Preparing for and responding to an FDA Inspection

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Disclosures

The speakers have no relevant financial and non-financial relationships to disclose.

The opinions presented are our individual opinions, based on our experience and do not represent those of anyone else, including the UTHSCSA, University Health System or their affiliates.
Breakout Session 501
Preparing for and responding to an FDA Inspection

• Moderator:
  – Frank Estala, BA, Research Compliance Manager, UT-Health Science Center at San Antonio

Introduction and General Overview

• Speaker:
  – Kathy James, CHC, CHSP, Assistant Compliance Officer, UT-Health Science Center at San Antonio
Learning Objectives

✓ 1. Types and scope of FDA inspection
✓ 2. Inspection logistics
✓ 3. Latest trends in FDA inspections
✓ 4. Inspection outcomes and common findings
✓ 5. Responding to 483 and Warning Letters

Key Terminology

- **FDA Inspection** – FDA conducts inspections not audits.
- **FDA 482** Notice of Inspection
- **FDA 483** Inspectional observations issued (if applicable) at end of audit in person/FDA
- **EIR**: Establishment Inspection Report—Official FDA Investigator Report (Freedom of Info Act)—other sponsors can see
  - NAI – No Action Indicated
  - VAI – Voluntary Action Indicated
  - OAI – Official Action Indicated
- **Warning Letter** – An FDA Correspondence that notifies the site inspected of violations documented during an inspection.
BIMO History

- Bioresearch Monitoring Program (BIMO)
- Established in 1977
- Created compliance programs
  - Clinical Investigators (7348.811)
  - Sponsors, CROs & Monitors (7348.810)
  - Institutional Review Boards (7348.809)
  - In-Vivo Bioequivalence Facilities (7348.001)
  - Non-Clinical Laboratories (7348.808)

Why are the inspections done?

- Protect the rights, safety and welfare of human subjects
- Assure quality and integrity of data
- Ensure compliance with regulatory requirements
- Compliant to Title 21 CFR part 312, 314, 511 and 514
When are inspections done?
When are inspections done?

- For clinical trials supporting primary claims of efficacy and safety or important efficacy supplements (Phase II & III studies)
- Studies of any phase if data integrity concerns exist
- Phase IV studies (post market/FDA directives)
- History of the Clinical Investigator

Reasons for Inspections

- Within the Center for Drug Evaluation and Research (CDER), the Division of Scientific Investigations (DSI) in the Office of Compliance has specific responsibility for overseeing the inspections that verify the integrity of application data and determine whether clinical trials supporting applications are conducted in compliance with current FDA regulations and statutory requirements.
Who can be selected?

- Top enrollers
- Single site study
- Studies with inconsistent data
- For cause (complaint, report, suspicions)

Types of FDA inspections

- Study focused – NDA/BLA/PMA
- Investigator focused
- Routine (Surveillance)
- Directed/For Cause
Inspection general plan

- Notification to PI
- Presenting with inspector’s credentials
- Upon arrival FDA investigator issues Form FDA 482, “Notice of Inspection”
- Conducts audit
- Form FDA 483, “Notice of Inspectional Observations”
- “Establishment Inspection Report” (EIR)

Managing FDA Visit

**FDA inspector is here. Now what?**
Managing FDA Visit

- **Speaker:**
  - Clara Vorpahl, BA, Senior Research Compliance Specialist, UT-Health Science Center at San Antonio

Once notified of the inspection…

- FDA announced/un-announced visit:
  - Speak directly with the FDA Inspector whenever possible to arrange the inspection date.
  - Make arrangements to accommodate the Inspector.
  - Notify regulatory offices (IRB, CTO, ORAC, VA).
  - Notify study sponsor.
“Ideal” Accommodations

- Ample workspace
- Low traffic
- Private area
- Accessible to assigned research staff
- Phone and research staff contact information
- Bare room
- Available Copier
- Internet Connection

Briefing the Research Staff

- Principal Investigator
- Sub-Investigators
- Research Nurse/Coordinators/Associates
- Research Fellows and Residents
- Research Pharmacist
- Research Administrative staff
- Research Volunteers/Interns
PI responsibilities and duties

• Discuss the Review of all approved protocols from the PI as PI and Sub-I
• Discuss the protocols in question with the PI
• Coordinate with PI and IRB to obtain all documentation and reconcile all(any outstanding items (submission, approvals, etc.)

