JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 9, No. 1, January 2013 "Happy Trials to You"

Successful FDA Inspections at Investigative Sites for Clinical Trials of Drugs and Biologics

By Swati Tendolkar

The United States Food and Drug Administration's (FDA's) Bioresearch Monitoring (BIMO) program provides regulatory oversight for clinical investigations performed in support of Investigational New Drug (IND) applications. BIMO's authority is set forth in 21 CFR 312.68: Inspection of Investigator's Records and Reports. The FDA conducts BIMO inspections globally.

The BIMO program has the following objectives:

- To protect the rights, safety and welfare of subjects involved in FDA-regulated clinical trials
- To verify the accuracy and reliability of clinical trial data submitted to the FDA in support of research or marketing applications
- To assess compliance with FDA regulations governing the conduct of clinical trials

Prior to starting a study, the clinical investigator completes a Form FDA 1572: Statement of Investigator that states, "I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68."

Types of Investigative Site Inspections

There are two types of FDA inspections:

- Study-oriented (formerly "routine") inspections confirm data used in a New Drug Application (NDA), without any suspicion of regulatory non-compliance.
- Investigator-oriented (formerly "for cause") inspections investigate possible regulatory violations. Investigator-oriented inspections may be triggered by high enrollment; a suspiciously high volume of clinical research at the site (especially outside the principal investigator's medical specialty); results that are inconsistent with that of other sites; a complaint by a subject, the sponsor, or the Institutional Review Board (IRB) / Institutional Ethics Committee (IEC); or other reasons.

In both types of inspections, the FDA investigator ("inspector") may be interested in one or more clinical investigators and studies. However, for simplicity, this article will discuss one inspector inspecting one study with one principal investigator (PI) / clinical investigator, one sponsor, and no contract research organization (CRO).

Notification of Inspection

FDA inspectors usually notify sites in advance of study-oriented inspections but not in advance of investigator-oriented inspections. Five-day notice is typical, but it could be much shorter. Should you receive advance notification, ask questions that will help you prepare for the inspection. In the absence of advance notification, ask these questions at the inspection's initial meeting. The inspector may be unable to answer some of these questions, but ask them all:

- Questions about the inspector(s):
  - How many inspectors will participate?

    - What are their names and contact information (address, phone, fax, email)?
    - What is the inspector's office (field office/review division, etc.)?
- Questions about the inspection:
    - What are the type and reason for the inspection?
    - Which clinical trial(s) will be inspected?
    - Which investigator(s) will be inspected?
    - Which location(s) will be inspected?
    - Will the studies of a particular sponsor be inspected?
    - What are the anticipated inspection visit start and end dates?
    - What are the anticipated daily inspection start and end times?
    - Who should be available for interviews?
    - What documentation should be available?

Preparation for Inspection

In a successful inspection, the site provides correct documents and answers in a timely and organized manner. The merits of providing correct information are obvious. Providing it in a timely and organized manner indicates to the inspector that the site is competent. In advance of the inspection, the site should therefore ensure that all study documentation is complete and ready for quick delivery at the inspector's request. Set aside enough time so the visit can proceed efficiently but without any sense of being rushed.

Notification of Personnel

FDA inspections can range broadly, so notify all pertinent personnel at the facility in advance of the inspection (or immediately at the start of an unannounced inspection) that an FDA inspector will be on site. For example, the inspector might want to tour and inspect records in the pharmacy, clinical laboratory, long-term records storage facility, and any satellite locations.

Notify the local or central IRB/IEC. It may be helpful during the inspection, and the FDA may inspect it concurrently.

Notify the study sponsor. The sponsor has a lot at stake in the inspection. Many sponsors can help the site prepare for the inspection by conducting a pre-inspection audit and training site personnel for the inspection. The sponsor might want to place an experienced employee at the site during the inspection to advise the site in real time (but not meet with the inspector). Even if no sponsor representative is on site, the sponsor will probably ask the site for a daily end-of-day briefing and discussion.

If there is a central IRB/IEC, the sponsor will normally notify it of the inspection.

Documents to Organize

Ensure that all study documentation, especially that likely to be the focus of the inspection, is accurate, complete, organized and available for review. FDA inspectors commonly request the following documents and often other information during an inspection:

- All versions of the study protocol
- All versions of the informed consent form and any subject information sheets
- The investigator's brochure and all updates
- Delegation of duties log (with signatures) and an organizational chart
- Curriculum vitae (CVs) and applicable licenses for personnel on the delegation of duties log

- Evidence that the study team has the appropriate qualifications, education and experience necessary to perform assigned study tasks, generally demonstrated by CVs, licenses and training records
- Evidence of training on the study
- A list of the investigator's past and ongoing studies, including protocol numbers and names, sponsors and dates
- Financial disclosure forms
- The name and contact information of the IRB/IEC chairman, as well as board composition and membership roster
- Evidence of adequate human subjects protection oversight, generally demonstrated by IRB/IEC submissions, approvals, reports and correspondence
- A list of facilities providing laboratory, imaging, ECG and other services for the study, including locations and any certifications.
- Normal ranges for laboratory tests
- A description of the subject recruitment process, including any printed or electronic advertisements and scripts (presumably all approved by the IRB/IEC)
- A description of the informed consent process as evidenced by an SOP and a note in each subject's source documents
- Signed informed consent forms
- Study screening and enrollment logs
- A description of the randomization scheme and blinding procedures
- Subject identification log/roster, listing subject names, initials and numbers
- Source documents and case report forms (not necessarily all at once)
- Medical records relevant to the clinical trial being inspected
- Serious Adverse Event (SAE) documentation
- Adverse event log
- Adverse event document submissions to the sponsor and IRB/IEC, along with related correspondence
- Protocol deviation log
- Sample of the test article (usually not present at the site during a routine, post-study inspection, but in a for-cause inspection during a study, the inspector may photograph or take a sample of the study drug and/or related items)
- A description of control article
- Accountability logs for the test article and controls
- Safety and other biosample logs (e.g., pharmacogenomics, pharmacokinetics)
- A description of the clinical monitoring program (normally obtained from the sponsor or CRO)
- Monitoring visit log, visit letters, and other correspondence with the sponsor
- Notes to file
- Evidence of Part 11 computer system compliance, including procedures, signatures, data collection methods, and security measures
- A description of the records retention system
- Standard operating policies and procedures
- Audit certificate(s) and dates, if any, along with audit plans (from sponsor or CRO)
- The entire set of regulatory binders

The Site's Inspection Team

The site's "inspection coordinator" manages and coordinates the inspection with the assistance of the "inspection team."

Team members and their responsibilities (Figure 1) can be adjusted for the scope of the inspection and the site's organization. The "primary team" consists of the PI, most or all persons listed on the delegation of duties log, and the inspection coordinator and inspection assistant(s). The primary team must be available full-time during the inspection. Other team members should be available when required.

Figure 1. Inspection Team Members and Responsibilities

Team Members	Responsibilities
Inspection coordinator	Lead inspection team. Serve as primary liaison to the inspector. Debrief interviewees.
Inspection assistant(s)	Manage control room. Obtain, personally copy, log, manage and return requested documents. Locate requested personnel. Chaperone inspector at all times. Take detailed notes during interviews and all other inspection meetings (internal and with the inspector) and activities.
Principal Investigator	Participate in a manner that demonstrates that he or she is personally in control of, and knowledgeable about, the study. Provide information regarding how site maintained subject safety and data quality and integrity during the study. Be available for interview(s) throughout the inspection visit.
Study coordinator(s)	Provide information regarding their delegated study duties. Be available for interview(s) and to provide requested documents throughout the inspection visit.
Research pharmacist(s)	Provide information regarding test article accountability/disposition. Be available for interview(s) and to provide requested documents throughout the inspection visit.
Laboratory personnel	Provide information regarding lab sample processing and any on-site lab testing performed.
Clinic/Institution receptionist(s)/Security	Properly greet the inspector.
Other team members: • Site Manager/ Director of the Clinical Trials Office • Sub-Investigator(s) • Service personnel (e.g., radiology lab manager, ophthalmologist) • IRB/IEC chairman • Regulatory attorney or expert • Sponsor representative	Provide documents and information, as required.

Inspection and Control Rooms

Two rooms are required for the inspection. The inspector works in the inspection room, and the inspection team works in the control room. The rooms should be in close proximity. Each should have suitable furniture, at least two telephones, and Internet access. They should also have convenient access to a photocopier, scanner, fax machine, snacks and beverages. (Do not offer the inspector anything of value, which might be interpreted as a bribe.) The rooms should provide a pleasant and efficient work environment. The inspection room should contain only documents requested by the inspector.

Documents and people are staged in the control room, moved to the inspection room as required, and then returned to the control room. Meetings can be held in the inspection room or elsewhere. Exposing the inspector to internal discussions and activities that do not relate directly to the inspection may create additional questions and issues to resolve.

Keep the door of the inspection room closed and assign someone to remain nearby to provide assistance.

The Inspection Visit

Arrival of the Inspector

Upon arrival, the FDA inspector should present his or her photo identification card and business card and issue a Form FDA 482: Notice of Inspection. You can write down the FDA Inspector's identification number, but photocopying his or her identification is not allowed. Following this initial introduction, escort the inspector to the inspection room so he or she can settle in and prepare for the opening meeting.

