Successful FDA Inspections
How to Prevent and Respond to Common FDA Observations in a Form 483 or Warning Letter

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Usual Disclaimers

- Our views are our own, and may not be attributed to our current or former employers.
- This is an educational session.
- We are not providing legal advice.
- Consult with your own attorneys for advice tailored to your individual needs.
Field Investigator

- Don’t call the field investigator “inspector”
- For clarity, we may use “inspector” in this presentation to minimize confusion with “clinical investigator”

Overview

- Part 1
  - Background
  - Prevention
  - Lessons Learned
- Part 2
  - Post-inspection letters
  - Common Observations
  - Responding
Part 1

- Background on BIMO inspections
- Prevention: What Happens During an FDA Inspection & How Best to Prepare
- Case Studies: “Lessons Learned” about Inspections

FDA Inspection Authority

- Each clinical investigator conducting FDA regulated research makes a personal, legal commitment to comply with FDA regulations
- FDA has authority to
  - inspect and copy study records, policies and SOPs
  - interview study staff
FDA’s BIMO Program

Office of Regulatory Affairs (ORA)
http://www.fda.gov/ora/

Goals of BIMO Inspections

- Protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials
- Verify the accuracy & reliability of clinical trial data
- Assess compliance with
  - FDA regulations
  - IRB policies
  - Study protocol
Types of Inspections

“Routine” (aka “Surveillance” or “Data Audit”)
- Typically done on large pivotal trials intended for a regulatory submission, sites randomly selected
- Usually target completed clinical trials and retrospectively review compliance with FDA regulations

<table>
<thead>
<tr>
<th>Types of Inspections</th>
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<tr>
<td>“Directed” (aka “For cause” or “Referral”)</td>
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<tr>
<td>Directed at PI</td>
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<tr>
<td>- PI conducts study outside his/her specialty area</td>
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<td>- PI conducts many studies</td>
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<td>- PI has significant financial interest in agent or with sponsor</td>
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<td>- Complaints or concerns about PI reported to FDA</td>
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<tr>
<td>Directed at Site</td>
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<tr>
<td>- Site is high enroller</td>
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<td>- Site has rapid or late enrollment</td>
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<td>- Site has inconsistent data or unusual safety profile</td>
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<td>- Site is terminated by a Sponsor</td>
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<tr>
<td>Directed at Test Article</td>
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<tr>
<td>- Test article of focused FDA interest (e.g. public health concern)</td>
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### BIMO Inspections Completed FY 2011

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</table>

* 3 IRB = RDRC; + 194 BEQ inspections (CDER specific)

** CFSAN’s BIMO Program is under reorganization

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### Increasing Inspection Activity:
University of Michigan Statistics

- **2004-2007**: 5 inspections
- **2008-2011**: 17 inspections
What Happens During an FDA Inspection?

FDA Inspection Process

**FDA Office**
1. Select Site
2. Contact Site
3. Schedule Site
4. Arrive (482)
5. Review Records
6. Interview Staff
7. Present Findings
8. Depart (483)

**Site Location**
9. Write Report (EIR)
10. Classify Inspection
ASK (politely):

- Why?
- Who will be coming?
- When? How long?
- Any specific requests?
FDA Inspection Manual Guidance

- "The field investigator should keep the time span between initial contact and actual inspection as short as possible. The field investigator should immediately report to the Center contact any attempt by the clinical investigator or sponsor-investigator to unduly delay an inspection, by more than ten working days, without sufficient justification."

( emphasis added )

Before the FDA Arrives—

**NOTIFY**
- Regulatory Affairs
- IRB
- Sponsor/Office of Sponsored Research
- Co-/Sub-Investigators
- Past study coordinators, if applicable and if available
- Division/Department Administration
- Other units supporting the conduct of the studies of interest
- Medical Records Dept
Before the FDA Arrives—

**SCHEDULE**

- Availability of
  - PI and study team for duration of inspection (and post inspection to prepare response)
  - Photocopier
  - Clerical support to promptly photocopy documents or retrieve off-site records
- Conference room for the entrance & close-out interviews
  - Invite representatives from IRB, Regulatory Affairs/Legal and support units
- Office or small conference room for inspection

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Before the FDA Arrives—

**COMPILE BACKGROUND INFO**

- Study Listing
- Organizational chart of pertinent study personnel
- CVs/resumes of all investigators, coordinators, and other key personnel
- Financial interest of clinical investigators
If FDA advises (in advance) that the inspection is of a specific study.....

Before the FDA Arrives—

**GATHER**
- Regulatory binders
  (“Accessible, available and organized”)
- Source documents/medical records
Before the FDA Arrives—

**REVIEW**

- Who is responsible for each step of study process (currently and historically)
- Regulatory binders & records to refresh memory & be familiar with organization of documents
  - study team documentation (qualifications, training, delegation logs)
  - pertinent study dates
  - pertinent study numbers
  - findings of recent monitor visits

Before the FDA Arrives—

**HUDDLE and CONSIDER**

- Lapses in IRB approval
- Tardy reports to Sponsor or IRB
- Voluntary holds or suspensions
- Deficiencies cited by monitors
- Prior findings of non-compliance
- Changes implemented without prior IRB approval

“It is what it is”
Before the FDA Arrives—

**CORRECT**

- Initiate and submit any missing reports due to IRB or Sponsor
- List any shortcomings identified for further discussion with IRB and Regulatory Affairs *before* the FDA inspection

Opening Interview—

- FDA inspectors present credentials & FDA Form 482 “Notice of Inspection”
- Introductory remarks offered by FDA
  - What FDA center requested this inspection?
  - Why?
  - Focus and scope of inspection
  - Logistics and expected duration
- PI should
  - introduce key support personnel
  - provide high level overview of study if targeted at specific study
Opening Interview —

- Questions regarding PI/study background
- Questions about study team
- Questions about study conduct

During Inspection —
Checking in & Updates

- “Check ins” to satisfy requests for documents, copies & interviews:
  - Clerical support  
    Hourly or upon request
  - Study Team Member  
    Every 2 hours or upon request
  - PI  
    Upon request, but AT LEAST daily
  - Regulatory Affairs  
    Daily
  - Supporting units *  
    Upon request

* FDA typically makes visits to supporting units

- If not provided, ask for a **verbal** review of findings **at the end of each inspection day.**
During Inspection—Answering Questions (1/2)

- Speak with “one voice”
- Avoid contradictions among study staff in front of inspector
- Take your time
- Repeat and clarify question asked (request made) before responding
- Be clear on the timeframe applicable to the question or request
- Be honest and forthright
- Stick to facts known (within your scope of expertise), AVOID speculating

During Inspection—Answering Questions (2/2)

- Resist urge to expand beyond question asked or fill the silence
- Be prepared, but AVOID over-coached appearance
- Follow through on promises to answer questions, deliver documents, arrange interviews
- Acknowledge obvious problems readily
- AVOID long delays & appearance of stonewalling
- AVOID signing affidavits (consult legal advice)
Lesson Learned —
Warning Letter to Leslie Diaz, MD (11/4/11)

Sample statements from affidavit:

- “I am admitting . . . that . . . I had a lack of involvement and oversight in the conduct of these clinical trials.”
- “In searching for study documentation, I also found letters that were sent to me that I had never opened and/or had seen before. These letters were from monitors, sponsors, and IRB’s, including some of which involved the termination of my clinical studies.”
- “I acknowledge that adverse experiences for . . . the trials . . . were not evaluated/graded as required by study protocols.”
- “I am also admitting to having ignored the clinical trials.”
- “I also did not keep track of the mail as far as what was coming in or going out.”
- “All study documentation ended in early December 2007 after my study coordinator left.”
- “I had no knowledge of how these studies were monitored.”

During Inspection —
Photocopying Do’s & Don’ts

- **Do**
  - expect lots of photocopying
  - complete copies promptly
  - make at least 3 copies (FDA, Study team, Regulatory Affairs)
  - keep a log of all documents copied and provided to FDA

- **Don’t**
  - assign a work study to do copying
  - disrupt inspector’s flagging convention
  - copy personnel data
FDA Inspection Focus

FDA Inspection Focus (1/2)

- Who performed various aspects of the study protocol?
  - FDA examines delegation Logs, 1572s (drugs) Investigator agreements (devices)
- Were study team members qualified for delegated task?
  - FDA examines CVs, professional licenses, training logs, and documentation of study-specific training
- Were rights, safety and welfare of subjects protected? Where all approvals in place and timely?
  - FDA examines approval dates, looks for timing problems/lapses
- Did PI timely obtain and document informed consent?
  - FDA examines all (if 25 or less subjects) or a sample of ICFs, looks for who did consenting, was correct version of IRB approved form used, was ICF dated & signed by appropriate person, were required elements present.
FDA Inspection Focus (2/2)

- **What is quality of Source Documents and CRFs?**
  - FDA assesses organization, condition, completeness & legibility of documents (FDA may compare data reported to FDA to source documents—medical record—doctor or nurse progress notes)

- **Did PI follow investigational plan?**
  - FDA assesses adherence to IRB conditions & protocol (Inclusion/Exclusion criteria, timing of study procedures etc)
  - FDA assesses whether protocol deviations and AEs were documented & reported appropriately

- **Did PI properly control and administer test article?**
  - FDA examines documentation on accountability of test article (amount shipped, received, used, returned destroyed)

- **What concerns were raised by monitoring reports? Did PI and study team act on findings?**
  - FDA seeks a copy of the any monitoring plans, the log of monitor reports and monitor visits and evidence PI followed up on monitor’s findings

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**FDA Inspection Process**

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3. Schedule Site
4. Arrive (482)
5. Review Records
6. Interview Staff
7. Present Findings
8. Depart (483)
9. Write Report (EIR)
10. Classify Inspection
Close Out Meeting —

- Schedule to ensure PI availability
- FDA inspectors present findings
  - “Inspectional Observations” on Form 483
    - “significant deviation” from regulations
    - The 483 does NOT reflect final FDA determination
  - “Discussion Items”
- Save rebuttal for the written response, with possible exception of correcting significant factual errors
- Ask for clarification
- Indicate intention to respond within 15 days

After Inspection...

FDA field inspector writes
Establishment Inspection Report (“EIR”)
- EIR has more detail than Form 483
- Sent to HQ within 15 working days of inspection with a “preliminary district classification” for inspection
- HQ reviews and makes a final determination on classification of inspection
FDA's Classification of Inspection

Classify Inspection

- NO Action Indicated
- Voluntary Action Indicated
- Official Action Indicated
  - Serious or pervasive findings

FDA Considers Response

- Untitled Letter
- Warning Letter
  - Adequate Response
  - Inadequate Response
    - NIDPOE
    - NOCH
    - Disqualification

Clinical Investigator Inspections
Final Classification* (FY 2011)

- No Action Indicated: 42%
- Official Action Indicated: 51%
- Voluntary Action Indicated: 7%

*(Based on Letter Issue date; Includes OAI Untitled Letters, [OSI database as of January 18, 2012]*)
What can you do NOW to prepare? Proactive Steps to Success

Proactive Step — Risk Assessment

KNOW your existing research portfolio

- Who are your clinical researchers?
- What types of studies are they doing?
  - Sponsor investigator studies?
  - Drug (what phase?) vs device studies?
  - Big industry sponsored?
  - Small start up sponsored?
  - Government or Cooperative sponsored?
Proactive Steps — Risk Assessment

**KNOW how things are going**
- Are subjects complaining or withdrawing?
- Are protocol deviations occurring?
- Are deadlines for submissions/reports being met?
- Is coordinator happy, overwhelmed, or not speaking to PI?
- Do monitor visits/audits have noncompliance findings?
- Has IRB, Sponsor, Lead Site, DSMB, DCC, Support units raised any concerns about study conduct?

Proactive Step — Personnel

- Hire well
- Train well
- Supervise well
Quote from Recent Warning Letter Failure to Adequately Supervise

“While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities.

Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects.”

The investigator is ultimately responsible.

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Proactive Step — Feasibility Analysis

SCRUTINIZE new studies before signing on

- Run mock subjects through protocol to test feasibility of protocol windows at your institution.
- Look for and remedy any inconsistencies in protocol, CRFs, investigator brochures, other study tools.
- Pilot CRFs
- Evaluate whether there are conditions/events that can occur during the study to disqualify a subject? Do you have processes to detect such events?
- Test performance of supporting electronic systems.
Proactive Steps — On-going

- Conduct on-going quality control/quality assurance/quality improvement efforts
- Heed monitor advice cautiously - Consult own legal and regulatory experts
  - Consult FDA
- Prep study team when inspection is *imminent* (aim to lower stress level)

Lesson Learned #1

**2011 483 Observation:** An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically, Dr. H. is not listed on the Form FDA 1572 as a Sub-investigator, but he conducted the screening visit, baseline visit and Day 7 visit for the enrollment of Subject 07 to the clinical study. Dr. H. is listed on the responsibility and training logs for the study.

**2009 Monitoring Report:** Identified this lapse and directed PI to include Dr. H (a clinical Fellow) on 1572.

**Lesson Learned:** A Clinical Investigator should thoroughly and timely review findings on monitoring reports and implement appropriate corrective and preventive actions.

**Audience Activity:**
How can you ensure appropriate corrective and preventive actions are timely taken on monitoring report findings?
Lesson Learned #2

2011 483 Observation: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically, blood pressure readings were not taken as required in the protocol.

Two blood pressure measurements in the designated arm are required at all visits and measurements must be separated by an interval of at least 2 minutes. If the 2 sequential readings differ by >5mm Hg (systolic or diastolic), repeat the measurement until consecutive readings are within 5 mmHg of each other.

Lesson Learned. Should have worked with sponsor to modify the protocol to allow more flexibility if measures would still be consistent with the science. Should have designed a data capture tool that was more accurate (re: sequential) and allowed more room for multiple measures and space to record rationale if efforts were aborted.

Audience Activity: How can you determine if the study is doable and the forms correct without inconsistencies?

Part 2

- Post-Inspection Letters
- Common observations
- Writing an “adequate” response
"Dr. Simpkins drew the short straw at the pre-inspection meeting."
FDA Post-inspection Letters

- Basic compliance observed (or no letter)
- Informational/Untitled Letter
- Warning Letter
- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

TO: Terence J. Walsh, Site Leader

Boehringer Consumer Health
Lincoln, NE 68517-9526

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

The responsibilities and procedures applicable to the quality control unit are not fully followed.

“This explanation is inadequate because your written procedures would allow research to be approved by the IRB without the approval of a majority of those members present at the meeting.”

“However, you have not provided documentation to show that this proposed corrective action has been implemented.”

“Creating multiple versions of meeting minutes is not an acceptable corrective action.”

Manish Mehta, MD Warning Letter
February 2012

“Your response states that you have decided to stop enrollment…pending further guidance from the FDA. Your response, however, is inadequate because it fails to acknowledge that a clinical study of a significant risk device requires an IDE and FDA approval of the IDE before allowing subjects to participate, which assures that subject risks are outweighed by anticipated benefits; that adequate monitoring is in place; and that the safety, rights, and welfare of research subjects are adequately protected. Thus, you have not provided an adequate correction to this violation to ensure that this problem will not recur.”
Common Observations

- Clinical Investigators
- Sponsor-Investigators
- IRBs

Clinical Investigator

- Failure to follow protocol
  - Ineligible subjects enrolled
  - Procedures not done
  - Out of window procedures
- Inadequate recordkeeping
  - Inadequate case histories
  - Inadequate accountability of investigational product
- Inadequate/untimely reporting to sponsor or IRB
Clinical Investigator

- Inadequate subject protection
- Inadequate informed consent process
  - Procedures done before consent obtained
  - Incorrect consent form
  - Missing signatures, initials, dates
- Failure to obtain IRB approval/follow conditions of approval
- Inappropriate delegation
- Failure to adequately supervise

Sponsor Investigator

- Failure to adequately monitor
- Failure to obtain IRB approval
  - Subject Materials
  - Changes in research
- Failure to obtain required FDA approval
  - DEVICE REGULATIONS!!!
- Failure to obtain investigator agreements from each participating investigator
- Failure to provide participating investigators with brochures, consent forms, or protocol documents
- Failure to submit progress reports/annual reports
IRB

- Inadequate meeting minutes
- Inadequate written procedures
- Not following written procedures
- Inappropriate use of expedited review
- Failure to conduct continuing review
- Failure to ensure basic elements of consent provided to subjects

IRB

- Failure to make device determinations
- Failure to make prompt reports to FDA
- Failure to have a majority of members present during convened meetings
- Failure to have a nonscientific member present
- Failure to maintain IRB member rosters
How to Respond

"As a general rule, a Warning Letter should not be issued if the agency concludes that a firm’s corrective actions are adequate and that the violations that would have supported the letter have been corrected."

*FDA Regulatory Procedures Manual*
When to Respond

15 DAYS!

What to Write?

- Thank you – set a polite tone
- Commitment to compliance
- Commitment to correcting all instances of noncompliance
- Corrective and preventive actions
What NOT to Write

- Don’t focus on the FDA Inspector
- Don’t downplay observations
- Don’t point fingers or make excuses

Respond to Each Observation Separately

- Note whether you agree or disagree
- Address the root cause
- Focus on regulatory requirements
- Outline specific corrective and preventive actions (CAPA) and dates for completion
- Supporting documentation
Corrective And Preventive Action (CAPA)

CORRECTIVE ACTION
Addresses specific instance(s) of the error

PREVENTIVE ACTION
Ensures the error is not repeated

Observation 1: Failure to obtain proper informed consent.

Specifically, Subject 001 was not reconsented after the IRB approved changes to the consent form requiring reconsent.
Corrective Action

- The subject signed the most recent consent form version at the next visit following discovery of this error.

- A note to file was placed in the subject’s file explaining that the subject did not sign it because the error was discovered after the study was completed.

- A copy of the most recent consent form has been placed in the subject’s file and the consent discussion will take place at the subject’s 12-month visit to take place on July 6, 2012.

Preventive Action

- When consent document changes are made that require reconsent, the Study Coordinator will place a copy of the current consent form in each subject’s file. An email is also sent to all staff involved in the consent process to notify them that a change has been made and communicate the instructions for reconsent. See Attachment 1, updated Informed Consent SOP. All staff involved in the consent process have already been retrained on this revised SOP. See Attachment 2, training log.
CAPA

- Specific actions for **every observation**
- Assign **responsibility** for each action to a specific person or group
- Specify **target dates** for actions not yet completed
- Ensure **completion** of each action
  - CAPA Table
  - CAPA Form
- Consider internal/QA audit to evaluate implemented CAPA

CAPA FORM

- To: appropriate stakeholder
- Describe the issue
- Identify data collected
- Root cause
- Short term action
- Long term action
- Results
- Sign off: by appropriate stakeholder
- Set due dates

CAPA is part of an effective quality management system
Observation 2: Investigational drug disposition records are not adequate with respect to dates, quantity and use by subjects.

Specifically, you did not maintain drug accountability records with respect to dispensing drug ABC and drug XYZ. There is no way to determine or verify which subject received what drug, which lot of drugs was dispensed, what quantity of vials was dispensed and when those vials were dispensed.

Adequate Response

- Timely
- Organized, concise
- Specific
- Corrective Action
- Preventive Action
- Documentation
- Respectful tone
Inadequate Response

- Doesn’t address the problem
- Not specific enough
- Not supported by documentation or evidence
- Blaming others (sponsor, CRO, your staff, FDA inspector)
- Lacks preventive action

Resources

- Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors
- FDA Running Clinical Trials Page
  http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm
- Writing an Effective 483 Response (2009 FDA Presentation)
- FDA Warning Letters
- EIR policies
  http://www.fda.gov/ICECI/inspections/fieldmanagementdirectives/ucm061430.htm
Resources (cont.)

- WIRB Online Seminars
  - Importance of an effective corrective and preventive action program
  - How to survive an FDA inspection of your clinical trial site
  - Feasibility issues – should I agree to do this trial?
  - Many other topics
- ICH Guideline E6: Good Clinical Practices
- CDRH Learn Courses
  [http://www.fda.gov/Training/CDRHLearn/ucm162015.htm](http://www.fda.gov/Training/CDRHLearn/ucm162015.htm)