U.S. FOOD & DRUG ADMINISTRATION

FDA Perspective on International Clinical Trials

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Outline

1. Global Distribution of Clinical Trial Data in FDA Submissions
2. Acceptance of Clinical Trial Data
3. Considerations for Inspections
4. GCP Inspection Findings and Metrics

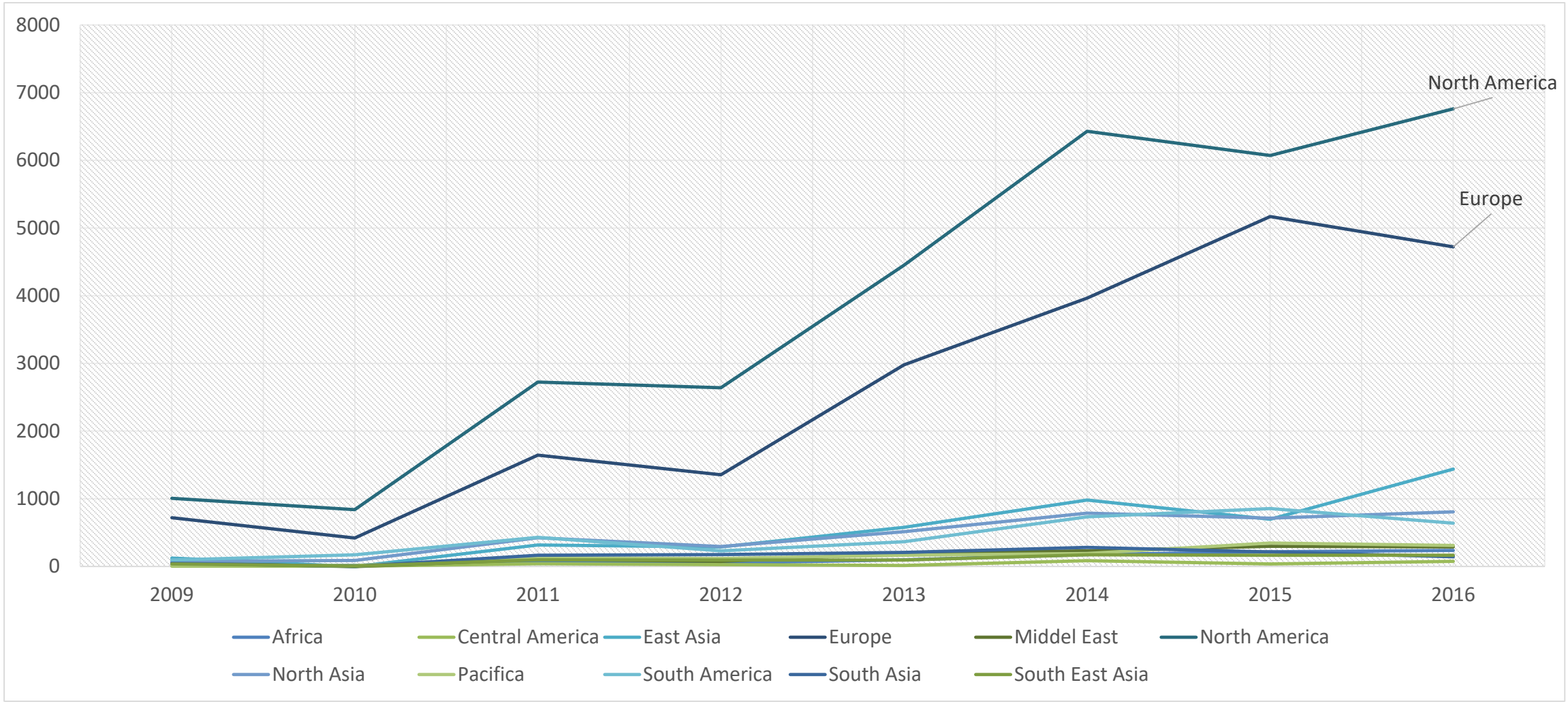
Disclaimer

The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration

International Clinical Trials

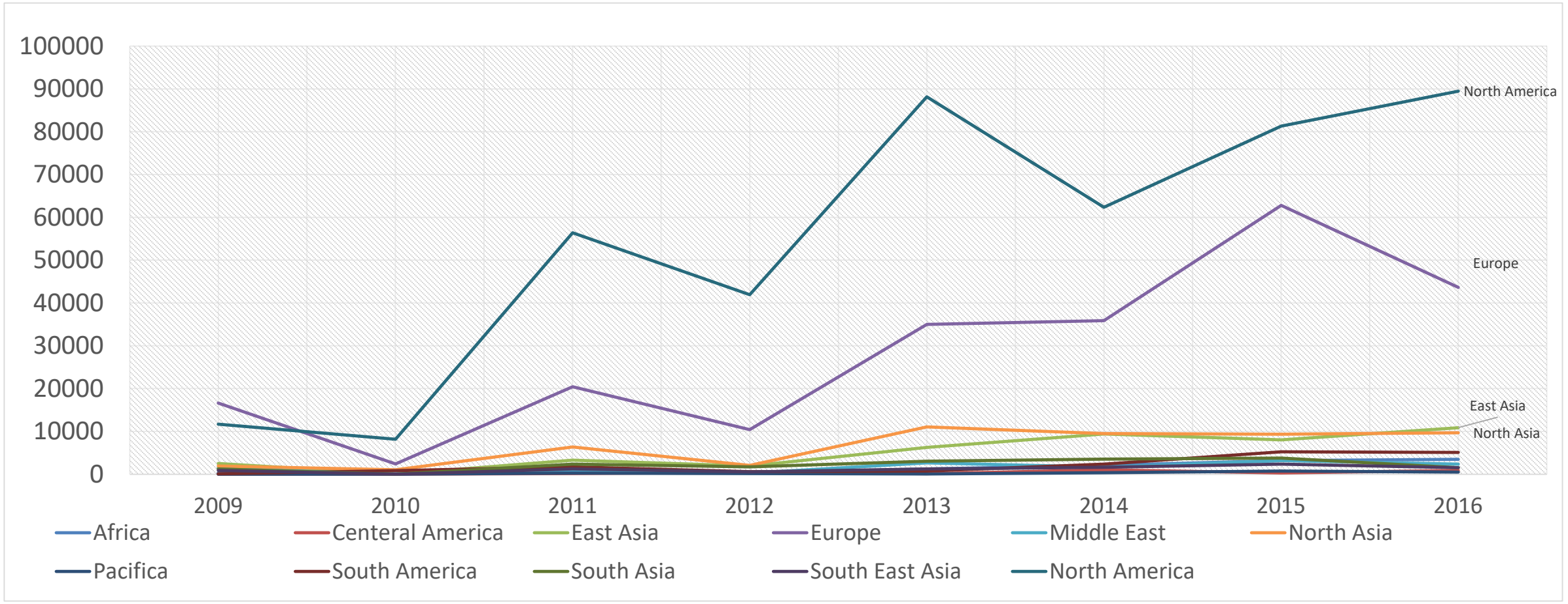
- The number of international sites and trial participants contributing data to support U.S. marketing applications for drug approval is increasing

Number of Clinical Trial Sites by Region Over Time



Source: CISST Database for 2009-2016

Number of Clinical Trial Participants by Region Over Time



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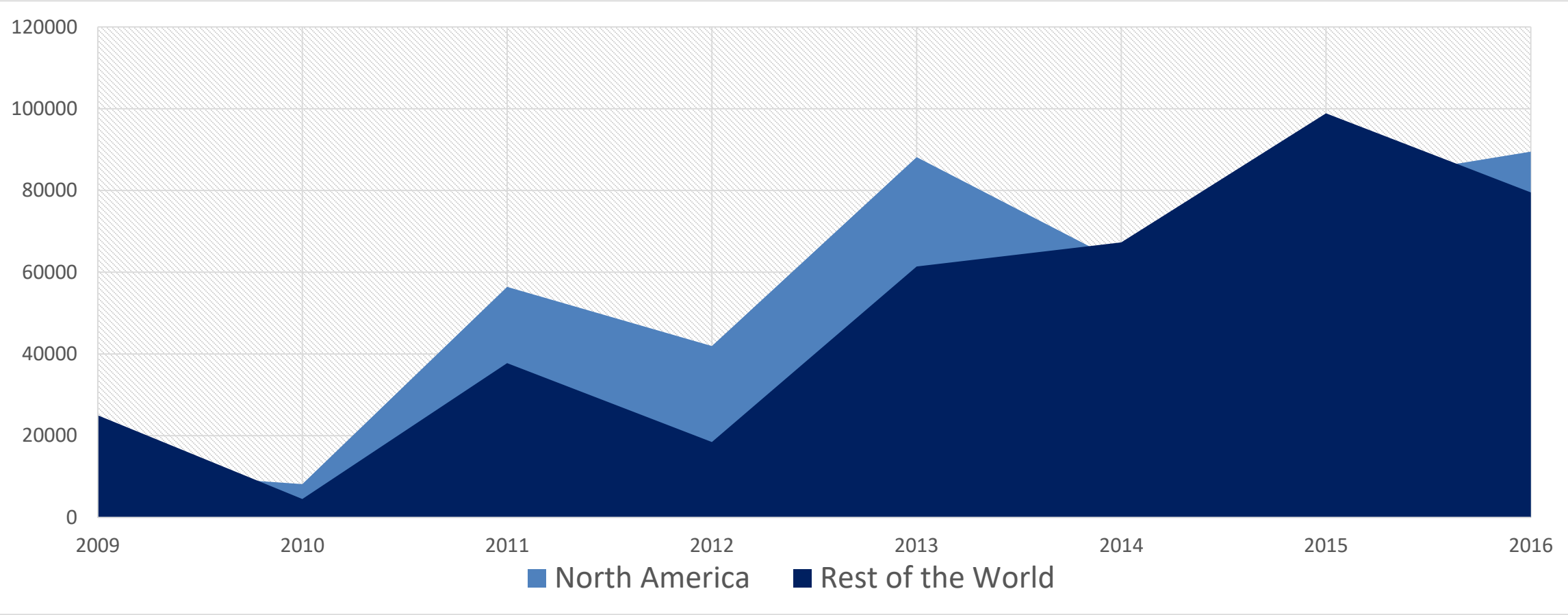

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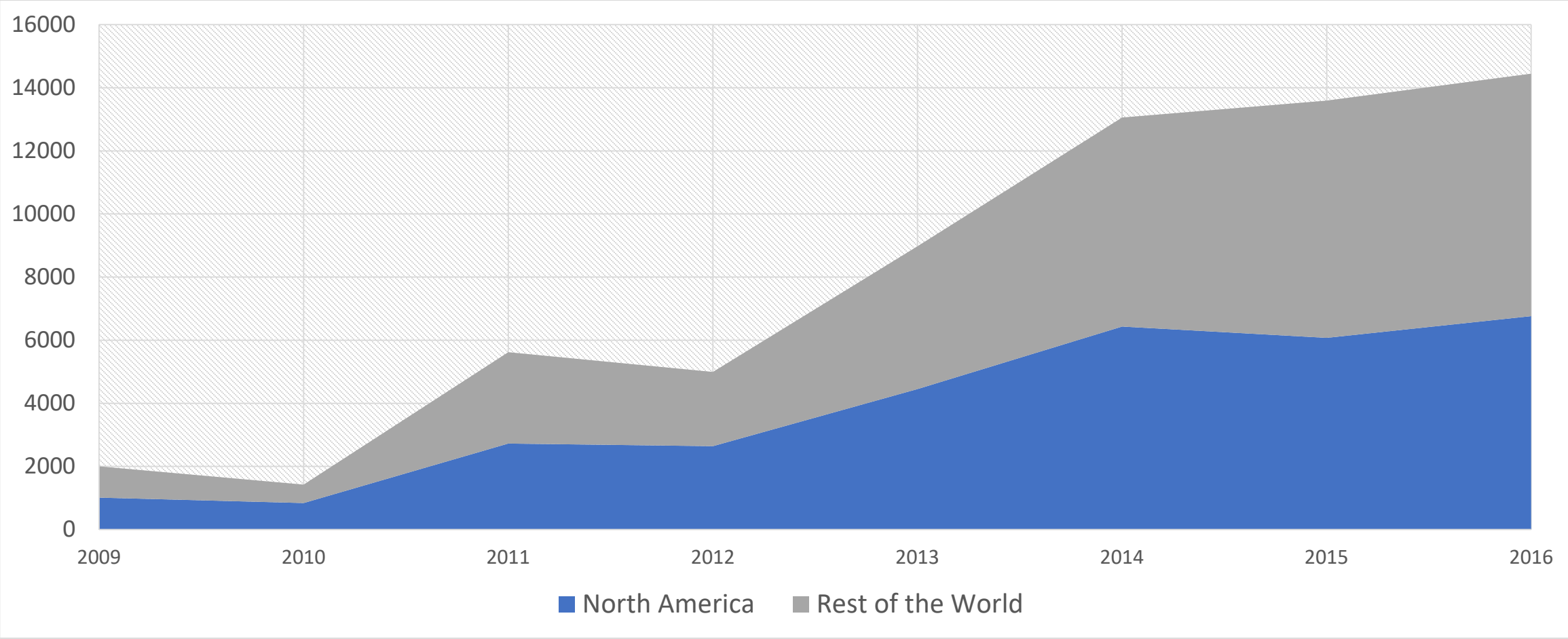


Source: CISST Database for 2009-2016

FDA Acceptance of International Clinical Trial Data

Acceptance of International Data

- FDA accepts data from studies conducted under Investigational New Drug (IND) application that adhere to IND regulatory requirements
- FDA also accepts data from foreign studies not conducted under an IND, but meeting criteria specified in FDA regulations
  - Study well designed and conducted
  - Performed by qualified investigators
  - Conducted in accordance with **Good Clinical Practices**
  - FDA is able to **validate data through onsite inspection** if necessary

Good Clinical Practice (GCP)

- Defined as the standard for the **design, conduct, performance, monitoring, auditing, recording, analysis, and reporting** of clinical trials in a way that provides assurance that the data & reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected

- In light of diverse regional practices, ensuring high quality of study design and conduct in accordance with E6 (GCP) in all regions are of paramount importance to ensure study results are reliable.

VALIDATION OF DATA THROUGH ONSITE INSPECTION

Medical Product Approval by FDA

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

Reliability of Clinical Trial Data

- Data in support of marketing applications should be complete, consistent, reliable, accurate and trustworthy

- Data should fulfill fundamental elements of data integrity (ICH):
  - Attributable, Legible, Contemporaneous, Original, Accurate

FDA's On-Site Data Audit

It determines the adequacy of

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

On-Site Data Audit Milestones

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

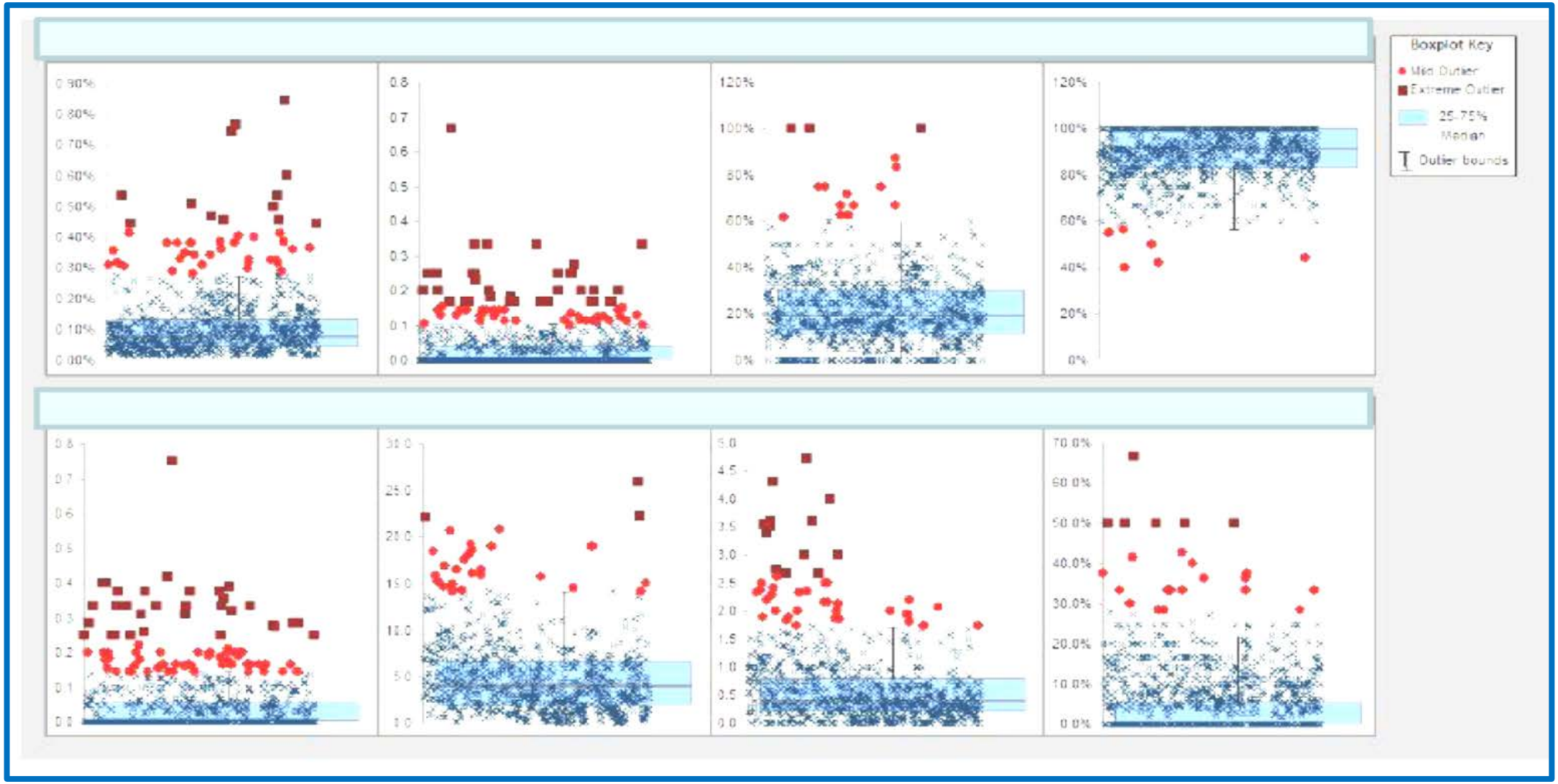
Approval Decision

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.

Considerations for GCP Inspections

- **Application Level**
  - Submission type, Population vulnerability, Severity of disease, Target population size, Impact of indication
- **Study Level**
  - Pivotal status, Trial design, Geography of the trial
- **Site Level**
  - Contribution of data
  - Outliers (efficacy and safety data)
  - Concern of scientific misconduct
  - Prior inspectional history , Financial Disclosure

Clinical Investigator Inspection Tool Outlier Displays



What does the FDA review at Clinical Investigator Sites?

- Verify source data
- 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
- Evaluate communications with monitors/sponsc
- Evaluate SAE/AE reporting

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

Impact of GCP Inspectional Findings

Impact on Review

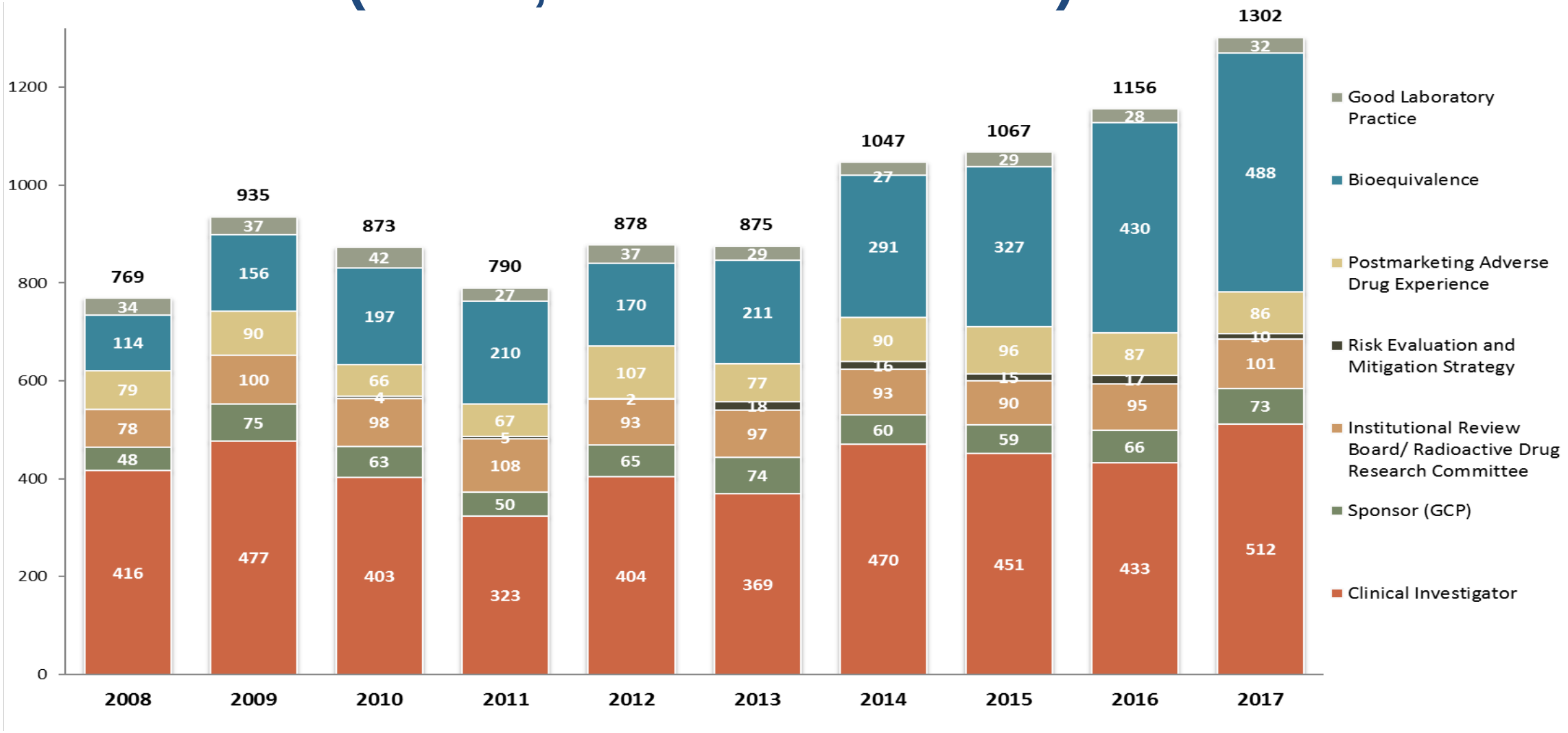
- Additional Inspections
  - CIs, sponsors/monitors, CROs
- Third Party Audits
- New Studies

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)

GCP Inspection Findings and Metrics

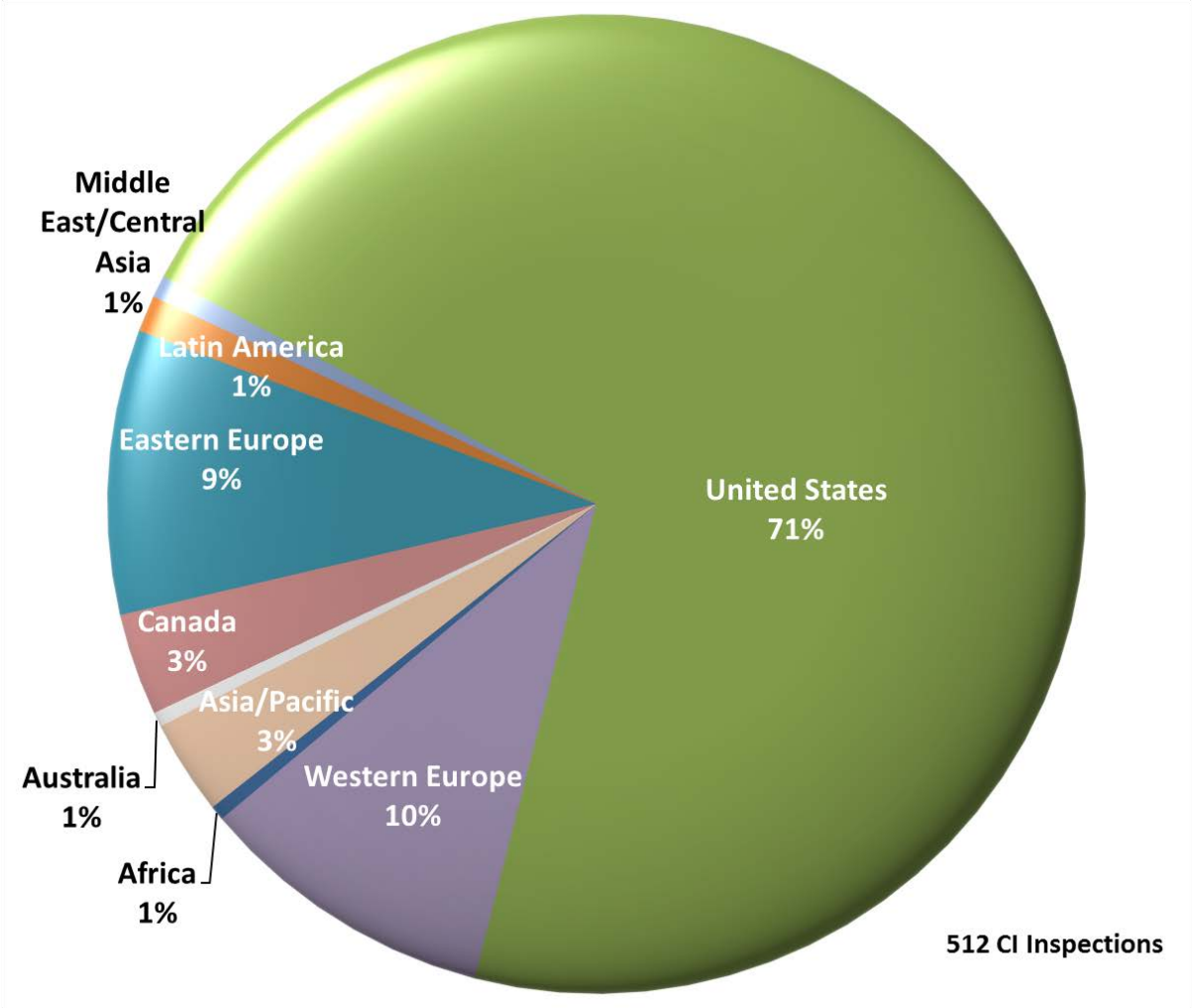
Application-Inspections Overseen by OSI/OSIS* (CDER, FY 2008 - FY 2017)



*Based on inspection start date – [Complis database as of December 29, 2017]

- Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
- BEQ Application-Inspections accomplished with 289 FY17 Site Visits
- Good Laboratory Practice and Bioequivalence inspection programs operated by OSIS as of January 2015

Clinical Investigator Inspections by Location*, (CDER, FY 2017)



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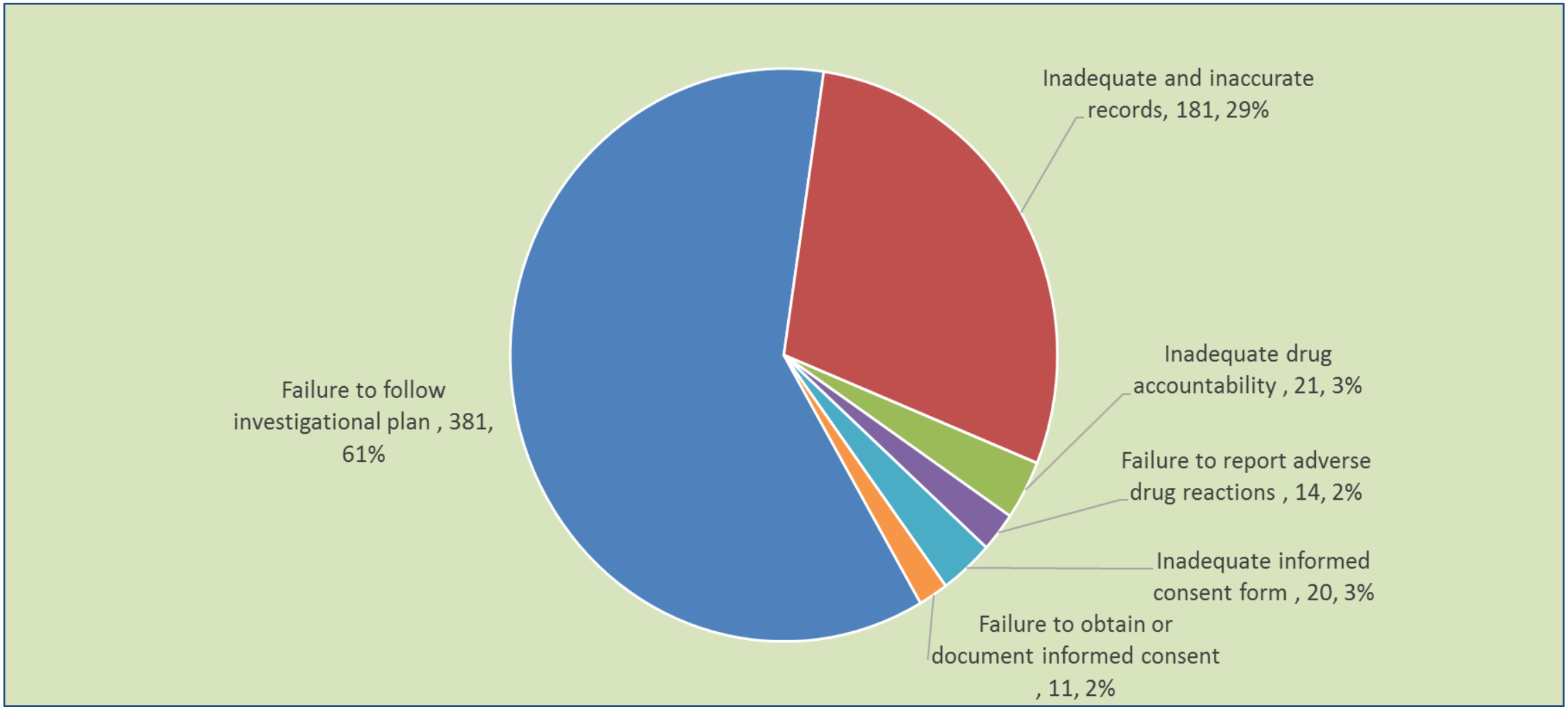
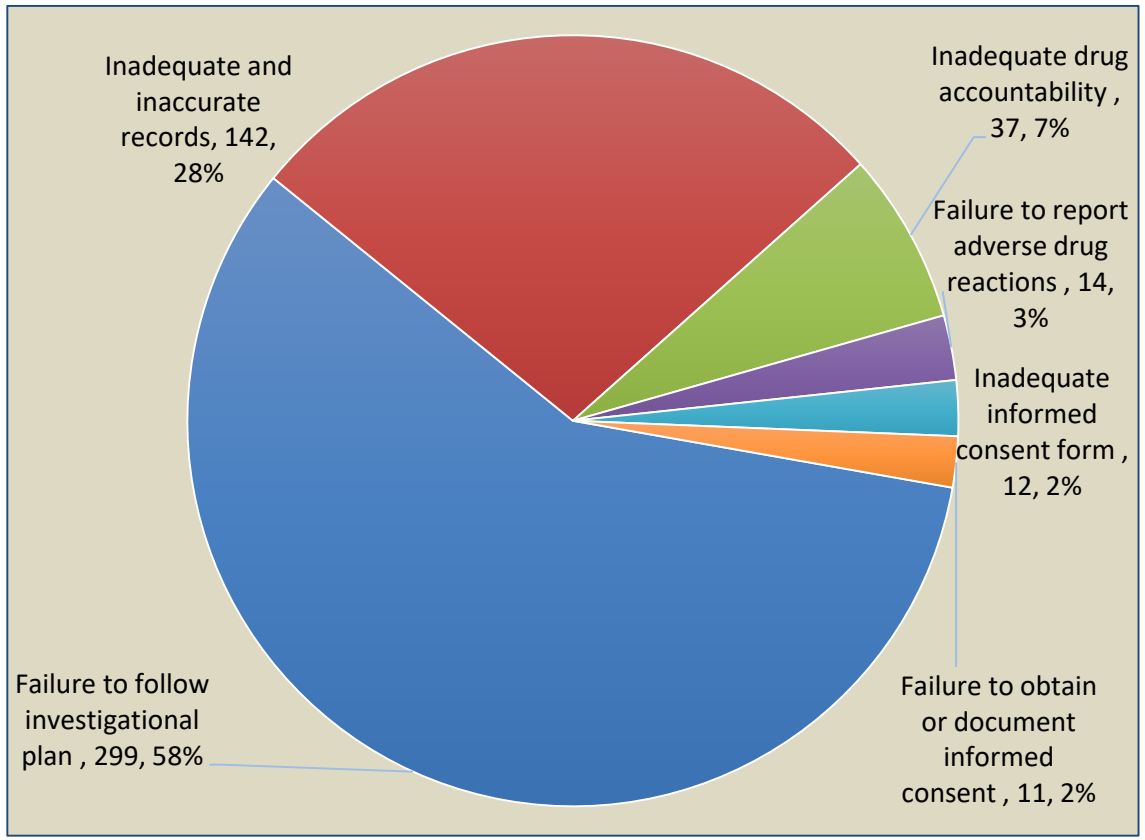
Frequency and Types of the Common Clinical Investigator GCP Deficiencies

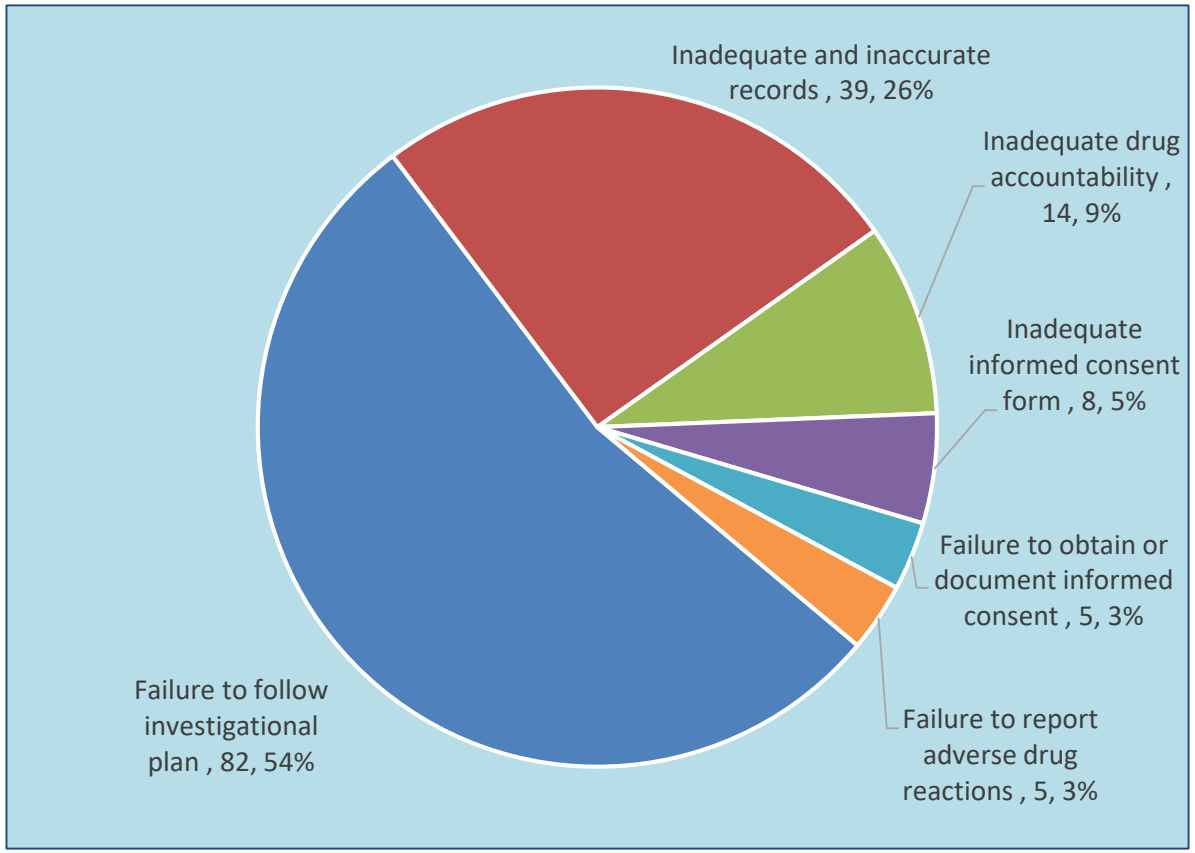


Based on Post-Inspection Correspondence Issued (FY 2015-17) for total of 628 inspections

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



U.S. Inspection



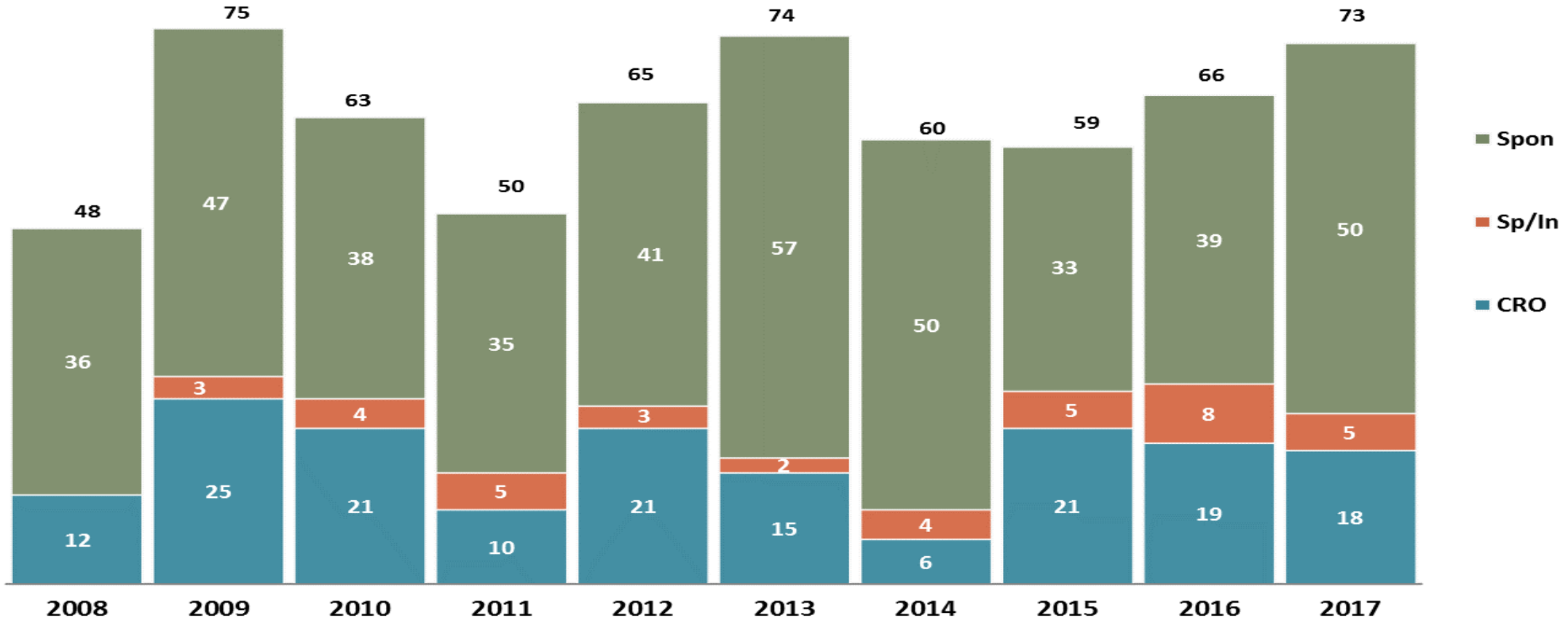
Non-U.S. Inspection

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

GCP-Related Sponsor/Contract Research Organizational Inspections*, (CDER)



*Based on inspection start date [Complis database as of December 29, 2017]
The Sponsor/CRO distribution shifted for FY09-12 in previous releases due to data corrections in the Complis Database.

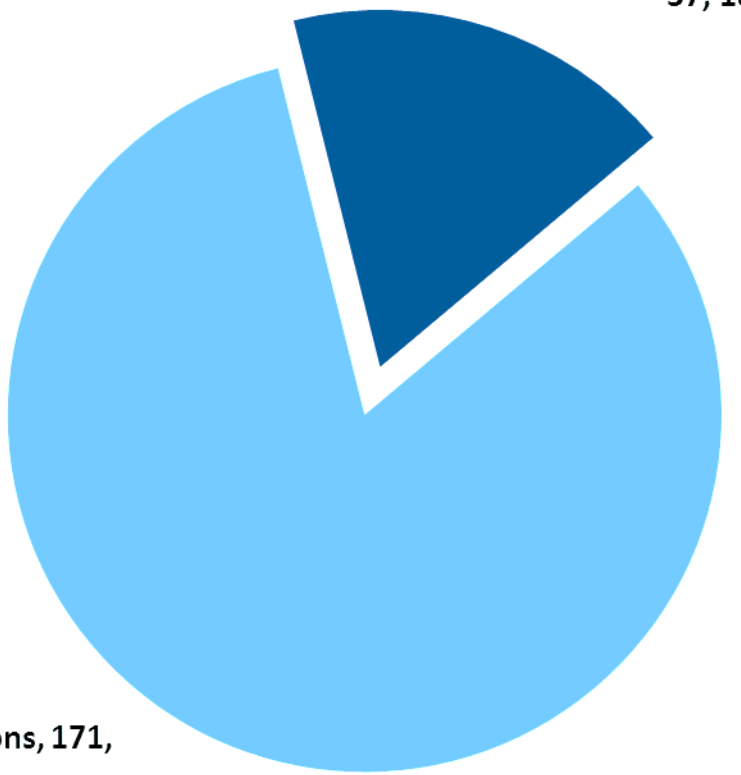
Common Sponsor GCP Related Deficiencies

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

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

Take Home Points

- It is important have clinical development programs that reliably produce high quality data acquired in a manner that does not jeopardize the rights, safety, or welfare of trial participants

Thank you!

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