Clinical Investigator Site Inspections: What to Expect

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United States Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of Compliance (OC)
Office of Scientific Investigations (OSI)
Division of Enforcement and Postmarketing Safety (DEPS)
Compliance Enforcement Branch (CEB)

FDA Clinical Investigator Training Course
November 15, 2018
Learning Objectives

• Describe the types of clinical investigator site inspections

• Summarize the clinical investigator inspection process
Discussion Topics

• Inspection Types

• Inspection Process

Opening Interview and Form FDA 482 (Notice of Inspection)

Inspection

Form FDA 483 (Inspectional Observations) and Exit Interview

Post-Inspection
Inspection Types

Routine/surveillance
- Pre-marketing application
- General compliance

For-cause/directed
- Investigate potential violations
- Sources
Inspection Process

Opening Interview and Form FDA 482
Pre-Announced and Unannounced Inspections

• Clinical Investigator inspections generally pre-announced unless otherwise instructed in the inspection assignment
  - For-cause generally unannounced

• All international inspections generally pre-announced
The best way to survive an FDA inspection is to always be prepared for one!
Opening Interview

- Performed by field investigator with or without Center subject matter expert
- Present credentials
- Issue Form FDA 482
- Describe the basis and scope for inspection
Form FDA 482 (Notice of Inspection)

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<th>DEPARTMENT OF HEALTH AND HUMAN SERVICES</th>
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<td>FOOD AND DRUG ADMINISTRATION</td>
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Notice of Inspection is hereby given pursuant to Section 7(q)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379(q)) and Part F of Title 21 of the Public Health Service Act (42 U.S.C. 265-445). As a small business that is subject to FDA regulation, you have the right to seek assistance from the U.S. Small Business Administration (SBA). This assistance includes a mechanism to address the enforcement actions of Federal agencies. SBA has a National Ombudsman’s Office that receives complaints from small businesses about Federal agency enforcement actions. If you wish to contact the enforcement action of FDA, CALL (888) 734-2447. The website address is www.sba.gov/ombudsman. FDA has an Office of the Ombudsman that can directly assist small business with complaints or disputes about actions of the FDA. This office can be reached by calling (301) 792-0552 or by email at ombuds@fda.hhs.gov. For industry information, go to www.fda.gov/industry.

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<th>9. TYPE OR PRINT NAME(S) AND TITLE(S) (FDA Employee(s))</th>
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Applicable portions of Section 7(q) and other Sections of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379) are quoted below:

Sec. 7(q)(4). For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon present examina-
tion of records, equipment, facilities, and operations, may seize or remove any article of food, drug, device, or cosmetic manufactured, processed, packed, or held for human consumption or for the use of which these products are used, provided such removal is necessary to prevent their introduction or further introduction into commerce. Articles subject to seizure must be stored in a safe place and made available for examination.

(Continued on reverse)
Inspection Process

Inspection
Inspection Logistics

- Time frame
- Work area
- Photocopier
- Daily discussions regarding inspection progress
Inspection Scope

• Inspection assignment

• Clinical Investigator Compliance Program (CP) – Program 7348.811
  https://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm255614.htm

• Investigations Operations Manual (IOM) – Section 5.10 Bioresearch Monitoring (BIMO)
  https://www.fda.gov/ICECI/Inspections/IOM/default.htm
Inspection Scope

• Examples of records reviewed
  - Protocol and amendments
  - Informed consent documents
  - Drug accountability records
  - Institutional review board approvals
  - Source documents
  - Case report forms

• A word about access to electronic systems

• Interviews

• Site walk-through
Inspection Process

Exit Interview and Form FDA 483
Form FDA 483

• Issued to highest management official available at end of inspection

• *Form FDA 483 items are field investigator’s observations of possible deviations from federal regulations, and not necessarily regulatory violations*
  - Center determines whether each observation is a regulatory violation, and if a regulatory violation, will determine violation’s impact on data integrity and subject safety

  - Verbal response to Form FDA 483
Form FDA 483 (Inspectional Observations)

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<th>INSPECTIONAL OBSERVATIONS</th>
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This document lists observations made by the FDA representative during the inspection of your facility. They are inspectional observations and do not represent an official agency determination regarding your compliance. If you have any questions, please contact FDA at the phone number and address above. During an inspection of your firm's OCP, observations were made.

Add Continuation Page
Inspection Process

Post-Inspection
Let’s take a look at post-inspectional steps from your end....
Form FDA 483 Written Response

• Received within 15 business days after the close of the inspection to the field investigator’s office

• What if you miss the 15-business day time frame?
Four Reasons to Submit a Well-Reasoned, Timely, and Complete Written Response to Form FDA 483

1. May be considered in an FDA compliance decision

2. Demonstrates your acknowledgment and understanding of the observations to the FDA

3. Demonstrates your commitment to correct the observations to the FDA (i.e., intent to voluntarily comply)

4. Establishes credibility with the FDA
How to Respond to Form FDA 483

• You should ensure that the communication provides an adequate response to FDA’s observations, is easy to follow, and there are corrective actions in place to fix the issues

• Each response should address the central issues raised in the observations and provide factual objective evidence that permits evaluation and aids in understanding of the response
How to Respond to Form FDA 483

• Include a commitment from senior leadership
• Address each observation separately
• Note whether you agree or disagree with the observations
• Provide both corrective and preventive actions
• Provide both completed and planned actions
• Provide timelines for completion of the actions
• Provide a method of verification or monitoring of the effectiveness of the actions
• Submit documentation (training, standard operating procedures, records)
Now let’s take a look at post-inspectional steps from FDA’s end....
EIR and exhibits → Center review and classification → Post-inspectional correspondence
Inspection Classification

No Action Indicated (NAI)

No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further FDA action).
Voluntary Action Indicated (VAI)

Objectionable conditions were found and documented, but the Center is not prepared to take or recommend any regulatory action since the objectionable conditions do not meet the threshold for regulatory action.
Official Action Indicated (OAI)

Objectionable conditions were found and regulatory action should be recommended.

If the inspection is classified OAI by the Center, the Center may issue one of the following types of letters....
OAI Letter Types

• Untitled Letter

• Warning Letter
  https://www.fda.gov/iceci/enforcementactions/warningletters/default.htm

• Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) Letter
  - Notice of Opportunity for Hearing (NOOH) Letter
Additional Resources

BIMO Program
https://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/ucm160670.htm

Regulatory Procedures Manual (RPM)
• Chapter 4 - Advisory Actions (Warning and Untitled Letters)
• Chapter 5 - Administration Actions (Chapter 5-9: Disqualification of Clinical Investigators)

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
• Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)
Challenge Question #1

Fill in the blank regarding the flow of the inspection process:

__________ → Inspection → Form FDA 483 and Exit Interview → Post-Inspection
Challenge Question #2

True or False:

All observations listed on Form FDA 483 are automatically regulatory violations.
Challenge Question #3

Which of the following should be included in your written response to Form FDA 483?

A) Corrective and preventive actions
B) Addressing each observation separately
C) Timelines for completion of corrective and preventive actions
D) Documentation (training, standard operating procedures, records)
E) All of the above
Contact Information

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