U.S. FOOD & DRUG ADMINISTRATION

International Clinical Trials: GCP Perspective

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Disclaimer

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

Objective

To learn about the evaluation and acceptance of international clinical trial data by FDA's from Good Clinical Compliance(GCP) perspective

Outline

- Introduction
- FDA's Good Clinical Practice (GCP) Expectations
- Validation Of Data Through an Onsite Inspection
- Site Selection for Inspection
- Clinical Inspection Approaches
- Inspection Metrics
- GCP Violations

Question 2

What proportion of applications for drugs & biologics contain data from ex-U.S. studies?

A) 80%

B) 50%

C) 35%

D) 20%

Question 1

Based on Office of Inspector General (OIG) report in 2010, how many of all clinical trial sites are outside the U.S?

A) >25%

B) >50%

C) >75%

Question 3

There is strong evidence that foreign sites or data present more issues in terms of compliance and data validity?

A) True

B) False

INTRODUCTION

Medical Product Discovery & Development

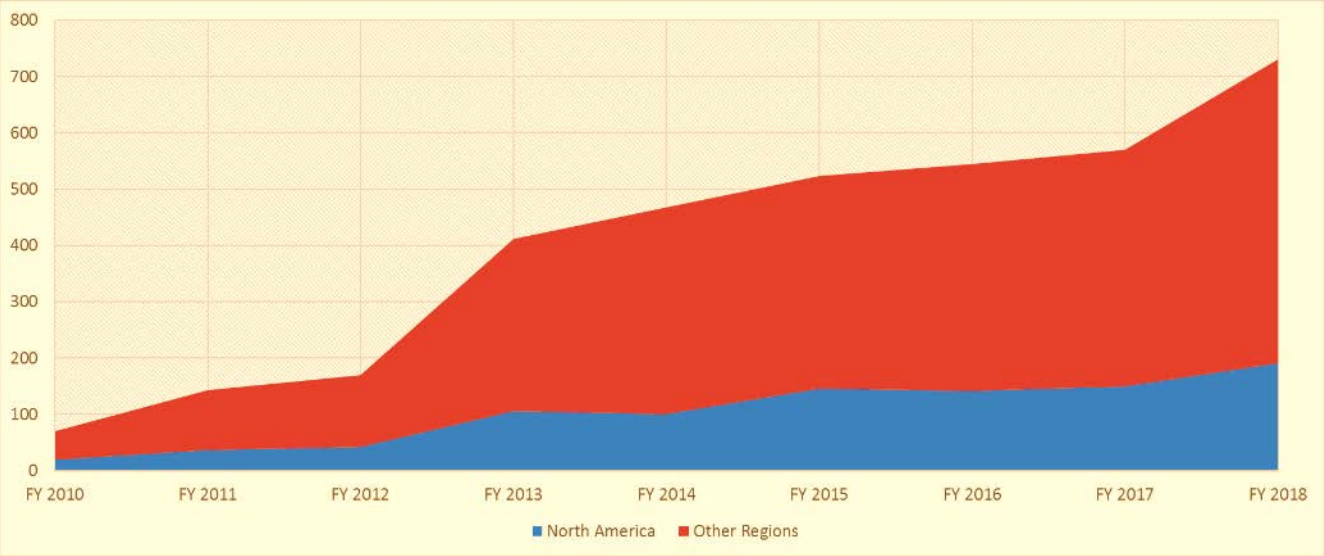
- The clinical development of pharmaceutical products has become a global undertaking
- Sponsors conduct clinical trials globally to use data as support for a new drug application (NDA)/biologics license application (BLA)
- Regardless of where trials are conducted, FDA's determinations on medical product approval depend on the demonstration of effectiveness and safety

History of Foreign Clinical Trial Data Submission

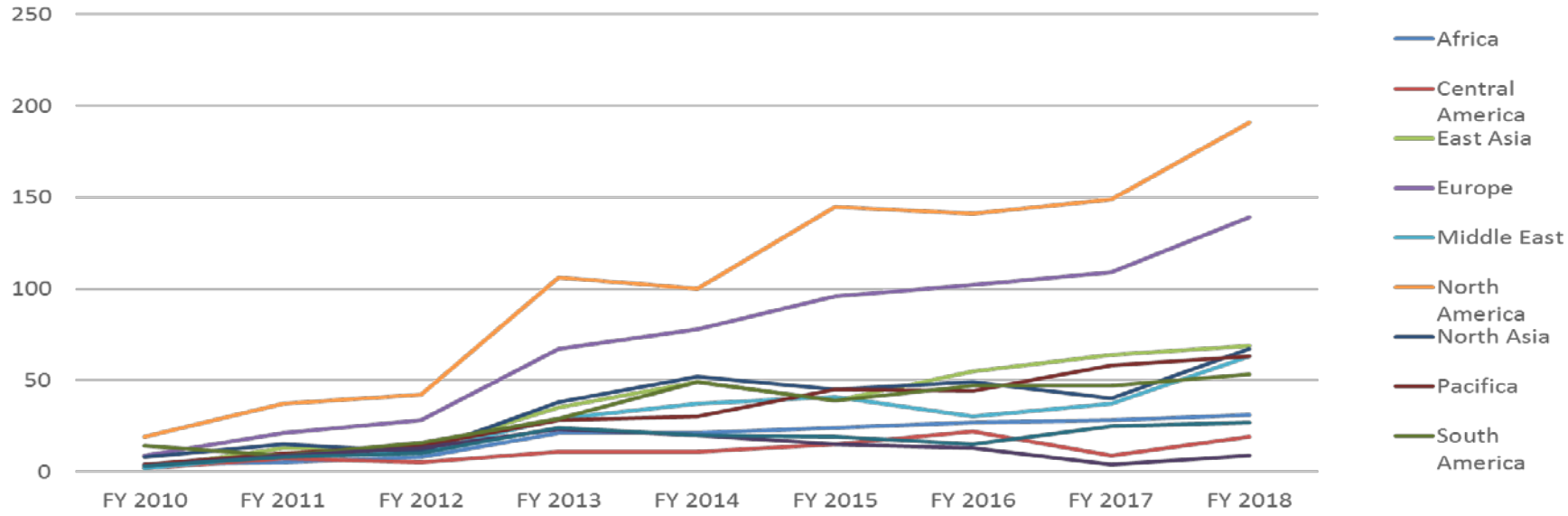
- It was uncommon for a Sponsor to submit foreign clinical trial data prior to the 1962 Kefauver-Harrison Amendments

- The 1975 provision codified in 21CFR312.120 permits submission of foreign clinical trial data not conducted under an IND

Number of Studies by FY (2010 – 2018)

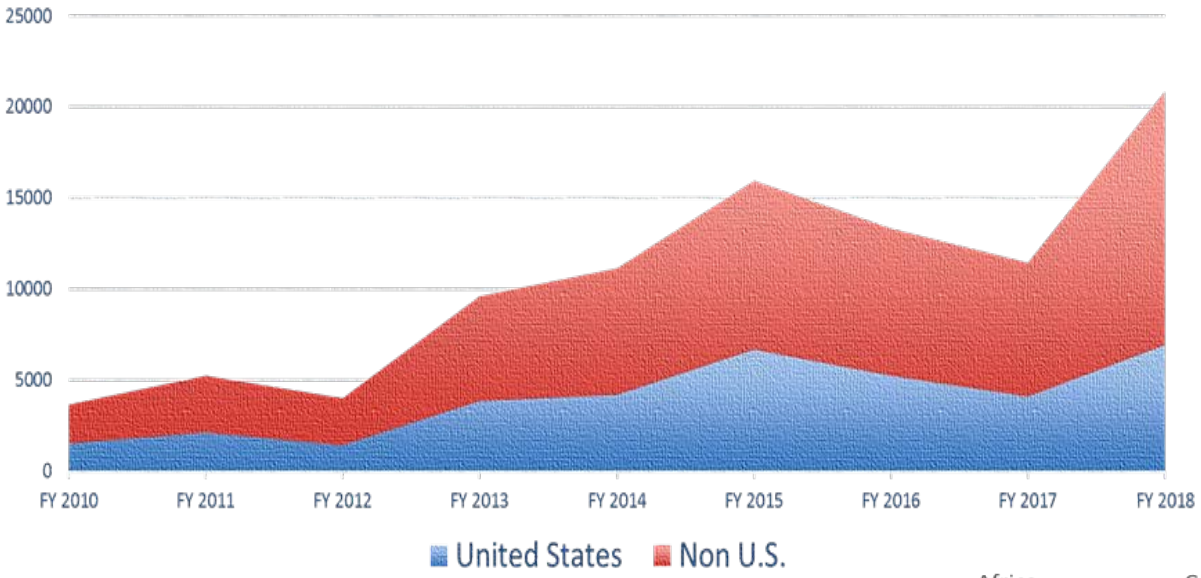


During the 8 year period, the number of Clinsite.xpt submissions to marketing applications have grown; most FDA regulated studies were conducted outside the U.S.



Source:
Data represented 577 unique datasets IDs /CISST that support one or more marketing application

Number of Sites by FY(2010 – 2018)



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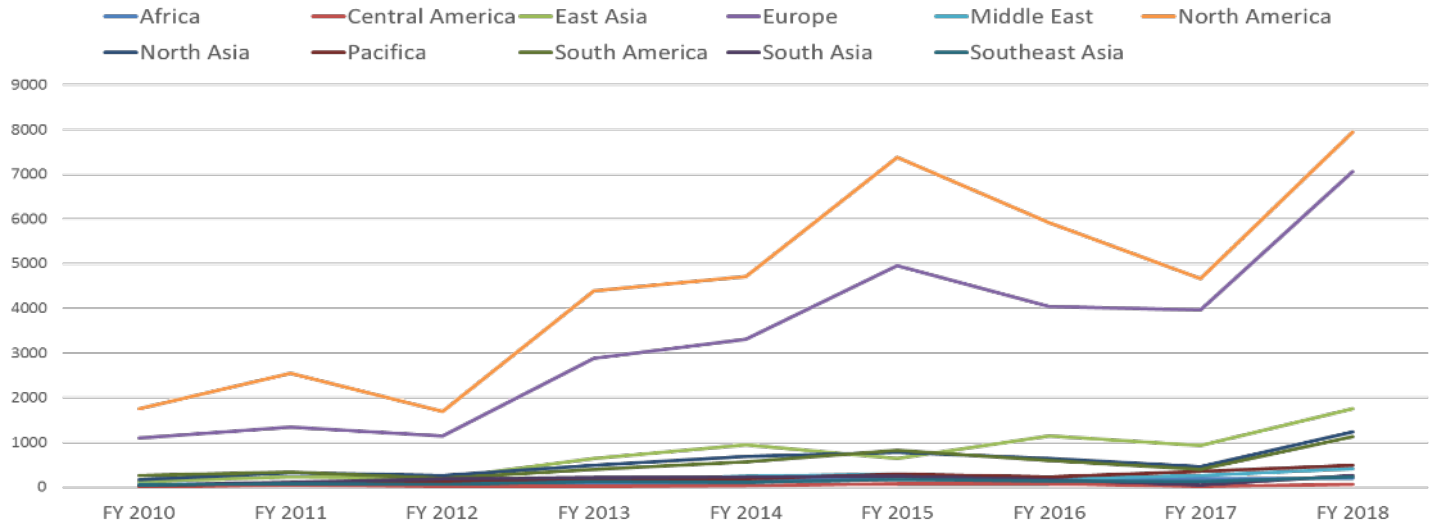

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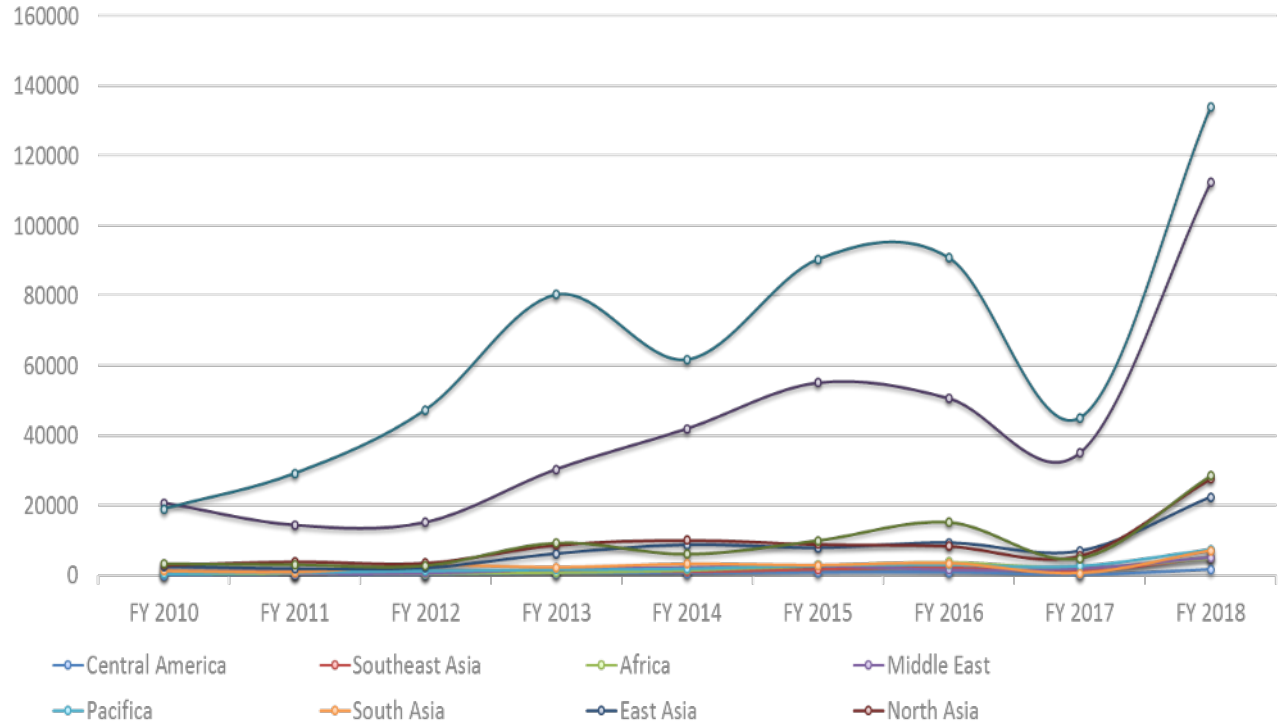
Patients Enrollment by FY(2010 – 2018)



During the 8 year period, the number of Clinsite.xpt submissions to marketing applications have grown; based on archived Clinsite data the total number enrolled patients has grown

Data represented 577 unique datasets IDs /CISST that support one or more marketing application

FDA'S GOOD CLINICAL PRACTICE (GCP) EXPECTATIONS

Conducting Clinical Trials

- Studies using investigational product that has not been approved by the FDA or for indications not in the approved labeling may require filing an investigational new drug (IND) application with the FDA
  - If a study meets specific regulatory exemption criteria, then an IND may not be needed

- When a study is conducted under an IND but is located outside of the United States, the study must meet all relevant FDA regulations as if it were being conducted within the United States

- Sponsors are not required to conduct their studies outside of the US under an IND in order to use them as support for an NDA/BLA.

Study Outside U.S Not Conducted Under an IND

- FDA accepts a well-designed, well-conducted, non-IND foreign study as support for marketing approval, under 21 CFR 312.120.

- The sponsor must ensure that the study complies with the requirements in 21 CFR 312.120 to use it as support for marketing approval.

Clinical Trials Not Conducted Under An IND: Acceptance of Clinical Data

- FDA accepts foreign clinical data from studies not conducted under an IND if the following conditions are met:

1. Study was conducted in accordance with Good Clinical Practice (GCP)

2. FDA is able to validate the data from the study through an onsite inspection

FDA expects that clinical trials are designed, conducted, performed, monitored, audited, recorded, analyzed, and reported in a way they provide assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

VALIDATION OF DATA FROM THE STUDY THROUGH AN ONSITE INSPECTION

Validation of Data Through Inspection

- To determine the quality, integrity, and acceptability of the data & the adequacy of the protection of rights & welfare of human subjects

- To ensure that FDA regulated research is conducted in compliance with applicable regulations

Types of Inspections

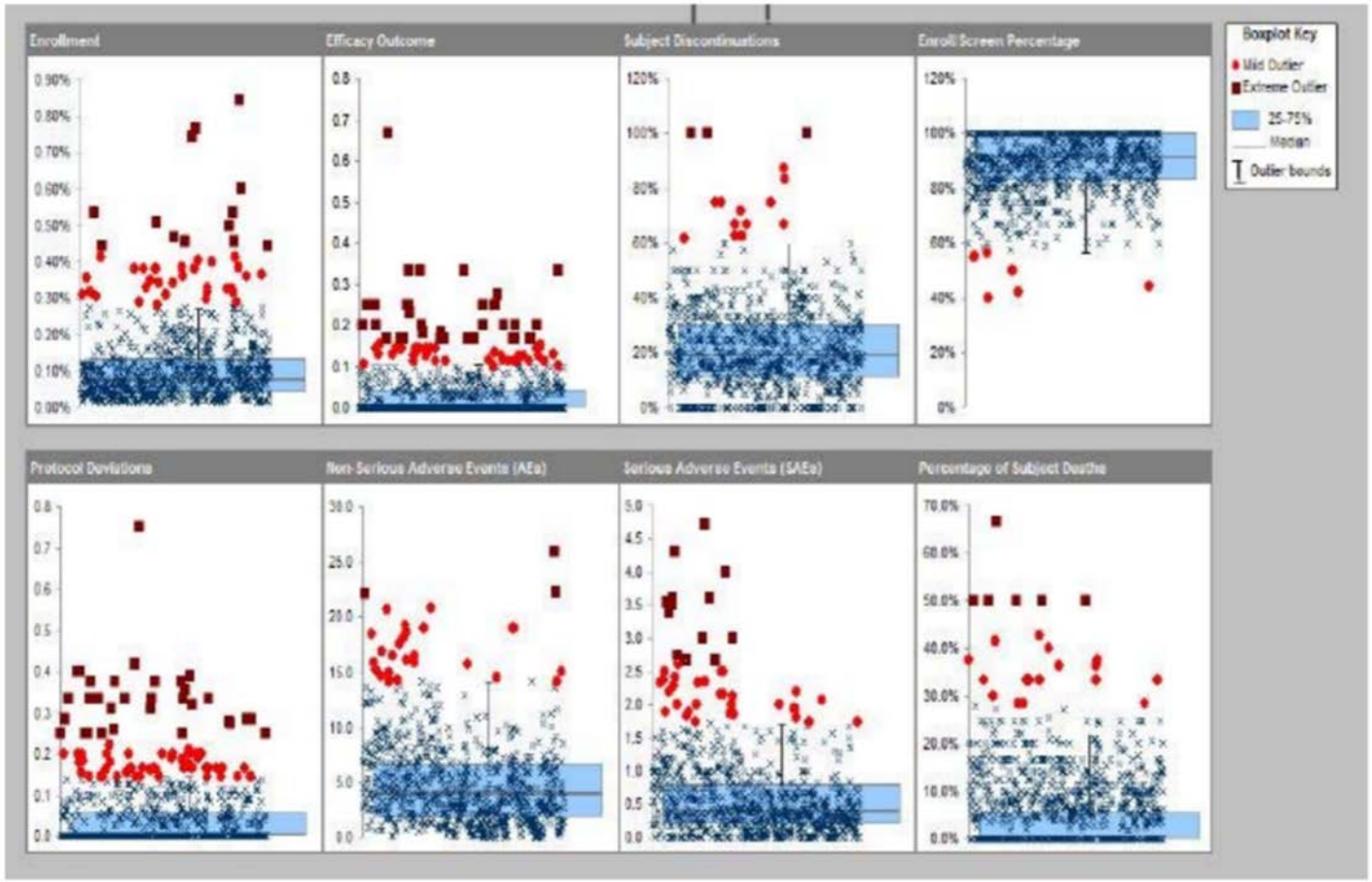
- PDUFA/BsUFA-related inspections: New medical product applications
- For-cause inspections: GCP complaints
- Surveillance inspections: Compliance enforcement

SITE SELECTION FOR INSPECTION

Risk-Based Site Selection for Inspection

- FDA uses risk based approach to identify and target sites for inspection (greater impact on public health or likely to have problems)
- The approach takes into account the risk of the application (new molecular entity [NME] vs non NME), site level attributes (comparative performance indicators) and study level attributes
- Using innovative strategies & tools to identify sites for clinical inspection

Site Selection Tool for Inspection



Factors to Consider: When to Inspect

Inspection approach is similar for domestic and foreign sites

Importance of the study	• Relevance to labeling/NDA/BLA • Contribution/size/outliers/concern of scientific misconduct, protocol violations, study discontinuations • Statistical impact of data from the site
History of the clinical investigator	• Frequency and prior classification(s) • Findings of previous inspection(s)
Data Contribution	• Domestic versus international

International Inspections

- Clinical sites likely to be audited when:
  - only foreign data are submitted to support an application
  - insufficient domestic data
  - domestic and foreign data show conflicting results pertinent to decision-making
  - there is a serious issue to resolve (e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations)

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Clinical Inspection Approach is The Same for non-U.S sites!

Inspection Focus

- Protocol – adherence
- Review of IC
- Comparison of line listings with source documents and verification of reported data and quality
- Review of enrollment process and signed consent from(s)
- Review of IRB oversights
- Review of monitoring activities

- Review of reporting to sponsor
- Review of compliance with applicable regulations (e.g., financial disclosure and updates as indicated)
- Review of test article control
- Review of records custody and retention

Inspections of Foreign Clinical Sites

- FDA has the authority to have access to and copy and verify any records and reports relating to a clinical investigation (study binder, drug accountability records, consents, medical records, tests and procedures, case report form data, qualifications of investigator and study staff, and all other documents that relate to a study (except financial records and payments)

- The firm is expected to provide a translator if key personnel do not speak English

- It is expected to have translations of spoken words, medical records, and study records

Waiver: Form FDA 1572 Signature Requirement and Local Laws

- A sponsor may seek a waiver from the Form FDA 1572 signature requirement for clinical investigators at foreign sites conducting studies under IND

- Sponsors are expected to provide documentation of the waiver to the clinical site(s) to which the waiver applies

- Investigators are responsible for complying with applicable laws and regulations of the country in which the study is being conducted

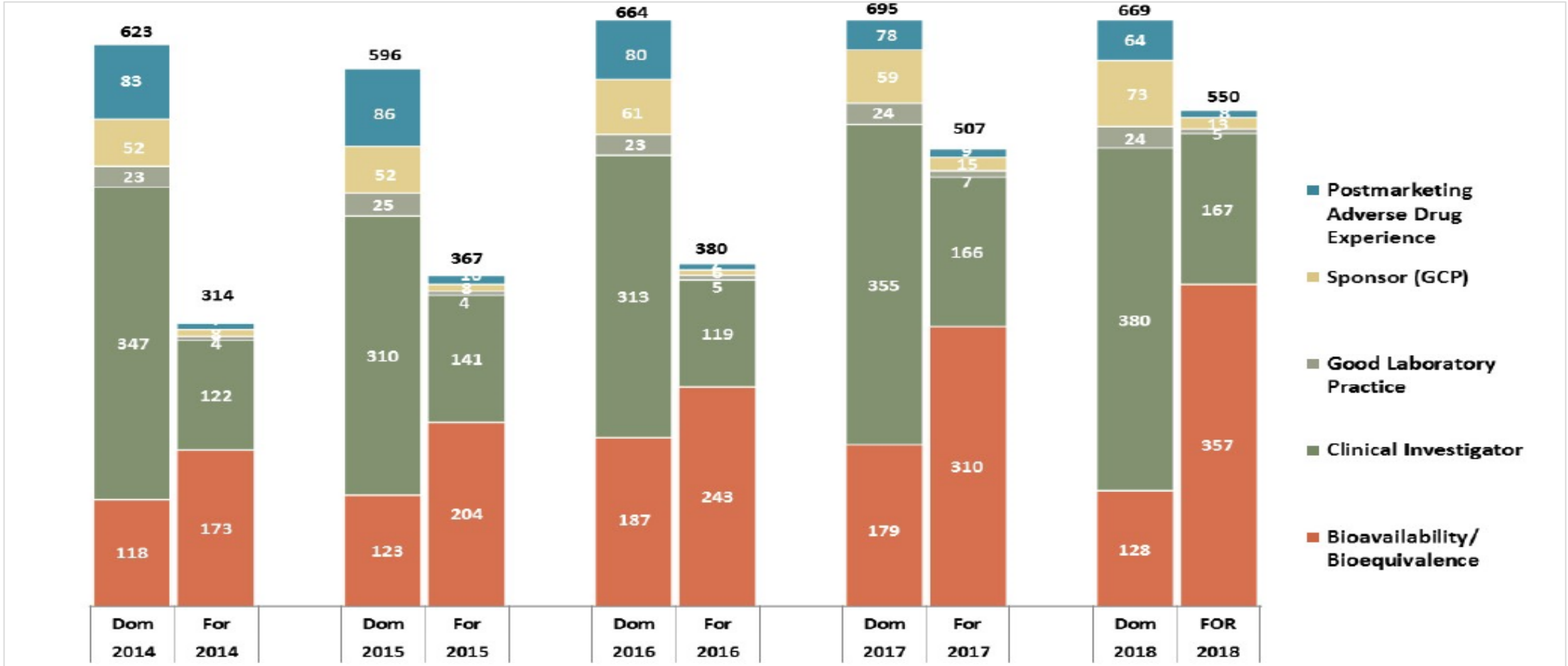
International GCP Collaboration

- FDA collaborates with international foreign regulators such as EMA (EU), MHRA (UK), PMDA (Japan) and Health Canada on GCP issues

- Purpose of GCP collaboration include:
  - Establishing common procedures for GCP inspections
  - Sharing information and relevant inspection findings as applicable
  - Conducting collaborative inspections for some shared marketing applications
  - Holding t-con meetings and GCP inspector discussions

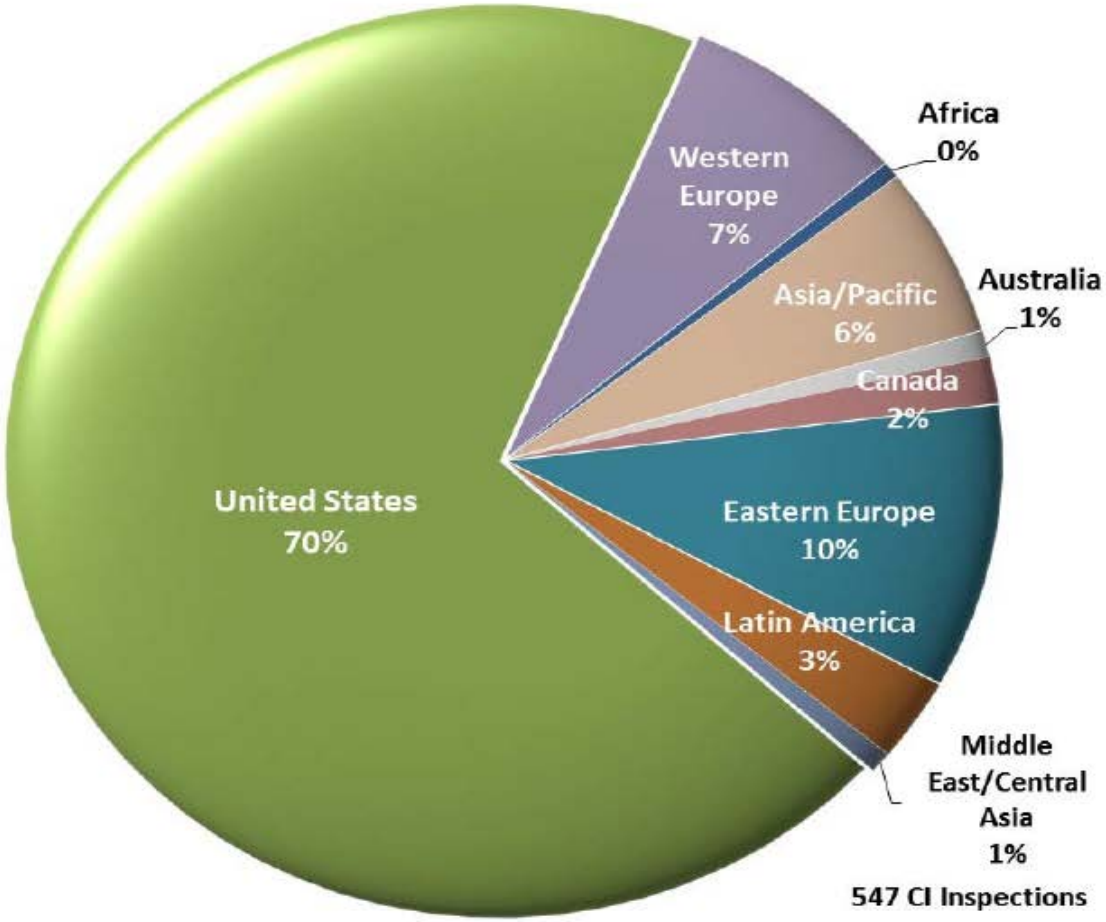
INSPECTION METRICS

Domestic vs. Foreign Inspections Overseen by OSI/OSIS* (CDER, FY 2014 - FY 2018)



*Based on inspection start date – [Complis database as of January 7, 2019]
- Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
- Good Laboratory Practice and Bioequivalence inspection programs operated by OSIS as of January 2015

Clinical Investigator Inspections by Location* (CDER, FY 2018)



*Based on inspection start date – [Complis database as of January 7, 2019]

Clinical Investigator Inspections by Country (CDER, FY 2019)

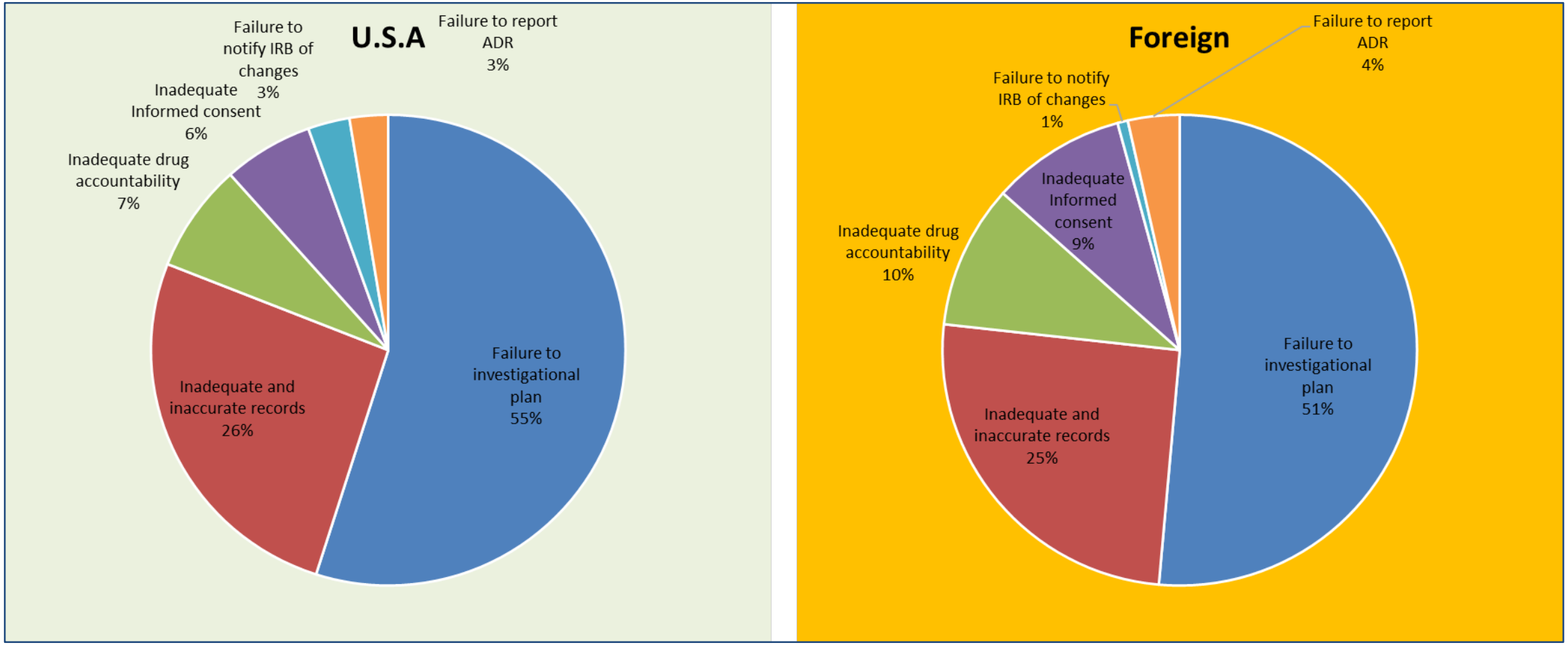
GCP VIOLATIONS

GCP Compliance in Foreign Sites

- No evidence that foreign sites or data present more issues in terms of compliance and data validity

