CBER's Bioresearch Monitoring Program: Clinical and Nonclinical Inspections

SLIDE 1
This presentation will cover Bioresearch Monitoring, abbreviated BIMO, at the Center for Biologics Evaluation and Research, or CBER.

The term "clinical" refers to studies in human subjects. The requirements for conducting clinical research are also referred to as Good Clinical Practice, or GCP. The term "nonclinical" refers to studies in animals or tissue cultures that are used to evaluate safety before the products are tested in humans. The regulations for nonclinical laboratories are referred to as Good Laboratory Practice, or GLP.

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BIMO is an agency program. All FDA headquarters product centers have BIMO staff working in Good Clinical Practice and/or Good Laboratory Practice compliance.

GCP and GLP compliance are enforced in the same way throughout the Agency. In addition, FDA has cross-cutting committees to develop GCP and GLP policies for the agency.

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The BIMO Program has three purposes: to ensure that the rights, safety, and welfare of the human research subjects are protected; to determine the accuracy and reliability of the clinical trial data; and to assess compliance with FDA's regulations throughout the study.

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FDA's BIMO inspections include the following: one, the clinical investigators who conduct clinical trials. Most of the GCP inspections in FDA are of clinical investigators. Two, FDA also conducts inspections of sponsors, monitors, and the contractors that sponsors hire to assume some or all of their research duties. Some of these inspections are based on complaints or concerns from FDA reviewers, complaints from outside of FDA, or from problems found during other inspections. Three, FDA also does inspections of Institutional Review Boards, which are similar to Independent Ethics Committees found in other countries. And finally, four, FDA inspects the nonclinical laboratories that perform testing in animal or tissue culture systems.

As I mentioned before, non-clinical laboratories perform studies to evaluate safety, before FDA allows investigational products to be used in humans.

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FDA investigators follow a Compliance Program for each of the inspection categories just noted. A compliance program is a step-by-step list of instructions for FDA field investigators to follow during an inspection.

A web link can be found at the end of this presentation, if you would like to read these documents.

SLIDE 6
The next few slides will explain the types of work that the Bioresearch Monitoring Branch does for CBER.

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A very important function is that the branch coordinates pre-approval inspections to verify data that sponsors have submitted in a marketing application.

The inspection assignment requests are written by the CBER BIMO staff. Inspections are performed by investigators in FDA's Office of Regulatory Affairs, known as ORA.

The Center BIMO staff also conducts inspectional follow-up activities.

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For marketing applications, CBER usually inspects from three to five clinical investigator sites to evaluate whether the sites followed the study protocol. During the inspection, FDA verifies the critical safety and efficacy endpoint data that the sponsor submitted in the marketing application. Sometimes, though, those first inspections might raise questions about how the entire study was conducted, so FDA might add additional inspections. There have been numerous inspections for a single application, including inspections of the sponsor and contractors, to try to understand the scope of problems in a study.

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The inspection assignments include a description of the product, and explain the goals of the study protocol. The branch includes this information so the FDA investigators have a good understanding of the study. The assignments also include specific questions written with input from the review committee for the application.

For example, there might be specific concerns about data from a particular site, or questions about a particular technical aspect of the study. The assignments include copies of the data from the selected study sites, and FDA compares those data to the site's own study records. The data verified are listings of the data for each subject, not combined or calculated data.

Questions about study drug accountability, subjects' disposition and follow-up, and monitoring and supervision of the study are also included in the assignment.

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FDA is frequently asked how it selects which sites to inspect. It is based on a number of factors. The distribution of the subjects is important. FDA will typically go to the larger sites, but also looks to see if there is something about a particular site that stands out or is unusual.

In certain specific product areas or for some rare diseases, there may be a few clinical investigators inspected several times. If FDA has a recent inspection history showing an investigator was recently in compliance, then investigators who have not been inspected will be selected, even if there are smaller numbers of subjects enrolled at that site. Review of the application might show that a site enrolled ineligible subjects, or that there was a high rate of protocol violations. These are also sites FDA might choose to inspect.

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The CBER BIMO staff looks at the list of protocol violations for investigators who had problems conducting the study. When the information is available, CBER tries to reconstruct the randomization plan to see if the sites followed the plan. That is becoming more difficult now that sponsors are using centralized, automated randomization software, but is still possible for some of the early- phase studies.

