action.

[**Narrator**]

It's important to remember what we mean by serious when we talk about adverse drug experiences. Let's look at the list:

- Death
- A life-threatening ADE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect, and
- Other important medical events that may not result in death, be life-threatening, or require hospitalization when, based upon appropriate medical judgment, the event may jeopardize the patient or subject and may require medical or surgical intervention to prevent a life-threatening outcome.

A life threatening ADE is any adverse drug experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse drug experience. It does not include an ADE, that had it occurred in a more severe form, might have caused death.

Let's look at what must be reported:

- Any spontaneous adverse event occurring within the U.S., and
- Any foreign reports, literature and study reports that involve serious and unexpected events.

Remember, we define an unexpected adverse drug experience as one that is not listed in the current approved U.S. labeling for the drug product.

Companies are required to report all adverse events associated with use of a drug, whether or not the company considers the event drug related … except for study reports where there must be a reasonable possibility that the drug caused the event.

There are three types of required reports. Audrey will describe them for us …

[**Thomas**]

Applicants, manufacturers, packers and distributors are required to submit an Expedited or 15-day alert report if a serious and unexpected event occurs. The regulatory clock for these reports should begin when the firm has knowledge of the following four basic elements: an identifiable patient, an identifiable reporter, a suspect drug, and an adverse drug experience that can be identified as serious and unexpected.

Applicants having drugs with approved applications are required to submit a postmarketing periodic safety report quarterly for the first 3 years after U.S. approval of the product, and annually thereafter. Individual cases of serious, expected adverse drug experiences and all nonserious adverse drug experiences are required to be included in these reports.

Follow-up reports are required if additional information is received or obtained by the firm after submission of an expedited or periodic report.

Mandatory reporting of individual cases by applicants, manufacturers, packers and distributors must be submitted on an FDA Form 3500A. Firms can use an FDA Form 3500A or CIOMS I form, developed by the Council for International Organizations of Medical Sciences, for reporting foreign events. Companies don't need FDA's prior approval to use the CIOMS I form.

[**Narrator**]

Thank you, Audrey. Another important part of the ADE program is maintaining records. Rick Blumberg will tell us more about what records must be kept.

[**Blumberg**]

Regardless of the Adverse Event Reporting process used by a company, under sections 310.305 and 314.80, companies are required to develop written procedures for handling ADEs. The procedures must provide for:

- surveillance
- receipt
- evaluation, and
- reporting.

A company's contractual agreements are considered part of the firm's written procedures. If company A is exchanging adverse event data with company B, the contractual agreement should cover a full description of each company's responsibilities regarding the exchange of ADE information which includes the following critical elements:

- receipt
- analysis
- storage and
- reporting of information.

It is improper to contract with a company to do less than what the regulations would require. And both companies could be held responsible under such circumstances.

The bottom-line is that firms should collect quality information, identify and confirm drug safety issues as soon as possible, and communicate the drug safety information to the FDA and the public efficiently and effectively.

Firms are required to maintain all ADE records, including all raw data, for 10 years.

The FDA considers the safety reporting requirements to be critical for drug manufacturers. Persons who do not comply with the safety reporting regulations may face seizure, injunction, prosecution and/or revocation of their applications to continue marketing the drug in the United States.

[**Narrator**]

In addition to the mandatory regulatory requirements, there is also a program of voluntary reporting of adverse events by consumers and health care professionals to the FDA. This is covered by the Agency's MedWatch Program. Here's Dr. Norman Marks, Director of the MedWatch Office, to explain.

[**Norman Marks, MedWatch**]

In the mid-90s, the FDA launched MedWatch, a program designed to promote and facilitate the voluntary reporting of serious adverse events and product problems with drugs. Form 3500 is intended for consumers and health care professionals.

Both FDA forms 3500 and 3500A can be obtained from the MedWatch Office web site:
http::/www.fda.gov/medwatch/how.htm
Types of information requested on the form include:

- Information about the patient
- Details about the event, and
- Information about the suspected medication.

Consumers and health professionals can send Form 3500 to the MedWatch office:

- By Mail: Use the postage-paid MedWatch form
- By Phone: Dial 1-800-FDA-1088
- By Fax: 1-800-FDA-0178
- And by the Internet

Only Form 3500 is sent to the MedWatch Office. This office will forward the voluntary forms to OPDRA for review and evaluation. Mandatory Form 3500A is sent to the FDA's Central Document Room and to OPDRA. All forms are entered into the Adverse Event Reporting System.

