



# What to Expect When You Are Inspected

Dorothy asks a former FDA Compliance Officer and Investigator about what you can expect when the FDA comes for a visit.

BY DOROTHY B. ABEL, WITH J. LAWRENCE STEVENS

*The views and opinions in this article are those of the author and do not necessarily reflect those of the US FDA, the US Department of Health and Human Services, or the Public Health Service.*



The recent focus on enforcement at the FDA has sparked much interest in FDA inspections. Although all investigators in clinical studies may be subject to inspections, few are familiar with the process by which investigations are conducted.

In an effort to introduce this process, J. Lawrence Stevens, currently the Director of Import Operations for the FDA in Los Angeles, has provided answers to some common questions regarding inspections. Mr. Stevens was formerly an FDA Compliance Officer and Investigator, specializing in medical device and bioresearch monitoring (BIMO) inspections. Part of his background includes 17 years in the medical device industry where he managed numerous clinical trials for cardiovascular devices.

## What are the reasons for being inspected?

There are two basic types of FDA inspections: surveillance and compliance. A surveillance inspection is a routine FDA inspection, concentrating on basic FDA requirements (ie, good clinical practice compliance).

A compliance inspection is based on a specific objective.

This type of inspection may be based on a complaint or another suspected specific problem, such as unreported adverse events, and also occurs as a follow-up to a previous violative surveillance inspection. Other types of compliance inspections can be prompted by the submission of a marketing application (eg, 510[k] or PMA) to the FDA that contains clinical data. These so-called BIMO inspections are initiated by the FDA headquarters and sent to the field for implementation.

## When will practices be notified that they will be inspected; that is, how much advanced warning do you get?

Advanced notification of an inspection is voluntary and is limited to medical device firms and BIMO inspections. Notification is usually provided 7 to 10 days before the scheduled inspection and is generally not negotiable. It is a notification of inspection, not a request for an appointment; however, the FDA investigator does have some flexibility regarding scheduling.

Compliance inspections, and for the most part all inspections of food, drug, or cosmetic firms, are unannounced. The Food Drug & Cosmetic Act authorizes unannounced inspections at any time the institution or firm is open for business.

## Will the facilities be told why the inspection is being conducted?

The FDA investigator is not required to state the rea-



son for the inspection. Some investigators choose to do so; others will not volunteer the information. A prudent person will ask the reason, and the investigator should be forthright with the reason, but will probably not provide any details.

#### **How many investigators will show up?**

Generally, inspections are performed by one person. If more than one person participates, it may be for training purposes or because some of the participants have specialized knowledge that the FDA believes is necessary to perform a thorough inspection. The specialists may be nurses, dentists, physicians, computer experts, microbiologists, chemists, or criminal investigators. It would be prudent to ask each FDA participant his particular area of expertise.

#### **What sort of background will the investigators have, and from what part of the FDA do they come?**

Investigators will generally have a background in natural or physical sciences or engineering. Although specialists may be brought in from other parts of the FDA, investigators work in the FDA field offices, that is, regional offices responsible for coordinating and conducting all inspections related to foods, drugs, cosmetics, and devices.

#### **What sort of preparation do investigators have before arrival?**

The assignment that is sent to the field by FDA headquarters will include pertinent documents. Generally, these will include the IDE protocol, the sample informed consent form, the data tables for the primary endpoints, a list of protocol deviations, and a listing of all reported adverse events. If specific issues are involved, the investigator may be provided with copies of FDA correspondence, IRB correspondence, or other related documents. In the written assignment, the investigator is instructed to call the Office of Device Evaluation reviewer to discuss the inspection strategy.

#### **What do investigators do once they arrive?**

The inspection will generally begin with a meeting with the principal investigator and would include the clinical coordinator. At that meeting, the investigator will issue the FDA-482 Notice of Inspection form, which is a required document that states the FDA's authority to inspect. The investigator will discuss the general conduct of the trial, including the sponsor's interaction with the site (eg, clinical investigator and/or site training, general correspondence, reporting of adverse events, monitoring). The actual inspection will include a comparison of

Case Report Forms data to source documents and a review of IRB correspondence, approval, and use of informed consent documents, protocol deviations, and site monitoring reports.

#### **What should the principal investigator do during the inspection?**

The principal investigator should be available throughout the inspection to assist the FDA investigator. It is useful to keep a log of all questions, requests, and answers. All documents should be marked as confidential and copies retained.

#### **How long will the investigator be there?**

BIMO inspections usually take 1 to 3 days. Generally, the more issues there are, the longer the inspection takes. Again, a prudent person will ask the FDA inspector how long they think the inspection will take and even suggest an inspection agenda so that appropriate persons may be made available. Also, it is acceptable to ask the investigator on a daily basis if they have observed any objectionable conditions.

#### **What will come out of the inspection, and are the results publicly available?**

At the conclusion of the inspection, the investigator will almost always ask to meet with the principal investigator and the appropriate staff to discuss findings. For minor issues, the investigator will not issue a form, but rather will discuss the findings orally. If more serious deviations are noted (eg, failure to report adverse events, clinical procedures done without proper informed consent), the investigator will issue an FDA-483 form that lists the specific deviations. It is very important that the observation be discussed to ensure that the issues are understood completely. Ideally, the investigator will have discussed any issues during the inspection and there should be no surprises when the FDA-483 form is issued. If there is disagreement and the investigator maintains his position, you should ask that your objection be placed in the written report.

The investigator will ask what corrective actions might be undertaken in response to the observations. It is best to speak only in generalities, unless the "fix" is quite obvious. The most common type of initial response is to tell the investigator that it is your intention to fully comply, and that you will submit a written response after a careful analysis of the issues, identification of root causes, and creation of effective corrective actions. When you write the response to the FDA-483 form, you should explain the observed deficiencies, as well as describe the corrective actions, both taken and planned.

The investigator will prepare a narrative report to accompany the FDA-483 form. He or she may also collect copies of documents that show the violation. All of those documents will be forwarded to FDA headquarters, specifically the CDRH Office of Compliance, for a review by the Division of Bioresearch Monitoring. Serious violations may be followed by a formal warning letter from the FDA. This letter demands creation of effective corrective actions, with the threat of legal penalties if the actions are not forthcoming. Serious repeat violators may be banned by the FDA from performing clinical research on FDA-regulated products. Additionally, the data from any clinical investigator's site could be rejected from consideration in the FDA submission it is intended to support.

Once the file is closed (ie, corrective actions are accepted or no FDA-483 form was issued), the report and any FDA-483 form become public information excepting any trade secret or patient information.

**Is there anything else that clinical investigators should be aware of?**

Those who are participants in FDA-regulated clinical trials should be well prepared for FDA inspections by the sponsors of the studies. Regulatory binders should be provided with all pertinent FDA-approved documents. Files should be set up to capture all sponsor and IRB communication. Standard operating procedures should be maintained on how to manage the study. Equally as important are regular monitoring visits by the sponsor and at least one mock FDA audit. It is, of course, very important that corrective actions deemed appropriate from monitoring visits or the mock FDA audit be completely implemented. This kind of preparation minimizes the possibility of any significant FDA violations that would be found by an FDA investigator. ■

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