One of the areas where problems were found is when a sponsor permits a clinical investigator to supervise many other satellite sites. CBER has seen a clinical investigator supervising over 20 satellite clinics enrolling subjects under a single investigator's name. FDA's concern is that the investigator might not be able to adequately supervise the study.

CBER is conducting more international inspections.

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During an inspection of a marketing application, such as a Biologics License Application or a Premarket Approval Application for a medical device, FDA looks at the data that was submitted in the application and compares it to the medical records and other records at the site.

Fortunately, most of the time those data match. But if they do not match, then FDA must find out why. Was there a problem with the computer system or with the way the staff entered the data into the computer system? It's important to account for why there might be discrepancies, because FDA wants to know that the system for capturing the data was sound.

For example, FDA found a situation where a contractor that was supposed to manage the data actually corrupted the entire study. When verifying data during an inspection, FDA looks for signals that might show problems with the performance of the clinical trial system rather than just isolated local events.

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This diagram shows you the Center's time schedule for reviewing a standard biological license application, or BLA. The milestones listed above the line in white are the Center's milestones. The Center has 10 months to review a standard application, or 6

months for a priority application. Device premarket approval applications have a 6 month review deadline.

The Bioresearch Monitoring activities are shown below the line. The BIMO reviewer is a member of the application review committee, so the reviewer participates in meetings with the sponsor before the application is submitted. CBER BIMO issues inspection assignments shortly after the committee files the application. ORA schedules and conducts the clinical data verification inspections, and then submits the inspection reports back to the Center as soon as possible.

If an inspection finds anything alarming, CBER BIMO notifies the rest of the review committee, and evaluates whether the problems are site-specific, or whether the problems might impact other sites or the whole study. This might result in phone calls to the sponsor to obtain more information.

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When the inspection is over, the problems that were found are evaluated. Most of the time, the problems are minor. However, when there are many problems, or potentially serious problems, CBER evaluates the significance and possible extent and the impact of the problems.

First, CBER evaluates whether the data are reliable and accurate, and therefore, directly impact the data that FDA is reviewing.

Second, CBER evaluates whether the problems were isolated at one site, or whether there was a flaw in the management across the study.

In addition, CBER verifies whether the sponsor reported these problems in the application. If the sponsor did not report these problems, the Center will ask for an explanation from the sponsor. This might result in concerns about the integrity of the data that were submitted to that application.

If significant problems are seen at a clinical site, it is important to know what other studies are, or were, conducted there. There might be a pattern of problems that impact every study at the site.

For example, if CBER learns that a particular contractor contributed to protocol violations at one site, it is reasonable for FDA to conclude that those problems or practices may cause similar problems at other sites. In a case like this, FDA would follow up with an inspection of the contractor and additional sites, and the sponsor.

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CBER's Bioresearch Monitoring Branch also requests inspections of ongoing clinical trials, usually in Phase 1 and Phase 2.

These are referred to as "surveillance" inspections.

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CBER started this type of inspection more than fifteen years ago, after the death of a subject in a gene therapy study. Since that time, the surveillance program has expanded to cover all of CBER's investigational product categories. These inspections are usually focused on a specific type of product or study population.

For example, CBER in recent years selected studies enrolling pediatric subjects, or specific types of influenza vaccine as a focus area. Also, in recent years, CBER inspected several sponsor-investigators who are conducting studies at multiple sites, because in the past it has been found that some of these sponsors do not conduct the required monitoring of the other sites.

The surveillance inspections are usually short - two to three days. The focus is on two or three subjects' records, to make sure they were eligible for the study, and whether or not the clinical investigator is following the protocol. There is no data audit for these inspections, because the studies are ongoing, no data have been submitted to FDA, and the study is usually still blinded.

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The BIMO branch also investigates complaints that relate to investigational products and institutional review boards, or IRBs.

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The CBER BIMO staff receives complaints from anyone who might be involved in conducting, managing, or participating in clinical trials. These complaints may first come to the FDA headquarters, or other FDA Offices. BIMO receives them by email, phone, and letters. Some are anonymous.

U.S. IRBs are required by regulations to report when they suspend or terminate a study, and sponsors are also required to report when they terminate the participation of a clinical investigator. CBER BIMO manages these notifications the same way as other complaints.