Companies may use an alternative reporting format for safety reports such as a computer generated facsimile of FDA Form 3500A, but they are required to obtain prior approval from FDA.

[**Narrator**]

Thank you, Dr. Marks.

Now let's get back to your job. One of the most important aspects of it is to keep aware of changing regulations, including harmonization with international safety reporting initiatives. The CDER Web Page will help you acquire the most up-to-date information. Visit the site regularly.

Section 3: Compliance Program Guidance

[**Narrator**]

More and more, the FDA is relying on information technology. We're also moving toward conducting an increasing number of inspections. Because we're growing, and because there are more than 700 pharmaceutical firms in the United States, your job as an investigator will depend more on computers and telecommunications.

Using the computerized databases, we select the companies and products for you to inspect. Regulations cover several broad industry categories:

- Drug manufacturers
- Applicant holders
- Packers and
- Distributors.

There are 2 types of inspections: "**for-cause or directed inspections**" and routine **surveillance inspections**. The degree and depth of attention may vary in both types of inspections. During a directed inspection, you may be required to cover specific safety reporting information related to one or more drugs to determine whether a particular suspected violation exists. During routine surveillance inspections, you may be assigned to a broad spectrum of drug products to determine the firm's compliance with the postmarketing safety reporting regulations.

Companies or particular products are selected, based on these criteria:

- A review of the Adverse Event Reporting System Database, called AERS
- Firms that have a history of violations, are on the Application Integrity Policy List, or that have a history of recalls
- Routine surveillance

- The drug is a new molecular entity or is on the Top 200 List
- Safety issues
- Bioequivalence issues and
- Special situations.

[**Narrator**]

The AERS database is a useful tool. The FDA system can sort data about all adverse drug events submitted by the company.

Other reports include:
- Timeliness reports that describe any serious and unexpected reports submitted beyond the 15-day time frame
- Direct reports vs. mandatory reports, that compare those reports submitted by consumers and health care professionals with the reports submitted by the manufacturers
- and completeness reports that list the reports with missing information submitted by manufacturers

In some instances, in the Office of Postmarketing Drug Risk Assessment, safety evaluators may forward specific safety reports to the Office of Compliance for inspectional follow-up, particularly when inconsistencies in the reported data are found or when initial adverse event reports have not been followed up properly by the company.

These reports are important in preparing for an inspection, but they are only some of the tools available to the investigator.

Now let's talk about getting ready to go on your inspection.

In addition to phone, fax and Internet links to your support team at Headquarters, here's a list of steps to help you get ready:
- Review previous establishment inspection reports
- Review information provided with the assignment, including 3500A forms, current approved labeling and AERS-generated ADE lists
- Review applicable CFR sections, Compliance Program information, and FDA guidelines included in your inspectional package
- Contact the staff member who initiated your assignment

You'll find all the reference documents you will need on your CD-ROM.

[**Haggard**]

An investigator needs to request numerous materials from the company under investigation. Here's a list of the major ones to ask for:

- All of the firm's written procedures that describe receipt, evaluation, and submission of ADEs during the time period under investigation.
- Organizational charts showing which persons were or are responsible for all complaint handling during the period under investigation.
- All written procedures describing who is responsible for changing complaint handling procedures during relevant time period under investigation
- All correspondence, meeting minutes, and documents relating to all unreported or late ADRs.
- A list of all the company's drug products and approval dates
- Package inserts for products covered under the inspection.
- A listing of all ADE complaints received over a specific timeframe, such as 2 years. The listing should include foreign and domestic events.
- Periodic reports, specific 3500A forms, and associated raw data
- List of collection sites, processing centers, and reporting units
- And copies of all contractual agreements related to the collection, evaluation and reporting of ADEs.

If possible, get the data on computer disks. Be aware that some companies don't have all their information computerized, so you may have to follow a paper trail.

Your handout CD lists several other basic documents you'll want to keep handy.

[**Narrator**]

The FDA relies on adverse drug event reports to make critical labeling and risk management decisions. We also need to have assurances that the pharmaceutical companies are complying with the law and have a system in place that will ensure the receipt, analysis and submission of these important reports to the FDA in a timely and complete manner.

We rely on you, the Investigator, to provide us with this assurance.

Are you beginning to see how vital a role you play on the Compliance Team? Next, you'll have the opportunity to meet with an experienced investigator.

Section 4: How to Conduct an Inspection

[**Cerenzio**]

Class, I'd like to introduce Christine Cerenzio.