Regulatory Reconciliation Process

• Regulatory details
  ➢ IRB Approvals, Correspondence
  ➢ Study site recruitment/promotional materials such as Radio/TV ads, phone scripts, flyers
  ➢ Sponsor Correspondence such as meetings, minutes, follow-up letters
  ➢ Research site’s DSMB/DSMP
  ➢ Review and brief research study staff on site’s Standard Operating Procedures. Please note that SOP’s should cover the duration of the study.
What will be reviewed

- **Protocol procedures and participant chart review**
  - Subject inclusion/exclusion criteria
  - Randomization process/scheme
  - Number of subjects enrolled
  - The administration of Investigational Product: Drugs/Biologics and/or Devices
  - Adherence to IRB approved protocol in contrast with the study visit schedule
  - Informed Consent Processes
  - Informed Consent Documentation (25 or less FDA reviews 100%)
  - Source Documents
  - Case Report Forms
  - Electronic Case Report Forms

Briefing the Medical and Ancillary Staff

- Medical and Ancillary staff are sometimes part of research which may not be listed on a 1572, Delegation of Duties/Authority log.

- Why is this important?
Briefing the Medical and Ancillary Staff

- **Examples of Medical/Clinical staff**
  - Registered Nurses – RNs
  - Licensed Vocational Nurses – LVNs
  - Pharmacy technicians
  - Laboratory assistants
  - Nutritionist/Dietician
  - Please note examples of these staff members are sometimes standard of care and are not engaged in research.

- **Examples Ancillary staff**
  - Records manager/File Clerk
  - Statistician (Bio, Data, etc.)
  - Data Entry staff
  - Standard of care administrative staff
  - Facility operators (i.e. a DEXA operator in a Diabetes clinic)
  - Please note examples of these staff members are sometimes standard of care and are not engaged in research.
Important points to remember

1. Cooperate with FDA inspector

2. Always notify senior officials (compliance, research and regulatory offices, IRB)

3. Assign a staff member to assist and document

4. Do not answer a question if you are not sure of the answer

Ensuring Smooth Flow of Inspection

• **Speaker:**
  – Kathy James, Assistant Compliance Officer, University of Texas Health Science Center at San Antonio
Assignment of Duties Recommendation

**Designate a Liaison**
- A primary staff person to oversee the inspection
- The liaison will serve as the institutional/site monitor, escort, guide and general study contact
- Designate a transcriber to assist the liaison in documenting items being requested by the inspector during the course of the visit

Scope of Inspection

**Important Point to Remember**

- “The following outline provides only the **minimum scope** of the inspection, and each field investigator should expand the inspection as the circumstances warrant. Inspections should be sufficient in scope to cover special instructions in the assignment and to determine if the clinical investigator’s practices and procedures comply with regulations.” FDA
Scope of Inspection

- Interviews with study staff
- Administrative documents
- Case Report Forms
- Informed Consent Forms
- Test article storage area
- Data Audit
- Part 11 Compliance

Scope of Inspection

- Critical issues of the study:
  - Is study entry recorded?
  - Is there a subject/diagnosis?
  - Is drug administration documented?
  - Is raw study data available?
  - Did an IRB approve all significant stages?
  - Did the subject meet all inclusion criteria?
Critical issues of the study:
- Were all screened subjects entered?
- Does amount of test article used coincide with number of subjects treated?
- Was test article properly disposed?
- Was blind maintained?
- Was randomization scheme followed?

Scope of Inspection

Pharmacy records:
- Drug dispensing/accountability log
- Shipment and receiving records
- Temperature/storage log
- Dispensed by an authorized person
- Pharmacy security
- Equipment maintenance records
Exit meeting with inspector

- Discuss inspection findings
- May issue an FDA-483
  - Represents deviations from federal regulations for clinical investigators
- Verbal response to FDA-483

What is FDA-483?

- The FDA-483 is the FDA Investigators’ report to management of the conditions or practices he/she observed which, in his/her opinion, may constitute violations of law
- The observations are not a final agency’s determination of noncompliance
- There is extensive further review before any decision to escalate the agency response is made
Responding to FDA-483

• Inspected sites have both oral and written opportunities during and after the inspection to make their views known, to dispute, or to offer corrective action plans.
• The 483 is the first step in what can become an escalating enforcement process. Effective response to the document is the key to preventing further regulatory action.

Inspection outcomes

• The inspection report is written by the FDA inspector and sent to the Center.
• The Center evaluates the report and determines the corrective action, and classifies the inspection:
  – No Action Indicated (NAI)
  – Voluntary Action Indicated (VAI)
  – Official Action Indicated (OAI)
When a 483 is issued with official action indicated (OAI), the appropriate FDA district or regional office may choose to follow up with a warning letter, which usually signals that serious violations have been observed during one or more inspections.

- If a Warning Letter is issued, the recipient must take immediate corrective action and respond formally to FDA.
- If the response is incomplete or inadequate, FDA may initiate further enforcement actions up to and including suspension of some or all FDA-regulated activities at the site.
Be inspection ready

- FDA investigator follows compliance program CP 7348.811 (clinical investigator inspections) and 21 CFR 312.60
- Have available:
  - All study documents
  - Person knowledgeable about the study
- Conduct self-audits
Trends in FDA Inspections

• **Speaker:**
  – Anna Taranova, MD, MS, CCRP,
  Senior Research Director,
  University Health System

What triggers inspections

• Application-focused
• Complaint-driven
• More recently*: CDER has been piloting a risk-based clinical investigator site selection tool
  – permits quantitative evaluation of an array of factors that may indicate a higher risk of data integrity concerns at a site.

*FDLI report March 2011
Current Inspections Focus:

- Current FDA focus:
  - Increasing inspections, targeting sponsors, CROs, and sites
  - Citing monitoring violations
  - Emphasis on meeting FDA's expectations of GCP and regulatory compliance
  - Risk-based inspections to ensure data integrity

Focus of site inspections

- Site management
- PI (qualifications, oversight)
- Data (consistency, reliability)
- IMP
- AEs (consistency with sponsor data)
Number of 483s issued in 2012

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<tr>
<th>Center Name</th>
<th>483s issued</th>
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<td>Actual Total in system 483s**</td>
<td>5797</td>
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<tr>
<td>Devices</td>
<td>1090</td>
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<tr>
<td>Drugs</td>
<td>787</td>
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<tr>
<td>Bioresearch monitoring</td>
<td>283</td>
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<tr>
<td>Veterinary medicine</td>
<td>243</td>
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<tr>
<td>Biologics</td>
<td>237</td>
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<tr>
<td>Radiological health</td>
<td>18</td>
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Official Action Indicated

FY2010 and 1Q FY2011*:
- 72% of OAI actions resulted from for-cause inspections
- 80% recommended rejection of data

*FDLI report March 2011
Common findings

- Protocol non-adherence
- Inadequate and inaccurate records
- Failure to report adverse events
- Failure to report concomitant therapy
- Inadequate drug/device accountability
- Lack of training/qualifications records
- Informed consent issues
- IRB problems
Clinical Investigator-Related Deficiencies Based on Post-Inspection Correspondence Issued (CDER, FY 2011)*

Based on letter issue date; does not denote number of inspections completed

When Inspection has repercussions

- Whether an inspection was complaint-driven or application-focused, the OAI classification generally resulted from systemic, critical errors that undermined the interpretability of primary endpoint data, created an immediate risk to the rights, safety, and welfare of enrolled subjects and/or impeded FDA in carrying out its oversight responsibilities
Common Reasons for OAI:

- Failure to complete or document study procedures and data necessary to interpret a primary endpoint
  - not conducting a protocol-required efficacy follow-up visit for any enrolled subject

Common Reasons for OAI:

- Discrepancies and omissions in study records related to investigational product administration
  - discrepancies make it difficult to confirm that subjects received the assigned investigational product in accordance with the protocol-defined dosing regimen
Common Reasons for OAI:

- Discrepancies between an investigator’s records and primary endpoint data reported by the investigator to the sponsor
- Underreporting of adverse events, bringing into question the completeness of data on which safety conclusions were based

Common Reasons for OAI:

- Inclusion/Exclusion Criteria
  – enrollment of study subjects in violation of key eligibility criteria designed to exclude subjects for whom participation posed significant risk
FDA 483 and Warning Letters Analysis

- In a recent analysis of all warning letters issued from 2006 to 2009, Centerwatch reported that almost 40% of the findings were related to monitoring violations.
What to do if FDA 483 was issued?

- Assemble the team
- Write a response
- Root-Cause analysis in action
- Create corrections plan
- Respond to findings

Response to FDA 483

Why Submit a response?
- Could possibly mitigate an FDA compliance decision for further action (e.g. untitled letter, Warning Letter)
- Demonstrates an understanding and acknowledgement of the observations
- Demonstrates a commitment to correct, i.e. the intent to voluntarily comply
- Establishes credibility with FDA
Response to FDA 483

• Timely response: 15 business days to submit a written response to FDA 483 observations before FDA moves ahead with the issuance of a Warning Letter (if FDA determines that a Warning Letter is appropriate)
• If unable to provide full response within 15 day time frame, provide at least partial response and include your intent to provide further response with time line for that response

What to Include in a Response

• Address each observation
  – Concentrate on specifics AND any system-wide or global implications
  – Include copies of any supporting documents referenced in response
  – Consider root-cause analysis for each issue
  – Communicate action plan with immediate, short-term, and long-term correction and prevention of recurrence
  – Provide time frames for correction (be specific!)
  – Provide method of verification and/or monitoring for corrective measures
Response to Warning Letter

• Why respond to the letter?
  – “Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.”

What to Include in a Response

• Address each violation:
  – Provide CAPA and include immediate, short-term, and long-term measures
    • Provide time frames for correction
    • Provide method of verification and/or monitoring of corrective measures
  • Consider submitting documentation demonstrating success of implemented CAPA, if possible and feasible
Response to FDA 483 and Warning Letter

• “In response to this letter, provide your updated corrective action and preventive action (CAPA) plan to ensure that ….”

Response to FDA 483 and Warning Letter

• Ensure response is timely - if additional time is needed to fully formulate response, formally request it.
• Be realistic and make sure you can follow through on your promises.
• If CAPA is extensive, propose realistic timeline and provide updates to FDA on accomplishments.
• If implemented CAPA does not achieve desired goal, discuss with FDA and consider other plans and actions.
You failed to ensure that the investigation was conducted according to …. the investigational plan [21 CFR 312.60].

- The protocol specified that subjects who miss any visit were to be contacted by telephone. There is no documentation that you attempted to contact Subject [redacted] after the subject missed the 6-Month visit.
- The protocol specified that clinical examinations were to be performed by the investigator (you). However, the clinical examinations for the following visits were performed by (b)(4), M.D. ….

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm340269.htm

Failure to maintain accurate, complete, and current research records [21 CFR 812.140(a)(1), (3), and (4)]

- “You failed to adhere to the above-stated regulations. Examples of these failures include, but are not limited to the following:
  - The Electronic Case Report Form (eCRF) lacks baseline vital signs, permanent pacemaker) interrogation findings, or laboratory values.
  - The post-procedure electrocardiogram and interpretation notes are missing from the study chart.
  - Part of the original screening worksheet is missing and the two copies that exist differ regarding exclusion criteria for mitral or tricuspid regurgitation and mitral stenosis.”

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm340269.htm
You failed to ensure that the investigation is conducted according to the investigational plan. [21 CFR 312.60].

- …The protocol’s "Site Reference Manual" states, "Laboratory test results must be initialed and dated by the Investigator indicating that they were reviewed." There are several examples of laboratory reports that were not signed or dated by you or a sub-investigator responsible to you.

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm340269.htm

Failure to maintain accurate, complete, and current records ……[21 CFR 812.140(a)(3)].

- You failed to adhere to the above-stated regulation. Examples of this failure include but are not limited to the following:
  - At least three subjects had documentation in their medical records of complications that were not reported to the study sponsor. Specifically:
    - For Subject# [redacted], the medical records for the visit indicate that the subject developed [redacted], but the Physical Exam case report form indicates there were no complications.…

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm340269.htm
Drug Accountability [21 CFR 312.62(a)]

“You did not maintain records of study drug disposition for Subjects [redacted] and [redacted].”

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm345472.htm

You failed to ensure that the investigation is conducted according to the investigational plan. [21 CFR 312.60].

• …the individuals who have prepared study drugs have not been registered pharmacists qualified by training and experience.
• Several study visits were conducted by personnel not medically qualified to evaluate the subjects’ disease status, including the study coordinator and Dr. [redacted].

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm345472.htm
Failing to obtain informed consent before research procedures 21 CFR Part 50 [21 CFR 312.60 and 21 CFR 50]

“Subject [redacted] was randomized to protocol on June 12, 2006. You did not obtain informed consent from this subject until June 26, 2006”.


The IRB failed to ensure that basic elements of informed consent are included in the IRB-approved consent form [21 CFR 56.109(b)].

– The IRB must require that information given to subjects during the informed consent process includes the fundamental elements ....in accordance with 21 CFR 50.25.

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm345472.htm
The IRB failed to notify investigators and the institution in writing of its decision to approve or disapprove… [21 CFR 56.109(e)].

– Your IRB failed to provide written communication …of its decisions to approve or disapprove research studies reviewed by the IRB. The FDA investigator was told that, clinical investigators were only verbally informed of IRB decisions during meetings.

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm345472.htm

The IRB failed to ensure that no member participated in the review of a project in which they had a conflicting interest. [21 CFR § 56.107(e)].

• The (IRB) procedures manual states that no member of the Committee shall be involved in the review of an activity in which he has a conflicting interest. The meeting minutes dated January 26, 2012, show that two of the committee members, including you as the Chairperson, participated in the initial review and approval of clinical studies sponsored by (b)(4). Both you and (b)(6) voted to approve protocols sponsored by (b)(4) even though you had both provided consulting services to (b)(4) for which payment was requested.

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm323868.htm#
Guidance for Industry 2013

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

- Guidance assists sponsors of clinical investigations in developing risk-based monitoring strategies and plans for investigational studies of medical products, including human drug and biological products, medical devices, and combinations thereof.
Inspection Readiness

• Gather “Inspection Intelligence” through the internet, regulatory guidance, 483’s to industry, etc.
• Know how your departments communicate important information
• Plan your inspection logistics in advance

Create and maintain “Inspector crash cart”:
• Inspection team list, back-ups, Regulatory, Clinical, and Legal contacts
• Inspection procedural document/manual/Inspection checklist
• Date/confidential/copy stamps, administrative supplies, empty flash drives, empty CD’s, extra laptop for inspector, etc.
• CFR Title 21 and ICH guidelines reference guide
• Tracking sheets/log,
• Copy of last EIR and any company responses
Inspection Readiness

- Conduct self-monitoring and mock-inspections.
- Is your terminology harmonized (is it a quality risk or a key risk indicator)?
- Is your company adapting to changes in the Regulatory landscape?
- Do you consider a “Note to File” a fix? It is not.
- Retraining is not always the answer – get to the root cause and fix that.
- Build audit trail.

Questions and Answers
Thank you!