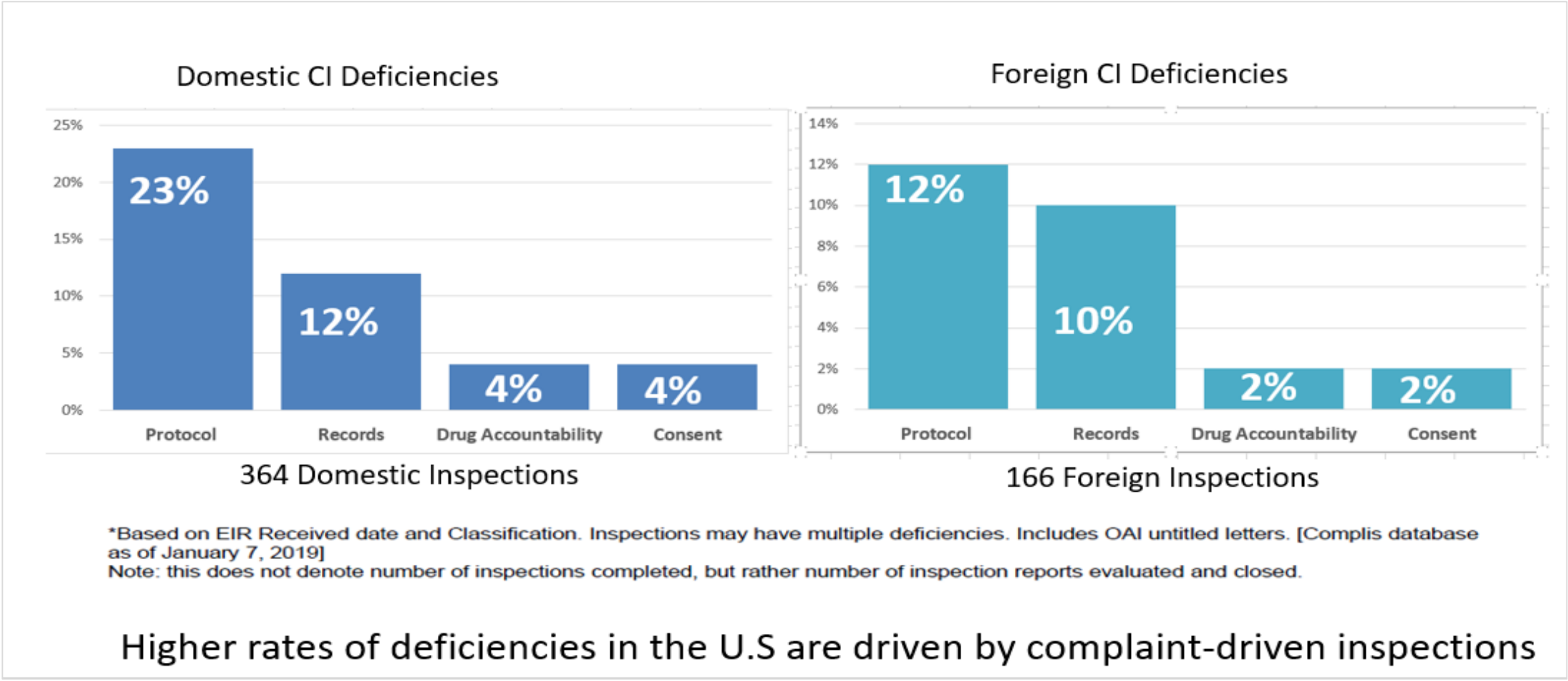
- Violations and rates of violations are similar to domestic sites

Frequency and Types of Clinical Investigator-Related Deficiencies Related to all Products in Routine Inspections, U.S.A vs. Foreign



Based on Post-Inspection Correspondence Issued (FY 2015-17) for total of 1192 inspections

Frequency of Clinical Investigator-Related Deficiencies Based on Post-Inspection Correspondence Issued* (CDER, FY 2018)



*Based on EIR Received date and Classification. Inspections may have multiple deficiencies. Includes OAI untitled letters. [Complis database as of January 7, 2019]
Note: this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed.

Higher rates of deficiencies in the U.S are driven by complaint-driven inspections

Post Inspection Letters to non U.S. Investigators

- Observations on Form FDA 483 are based on regulations.
- FDA does not have regulatory authority outside of the U.S.
- FDA's ability to inspect a non-US entity comes from submission of the data.
- When observations indicate serous breach of GCPs, FDA issues administrative correspondence letters to investigators outside of the U.S. However the letters do not not hold the same meaning as one issued to an investigator in the U.S.

Useful Guidance

- FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions
  - Issued March 2012
  - Provides clarifications for sponsors and applicants on how to demonstrate compliance with the requirements of 21 CFR 312.120

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf

Thank you!

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