Christine, the class has tried to think up some questions that would help us to better understand the role of the investigator. Let's start with a basic one. Is there a difference between a GMP inspection and a postmarketing ADE inspection?

[**Christine**]

Yes. There is a difference. A GMP inspection includes evaluating processes related to the manufacturing, packing and testing of drug products. An ADE inspection is a directed inspection which evaluates the firm's handling and reporting of adverse drug experience complaints.

An ADE inspection starts long before an on-site visit to the firm. It begins with a review of agency regulations and guidance documents, a review of data and reports generated by CDER, and a thorough review of the company's establishment file.

[**Narrator**]

Christine, can you tell us what is the main objective of these ADE inspections?

[**Cerenzio**]

The main objective of an ADE inspection is to determine whether the firm has filed all reports to the agency and to assure that these reports are complete, accurate and timely.

To do this, we need to identify problem areas for inspectional coverage. We also need to identify what system failures and persons caused the firm not to comply with the federal regulations.

We also need to determine the flow of the firm's adverse event process. Investigators need to question as many people as needed to learn this information.

You need to find out which persons in the company are responsible for collecting ADEs , evaluating adverse events for significance, and reporting to the FDA, and during what precise periods of time each person held his or her responsibility. This can be done with responsibility charts, organizational charts, standard operating procedures or forms.

[**Narrator**]

What are some of the questions you typically ask while interviewing representatives of the company?

[**Cerenzio**]

It's a long list … but here are the basic questions:

- How do they do their job when each type of ADE comes into the company?
- Are there meetings on ADEs? Who presides; how often; what topics are discussed?
- Which persons in the company are responsible for labeling and making sure that the labeling reflects the ADEs that are coming into the company?

- How does the process work for assuring that labeling reflects ADEs?
- Who first receives the incoming mail or calls relating to ADEs?
- Where are and how are ADEs logged in?
- Who performs the medical evaluations?
- Who performs follow-up?
- Who assesses seriousness?
- Who determines if the ADE is a labeled or unlabeled event?
- Who determines if the ADE is a 15-day or a periodic report?
- Who transmits or sends the 3500A Form to FDA?
- How is information shared among departments? Be aware that the legal department might be receiving and maintaining ADEs too.
- How are ADE reports tracked?
- How are control numbers assigned?
- Does the firm use a computerized database for tracking?
- Is this database national or global? What information is kept in the database?
- Is there an audit trail? How does the firm track ADE receipt and submission?

[**Narrator**]

What about a firm's written procedures, Christine?

[**Cerenzio**]

It's important to review the firm's written procedures for ADEs. Written procedures should reflect current practices and should identify how ADEs are evaluated, investigated, and sent to the FDA. These procedures should address how and when follow-up information will be collected. When written procedures don't conform with the ADE regulations, determine how SOP deficiencies resulted in the firm's failure to submit an adverse event or how it impaired the firm's ability to submit safety data to the agency.

Spend time interviewing company employees. You may want to spend some time observing their processes including the data entry and assess how uncertain situations are handled by the data entry personnel.

You also need to determine the rates of errors in the company's information system. Keep in mind that when an electronic record of an adverse drug experience is created, modified, archived, retrieved or transmitted, the drug manufacturer is required to employ certain procedures.

[**Narrator**]

What kind of procedures do you mean?

[**Cerenzio**]

I mean validation of their computer systems to ensure the accuracy, reliability, consistent intended performance and the ability to discern invalid or altered records. This requirement is covered in 21 CFR Part 11 – Electronic Records, Electronic Signatures, and it's in your CD-ROM.

[**Narrator**]

What are some of the common deficiencies found in these inspections?

[**Cerenzio**]

Some of them are…

- A firm's failure to submit or the late submission of a 15-day report.
- Failure to submit or the untimely submission of periodic reports.
- Submission of inaccurate or incomplete ADEs.
- Failure to conduct follow-up investigations into the outcome of serious and unexpected ADEs.
- No written SOPs; inadequate SOPs, or failure to follow SOPs and
- Failure to validate computer systems used to generate ADE reports.

[**Narrator**]

Thanks, Christine, for all that helpful information.

So class, during your inspections, you may have questions or just need additional information from the FDA AERS database. While field offices don't have direct access to the database, this information can be obtained from CDER's Office of Compliance. Just call the Division of Prescription Drug Compliance and Surveillance in the Office of Compliance at 301-594-0101.

In fact, for any question or when in doubt, contact the Division.

Section 5: Tips

[**Narrator**]

To help you during the inspection in your role as investigator, here are some tips and hints from the Compliance Team to help you be more productive and effective on the job.

