



U.S. Food and Drug Administration

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Good Clinical Practice (GCP) Roles, Responsibilities and Inspections

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Disclaimer

- This communication constitutes an informal communication that represents the best judgment of the speaker at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

CDER's BioResearch Monitoring ("BiMo") Inspection Program

- Evaluates adherence to applicable regulations with respect to:
 - Good Clinical Practice (GCP)
 - Clinical Investigators
 - Sponsors, Monitors, Contract Research Organizations
 - Institutional Review Boards
 - Good Laboratory Practice (GLP)
 - *In vivo* Bioequivalence (BE)

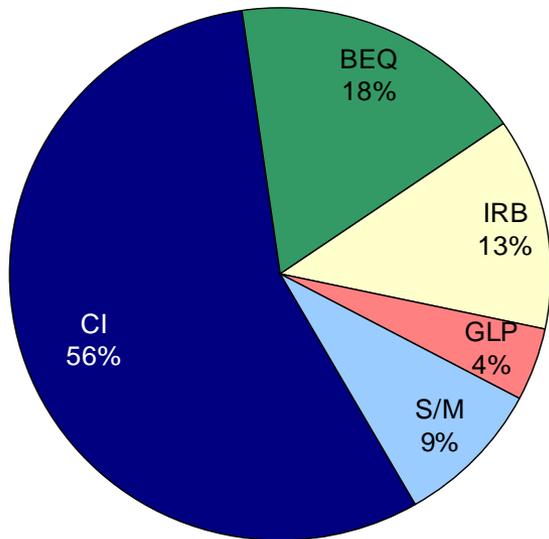
Compliance Program Guidance Manuals (CPGM)

- Provide guidance and instructions to FDA staff conducting inspections
 - 7348.001 In Vivo Bioequivalence
 - 7348.808 Good Laboratory Practice (Nonclinical Laboratories)
 - 7348.809 Institutional Review Board
 - 7348.810 Sponsors, Contract Research Organizations, and Monitors
 - 7348.811 Clinical Investigators

<http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/default.htm#bimo>

Bioresearch Monitoring Program Inspections* (CDER, FY 2009-2010)

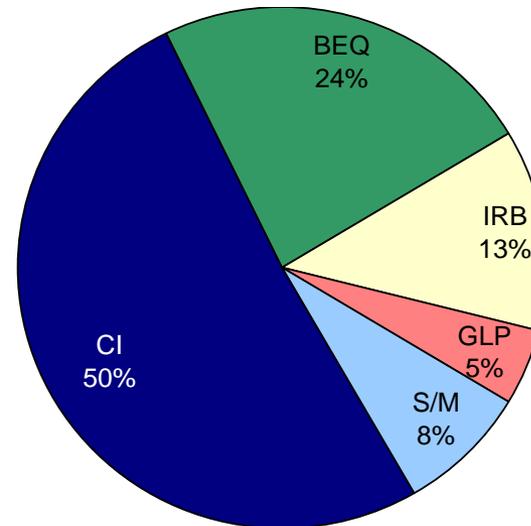
FY 2009 (N= 843)



CI = 474
BEQ = 150
IRB = 107
GLP = 37
S/M = 75

Total 843

FY 2010 (N= 778)



CI = 398
BEQ = 183
IRB = 98
GLP = 37
S/M = 62

Total 778

*Based on inspection start date [4/01/2011]

