Chrissy J. Cochran, PhD
Director (acting)
Division of Enforcement and Postmarketing Safety
FDA/CDER/OC/OSI
May 12, 2015
Learning Objectives

• To describe the BIMO inspection program purpose and process.
• To identify recent trends in CDER’s BIMO inspections of clinical investigators and sponsors.
• To identify key strategies for responding to Form FDA 483s and Warning Letters.
Bioresearch Monitoring (BIMO) Program

A comprehensive, agency-wide program of on-site inspections and data audits, designed to monitor all aspects of the conduct and reporting of FDA-regulated research
Bioresearch Monitoring (BIMO)

Clinical Investigator

Nonclinical Laboratory

Institutional Review Board

Sponsor
Regulatory Requirements

• Protection of Human Subjects
  – 21 CFR Part 50

• Financial Disclosure
  – 21 CFR Part 54

• Institutional Review Boards
  – 21 CFR Part 56

• Good Laboratory Practice
  – 21 CFR Part 58

• Investigational New Drugs
  – 21 CFR Part 312

• New Drug Applications
  – 21 CFR Part 314

• Bioequivalence
  – 21 CFR Part 320
BIMO Program Objectives

• To protect the rights, safety, and welfare of human research subjects

• To ensure the quality, reliability, and integrity of data collected

• To maintain the integrity of the FDA review process by ensuring that FDA-regulated research is conducted in compliance with applicable regulations
OSI Inspections: 2005-2014

*Based on inspection start date – [OSI database as of January 20, 2015]*
- IRB includes only CDER numbers – previously reported metrics may have used combined data across CDER, CBER and CDRH.
- Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
- Postmarketing Adverse Drug Event and Risk Evaluation and Mitigation Strategy inspection programs incorporated into OSI June 2011
BIMO Inspections – CDER, FY2014

- Clinical Investigator: 50%
- Bioequivalence: 32%
- Sponsor (GCP): 6%
- Institutional Review Board/Radioactive Drug Research Committee: 9%
- Good Laboratory Practice: 3%

*Based on inspection start date – [OSI database as of January 20, 2015]*
- IRB includes only CDER numbers – previously reported metrics may have combined data across CDER, CBER and CDRH
Inspection Process

- Regulatory Correspondence/Follow-up
- Center Review Division
- Center BIMO Staff
- Inspection Assignment
- District Office
- EIR
Inspection Process
What can you expect?
What should you do?
What do we look for?

- Verify Primary Efficacy and Safety Data
- Source of subjects; did subjects exist?
- Did they meet inclusion/exclusion criteria?
- IRB Review obtained? Consent obtained?
- Adherence to protocol?
- Verify primary efficacy measure
- Adverse events?
- Safety data: Labs, EKG, etc.
- Drug Accountability? Blinding of data?
- Informed consent – substance, process, documentation
What do we find?

**Frequency of Clinical Investigator-Related Deficiencies Based on Post-Inspection Correspondence Issued***
(CDER, FY 2014)

*Based on letter issue date; Inspections may have multiple deficiencies, [OSI database as of January 20, 2015]*

Note: This does not denote number of inspections completed, but rather number of inspection reports evaluated and closed in FY2014.

*39%*

356 Domestic Inspections

- Protocol: 39%
- Records: 25%
- Drug Accountability: 8%
- Consent: 5%
- IRB Communication: 3%
What do we find?

• Sponsors/Monitors/CROs
  – Inadequate monitoring
  – Failure to ensure investigational plan followed

• Records
  • Investigational product
  • Financial disclosure
  • Retention
Compliance Classifications

• No Action Indicated (NAI)
  – No objectionable conditions or practices

• Voluntary Action Indicated (VAI)
  – Objectionable conditions or practices
  – Not at threshold to take or recommend administrative or regulatory action

• Official Action Indicated (OAI)
  – Serious objectionable conditions found
  – Regulatory action recommended
Official Action Indicated (OAI)

- Regulatory violations uncovered during the inspection are repeated, deliberate, and/or involve submission of false information to FDA or the sponsor in any required report.

- Regulatory violations are significant/serious and/or numerous, and the scope, severity, or pattern of violations support a finding that:
  - Subjects have been (or would be) exposed to an unreasonable and significant risk of illness or injury.
  - Subjects’ rights have been (or would be) seriously compromised.
  - Data integrity or reliability has been compromised.

CPGM – Clinical Investigator Inspections:
http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133571.htm
Warning Letters

15 Days

Response

Reinspection

Close-out Letter
Responding to FDA 483 or WL

• Response basics

• **Four reasons** to submit a well-reasoned, complete, and timely written response

• **Nine suggestions** for an effective written response
483 Responses

• There is no regulatory requirement for you to respond to the FDA 483.

• However, a well-reasoned, complete, and timely 483 response is in your best interest.
Form FDA 483 Inspection Observations

• List of inspection observations

• 483 language:
  – “This document lists observations made by the FDA representative during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance.”†

• Additional 483 information available from FDA Investigations Operations Manual (IOM) 5.2.3 at www.fda.gov/ora/inspect_ref/iom/
FDA’s Expectations During the Inspection

“... [FDA] Investigators should make every reasonable effort to discuss all observations with management ... as they are observed, or on a daily basis[,] to minimize surprises, errors, and misunderstandings when an FDA 483 is issued.”

-- IOM 5.2.3
4 Reasons to submit a complete and timely written response

1. A complete and timely response could mitigate an FDA compliance decision.
   - It MAY make a difference in the final classification or in the type of regulatory correspondence issued.
   - “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.”

4 Reasons to submit a complete and timely written response

2. A complete and timely response demonstrates your acknowledgment and understanding of the observations to the FDA.

3. A complete and timely response demonstrates your commitment to correct the observations to the FDA.

4. A complete and timely response establishes credibility with the FDA.

✓ Initial response & follow-up
9 Suggestions for 483 Responses

1. Include a commitment from senior leadership.
2. Address each observation separately.
3. Note whether you agree or disagree [documents?].
4. Provide both corrective and preventive actions.
5. Provide both completed and planned actions.
6. Provide timelines for completion.
7. Provide a method of verification or monitoring the effectiveness of the actions.
8. Submit documentation (training, SOPs, CAP, records).
9. SUBMIT THE RESPONSE WITHIN 15 WORKING DAYS.
What if I miss the 15-day deadline?

We acknowledge receipt of your written response dated [Month dd, yyyy,] to the Form FDA 483 but note that this response was received past the fifteen (15) business days from close of the inspection. Thus, while we have reviewed the response, we have not included a discussion of the response in this letter as per the Commissioner’s Enforcement Initiative announced August 11, 2009.
Example of an **Inadequate Response**

Failure of the clinical investigator to obtain informed consent, follow the study protocol, and comply with the commitments of FDA-regulated research

**Verbal Response:** “... I signed the Investigator Agreement, but I never read it... during a real estate settlement, do you read all those documents before signing them?”
Example of an Inadequate Response

Failure to obtain informed consent properly

Response: “As to the [forged] signatures of four persons out of eighty patients, suffice it to say...we are talking of a margin of error of 5%...this is well within recognized statistical limits.”
Example of an **Adequate** Response

Failure to follow the investigational plan

**Response:** “We prepared and adopted a written procedure that will help staff to assure compliance with written study protocols and the obligations we accept as clinical investigators for FDA-regulated trials. A copy of the approved SOP is attached. We have reviewed this new procedure at a meeting held on _____ with all research staff (attendance sign-in sheet attached) and implemented it on ____. After 3 months, we will evaluate these new practices to determine if this corrective action assists with protocol adherence.”
Documentation

- Description of non-compliance, data irregularities, other deficiencies
- Corrective and preventive plan
- Data and/or activities reviewed
Summary

Clinical Investigator

Sponsor

15 Days

Response

Corrective and preventive plan
References

Office of Scientific Investigations (OSI)
   – www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090085.htm

Regulatory Procedures Manual

FDA Investigations Operations Manual (IOM)
   – www.fda.gov/ora/inspect_ref/iom/

CPGM – Clinical Investigator Inspections
   – www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133571.htm

FDA Guidance Documents
Chrissy J. Cochran, PhD
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Building 51, Room 5364
Silver Spring, MD 20993
Chrissy.Cochran@fda.hhs.gov