[**Haggard**]

Failure to report serious and unlabeled events is the most serious problem.

[**Thomas**]

Remember that the firms are required to report adverse events associated with the use of a drug, whether or not the company considers the event drug-related except study reports.

[**Cerenzio**]

As Scientific Investigators, we need to recognize the impact that the firms noncompliance has on the agency's ability to reach timely scientific evaluations concerning matters of drug safety.

[**Honig**]

The firm should have knowledge of four basic elements before submitting a report to FDA: a suspect drug, the adverse event or fatal outcome, an identifiable reporter and an identifiable patient.

[**Cerenzio**]

Know how to analyze a company's processes and how to locate the data you need. This may require solid computer skills so you can understand the firm's network, electronic capabilities, information systems and their document tracking system.

[**Haggard**]

Be aware of reporting responsibilities by a firm's foreign affiliates and also the complexities of multi-national systems. If safety data are transmitted electronically from foreign affiliates to the processing center and reporting units, check to learn whether the firm has a mechanism to ensure that the transmission is properly conducted and whether there is a feedback mechanism among the units to ensure all data were actually transmitted. Be aware that in some instances their global adverse event database may not match their regional or local database.

[**Honig**]

Have a clear understanding of which persons were and are responsible within the firm for collecting the data, evaluating the adverse event, and for submitting the report. Know who was responsible when the first ADE was logged in.

[**Cerenzio**]

Be sure a firm's reports are accurate. If you suspect they aren't, use your scientific investigation skills and determine whether it was an isolated event, a pattern or whether it was intentional. We need to ask ourselves whether the reporting error has materially or significantly changed how the FDA may view the safety of the drug.
[**Blumberg**]

Pay particular attention to how reports are investigated by companies. Sometimes companies may not diligently follow-up on adverse drug reaction reports.

[**Honig**]

Pay attention to the quality of the firm's reports. Determine how the firm monitors the quality of these adverse event reports as they come in from their affiliates, outside partners or as the forms are completed by their reporting units. Determine whether any omissions in the adverse event reports are related to poor quality reporting.

[**Blumberg**]

If you discover that a firm has failed to submit ADE reports, determine what incentives there were to not report or to delay reporting.

[**Thomas**]

Keep in mind that recent or ongoing deviations from the regulations are the most significant.

[**Blumberg**]

Keep these regulatory considerations in mind:

- Does the firm have a chronic history of indifference?
- Is the unreported or late ADR not in the label?
- Is there a large number of ADE reports?
- How serious are the reports?
- What is the length of delay in filing the reports?

- Do the unreported data reflect a significant increase in the number of ADEs of this type or an increase in severity of the type of ADE?

- Is there a pattern of behavior such as selectively not reporting serious events?

- Is the unreported or late ADE report material, relevant to the decision making or capable of influencing a decision in FDA?

[**Honig**]

Don't make medical evaluations of the adverse event. And don't make labeling change recommendations.

[**Thomas**]

Did you know that a firm is required to report adverse drug events even if the drug is not marketed in the U.S.? If the firm has an active approved application in the United States and the drug is marketed overseas, then the firm is required to submit foreign serious and unlabeled events to the FDA.

[**Haggard**]

The firm should take appropriate actions to correct the deficiencies. These corrective actions should be reported to FDA. In some cases it may include training of employees, an in-depth review of the ADE handling procedures, and quality audits. Follow-up inspections are conducted to verify the firm's corrective actions.

[**Thomas**]

Become more familiar with the FDA's safety reporting requirements and how they relate to your inspections.

[**Blumberg**]

Proper documentation of ADE reporting violations by you is critical for the development of legal evidence.

[**Narrator**]

Exciting changes are ahead for the inspection program… changes that will help to streamline some of our activities, make us more productive, and improve how we communicate. And there are changes underway in how companies may report to the FDA.

The FDA and industry are engaged in a pilot program allowing companies to electronically submit ADRs. Eventually, we plan to eliminate paper submissions of ADRs. New regulations and guidance for industry are currently being written to assure that we can move toward this quickly.

When we began this presentation, Field Investigators were described as detectives – Scientific Investigators on the front lines of protecting public health and safety. Your job has never been more important. With the growing number of drug products becoming available and our focus on conducting a higher number of investigations annually, Field Investigators have a critical challenge ahead.

Your headquarters team is ready to support you throughout the course of each investigation. We're as close as a phone call …or a mouse click to the Internet.