An FDA Update on Clinical Trial Site Inspections: A View One Year Later

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Faculty Disclosure

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I do not have financial or other relationships with the manufacturer(s) of any commercial services(s) discussed in this educational activity.

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Overview

I. FDA CDER Clinical Research Inspection Program Changes & Compliance Trends

II. Globalization of Clinical Studies and EMA-FDA Collaborations

III. Enhancing Clinical Trial Quality Through Collaboration: FDA Participation Highlights

IV. Trends in Use of Technology to Support Clinical Trials
I. Inspection Program Changes

FDA Program Alignment Group

- Hamburg Memo -- September 2013
- PAG Recommendations -- February 2014
  - Commodity-Based and Vertically-Integrated Regulatory Programs
  - Action Plans -- October 2014
- Some information on the process is available on FDA’s website www.fda.gov
Issues to be Addressed by PAG groups

- Specialization
- Training
- Work Planning
- Compliance Policy and Enforcement
- Imports
- Laboratory optimization
- Delayering
BIMO PAG process

• BIMO – the unusual Commodity Group
  – Small comparatively, but extremely important

• BIMO Action Plan 10/7/2014
  – BIMO Specialization
  – BIMO Training and Development
  – BIMO Program Processes

• Currently all of these areas have sub-groups which are developing work products.
CDER BIMO

- Office of Scientific Investigations (OSI) reorganized
- Office of Study Integrity and Surveillance (OSIS) created
- OSI – Enforcement (DEPS/CEB) and Enforcement Policy (IO/Policy Staff) for BE and GLP programs
- OSIS – Inspections for BE and GLP programs
Finding OSIS

CDER

Office of Translational Sciences (OTS)

Office of Computational Science

Office of Biostatistics

Office of Study Integrity & Surveillance

Office of Clinical Pharmacology
CDER OC
Office of Scientific Investigations (OSI)

Office Director

Deputy Director

Policy Staff

Division of Enforcement and Postmarketing Safety

Division of Clinical Compliance Evaluation

Compliance Enforcement Branch

Postmarketing Safety Branch

GCP Compliance Oversight Branch

GCP Assessment Branch
I. Research Compliance Trends: What Triggers an FDA Inspection?

• New Drug Application (Data Validation)
  – ~70% of clinical investigator inspections are associated with NDA/BLA
  – May be linked with a sponsor/CRO inspection

• Complaints/Referrals (“For Cause” Inspection)
  – Can come from any source
  – ~30% of clinical investigator inspections follow a complaint

• Routine Surveillance Inspections
  – Institutional Review Boards & GLP facilities
FDA Inspections: 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
Inspections Overseen by CDER, OSI*
CDER, FY 2005 – FY 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
Clinical Investigator Inspections*
(CDER, FY 2005 – FY 2014)

*Based on inspection start date – [OSI database as of January 20, 2015]
Foreign Clinical Investigator Participation has Increased while Domestic has Decreased

- Based on Signed Form FDA 1572 that CDER Received in BMIS
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 is/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
Clinical Investigator Inspections Final Classification*(FY 2014)

472 CI Inspections

- No Action Indicated: 53%
- Voluntary Action Indicated: 40%
- Official Action Indicated: 7%

*Based on Letter Issue date; Includes OAI Untitled Letters, [OSI database as of January 20, 2015]
Frequency of Clinical Investigator-Related Deficiencies Based on Post-Inspection Correspondence Issued* (CDER, FY 2014)

Domestic CI Deficiencies

- Protocol: 39%
- Records: 25%
- Drug Accountability: 8%
- Consent: 5%
- IRB Communication: 3%

356 Domestic Inspections

Foreign CI Deficiencies

- Protocol: 28%
- Records: 20%
- Consent: 7%
- Adverse Events: 3%
- Other: 2%

116 Foreign Inspections

*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.
Frequency of Clinical Investigator Related Deficiencies Based on Post-Inspectional Correspondence Issued: Official Action Indicated (OAI) Final classification*

- Protocol: 67%
- Records: 55%
- Submission of False Information: 12%
- CI Supervision: 12%
- Drug Accountability: 9%

*Based on letter issue date. Inspections may have multiple deficiencies. Includes OAI untitled letters. [OSI database as of January 20, 2015] Note that this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed in FY2014.
Challenges in FDA Inspections

• Increasing globalization of clinical trials
  – Increase in numbers of non-U.S. based clinical investigators conducting research

• Finite inspection resources
  – Breadth of international inspections coupled with finite inspection resources result in inspection of a limited number of sites
Addressing Research Challenges Requires

- Collaborative effort such as engaging with regulatory organizations
- Building quality management approach to clinical studies & their oversight
- Encouraging sponsors to utilize data standards to improve analysis & site selection for inspection
- Converging regulatory approaches to FDA inspection process
II. Globalization and Collaborations

Trial Sites*

*Data Source: CDER’s Clinical Investigator Site Selection Tool (2009-2015)
CDER’s Clinical Investigator Site Selection Tool (2009-2015)

Number of Clinical Investigator Sites: 40,524
Number Trial Participants: 650,215

- Subject Enrollment
- Number of Sites
CDER’s Clinical Investigator Site Selection Tool (2009-2015)
Based on inspection start date – [OSI database as of January 20, 2015]

- Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
- As of June 2011, Postmarketing Adverse Drug Event inspection programs were incorporated into OSI
Clinical Investigator Inspections by Location* (CDER, FY 2014)

*Based on inspection start date – [OSI database as of January 20, 2015]
International Clinical Investigator Inspections by Location* (CDER, FY 2014)

*Based on inspection start date – [OSI database as of January 20, 2015]
EMA-FDA Collaborations
GCP Inspection Initiative