OSI's Role in CDER's GCP Inspections

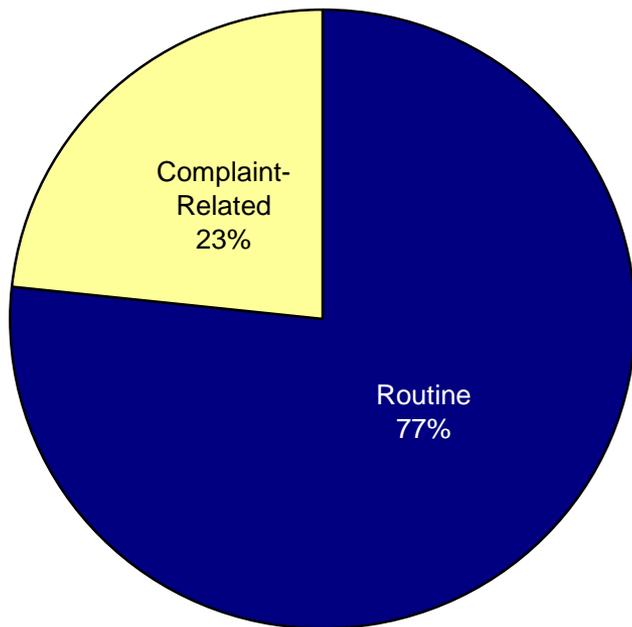
1. Determine need for inspection
2. Assign and perform inspections through Office of Regulatory Affairs (ORA)
3. Critically evaluate ORA inspectional findings and proposed classification (NAI, VAI, OAI)
4. Make final classification of the inspection
5. Prepare written communication to inspected party
6. Provide a summary of inspectional findings and recommendations to OND Review Division regarding the reliability of data

When Are Inspections Needed?

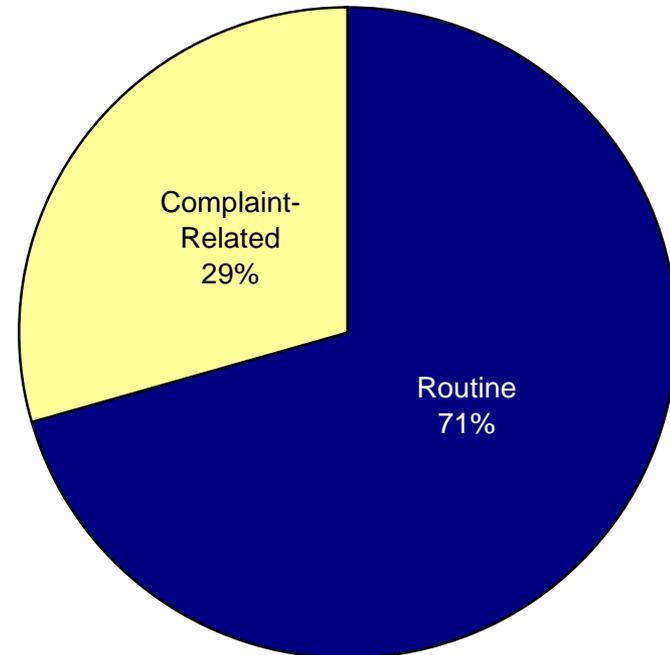
- For Cause
 - To evaluate allegations that raise concerns about data integrity or concerns about compromise of the rights, welfare, and safety of study subjects
- Marketing application related
 - All New Molecular Entities (NMEs)
 - Clinical Investigators
 - Sponsors / CROs
 - NDA/BLA Supplements
 - Inspections not always required
 - Significant expansion of the indication
 - Significant expansion of the patient population
 - Significant safety concern(s)
 - Data integrity issues

Clinical Investigator Inspection Assignments* (CDER, FY 2009-2010)

FY 2009 (N= 496)



FY 2010 (N= 473)

