FDA Presentation - Society for Clinical Research Sites

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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 & Compliance Trends

II. Globalization of Clinical Studies

III. EMA-FDA Collaboration GCP Inspections

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

V. Trends in Use of Technology to Support Clinical Trials (e.g.-eSource & EHRs)
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 come from any source
  – Complaint (“For Cause” Inspection)
  – ~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 2004 – FY 2013

*Based on inspection start date – [OSI database as of January 31, 2014]
- 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 Inspections*: CDER 2004-2013

- U.S. & Non-U.S. Investigators
- Non-U.S. Investigators
- Sponsor/CRO

Yearly inspections count from 2004 to 2013.
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
• 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 2013)

349 CI Inspections

- No Action Indicated: 54%
- Official Action Indicated: 3%
- Voluntary Action Indicated: 43%

*Based on Letter Issue date; Includes OAI Untitled Letters, [OSI database as of January 31, 2014]
Frequency of Clinical Investigator-Related Deficiencies Based on Post-Inspection Correspondence Issued*
CDER, FY 2013

Domestic CI Deficiencies

- Protocol: 34%
- Records: 21%
- Consent: 9%
- Drug Accountability: 5%
- Adverse Events: 5%
- IRB Communication: 3%

Foreign CI Deficiencies

- Protocol: 33%
- Records: 25%
- Consent: 8%
- Drug Accountability: 4%
- Other: 2%
- Adverse Events: 2%

*Based on letter issue date; Inspections may have multiple deficiencies, [OSI database as of January 31, 2014]
Note: this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed in FY2013.
Frequency of Clinical Investigator Related Deficiencies Based on Post-Inspectional Correspondence Issued: Official Action Indicated (OAI) Final Classification*
(CDER, FY 2013)

*Based on letter issue date. Inspections may have multiple deficiencies. Includes OAI untitled letters. [OSI database as of January 31, 2014] Note that this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed in FY2013.
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 of Clinical Studies

- **Subjects Enrolled**
  - Africa: 1%
  - Australia: 1%
  - Middle East/Central Asia: 2%
  - Canada: 4%
  - Latin America: 7%
  - Asia/Pacific: 8%
  - Eastern Europe: 16%
  - Western Europe: 17%
  - United States: 39%

- **Sites**
  - Africa: 1%
  - Australia: 2%
  - Middle East/Central Asia: 2%
  - Canada: 4%
  - Latin America: 7%
  - Asia/Pacific: 10%
  - Eastern Europe: 15%
  - Western Europe: 20%
  - United States: 44%
Global Coverage of FDA GCP Inspections

*Conducted by FDA/CDER from 1984 through Sept 3, 2013; based on inspections with a start date in the CDER/OC/OSI database*
Highest Enrollment: Top 10 Non-US Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Enrollment</th>
<th>% of Total Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>38109</td>
<td>4.0%</td>
</tr>
<tr>
<td>Germany</td>
<td>37830</td>
<td>4.0%</td>
</tr>
<tr>
<td>Russia</td>
<td>35304</td>
<td>3.7%</td>
</tr>
<tr>
<td>Poland</td>
<td>28470</td>
<td>3.0%</td>
</tr>
<tr>
<td>India</td>
<td>22550</td>
<td>2.4%</td>
</tr>
<tr>
<td>Brazil</td>
<td>20272</td>
<td>2.1%</td>
</tr>
<tr>
<td>Ukraine</td>
<td>18814</td>
<td>2.0%</td>
</tr>
<tr>
<td>China</td>
<td>18122</td>
<td>1.9%</td>
</tr>
<tr>
<td>Argentina</td>
<td>17980</td>
<td>1.9%</td>
</tr>
<tr>
<td>Czech Rep</td>
<td>17844</td>
<td>1.9%</td>
</tr>
</tbody>
</table>
Domestic vs. Foreign Inspections*
(CDER, FY 2009 - FY 2013)
Clinical Investigator Inspections by Location* (CDER, FY 2013)

*Based on inspection start date – [OSI database as of January 31, 2014]
III. EMA-FDA Collaboration
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
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 Inspections

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

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

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

**Results**
- 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 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.
IV. 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 Project Roster 2014
### GCP Training

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<tr>
<th>Objectives</th>
<th>Deliverables</th>
<th>Anticipated Impact</th>
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</table>
| - To improve the efficiency of GCP training imparted to investigators and site personnel conducting clinical trials | - Summary of current practices and issues related to GCP training  
- Recommendations on key elements of GCP training content and frequency  
- Recommendations to facilitate more efficient GCP training | - Improve the efficiency and reduce the cost of clinical trials by streamlining the GCP training requirements |
# Site Performance & Quality (PI Turnover)

<table>
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<tr>
<th>Objectives</th>
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<tbody>
<tr>
<td>- Obtain a more thorough understanding of issues underlying investigator attrition</td>
<td>- Recommendations to increase the number of experienced principal investigators participating in clinical trials</td>
<td>- There will be a decreased attrition rate of experienced clinical investigators leading to increased efficiency in clinical trial start-up and conduct.</td>
</tr>
</tbody>
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New Project: Facilitating Remote Clinical Trials

Technical/Clinical
- Catalog remote technologies used for data collection and communication with potential to facilitate trial conduct
- Outline best practices for conducting trials using such technologies
- Identify approaches to ensure integrity of remotely collected data

Fostering Patient Participation
- Assess patients’ interest and understand factors that impact on their willingness to participate in non-traditional trials
- Develop strategies to address barriers to patient acceptance, enrollment, and retention

Legal and Regulatory Issues
- Catalog federal and state laws and regulations that impact trial conduct
- Identify any additional perceived legal barriers to conducting off-site trials
- Develop framework for conduct of remote trials
CTTI Projects

- Quality by Design/Quality Risk Management in Clinical Trials
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: 03/31/2016
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.
V. eSource = Paperless Clinical Trail
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