FDA inspectors do not require search warrants for routine regulatory inspections. However, if the inspector does not issue an FDA Form 482 and declines to confirm in writing that the basis of the inspection is Section 704 of the Federal Food, Drug and Cosmetic Act, the inspection may be part of a criminal investigation. In this case, ask the inspector if the FDA has referred a recommendation for prosecution of the site to the Justice Department. Inspections intended to gather evidence to support such a recommendation require a search warrant.

The Opening Meeting

The opening meeting sets the stage for the entire inspection visit. Limit attendance to the PI and other primary team members. At the beginning of the meeting, everyone should introduce themselves. The inspector will then provide an overview of the inspection purpose and scope. The inspector may want to know about each person's role in the study and their other duties, so have the organization chart and information, as well as personnel CVs, available. Typically, the meeting will generate a tentative agenda for the visit and initial requests for documents, interviews and/or a tour of the facility. If the inspector's document request appears excessively burdensome, discuss the issue with him or her; a smaller initial set of documents might satisfy his or her requirements, assuming no problems are found. Use a sign-in sheet to document attendance at this and other meetings with the inspector (and internal meetings, as well).

Interviews

Inspectors typically interview numerous personnel who conducted or supported the trial. Rehearse likely interviewees, focusing on likely questions, e.g., who did what, and how, when and where they did it. Any statements made to the investigator can and will be used for enforcement purposes.

Interviews can be stressful, especially if you are aware of problems that the inspector might find. The inspector is very sensitive to the site's attitude and wants to feel comfortable that the site is not hiding anything and will work to address any shortcomings that are found. Honesty and professionalism thus work better than deception, evasiveness, defensiveness or hostility. A professional demeanor and a solid understanding of ICH GCP principles, study protocol, regulations and assigned study tasks provide evidence of competence. The inspector will be sensitive to inconsistencies between interviewees, so all personnel should be well-prepared.

Answer questions directly, accurately and completely, but do not volunteer information the inspector does not request. If a question is broad or unclear, ask for clarification, but take care to not appear evasive. Have the most knowledgeable person answer questions that require specialized expertise. It is generally acceptable to temporarily defer answers, within reason, but the inspector expects all study personnel to demonstrate the knowledge and capabilities necessary to perform their assigned clinical trial responsibilities. It is perfectly acceptable to address an inspector's question with a statement like, "Let me check that and get back to you with a response later today." An inspection assistant (or two) should take detailed notes on the interview. Interviews should not be recorded by audio or video.

Documents

Provide in a timely manner all documents that the inspector specifically requests. Inspectors have the right to inspect both paper and electronic records. If the inspector agrees, provide paper copies of electronic records. Provide electronic documents on a "clean" computer or storage device. However, if the inspector wants or needs to access files within a computer system, ask the inspector which specific files will be viewed. Have a staff member operate the keyboard.

Mark all documents as "confidential." Otherwise, they may be accessible through Freedom of Information Act requests. Document the location of any "stickies" and remove them from study documentation, since they will serve as red flags for the investigator.

If the inspector is not satisfied that the source documents provide adequate medical information about the subjects (e.g., in shadow charts), he or she can access private medical records per standard language in informed consent forms.

Inspectors do not have the right to see financial documents like study budgets and personnel records (other than CVs and training records). However, the inspector can review payment records for clinical trial subjects. If the inspector asks to see any contractual documents like clinical trial agreements, consider redacting the financial information.

The inspector has the right to inspect the original versions of documents. If you plan to provide photocopies, confirm with the inspector that they will be acceptable. After inspecting documents, the inspector may want additional photocopies or electronic copies. In most cases, the inspector will rely on site personnel to make photocopies. Regardless, make a paper or electronic copy of all documents provided to the inspector. Do not volunteer documents the inspector does not request. Check any file folders and binders for extraneous documents. If a document cannot be found, explain that you will attempt to locate it. (The inspector will immediately report any refusal to provide a document.) Return original records to their normal locations as soon as the inspector indicates it can be done.

Tours

If the inspector requests a tour of the facility, ask if there are specific areas of interest, e.g., the pharmacy or records storage facility. However, the inspector might decide mid-tour to

visit other areas. All likely areas should therefore be prepared for a visit, with a person in each area available on short notice and ready to answer questions.

If noncompliance is suspected, the inspector might want to take photographs. If so, explain any written policies that cover taking photographs.

Request Tracking and Resolution

FDA inspectors can request so many documents, interviews and tours that it can be hard to remember them all and make sure they are all delivered to the satisfaction of the inspector. After the inspection, it may become very important to know what information the inspector requested and received. Use a request tracking log (Figure 2) or, if available, a database to record requests and responses. If a computerized system is available, maintain the log on a shared computer drive, with appropriate access controls, to allow inspection team members and site management to view inspection progress in real time and calculate metrics like resolution completion percentage.

Figure 2. Example Request Tracking Log

#	Request	Requested	Provided	Status	Comments
1	List of PI's trials	10 Oct 12	10 Oct 12	Retained	
2	All signed informed consent forms	10 Oct 12	10 Oct 12	Returned	
3	Protocol and amendments	10 Oct 12	11 Oct 12	Retained	Amendment 2 missing – requested from sponsor
4	Interview: informed consent process	11 Oct 12	11 Oct 12	Not applicable	Verbal description by John Doe
5	Test article accountability logs	11 Oct 12	11 Oct 12	Returned	

End-of-Day Meetings

Request a meeting with the inspector at the end of each day. During this meeting, seek the inspector's feedback regarding any items of concern. The inspector may or may not share such concerns. Addressing these items during the visit might avoid inspection findings and improve the inspector's opinion of the site. After the inspector departs each day, convene a meeting of most or all team members to brief them on the day's activities and plan for the following day.

The Exit Meeting

At the conclusion of the inspection, the inspector will conduct an exit (close-out) meeting to review potential findings and recommendations. Listen carefully, take detailed notes, request clarifications, and answer questions if you know the answers.

If the inspector has discovered any noncompliance during the inspection, the inspector will issue a Form FDA 483: Inspectional Observations. The Form 483 will detail the inspector's findings and usually provide sub-points or examples as supporting evidence. Ask for necessary explanations and clarifications to make sure you understand the findings. Make sure the form accurately describes the documents and information you provided. Verify that any deficiencies that have already been corrected are not on the form or have been noted as corrected. Provide supporting documents, as appropriate. After understanding each finding, offer clarification. The inspector may amend the 483 or incorporate your points in the Establishment Inspection Report (EIR), which is issued when the inspection is fully

closed per 21 CFR 20.64(d)(3). However, the inspector will give no weight to the investigator's apologies, claims of ignorance, or deferrals of responsibility.

Inspectors rarely cite noncompliance with FDA guidance documents or site standard operating procedures in a Form 483 or EIR. However, he or she may discuss such matters during the exit meeting.

Communicate to the inspector that you have heard what he or she had to say and will take appropriate corrective actions and respond in a timely and professional manner. At the end of the meeting, thank the inspector for the educational experience, etc., as appropriate.

Following the inspector's departure from the site, conduct an internal close-out meeting with the inspection team to review the events of the inspection, any Form 483 findings, and the inspector's closing comments. If a sponsor representative is not present, brief the sponsor in a timely manner. Formulate an official response to each finding, listing each finding and then providing explanations, clarifications and/or corrective actions taken or to be taken, with proposed completion dates. Submit your written response within 10 working days. Confirm with the inspector that it should be sent to the address on the Form 483. Note that 483 forms and subsequent correspondence become part of the public record, discoverable under the Freedom of Information Act.

Compile an inspection file, consisting of the request-tracking log, copies of documents provided, notes, Forms FDA 482 and 483 (if applicable), response to the Form FDA 483 (if applicable), and any other relevant documents. The inspection file will be a valuable resource during the Form FDA 483 response process, if any, and any subsequent enforcement actions or legal proceedings. It will also serve as a training aid for future inspections.

Conclusion

Preparing for and hosting an FDA inspection can be a formidable task, even with advance notice. The notice may not allow much time to prepare and certainly will not explain what to do with all the other work in process. It is thus important to maintain an inspection-ready state at all times, which primarily means complying with the regulations and keeping study records in good order. Ensuring site readiness ensures not only smooth inspections but also ongoing compliance during the trial.

References

FDA Investigations Operations Manual, Ch. 2: Regulatory (2009).

Federal Food Drug & Cosmetic Act, Chapter VII, Section 704: Factory Inspection (2008).

FDA Compliance Program Manual 7348.811 Bioresearch Monitoring: Clinical Investigators, Part I Background (2008).

FDA Compliance Program Manual 7348.811 Bioresearch Monitoring: Clinical Investigators, Part II Implementation (2008).

FDA Form FDA 1572: Statement of Investigator.

FDA Investigations Operations Manual, Ch. 5: Establishment Inspections (2009).

FDA Bioresearch Monitoring Program CP 7348.811, Chapter 48 (2008).

Clinical Trials Audit Preparation, Vera Mihajlovic-Madzareevic, Wiley (2010).

Author

Swati Tendolkar is a Program Manager, Quality Assurance, at Johnson & Johnson. Contact her at 1.908.707.3492 or stendolk@its.jnj.com.

This article is intended for informational purposes only and does not replace independent professional judgment. Statements of fact and opinions expressed are those of the author and, unless expressly indicated to the contrary, are not the opinion or position of Johnson & Johnson, Janssen Research and Development LLC, or their affiliates.