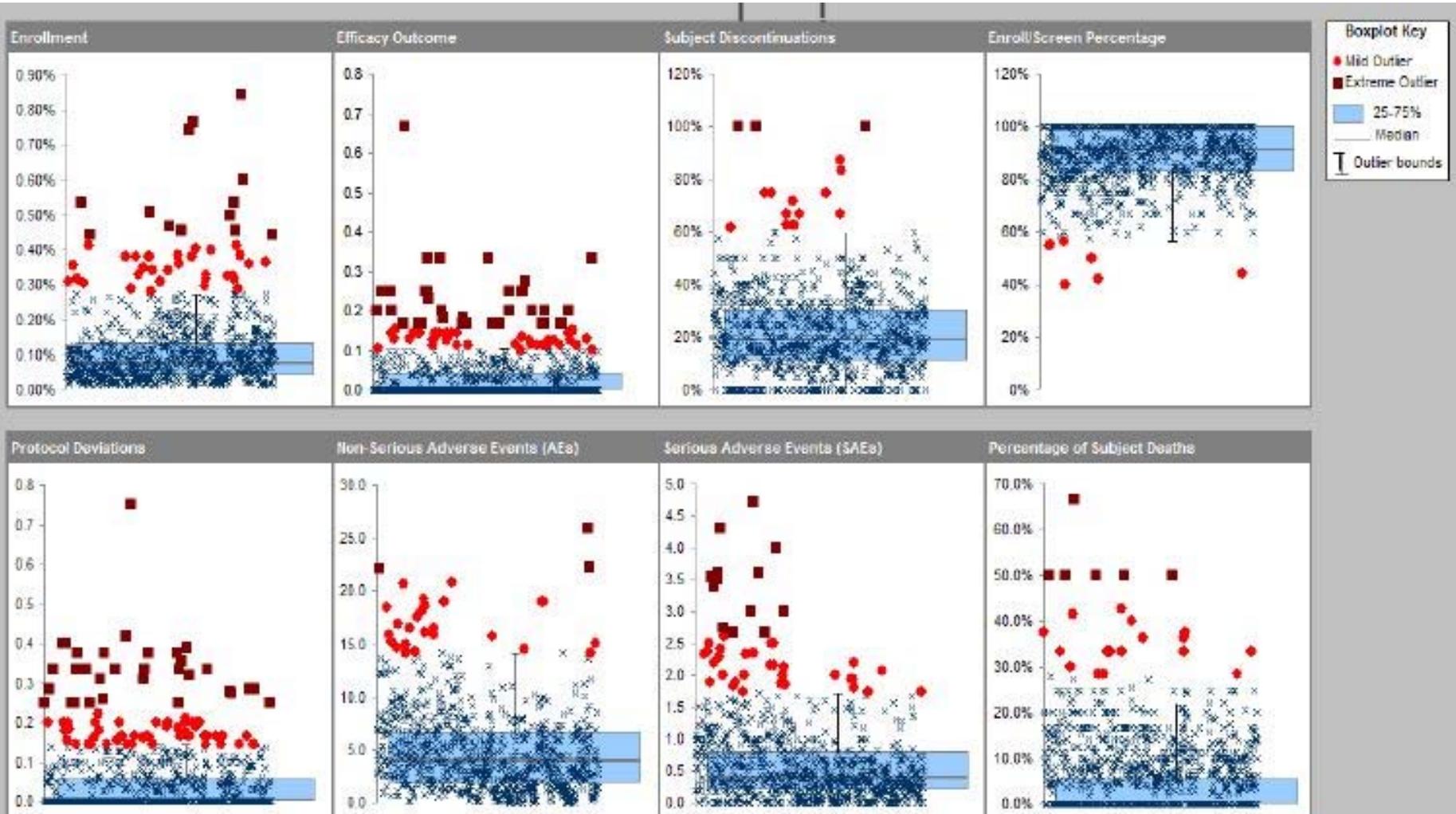


*Based on assignment issued date [4/01/2011]

Rationale For Clinical Investigator Selection

- A specific safety concern at a particular site or sites
 - Based on review of adverse events (AEs, serious AEs, 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 sites based on review of
 - financial disclosures,
 - protocol violations,
 - study discontinuations,
 - safety and efficacy results

CDER Risk-based Site Selection Tool Pilot



Inspection Conduct

- OSI assigns and performs inspections through the Office of Regulatory Affairs (ORA)
- OSI reviewers or other subject matter experts from CDER may accompany ORA investigators on inspections on an as needed basis

Post-Inspection Outcome and Evaluation

- ORA investigator may issue a Form FDA 483 at close of inspection, which lists inspectional observations (immediately available via FOI)
- ORA investigators prepares an Establishment Inspection Report (EIR)
 - Includes exhibits supporting all observations including deficiencies
 - Recommends inspection Classification (NAI/VAI/OAI)
 - Submitted to Division of Scientific Investigation for review

Post-Inspection Outcome and Evaluation

1. OSI reviews EIR and pertinent exhibits
2. OSI provides a summary of inspectional findings and recommendations to Office of New Drugs (OND) Review Division regarding the reliability of data generated by inspected entities:
 - Did observed violation affect:
 - Efficacy or safety data?
 - Subject safety, rights, or welfare?
 - Frequency of observed deficiency
 - Source of observed deficiency:
 - Isolated occurrence at CI site?
 - Systemic issue relating to study planning or oversight?
3. OSI makes final classification of the inspection and prepares written communication to inspected party

Inspection Follow-up

- At the inspection close-out meeting with FDA, use this opportunity to ask questions about the observations, request clarification, and inform the inspection team what corrections have been or will be made
- FDA will consider any written response received within 15 business days of the issuance of a 483 when determining appropriate action
- Recommendations for an effective response:
 - Assess each observation
 - Focus on the regulatory requirement(s) associated with the observation
 - Consider root-cause analysis – are there system-wide and global implications
 - Be specific (e.g. observation-by-observation), complete and realistic
 - Provide time frames for correction
 - Provide method of verification and/or monitoring for corrections

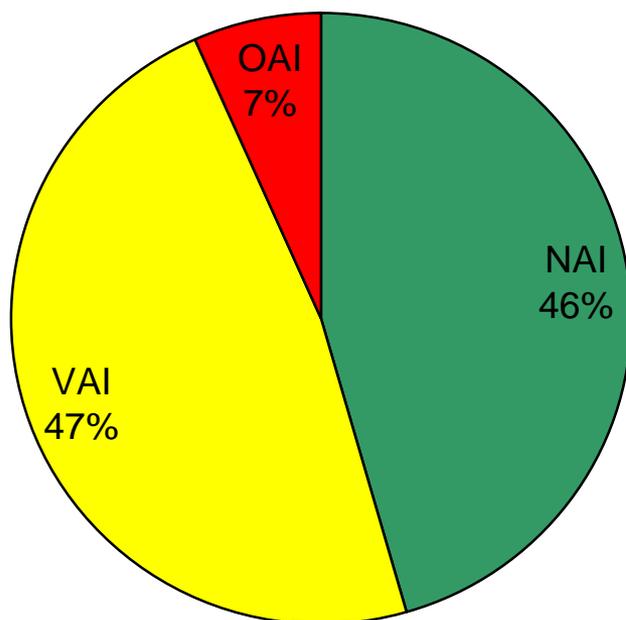
Inspection Outcomes

- **NAI:** No Action Indicated
- **VAI:** Voluntary Action Indicated
- **OAI:** Official Action Indicated

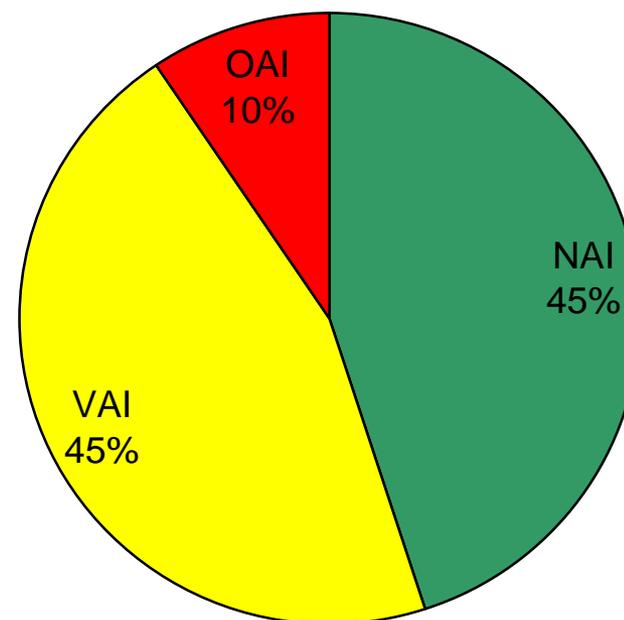
*Based on Letter Issued Date

Example: Clinical Investigator Inspections Final Classification* (CDER, FY 2009-2010)

FY 2009 (N= 460)



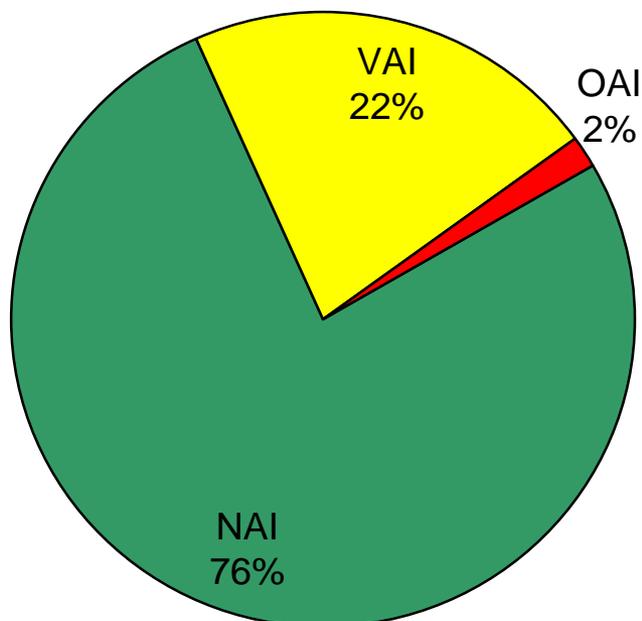
FY 2010 (N= 418)



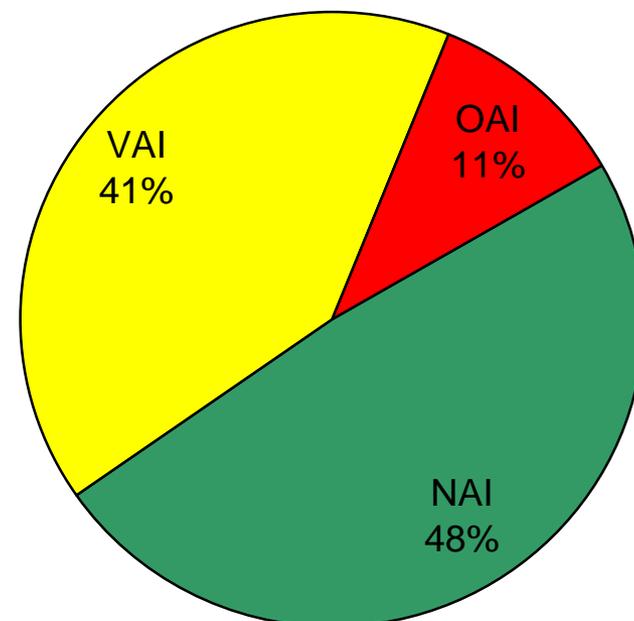
*Based on letter issue date; Includes OAI Untitled Letters, [04/01/2011]

Sponsor/CRO Inspections Final Classification* (CDER, FY 2009-2010)

FY 2009 (N=60)



FY 2010 (N=66)

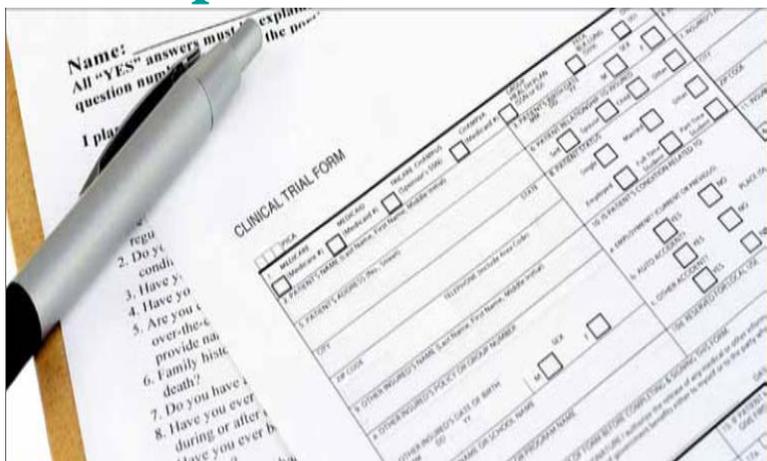


*Based on letter issue date; Includes OAI Untitled Letters, [4/01/2011]

Role of Inspection Results

- In aggregate, inform OSI/review decisions about data integrity and approvability for the application as a whole
 - Isolated occurrences at individual clinical sites, effectively addressed?
 - Or systemic issues relating to study planning or oversight?
- Public Health Impact
 - Regulatory Action by FDA/OSI
 - Warning Letters
 - Notice of Initiation of Disqualification Proceedings
 - Disqualification of CI
 - Criminal Investigation by Office of Criminal Investigations (OCI)

Impact of Non-Compliance¹



Current Trends in FDA Inspections Assessing Clinical Trial Quality: An Analysis of CDER's Experience

by Ann Meeker-O'Connell and Leslie K. Ball

Analysis of 104 original NDAs and sNDAs and BLAs inspected from 1Q FY2010 through 1Q FY2011

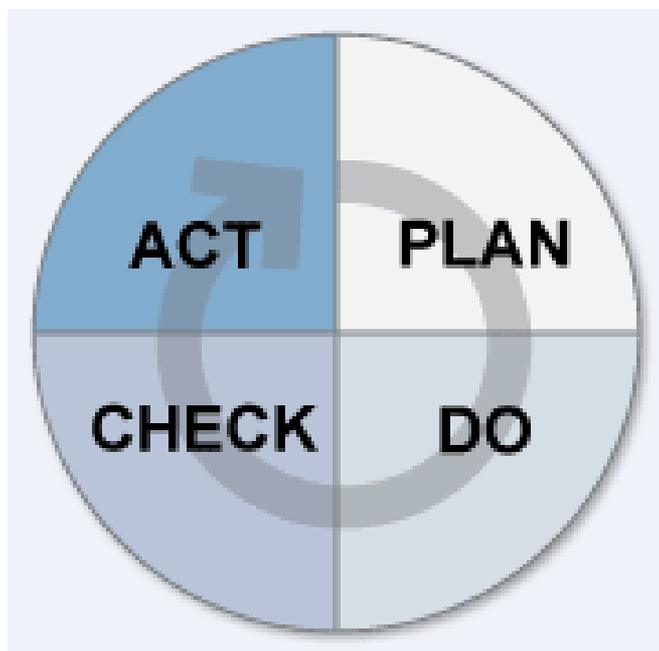
- OSI assessment focused on reliability of data for key efficacy and safety parameters
- OSI recommended the rejection of data for 13 of the 333 (4%) of clinical investigators inspected
- Resulted in delays in approval/CR letters for 5 of 104 (4.8%) applications

1. Meeker-O'Connell and Ball
FDLI Update 2011;2: 8-12

Impact of Non-Compliance (cont.)

- For these 5 applications, data integrity concerns led to refusals to file, rejection of data, and/or request for actions to demonstrate data reliability
 - Resulted in Complete Response letter, third party audit, additional inspections, reanalysis
- Some systemic errors persisted due to deficits in sponsor monitoring, but had a root cause in study design and planning
- In 2/5 cases, concerns arose **from internal data management processes at the sponsor and CRO**, *not from errors at the site*
- Sponsors who successfully address data quality concerns demonstrate a comprehensive approach

Successful Inspections and Quality as a Culture



Plan – Quality objectives and metrics; risks to quality; quality management plans

Do – Study conduct

Check – Measure/monitor

Act – Respond to deviation

http://www.iso.org/iso/catalogue/management_standards/understand_the_basics.html

Information Resources

OSI

<http://www.fda.gov/cder/offices/dsi>

List of Disqualified or Restricted Investigators

http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

OSI Warning Letters Archive

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm247881.htm>

NIDPOE Letters

<http://www.fda.gov/foi/nidpoe/default.html>

Debarment List

http://www.fda.gov/ora/compliance_ref/debar/default.htm