Shedding Some Light on FDA Inspections of Clinical Drug Trials

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Office of Compliance
CDER/FDA

National Cancer Institute/NIH
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Objectives

- Describe the purpose of the FDA's bioresearch monitoring (BIMO) program
- Identify the federal regulations covering clinical research and clinical investigator obligations
- Discuss what to expect during and after an FDA inspection
- Discuss specific problems seen during recent FDA inspections at clinical sites
- Discuss various methods that can be used to ensure compliance with federal regulations and study protocol requirements
FDA’s Biores research Monitoring Program

- **FDA’s Biores research Monitoring Program (BIMO)** - A comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research.

- The Program was established in 1977 to verify the data submitted in support of marketing applications and to provide oversight of the conduct of studies with regulated products.
DSI Mission (Purpose)

- To verify the integrity of efficacy and safety data submitted to the FDA in support of new drug applications.

- To assure that the rights and welfare of human research subjects are protected.
DSI/CDER’s BIMO Program Responsibilities

- Ensure adherence to applicable regulations with respect to:
  - Good Laboratory Practice (GLP)
    - *In vivo* Bioequivalence
  - Good Clinical Practice (GCP)
    - Clinical Investigators
    - Sponsor-Monitors, CROs
  - Human Subject Protection
    - Institutional Review Boards
CDER BIMO Inspections*
FY 2002-2009**

*Based on inspection start date
**FY09 to Date

1/5/10
CDER BIMO Inspections*(FY 2009**)

CI = 458
BEQ = 128
IRB = 102
GLP = 27
S/M = 73
Total = 788

*Based on Inspection Start Date
**FY09 to Date
Sponsor Inspections*

- 73 in FY 2009**
- 43 in FY 2008
- 25 in FY 2007

*Based on Inspection Start Date
**FY09 to Date
Clinical Investigator Inspections*  
CDER FY 2001-2009**

*Based on inspection start date  
**FY09 to Date

1/5/10
CDER IRB Inspections*
FY 2001 – 2009**

*Based on Inspection Start Date
**FY09 to Date

1/5/10
Clinical Investigator Inspections*
All Centers - FY2009**

- CDER: 458
- CBER: 83
- CDRH: 163
- Total: 704

*Based on Inspection Start Date
**FY09 to Date

1/5/10
“The Field”

- Refers to FDA offices within the Office of Regulatory Affairs (ORA)
- Under the jurisdiction of ORA, not CDER
- Located in 5 major regions of US:
  - 5 “Regional Offices”
  - 20 “District Offices”
    - 50 - 100 staff per office
    - 1 “District Office” is imports only
- Over 200 locations across the country
  - Includes approximately 140 “Resident Posts”
Office of Regulatory Affairs
Field Locations

Regional Offices - 5
District Offices - 20
Resident Inspection Posts/Border Stations - 140
OCI Field Offices - 6
OCI Resident Offices - 6
OCI Domiciles - 13
Ch. 1 - Regulatory Organization
Ch. 2 - FDA Authority
Ch. 3 - Commissioning and Work Sharing
Ch. 4 - Advisory Actions
Ch. 5 - Administrative Actions
Ch. 6 - Judicial Actions
Ch. 7 - Recall Procedures
Ch. 8 - Emergency Procedures
Ch. 9 - Import Operations And Actions
Ch. 10 - Other Procedures
Section 505(k)(2) of the Food, Drug, and Cosmetic Act mandates that FDA shall have **access** to and **copy** and **verify** the required clinical study records.

21 CFR 312.68

“An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator…”
### FDA/CDER GCP Regulations

<table>
<thead>
<tr>
<th>Inspections apply to:</th>
<th>FDA regulated <strong>CLINICAL</strong> and non-clinical research</th>
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<tbody>
<tr>
<td>Regulatory oversight</td>
<td>Institutional Review Boards (IRBs), Sponsors, CROs/Monitors, Clinical Investigators</td>
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</table>
| Relevant Regulations include (but not limited to) | 21 CFR  
- Part 11: Electronic Records; Electronic Signatures  
- Part 50: Protection of Human Subjects  
- Part 54: Financial Disclosure  
- Part 56: Institutional Review Boards (IRB)  
- Part 312: Investigational New Drugs (IND)  
- Part 314: New Drug Applications (NDA) |

**These are legally enforceable requirements!**
GCP Guidance Documents

- Part 11, Electronic Records; Electronic Signatures — Scope and Application (2003)
- Waiver of IRB Requirements for Drug and Biological Product Studies (2006)
- Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (2006)
- Protecting the Rights, Safety, and Welfare of Study Subjects- Supervisory Responsibilities of Investigators (2007-draft)
- Guidance for Sponsors, Clinical Investigators, and IRBs; Data Retention When Subjects Withdraw From FDA-Regulated Clinical Trials (2008)
- Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection (2009)

http://www.fda.gov/cder/guidance/index.htm
PDUFA (Prescription Drug User Fee Act)-Related Inspections vs For-Cause

- **For-Cause Inspections (Complaints)**
  - Based on complaints from any source
  - Allegations that raise concerns regarding data integrity or the rights, welfare, and safety of study subjects have been compromised

- **PDUFA-Related Inspections (NDA/BLA)**
  - FDA receives a Marketing Application
  - Drug is typically a new molecular entity (NME)
  - Pivotal studies not conducted under IND (Foreign)
  - Data in support of application is only from foreign sites
  - Also may be referred to as “Routine” Inspections
CDER Clinical Investigator Inspection Assignments*
FY 2009**

- Routine: 77%
- Complaint-Related Inspections: 23%

n=492*

*Based on assignment issued date
**FY09 to Date

1/5/10
Complaints Received*
FY 2001-2009**

*Includes All Branches
**FY09 to Date

1/5/10
CI Complaint-Related Inspection Assignments*
CDER, FY 2001 – 2009**

*Based on Assignment Issued Date
**FY09 to Date
1/5/10
Timing and Targets of PDUFA-Related Inspections

- Inspections can be conducted at any point in the drug development process.
- Inspections typically occur during the NDA phase.
- May include Clinical Investigator (CI), Sponsor/Monitor (S/M), Contract Research Organization (CRO), Institutional Review Board (IRB), Good Laboratory Practice (GLP), and Bioequivalence (BEq) inspection of FDA regulated research.
Site selection is a joint process: Review Divisions & DSI

Site selection considerations:
- A specific safety concern at a particular site or sites
  - Based on review of AEs, SAEs, deaths, or discontinuations
- A specific efficacy concern based on review of site specific efficacy data
  - Efficacy differential between sites
  - Final outcome driven by a particular site or sites
  - Efficacy outcome different than expected based on mechanism of action of drug
- Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results
Factors Affecting Selection - PDUFA Inspections

- **Importance of the study**
  - Relevance to labeling/NDA
  - Contribution/size/outliers

- **Statistical impact of data from the site**

- **History of the clinical investigator**
  - Frequency and prior classification(s)
  - Findings of previous inspection(s)
Criteria for PDUFA
International Inspections

- Insufficient domestic data
- **Only** foreign data are submitted to support an application;
- Domestic and foreign data show conflicting results pertinent to decision-making; or
- Serious issues that need resolution, e.g., suspicion of fraud, scientific misconduct, human subject protection violations.
Clinical Investigator Inspections – International* (CDER, FY 2002 – 2009**)

*Based on Inspection start date
**FY09 to Date

N=119
Request from Review Division

DSI evaluates & generates assignment

Assignment Request forwarded to DFI (foreign) or District Office

Inspection performed and EIR submitted for review by DSI

DSI makes overall decision for approval or non-approval recommendation
Preparing for the Inspection

FDA Inspectors use Compliance Programs

- Clinical Investigator
  http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm

- Sponsor/Monitor/CRO
  http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm

- IRB
Goals of Inspections: PDUFA

Assessment of the following:

- Clinical Investigator Qualifications
  - Training/Experience/CV review
- Clinical investigator oversight of study
  - In-depth knowledge of protocol/study plan
  - Selection of competent staff for delegation of responsibilities
- Clinical Study Center/Site
- Informed Consent Procedures
- IRB approval
- Adherence to study protocol
- Test article accountability
- Recordkeeping
Focus of Inspection

The FDA Inspection (Audit) compares

- Source Document Medical Record Data vs
- Case Report Forms vs
- Data Listing Submitted to NDA

Verify

- Source of subjects; Did subjects exist?
- Did they have the disease under study?
- Did they meet inclusion/exclusion criteria?
- IRB Review Obtained? Consent obtained?
- Adherence to protocol?
- Verify primary efficacy measurements
- Adverse events?
- Safety data: Labs, EKG etc.
- Drug Accountability? Blinding of data?
Fraud Still Occurs...

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<td></td>
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Inspections...

- Are FACT finding
- Require EVIDENCE
- Require ORGANIZATION and TIME MANAGEMENT
- Are REGULATORY
  - What is said could end up in court
To Lawfully Inspect (per 501(a)(1)(B)), FDA Must...

- **Show credentials**
  - Required by law to be shown upon starting an inspection
  - Displayed to the top management official ("owner, operator, agent in charge")
  - Management may examine credentials and record the number and name
  - Credentials are **not** to be photocopied

- **Issue Notice of Inspection**
Notice of Inspection

- Also known as the FDA-482
- Must be issued to start the inspection (except for international sites)
- All team members must sign
- Original given to firm and copy included in the Establishment Inspection Report
The FDA inspection ends...

- Formal Close Out

- May include:
  - Sample Collections
  - Affidavits (domestic)
  - Issuance of FDA 483, Inspectional Observations
After an Inspection Is Completed

- ORA may issue a Form FDA-483 at close of inspection
  - The observations listed on a Form FDA 483 lists inspectional observations
  - Immediately available via FOI
- ORA Prepares the Establishment Inspection Report (EIR)
  - Prepared by field investigator
  - Includes exhibits supporting all observations including deficiencies
  - Recommends inspection classification
  - Submitted to DSI for review
- DSI Prepares Review of EIR and pertinent exhibits
  - Makes final classification of the inspection
  - Informs the Review Division (NDA review) via internal report (Clinical Inspection Summary). Includes recommendation on data reliability…
- DSI Prepares written communication to inspected party:
  THE LETTER
Form FDA 483

- Observations listed in order of significance
- Must be objective and supported by evidence
- Guidance documents cannot be referenced on FDA 483
- Everyone present at issuance signs the first and last page of the FDA 483 and initials each intervening page in the signature block
Compliance Classifications

**NAI** - No Action Indicated  
Inspected Entity is in compliance

**VAI** - Voluntary Action Indicated  
Minor deviation(s) from the regulations  
Voluntary correction is requested

**OAI** - Official Action Indicated  
Serious non-compliance requiring regulatory or administrative action by FDA
Clinical Investigator Inspections
Final Classification*
FY 2009**

Total inspections with final classification = 624
Includes OAI Untitled Letters

*Based on Letter Issued Date
**FY09 to Date

1/5/10
Sponsor/CRO Inspections*
Final Classification FY 2009**

Total inspections with final classifications = 60
Includes OAI: Untitled Letters

*Based on Letter Issued Date
**FY09 to Date
Consequences of Non-Compliance: OAI
(not all inclusive)

IRBs:
- Administrative actions;
- Disqualification

Sponsors/CROs/Monitors:
- Rejection of data;
- Clinical Holds;
- Termination of IND;
- Application Integrity Policy

Clinical Investigators:
- Warning Letters
- NIDPOE Letters
- Disqualification
## CDER/DSI
### Clinical Investigator Regulatory Actions

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</table>

WL = Warning Letter  
NIDPOE = Notice of Initiation of Disqualification Proceedings and Opportunity to Explain  
NOOH = Notice of Opportunity for Hearing  
CA = Consent Agreements (Restricted Agreements)  
CA = Consent Agreements (Full Disqualification)  
DQ = Disqualification by Hearing  
DQ = Disqualification by Commissioner

*FY09 to Date  
1/5/10
CDER Clinical Investigator
OAI Actions
(Warning/NIDPOE Letters*)
FY 2001-2009**

*Based on Letter Issued
**FY09 to Date
1/5/10
Clinical Investigator Deficiencies
CDER Inspections - FY 2009**

*Based on Letter Issued Date
**FY09 to Date

Foreign n = 120*
Domestic n = 401*

1/5/10
CI Deficiencies - CDER; FY 2009**
Final Classification of OAI*

(% of total inspections with final classification of OAI; includes OAI:Untitled Letters)

*Based on Letter Issued Date
**FY09 to Date
Enforcement Initiatives

http://www.ConnectLive.com/events/fda080609/archive.asx

- Establishment of Timeframe for Submission of Post-Inspection Responses
- Shift in Office of Chief Counsel’s (OCC) Review of Warning and Untitled Letters
- Development of Risk Control and Enforcement Strategies with our Regulatory Partners
- Warning Letter and Recall Follow-Up Inspections
- Swift, Aggressive, and Immediate Enforcement Action
- Warning Letter Close-Out Process
Timeframe for Submission of Post-Inspection Responses

- Intended to facilitate the timely issuance of Warning Letters (WLs) by establishing a timeframe for the submission of post-inspection responses to an FDA-483.
- Industry has no more than 15 working days to respond to a 483 before FDA moves ahead with the issuance of a WL (if FDA determines that a WL is appropriate).
- Meant to eliminate delays in Agency’s ability to take prompt enforcement action.
Development of Risk Control and Enforcement Strategies with Regulatory Partners

- FDA will be working more closely with our regulatory partners to develop risk control and enforcement strategies.

- In some situations, local, state, and international officials may have the authority to take action more quickly than FDA.

- When the public health is at risk, FDA will reach out to these partners to take rapid action while we alert the public and prepare longer-term responses.
Do’s and Don’t For Investigators: DO

- Follow the current protocol
- Personally conduct or supervise investigation(s)
- Ensure that all persons assisting in conduct of studies are informed of their obligations
- Ensure informed consent (21 CFR 50) and IRB review, approval, and reporting (21 CFR 56) requirements are met
- Obtain the informed consent of each human subject to whom the drug is administered
Do’s and Don’t For Investigators: DO

- Notify the sponsor before making changes in the protocol.
- Notify the IRB and obtain IRB approval before making changes in the protocol.
- Report adverse events to the sponsor.
- Maintain adequate and accurate records.
- Make records available for inspection.
- Comply with all other requirements in 21 CFR 312.
- Report Financial Interests to the Sponsor (21 CFR 312)

*(Form FDA 1572: #9. Commitments)
8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:
FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.
FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:
I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
I agree to personally conduct or supervise the described investigation(s).
I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
I have read and understand the information in the investigator’s brochure, including the potential risks and side effects of the drug.
I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
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.
I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:
1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

“An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.”
Do’s and Don’t For Investigators: DON’T

- Over-delegate to non-physicians (e.g., diagnosis that qualifies/determines eligibility for entry into the study)
- Erase, white-out or obliterate original data entry either in CRFs or medical charts
- Accept suggested changes to study data without checking the source documents or without justification for such changes
- Backdate the consent forms and signatures
- Forget to obtain IRB approval of consent form revisions
- Revise the protocol without obtaining the sponsor’s written concurrence
Case Study #1: Failure of Due Diligence

- Drug developed through phase 3 by Sponsor X
- Rights of reference sold by Sponsor X to Y
- NDA submitted by Y
  - Multicenter, multinational non-inferiority trial
- Routine data audit inspections
  - Records not available for several sites
- WL issued to Y
  - Failure to make available underlying raw data for FDA audit
    [21 CFR 314.3(b)]
  - Failure to adequately verify data at sites prior to submitting NDA
    [21 CFR 31.50(d)(d)(iv)竞争优势。
Case Study #2: Data Validation Inspection for NDA--Clinical Investigator Sites

- Failure to prepare and maintain adequate case histories and retain records [21 CFR 312.62(b) and (c)]
  - eCRFs were source documents; Site data for inspection consisted of CD provided by sponsor, no evidence that CI prepared or maintained subject records or signed off on subject data in real time
  - Clinical signs such as breath sounds and chest exam were assessed during phone call to subjects
  - Data in eCRF inaccurately carried over from visit to visit
### Case Study #2: Data Validation Inspection---Sponsor Inspection

#### SIGN / SYMPTOMS

**KEY:**
- (5) Resolved
- (4) Worse
- (3) Improved
- (2) Same
- (1) New
- (0) Not Assessed

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Case Study #2: Data Validation Inspection for NDA--Sponsor Inspection

- eCRF design flaws resulted in erroneous data collection
  - Screen design confused sites, with assessment of signs and symptoms erroneously recorded

- Audit Trails were incomplete

- EDC system allowed some data to be pre-recorded
Case #2: Data Validation Inspection—Sponsor Inspection

- Monitoring reports – “study site’s laptop was not functional” during several weeks during which electronic data was reportedly captured
- Several electronic (word document) monitoring reports were backdated and misrepresented
- The sponsor’s EDC system did not allow investigators to “prepare, maintain, and retain” a copy of the eCRFs via which data was submitted to the sponsor
Improve Process — Be Proactive

- **Address human factors in systems**
  - Hire experienced, qualified staff
  - Avoid conflicts of interest/financial incentives
  - Decrease number of times data are handled

- **Create systems that limit opportunity for errors**
  - Simplify protocol and outcomes assessed
  - Be realistic about the amount of data to be collected
  - Standardize systems and formats where possible
  - Use validated instruments/definitions
  - Write down all procedures (SOPs). Use checklists.
  - Don’t re-invent the wheel
  - Keep amendments to a minimum and check the CRFs and consent form against each change
Improve Process — Be Proactive

- Develop an integrated framework
  - Data and Safety Monitoring Plan, Data Management Plan, Quality Assurance Plan, Data Analysis Plan
- Insist on training and then test it
- Think very carefully about unblinding procedures
- Have a disaster plan
- Do beta-testing/dry-runs
- Have weekly team meetings/calls
- Do real-time cleaning of the data
- Audit yourself — be open and honest
QUESTIONS

- What triggers an FDA audit?
- What type of regulatory review do the FDA inspectors perform on an FDA audit?
- What documents are they looking for in our regulatory files, specifically? Is an electronic regulatory binder/file acceptable?
- Will the FDA review each FDA IND submission, or are they more concerned with IRB documentation and other regulatory files like CVs, 1572, lab normal, etc.?
Helpful Websites

- **DSI Homepage**: [www.fda.gov/cder/offices/dsi](http://www.fda.gov/cder/offices/dsi)
  
  Includes links to the Clinical Investigator Inspection List (NEW), Bioresearch Monitoring Information Systems (BMIS) files (NEW), Warning Letters, NIDPOE Letters, Lists of Disqualified or Restricted or Debarred Investigators, Code of Federal Regulations, etc.

- **FDA Homepage**: [www.fda.gov](http://www.fda.gov)
  
  Includes links to the Federal Register Notices, FDA guidance documents.

- **Compliance Programs**: [www.fda.gov/ora/compliance_ref/default.htm](http://www.fda.gov/ora/compliance_ref/default.htm)
Contact Information

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