Sometimes the complaints are very general or vague, so there may not be enough information to allow CBER to conduct an inspection. Sometimes CBER will not even know what kind of product is involved, so it's unknown which FDA Center should be involved. Some complaints are very specific, and show that the person has knowledge of the operations of the institution. Sometimes there are current employees, or former employees who quit or whose job was terminated.
If CBER has the opportunity to talk to the person, as much information as possible is gathered. When CBER can speak with the complainant, the staff thanks them for telling FDA about the problems, and encourages them to tell more or even to send in copies of documents, if possible, to help focus an inspection.

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CBER BIMO also conducts inspections based on information received from FDA staff. These are examples of referrals received from other CBER employees.

For example, several times a year, reports are received from CBER's pharmacologists that a study had problems or the study report is flawed. They wonder how a particular laboratory could
be compliant with the Good
Laboratory Practice Regulations for nonclinical laboratories. These regulations are found in Title 21 of the Code of Federal Regulations, Part 58.

In one case, an FDA product reviewer attending a conference saw a poster presentation for a product that would require, but did not have, an Investigational New Drug Application, or IND. FDA conducted an inspection, and issued the investigator a warning letter for not having an IND for the research.

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CBER BIMO also writes inspection assignments and reviews the inspection reports for quality system inspections of Nonclinical Laboratories that conduct GLP studies.

SLIDE 21
CBER issues GLP assignments based on FDA referrals or complaints, and several have resulted in compliance actions, including warning letters.

SLIDE 22
There are several options for actions to be taken to obtain compliance with the Good Clinical Practice and Good Laboratory Practice regulations. Some of this information will repeat what you may have heard in other presentations.

SLIDE 23
The FDA investigator or the inspection team writes the inspection report and submits it to the Center's Bioresearch Monitoring staff. The BIMO staff reviews the report, decides what corrective actions are necessary, and classifies the inspection according to these three categories: one, "no action indicated," or NAI; two, "voluntary action indicated," or VAI; or three, "official action indicated," or OAI.

These three classifications apply to all FDA inspections in all product areas.
In the next two slides, you will see the possible actions for inspections classified OAI.

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This slide lists the possible actions for the inspected party. This could mean the clinical investigator, a sponsor or contractor, an institutional review board, or a nonclinical laboratory.

The most common action is a warning letter. Warning letters list violations of FDA regulations, not guidance, and request a reply within 15 days. These letters are posted on FDA's web page.

Much less common, FDA can initiate a process to disqualify a clinical investigator. This means that FDA intends to prohibit an investigator from participating in clinical trials of investigational products. The letter initiating the process is available on FDA's web page. While the proceeding is ongoing, the investigator can still conduct studies. FDA will not initiate the disqualification of a clinical investigator outside of the U.S.

The regulations also allow FDA to disqualify institutional review boards. FDA only recently had the first IRB disqualification. Most non-compliant IRBs quickly come into compliance or disband their operations after a violative inspection. Injunctions and seizures are court orders to stop a prohibited action or to take control of a product. CBER may refer matters to FDA's Office of Criminal Investigations, which has different authority for gathering evidence, and this might lead to prosecution. If someone is convicted of a crime, then FDA can debar the person from working on FDA matters.

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FDA also has a number of actions it can take for applications that have been submitted for review. An inspection might show that there are problems with an investigational biologic drug, or that the study is not being properly conducted, so there is the option of putting drug and biologic studies on clinical hold. A similar action, called a disapproval, can be imposed for an investigational device. There is also the option of rejecting data, either for a whole study or from particular clinical sites. As a result, the sponsor might have to conduct another study.

The other actions listed on this slide are rarely used.

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CBER's Bioresearch Monitoring staff answers questions about good clinical practice and data integrity. BIMO answers questions from industry, with the goal of preventing problems in clinical trials. BIMO is also a resource for CBER staff who find problems in investigational product applications.

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The first website contains information regarding Inspections, Compliance, Enforcement, and Criminal Investigations.

The second website contains information regarding Clinical Trials and Human Subject Protection. The Bioresearch Monitoring Program link takes you to the compliance programs that are instructions for how FDA inspects clinical investigators, sponsors and their contractors, IRBs, and nonclinical laboratories.

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This concludes the presentation, "CBER's Bioresearch Monitoring Program: Clinical and Nonclinical Inspections." We would like to acknowledge those who contributed to its development. Thank you.