• Initiated in Sept. 2009 as pilot to:
  - Develop a joint GCP program
    • Plan, coordinate, schedule, and conduct collaborative GCP inspections
  - Establish joint procedures
    • Share information related to drug applications

• Goals
  - To Conduct Periodic Information Exchanges on GCP
  - To Conduct Collaborative GCP Inspections
    Build mutual understanding and confidence in inspection process and share best practice knowledge
  - To Share Information on Interpretation of GCP
EMA-FDA Initiative Goals:

• To Conduct Periodic Information Exchanges on GCP-Related Activities
  – Streamline info sharing relevant to inspection (study/site selection) to improve coverage; communicate inspection outcome
  – Orphan designation, pediatric investigational plans, scientific advice

• To Conduct Collaborative GCP Inspections
  – Build mutual understanding and confidence in inspection process
  – Share best practice knowledge

• To Share Information on Interpretation of GCP
  – Inform regulatory guidance, legislation, policy and position papers
  – Identify and act on areas where greater convergence could be achieved to the benefit of the clinical research
Collaborative GCP Inspections

Pilot: September 2009 - March 2011
Post-Pilot: April 2011 – October 2014
Information Exchanges/Meetings

- Inspection plans & findings
- Lists of current applications
- Advisory Committee briefing documents
- Policies
- Guidances
- Procedures
- Templates

- Participation in annual EMA Inspectors Working Group training
- Basic & Advanced GCP Inspectors Training
- Inspectors’ local & teleconference presentations

- Minimized duplication of inspections
- Influenced inspection decision-making process (triggering/canceling inspections)
- Better understanding of each other’s inspection procedures & processes
- Improved inspection coverage
FDA’s Use of EMA GCP Inspection Reports

- If an EMA inspection report shows no serious problems, we may choose not to inspect the same site. Instead, we may inspect other sites to widen our coverage.

- If EMA’s inspection report shows serious problems, we may re-inspect the site or use the information to select additional sites.
The Way Forward

• Strengthen collaboration to help us identify & improve gaps
• Strengthen confidence building to reach mutual recognition & mutual reliance on each other’s inspection findings
• Expand the initiative outside the U.S. & E.U.
• Ongoing inspection collaboration and inspectional findings analysis
III. Enhancing Clinical Trial Quality:

- Clinical Trials Transformation Initiative (CTTI) Projects
- Risk-Based Monitoring
- ICH E6 Addendum Working Group
Clinical Trials Transformation Initiative

- **Overview:** public-private partnership established by FDA and Duke University in 2008
  - Members include stakeholders from government, industry, academia, patient and consumer representatives, clinical investigators, professional societies, and clinical research organizations

- **Goals:** To identify and promote practices that will increase the quality and efficiency of clinical trials

- **CTTI’s Vision:** A high quality clinical trial system that is patient-centric, efficient, and produces timely access to evidence-based prevention and treatment options
CTTI Projects – Quality by Design

“Quality” in clinical trials is defined as the absence of errors that matter

- Recommendations released

- Toolkit created to assist organizations put QbD into practice
  http://www.ctti-clinicaltrials.org/qbd
FDA Risk-Based Monitoring Guidance

Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)
August 2013
Procedural

OMB Control No. 0910-0733
Expiration Date: 03/31/2018
See additional PRA statement in section VII of this guidance.
FDA Risk-Based Monitoring Guidance

• Intent to assist sponsors in developing risk-based monitoring strategies and plans
  – Tailored to the specific human subject protection and data integrity risks of the trial
  – Focus on critical study parameters
  – Encourages use of a combination of monitoring activities, including a greater reliance on centralized monitoring practices, where appropriate

• Considers the protocol to be the blueprint for quality
  – Emphasizes need for a well-designed and articulated protocol

• Recommends
  – Conduct of a risk assessment to identify and evaluate risks to critical study data and processes
  – Monitoring plan be designed to address important and likely risks identified during risk assessment
ICH E6 Good Clinical Practice: Consolidated Guidance amendment

• FDA proposed update to address changes in clinical trials since original 1996 Guideline adopted

• To keep pace with the scale and complexity of clinical trials and to ensure appropriate use of technology
  – GCP should be modernized to enable implementation of innovative approaches to clinical trial design, management, oversight, conduct, documentation, and reporting that will better ensure human subject protection and data quality.

• E6(R2) Integrated Addendum open for comment through 31 January 2016  
IV. eSource = Paperless Clinical Trial
FDA eSource Guidance:
“…promotes capturing source data in electronic form…,”

[assists] “in ensuring the reliability, quality, integrity, and traceability of electronic source data.”

Use of Electronic Health Records (EHRs) in Clinical Research

Possible uses of EHRs in Clinical Trials:

• Retrospective analyses
  • Comparative Effectiveness Research (CER)
  • FDA’s Mini-Sentinel Initiative

• Subject recruitment tool

• “Auto-population” of a Subject’s data from EHR to eCRF and/or MedWatch/Adverse Event Report form
  – CDISC’s RFD Pilot Program
CDER’s Interests in Use of EHRs

• Drug Label available for view in EHR
• Automated Black-Box Warnings to Clinicians
• Electronic Prescribing capabilities
  – Alerts for Contraindications of Con-Meds
• Adverse Event Reporting facilitation
• Identifying Subjects actively enrolled in studies within EHRs
• Availability of Subjects’ complete EHR for review by FDA site inspectors
• Interoperability considerations
Additional Metrics Available at:  
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm256374.htm

- Sponsor/Monitor/CRO
- Institutional Review Boards
- Radioactive Drug Research Committee
- Postmarketing Adverse Drug Event Inspections
- Risk Evaluation and Mitigation Strategies
- Postmarketing Requirements
- Bioequivalence
- Good Laboratory Practice
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
- www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm