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Good Clinical Practice Assessment of Data Reliability in Registration Trials

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Outline

- Medical Product Approval and Reliability of Data
- Considerations and Milestones for Clinical Inspections
- GCP Related Inspections and Deficiencies
- Take Home Points

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Medical Product Approval

- Medical product approval depends on:
  - Demonstration of the effectiveness and safety through adequate and well-controlled clinical trial

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Reliability of Clinical Trial Data

- Reliability of clinical trial data is crucial to the approval decisions of new medical products applications

- Source data should be:
  - Attributable, Legible, Contemporaneous, Original, Accurate and Complete

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FDA's Clinical Trial Inspection Program

To determine

- Human research subjects protection
- Data integrity and reliability
- Regulatory compliance

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CONSIDERATIONS AND MILESTONES FOR CLINICAL INSPECTIONS

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Milestones for GCP Inspections

Applicant submits NDA/BLA

Site Selection

Reviewers identify site for Inspection

Inspection Assignment

Reviewers issue inspection assignment to field inspectors and provide background material needed for inspection

Inspection

FDA field investigators conduct inspections

Recommendation

- Recommendations on data reliability and quality will be made
- Post-inspectional correspondence to the inspected entity

Approval Decision

On-site data-audit inspections are conducted to verify the quality and integrity of data and to protect the rights and welfare of human research subjects.

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Inspection Targets

- Clinical Investigator (CI)
- Sponsor/Monitor (S/M)
- Contract Research Organization (CRO)
- Institutional Review Board (IRB)

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Considerations for GCP Inspections

- **Application Level**
  - Indication
  - Population
- **Study Level**
  - Importance of the study for the intended claim
- **Site Level**
  - Contribution of data
  - Outliers (efficacy and safety data)
  - Concern of scientific misconduct
  - Prior inspectional history

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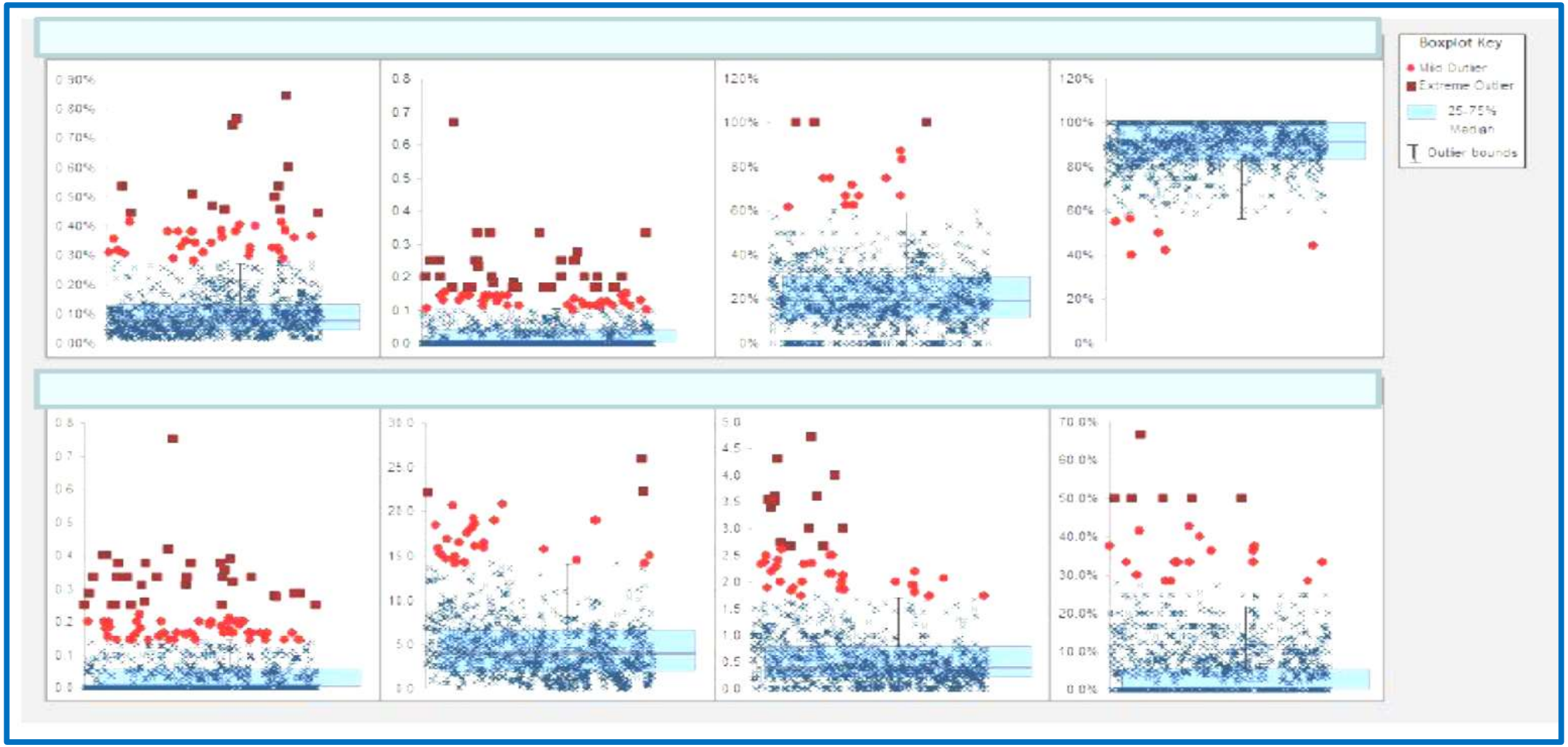
Clinical Investigator Inspection Tool – Outlier Displays



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FDA Inspection of Clinical Investigator Sites

- Source data verification
- Assess CI's
  - Qualifications and oversight of study
  - Knowledge of the protocol
  - Adherence to study protocol
  - Recordkeeping
  - Test article accountability
- Evaluate informed consent/IRB approval
- Communications with monitors/sponsors
- AE reporting

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FDA Inspection of Sponsor/CRO Sites

- Review sponsor's:
  - Roles/responsibilities
  - Oversight of the target study[ies]
  - Handling of study data
  - Handling/accountability of investigational product
  - Adverse event reporting
  - Study monitoring, relevant communications (with investigators, with CROs)
  - Recordkeeping and record retention

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Post-Inspectional Activity

- Review and evaluate inspectional observations, evidence provided in inspectional report
- Provide recommendations to CDER review divisions regarding data reliability and integrity in clinical inspection summaries (CIS)
- Issue post-inspectional correspondence to inspected entity

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Impact of Inspectional Findings

Impact on Review

- Additional Inspections
  - CIs, sponsors/monitors, CROs
- Third Party Audits
- New Studies

Impact on Approval

- Depending on the scope, nature and risk
  - Approval may be delayed for further inspections and analyses
  - Post-marketing studies may be required
- Non-approval (Complete Response)

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U.S. FOOD & DRUG ADMINISTRATION

GCP Related Inspections and Deficiencies

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Types of GCP Related Inspections, CDER FY 2015-2017

Based on Post-Inspection Correspondence Issued (FY 2015-17) for total of 1767inspections

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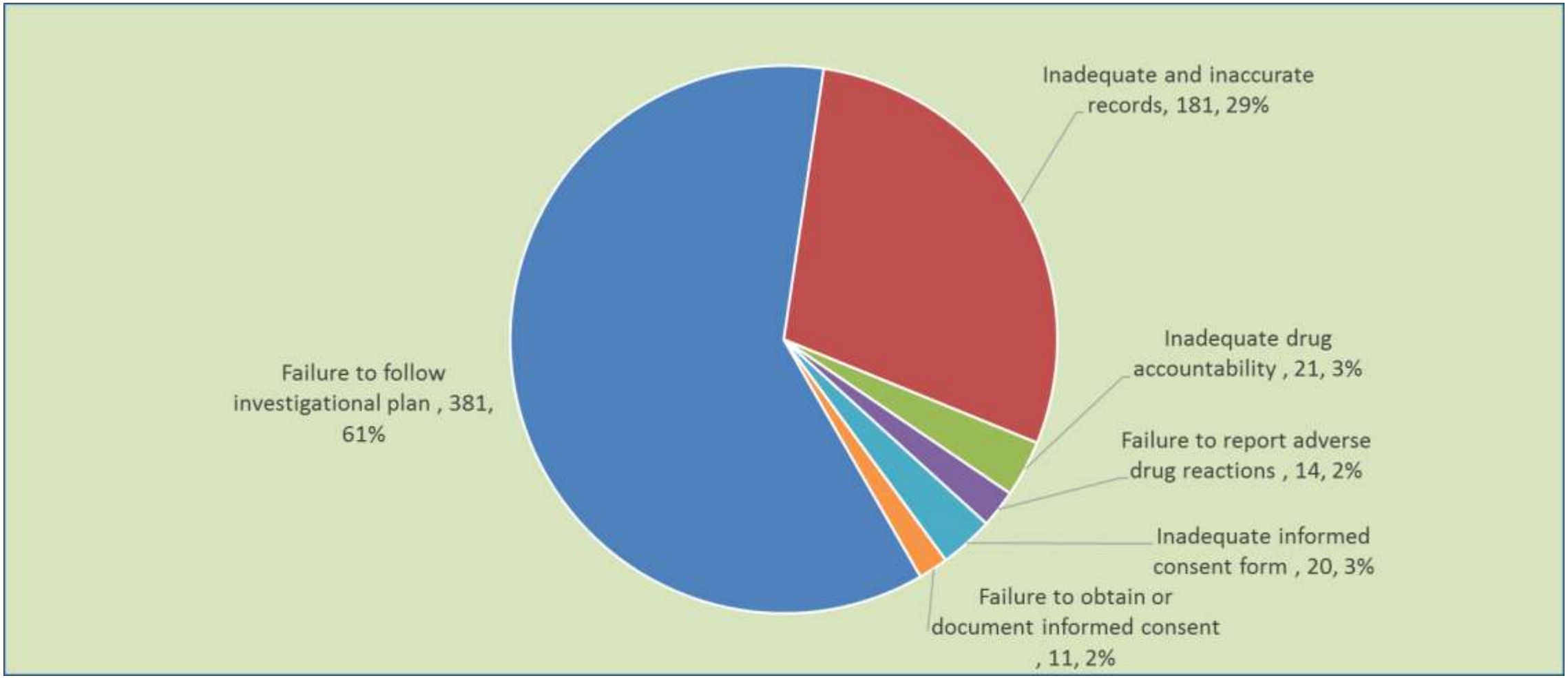
Frequency and Types of the Common Clinical Investigator GCP Deficiencies



Based on Post-Inspection Correspondence Issued (FY 2015-17) for total of 628 inspections

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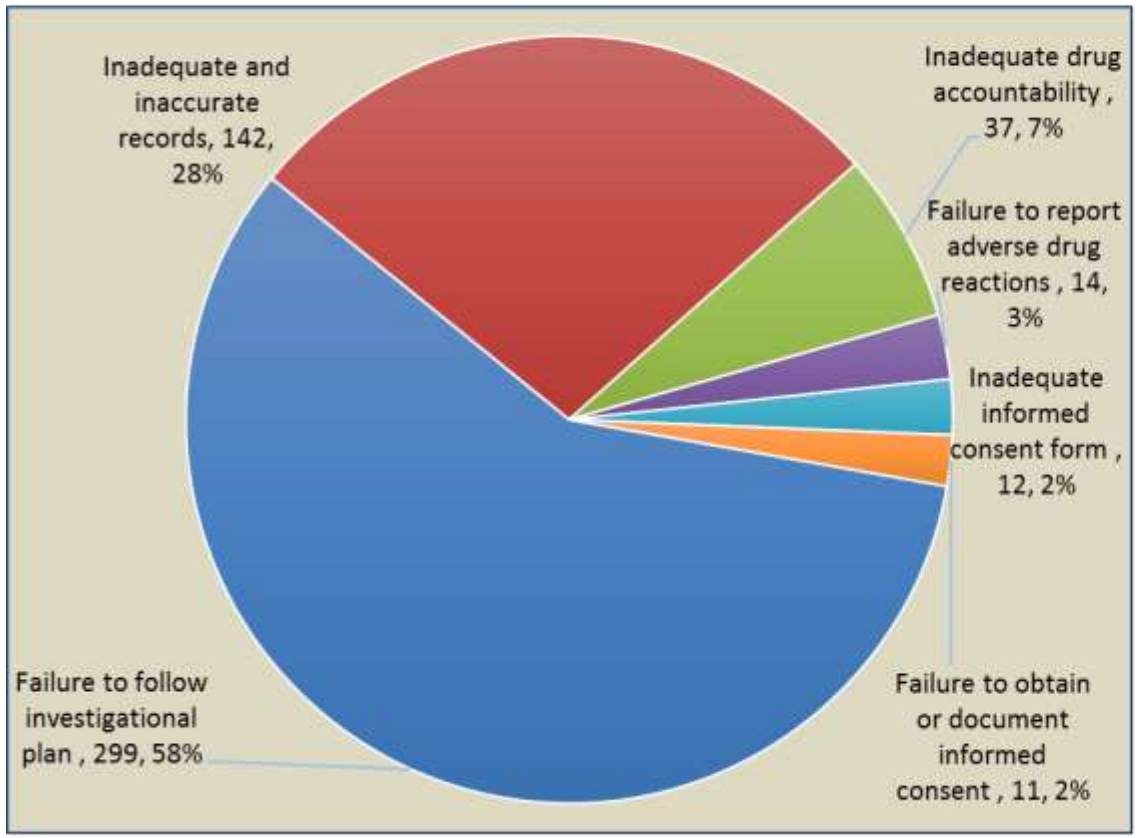
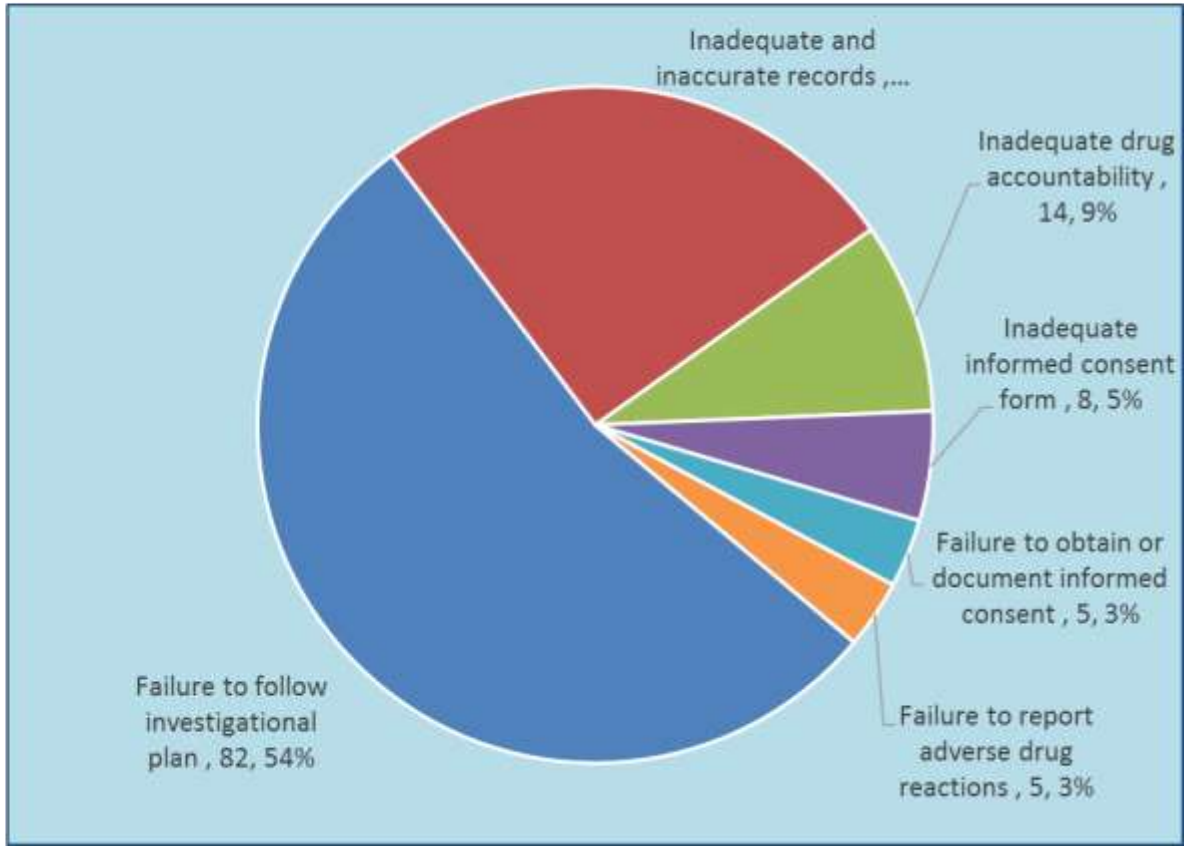
Common Clinical Investigator GCP Deficiencies
U.S. vs. Non-U.S.

U.S. Inspection



Non-U.S Inspections



Based on Post-Inspection Correspondence Issued (FY 2015-17) for total of 628 inspections

Common Clinical Investigator-GCP Related Deficiencies

- Failure to Follow Investigational Plan
- Inadequate and Inaccurate Records
- Inadequate Drug Accountability

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Common Sponsor GCP Related Deficiencies

- Inadequate Monitoring
- Failure to Follow Investigational Plan
- Inadequate and Inaccurate Records

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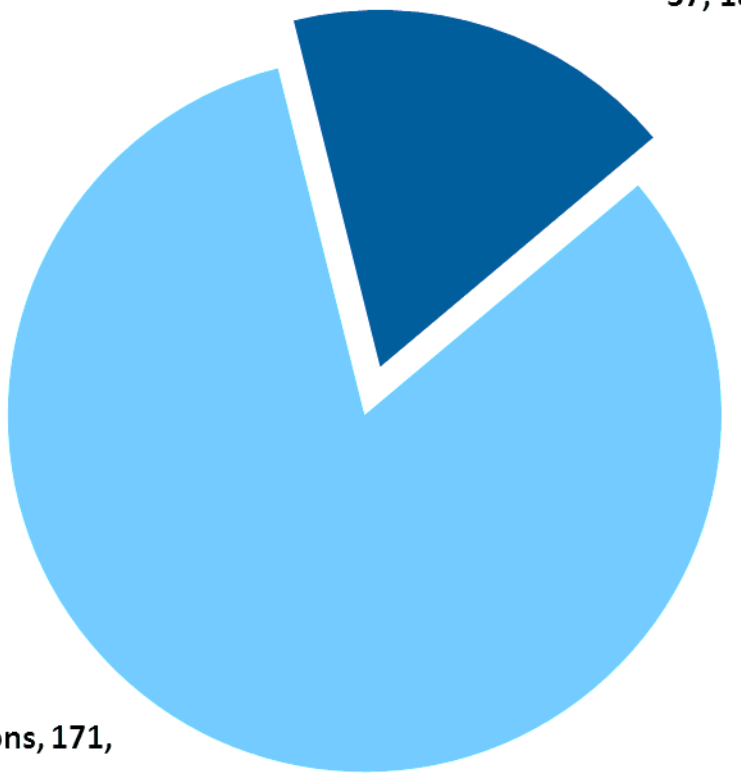
Recommendations to Review Divisions in CDER FY2015-2016

37 of 208 CIS had GCP Related Recommendations

= 18%



Recommendations include:

- Sensitivity Analysis
- Additional inspections
- Excluding data from site
- New study
- Independent third party audits

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Take Home Points

- GCP assessment through on site inspection helps to ensure that the safety and efficacy of investigational new medical products are accurately assessed

- It is important have clinical development programs that reliably produce high quality data (the absence of errors that matter) acquired in a manner that has not jeopardized the rights, safety, or welfare of trial participants

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