FDA U.S. FOOD & DRUG ADMINISTRATION

Clinical Investigator's General Responsibilities

Faranak Jamali, M.D.
Office of Compliance
Office of Scientific Investigations
Division of Enforcement and Postmarketing Safety
Compliance Enforcement Branch

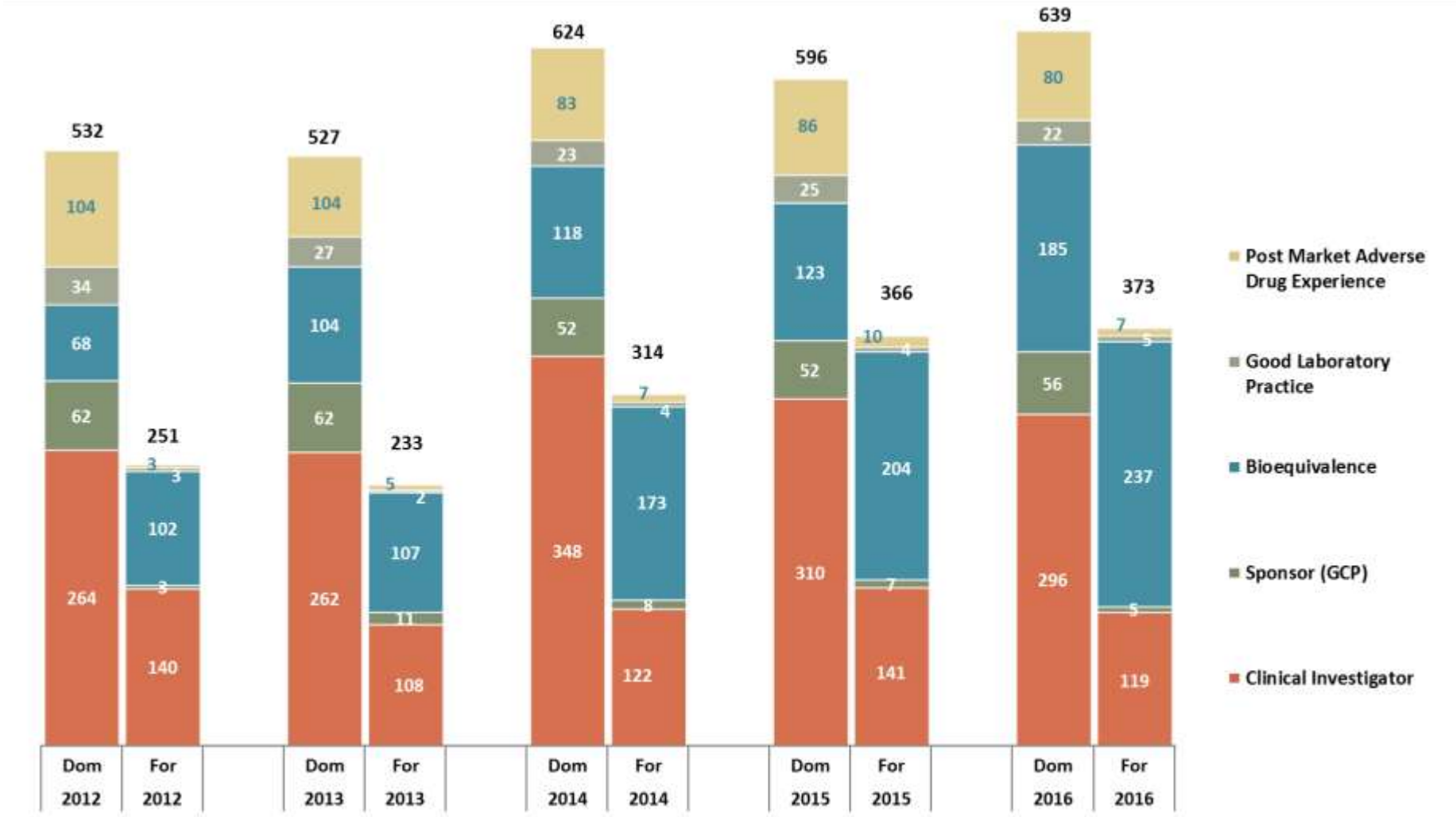
Disclaimer

The views expressed in this talk are those of the speaker and not necessarily those of the US Food and Drug Administration (FDA).

Objectives

- What is reviewed in a Clinical Investigator (CI) Inspection?
- Metrics on CI Inspections and Regulatory Actions
- Examples of Common GCP Regulatory Violations
- Tips for Clinical Investigators (CIs)

CDER Domestic vs. Foreign Inspections



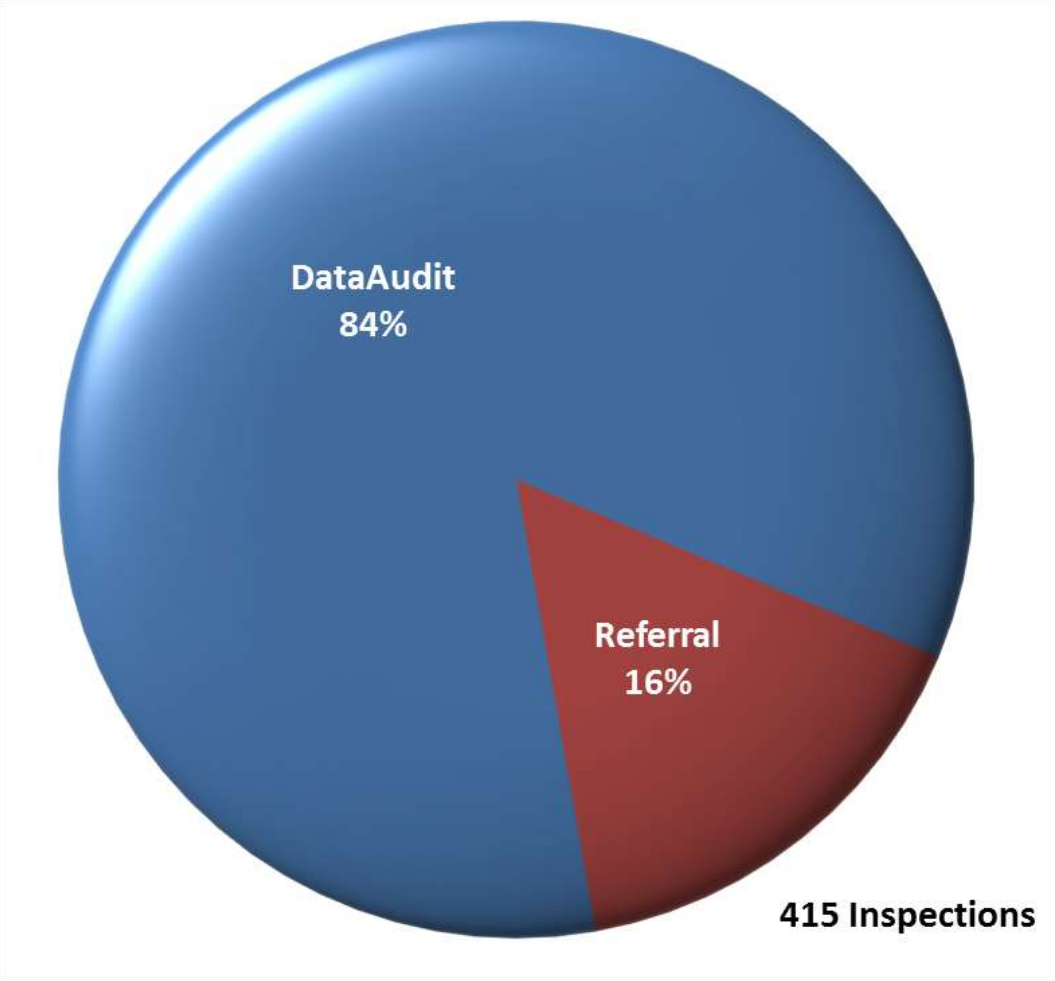
(CDER, FY 2012 - FY 2016)

*Based on inspection start date – [Complis database as of December 20, 2016]

• Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator

• Good Laboratory Practice and Bioequivalence inspection programs operated by OSIS as of January 2015

Clinical Investigator Inspections CDER FY-2016



Pre-approval/Data audit/Surveillance

For-cause/Referral

Follow-up

Based on inspection start date – [Complis database as of December 20, 2016]
Referrals include Complaints, Required Reports, IRB/Sponsor Notifications, and other referrals-internal and external for All OSI Branches

Document review – CI inspection

- CDER regulated clinical studies:
  - Form FDA 1572
  - Informed consent processes
  - Subjects' records and Case Report Forms (CRFs)
  - Protocols and amendments
  - Sponsor and IRB correspondences
  - …

Poll Question

For how long is a clinical investigator is required to retain the study related records?

- 2 years
- 4 years
- 10 years
- Indefinitely

Form FDA 1572 –Commitments

- **Conduct** the study in accordance with the protocol
- **Personally conduct** or **Supervise**
- **Inform patients** about investigational purposes
- **Report** adverse experiences to sponsor
- **Inform Staff** about their obligations

You commit when you sign:

Form FDA 1572

21 CFR 312.60
21 CFR 312.50,56
21 CFR 312.64

Poll Question

When does a Form FDA 1572 need to be completed?

- Any time during the study
- Every month during the study
- Any time a new clinical investigator is selected by the sponsor to conduct the study

Form FDA 1572 –Commitments

- **Maintain** adequate/ accurate records; and and **Retain** records
- **Make records** available for inspection
- **Ensure IRB review** of the initial & continuing application
- **Comply** with all other obligations of CI's

Form FDA 1572

21 CFR 312.62
21 CFR 312.68
21 CFR 312.66

By a show of hands:

Do you have to be a physician to conduct a clinical study as a clinical investigator?

- Yes
- No

Adequate Informed Consent

- Approved by IRB
- Signed/dated by subject or subject's LAR
- Provide basic information
- Language understandable to subjects

50.20: General Requirements
50.25: Basic Elements
50.27: Documentation of Informed Consent

Adherence to investigational plan

- Screening evaluations
- Subject eligibility
- Study procedures
- Dosage and administration
- Reporting Serious Adverse Events (SAEs)

Adequate documentation

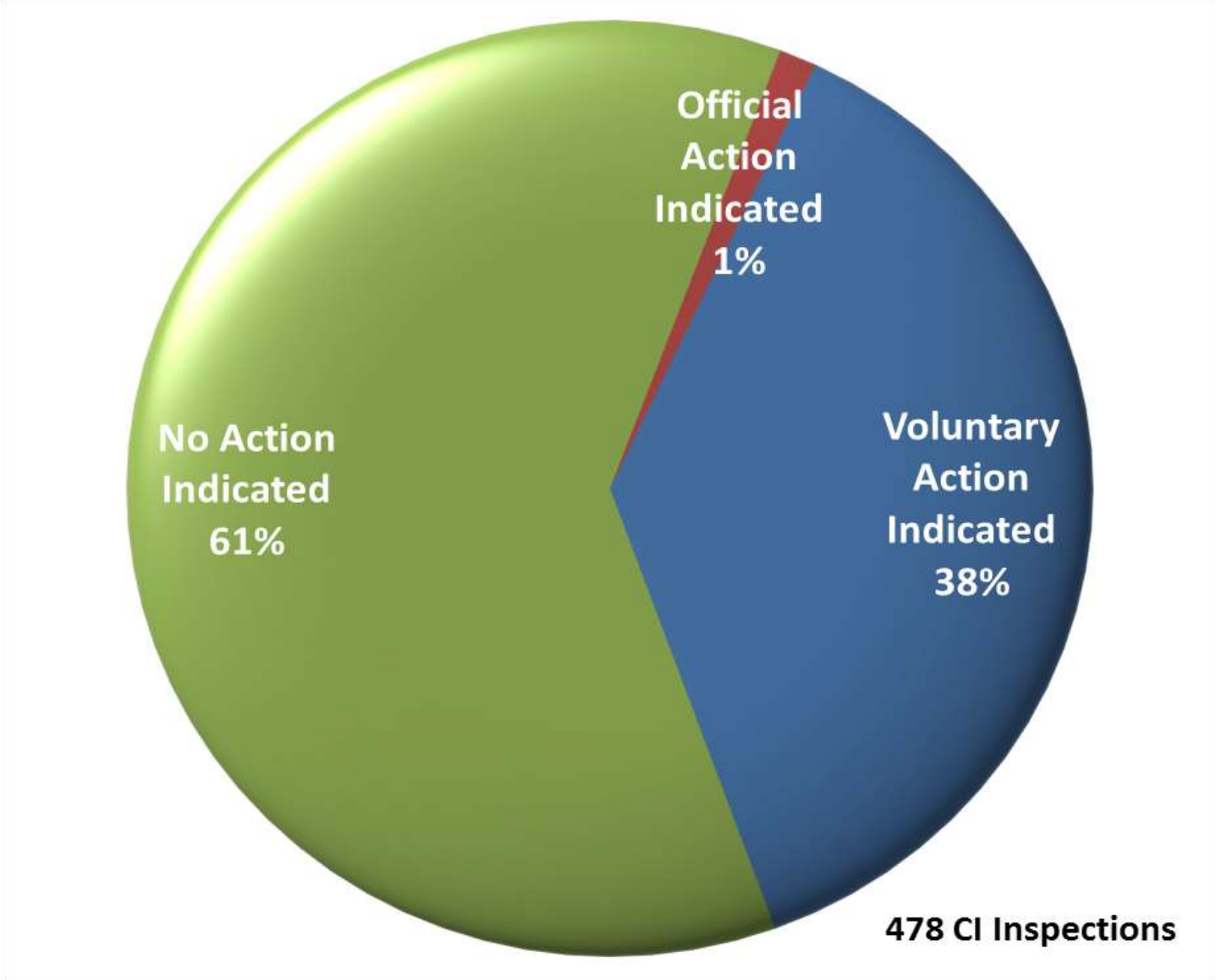
- ✓ Correct, original, clear, legible, contemporaneous
- ✓ Initialed/signed and dated
- ✓ Study data transferred correctly into Case Report Forms (CRFs)

Assurance of IRB Review

- Review and approval of
  - original protocol
  - any changes to the protocol
  - revisions in informed consent document
- Reporting all unanticipated problems involving risks to human subjects

CI Inspections by Classification

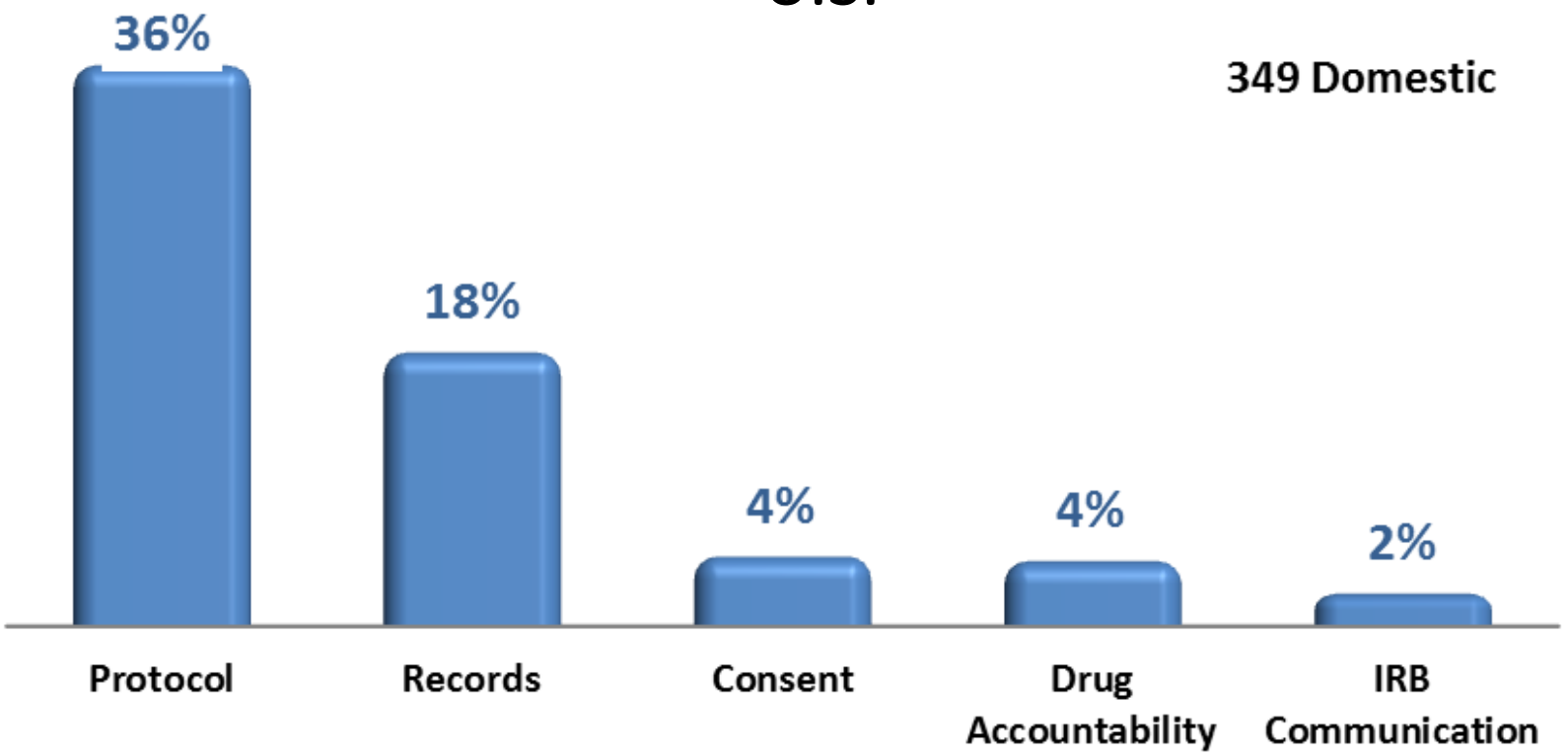
CDER- FY 2016



Regulatory Violations – All Letters

CDER- FY 2016

U.S.

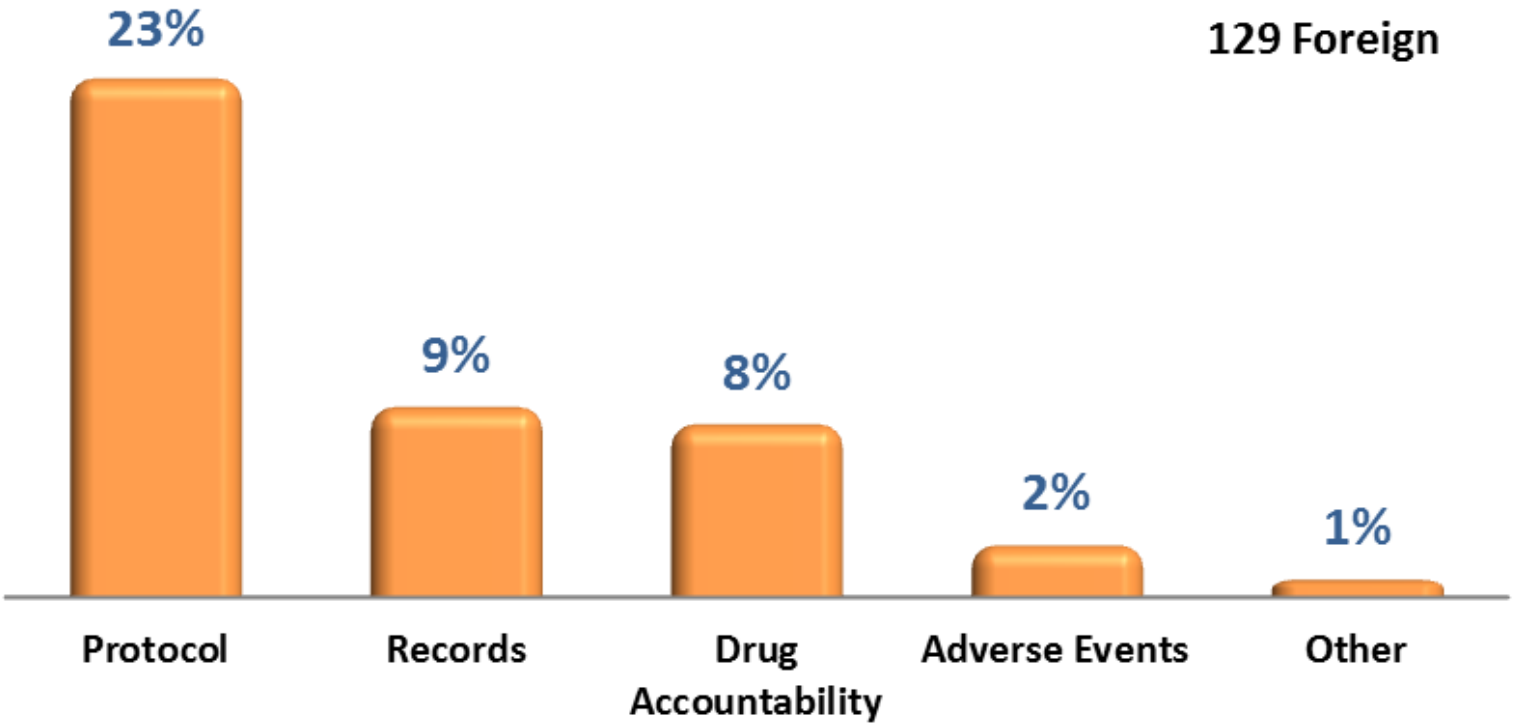


Based on letter issue date. Inspections may have multiple deficiencies. Includes OAI untitled letters. [Complis database as of December20, 2016]
Note: this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed.

Regulatory Violations – All Letters

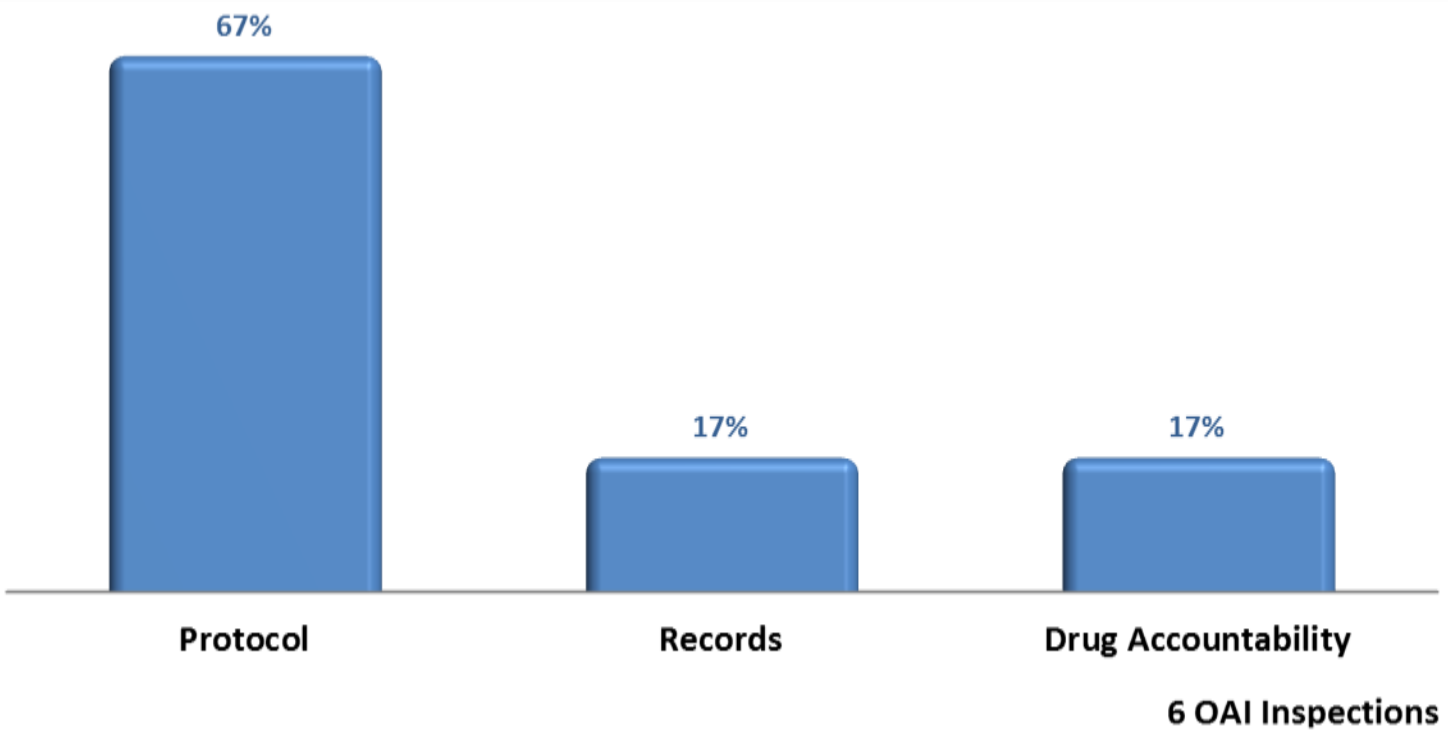
CDER- FY 2016

International



Based on letter issue date. Inspections may have multiple deficiencies. Includes OAI untitled letters. [Complis database as of December20, 2016]
Note: this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed.

Regulatory violations – OAI letters

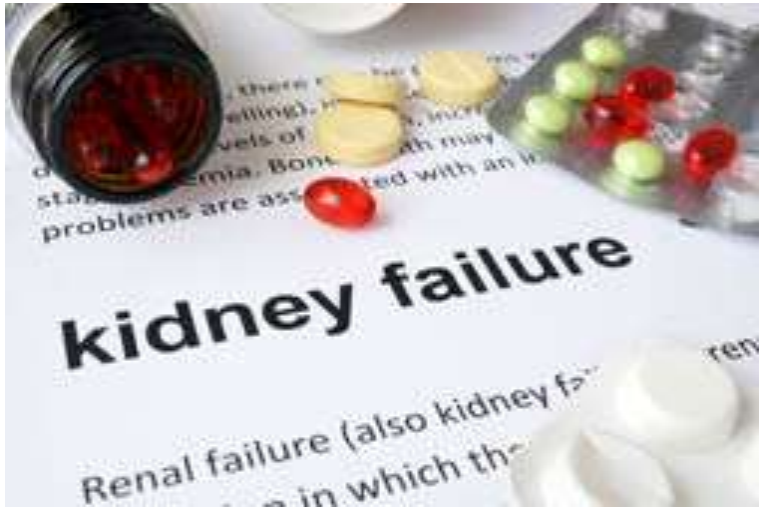


Based on letter issue date. Inspections may have multiple deficiencies. Includes OAI untitled letters. [Complis database as of December 20, 2016]
Note: this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed.


EXAMPLE

Protocol Violations - Eligibility

- Protocol required exclusion of subjects with severe renal insufficiency

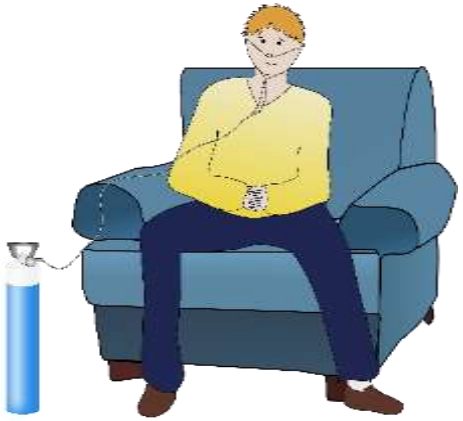


- Medical history records showed that subject had chronic renal failure prior to enrollment into the study.

Protocol Violations - Eligibility

- Protocol excluded severe Chronic Obstructive Pulmonary Disease (COPD):
  - Hx of repeated exacerbations
  - Requiring systemic corticosteroid maintenance tx
  - On Oxygen therapy

- 5 Subjects with COPD symptoms requiring oxygen, and on corticosteroid maintenance therapy were enrolled.



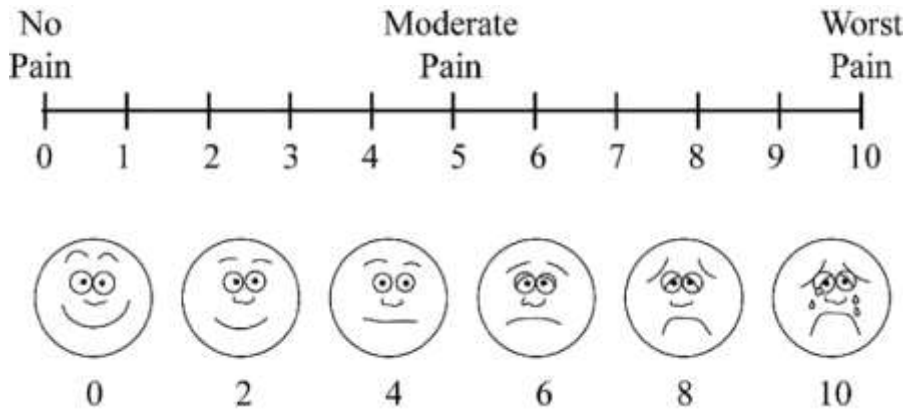
Protocol violations – Screening

- Protocol required collection of serum creatinine values at screening and randomization visit

- 20 subjects were enrolled and received study drug prior to receipt of their serum creatinine values.

Protocol violations – Study Procedures

- Protocol required that pain assessment be documented by the subjects on an electronic handheld device prior to surgery.
- Pain assessments for subjects were entered by the study coordinator, rather than by the subjects.



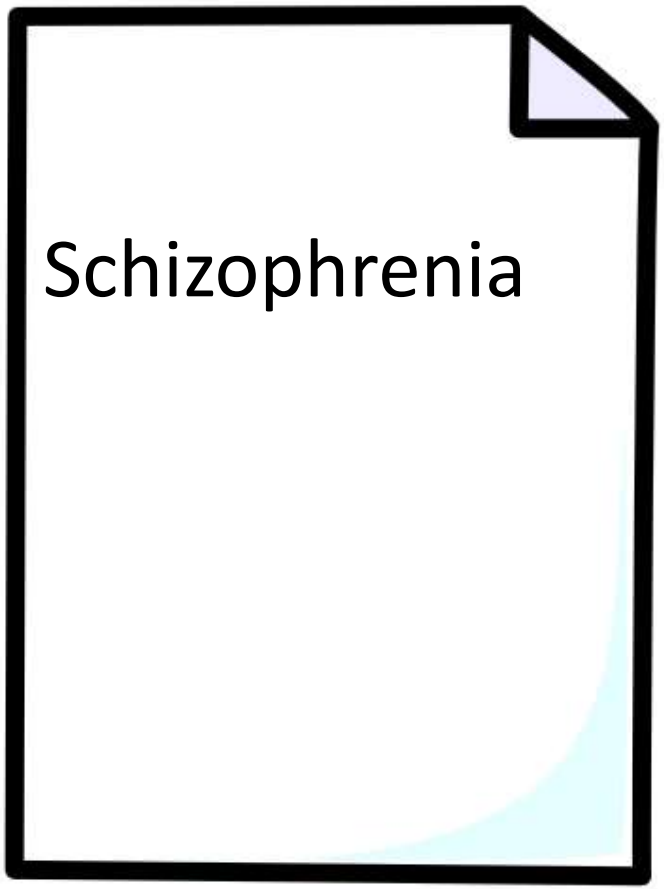
Protocol violations – Subject Safety

- If Fasting Plasma Glucose (FPG) ≥ 250 mg/dL → administer hyperglycemia rescue medication

- Subject had FPG levels: 350 mg/dL, and 304 mg/dL
- No rescue medication administered

Inadequate documentation

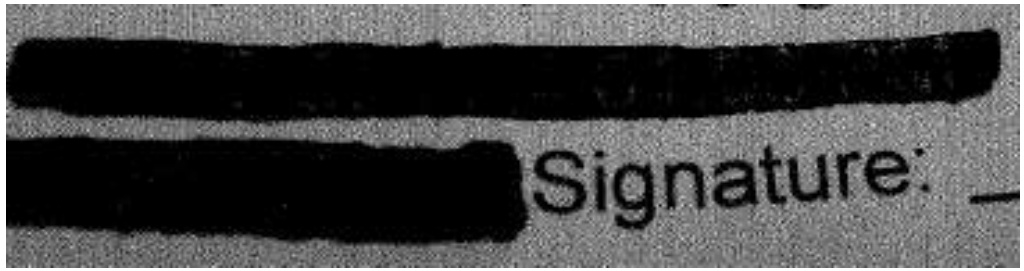
Source document



CRF

Inadequate documentation Case 2

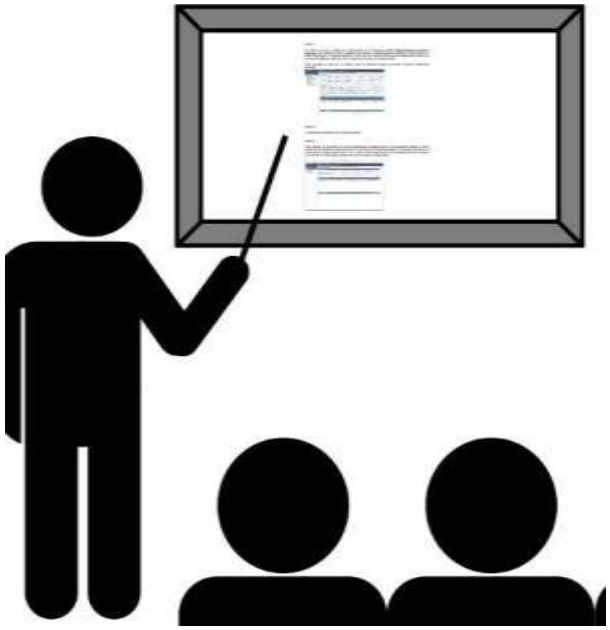
- Obscured original subject ID data for multiple subjects
- Different subject ID handwritten on those records on which original data was obscured



If you don’t strategize…

Root Cause Analysis

- Insufficient training/awareness
- Overlapping responsibilities
- Fear/desire
- Misunderstanding of the regulations
- Inadequate delegation

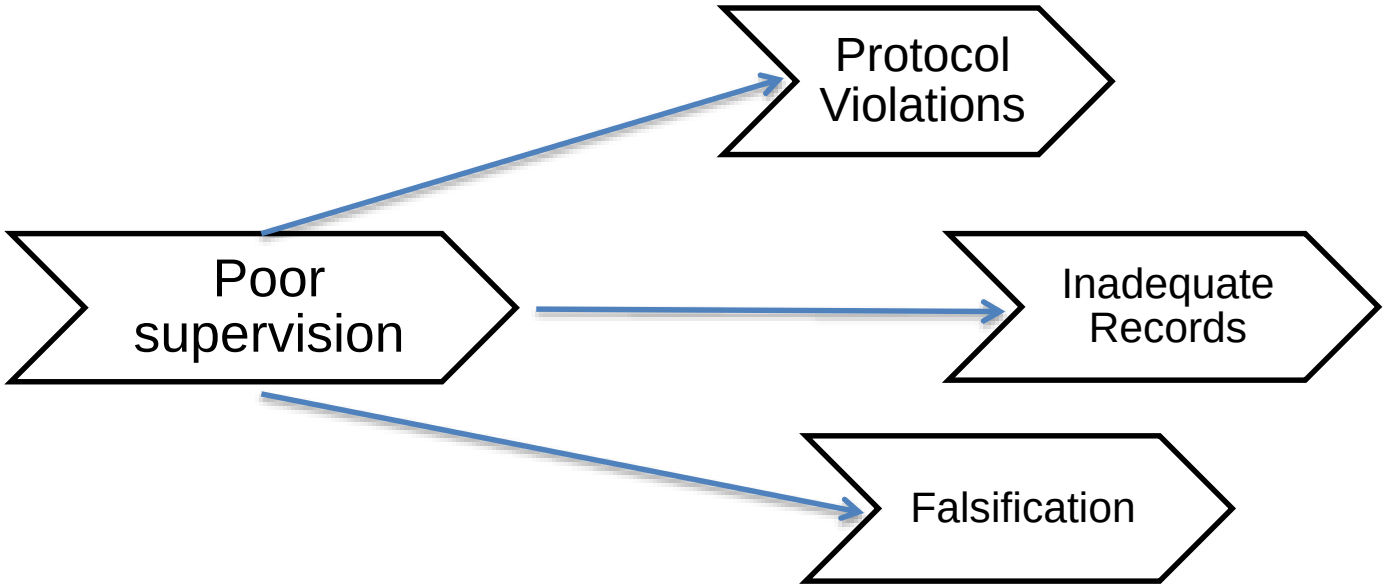


Unqualified Study Team

- Lymphoma
- Pre-eclampsia
- Bone fractures
- Periodontitis

- Dentist
- Podiatrist
- Ophthalmologist
- Physical therapist

Chain Reaction



What can you do to correct?

A Few Tips

- Commit to change or stop
- Make a comprehensive plan with defined steps
- Support with documentation (SOP, work instructions, training)
- Set a timeline for completion of your CAPs
- Implement your CAP
- Evaluate the implementation of CAP

Key Elements

- Write a complete and articulated protocol
- Select a qualified team
- Train your staff
- Adhere to the protocol
- Supervise
- Communicate
- Anticipate
- Correct
- Re-evaluate

Summary

- CDER GCP BIMO Program
- Regulatory Requirements for CIs
- Inspection Classifications and Regulatory Actions
- Common Regulatory Violations and Examples
- Root cause analysis and Tips for CIs

Please complete the session survey:

surveymonkey.com/r/DRG-D2S05

Helpful Resources

- Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

- FDA Inspections of Clinical Investigators- Information sheet

  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf

- Guidance for Industry-Investigator Responsibilities

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

- Clinical Investigator Administrative Actions – Disqualification

  https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidanceInformationSheetsandNotices/default.htm

Thank You

Faranak Jamali
CDER OC/OSI/DEPS/CEB
Phone: (301) 796-2289
E-mail: faranak.jamali@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION