U.S. FOOD & DRUG ADMINISTRATION

Sponsor Responsibilities

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Disclaimer

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

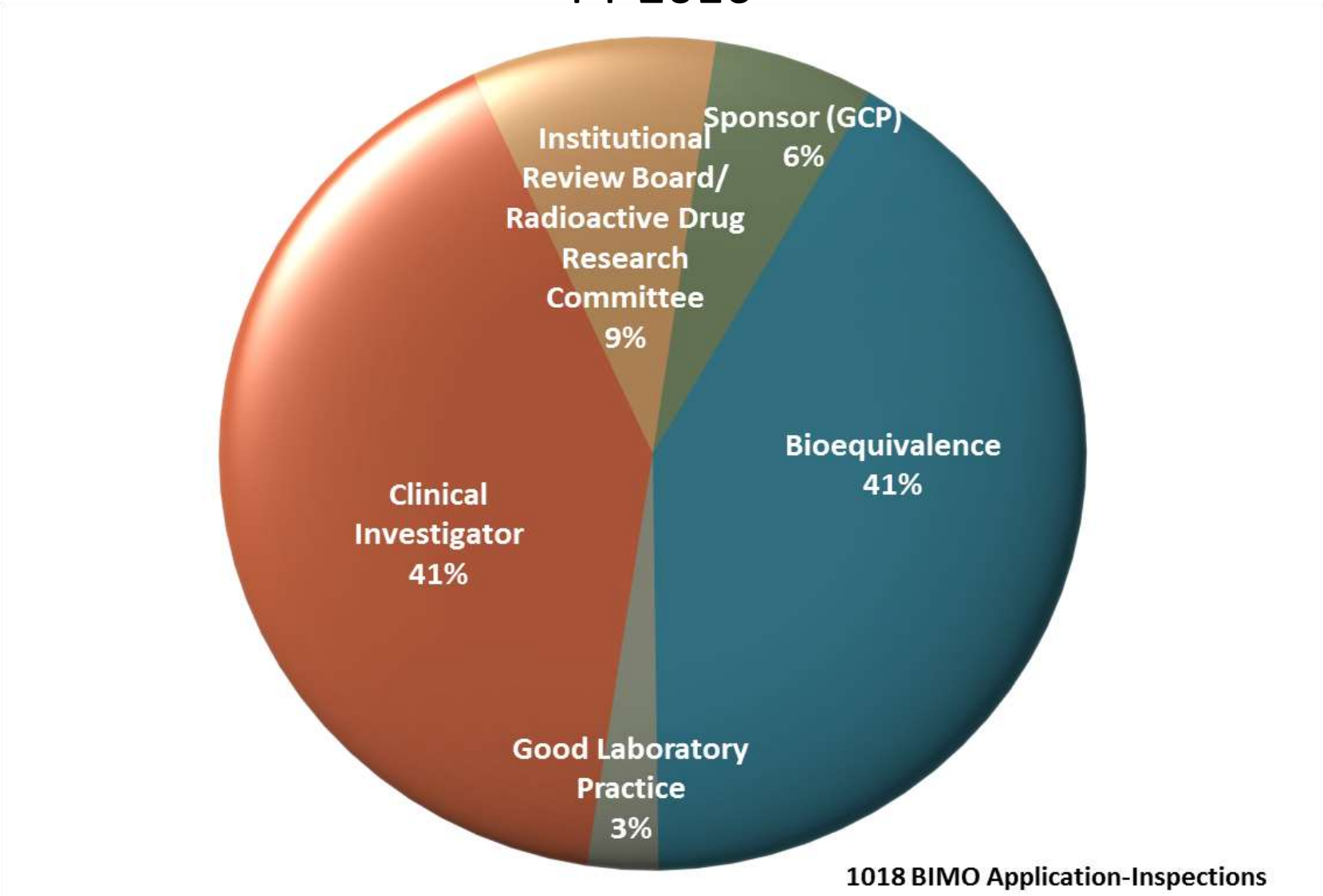
Objectives

- CDER BIMO GCP Inspections
- Definitions: Clinical Investigator and Sponsor
- Inspection Classification and Regulatory Actions
- Sponsor and Sponsor-Investigator (SI) responsibilities
- Common Sponsor and SI Violations
- Case Example
- Summary

CDER: Center for Drug Evaluation and Research
BIMO: Bioresearch Monitoring
GCP: Good Clinical Practice

CDER-BIMO Inspections

FY 2016



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

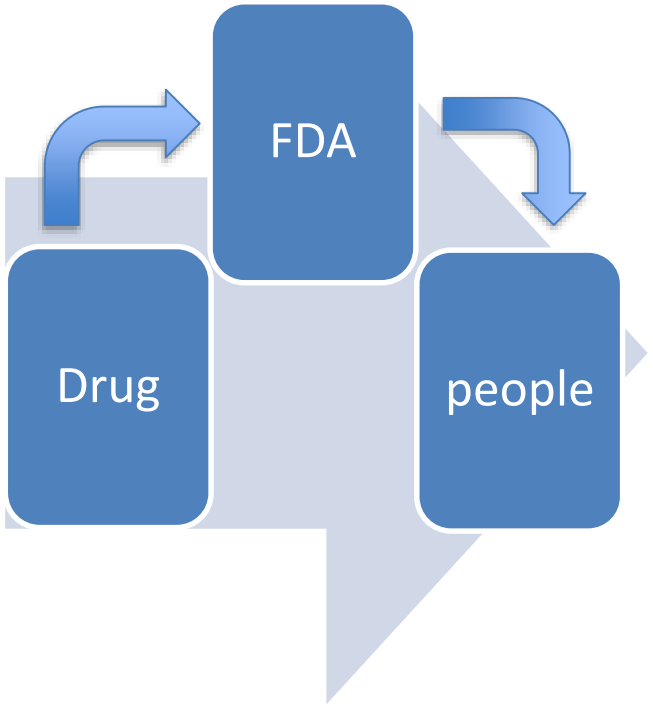
GCP Compliance Program
BIMO Coverage

- Sponsors and monitors
- Clinical Investigators (CI)
- Sponsor-Investigators

- In-vivo bioequivalence facilities
- IRBs
- Nonclinical Laboratories

BIMO GCP Objectives

- To ensure data reliability and integrity
- To protect rights, safety, and welfare of human research subjects
- To ensure FDA-regulated research is conducted in compliance with applicable regulations



Poll: Role Category

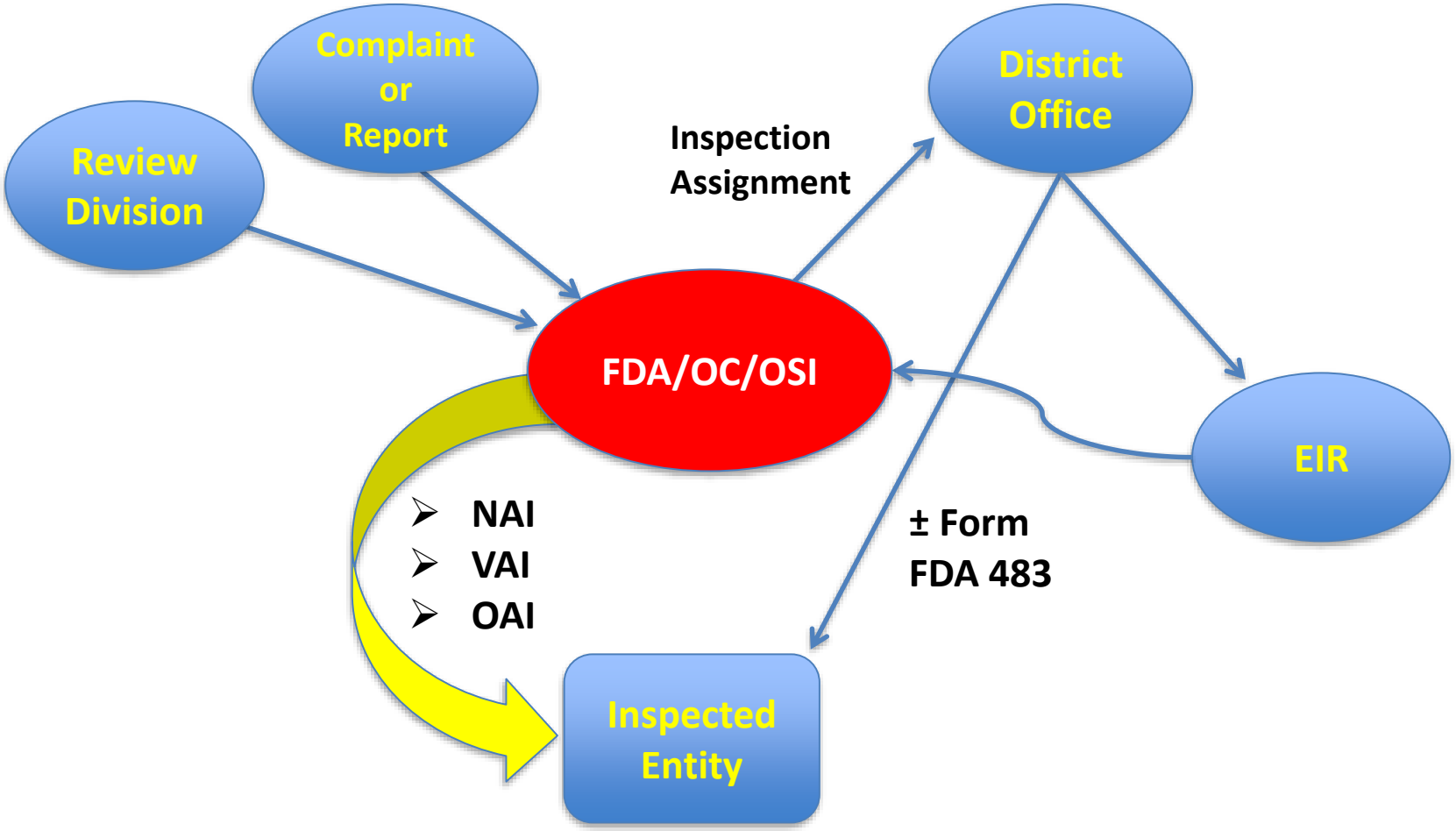
Into which of these categories do you best fit?

- Sponsor
- Monitor/Contract Research Organization (CRO)
- Clinical investigator
- Sponsor-investigator
- Other

Definitions

- Sponsor: individual or entity that takes responsibility for and initiates a clinical investigation
- Clinical investigator: individual who conducts a clinical investigation
- Sponsor-Investigator: individual who both initiates and conducts an investigation

BIMO GCP Inspection Process

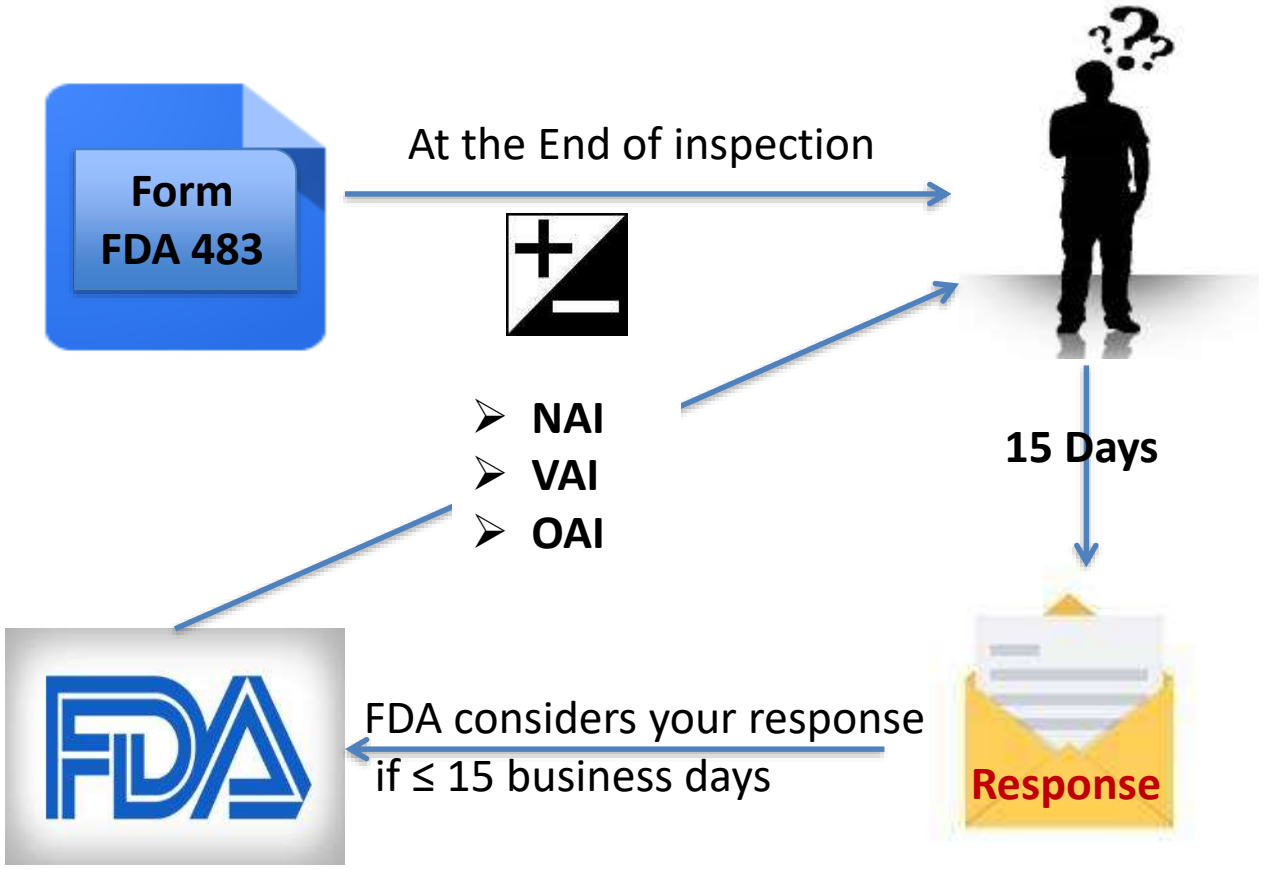


By a show of hands:

If you receive a Form FDA 483 at the end of an inspection, are you required to respond to the FDA?

- Yes
- No

Form FDA 483 Issued?



Does your response help?

Form FDA 483 and EIR

Response

- Change significance
  - Disproves
  - Mitigates
- No change

Final Inspection Classification

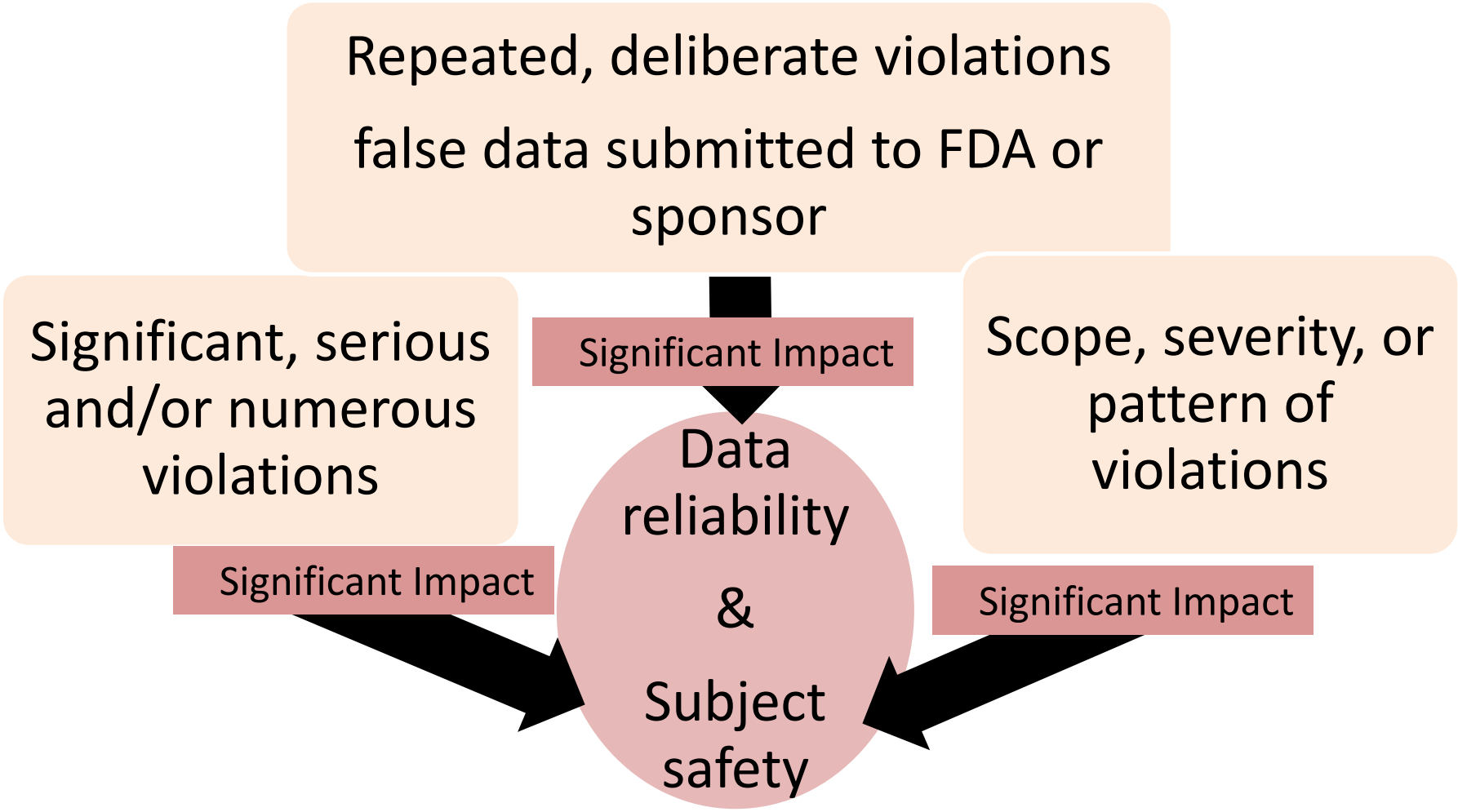
NAI: no violations identified

VAI: violations identified but no or minimal impact on data integrity and/or subject safety

OAI: violations identified that have significant impact on data integrity and/or subject safety

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

OAI Classification



OAI – Warning Letters (WL)

- Informal and advisory
- Issued for: violations of regulatory significance
- Purpose: to give opportunity to take voluntary and prompt corrective action before an enforcement action is initiated.
- Does not commit FDA to take enforcement action
- Is not a pre-requisite to take enforcement action

Follow-up Inspection

- ✓To ensure violations are not repeated
- ✓To verify promised CAs are implemented
- ✓To ensure compliance is sustained

Close-out Letter

Sponsor Responsibilities

- Know when to submit an IND or ask
- Transfer obligation in writing
- Select qualified investigator and monitor
- Obtain signed 1572, curriculum vitae & financial disclosure
- Give each investigator an investigator brochure

312.2(b)
312.20(a)
312.50
312.52
312.53
312.55

Sponsor Responsibilities

- Monitor the progress of the studies
- Maintain and retain records
- Promptly secure compliance or discontinue CI participation
- Promptly notify FDA, IRB and CI of risks
- Discontinue the study if needed
- Assure return of unused drugs

312.56
312.57
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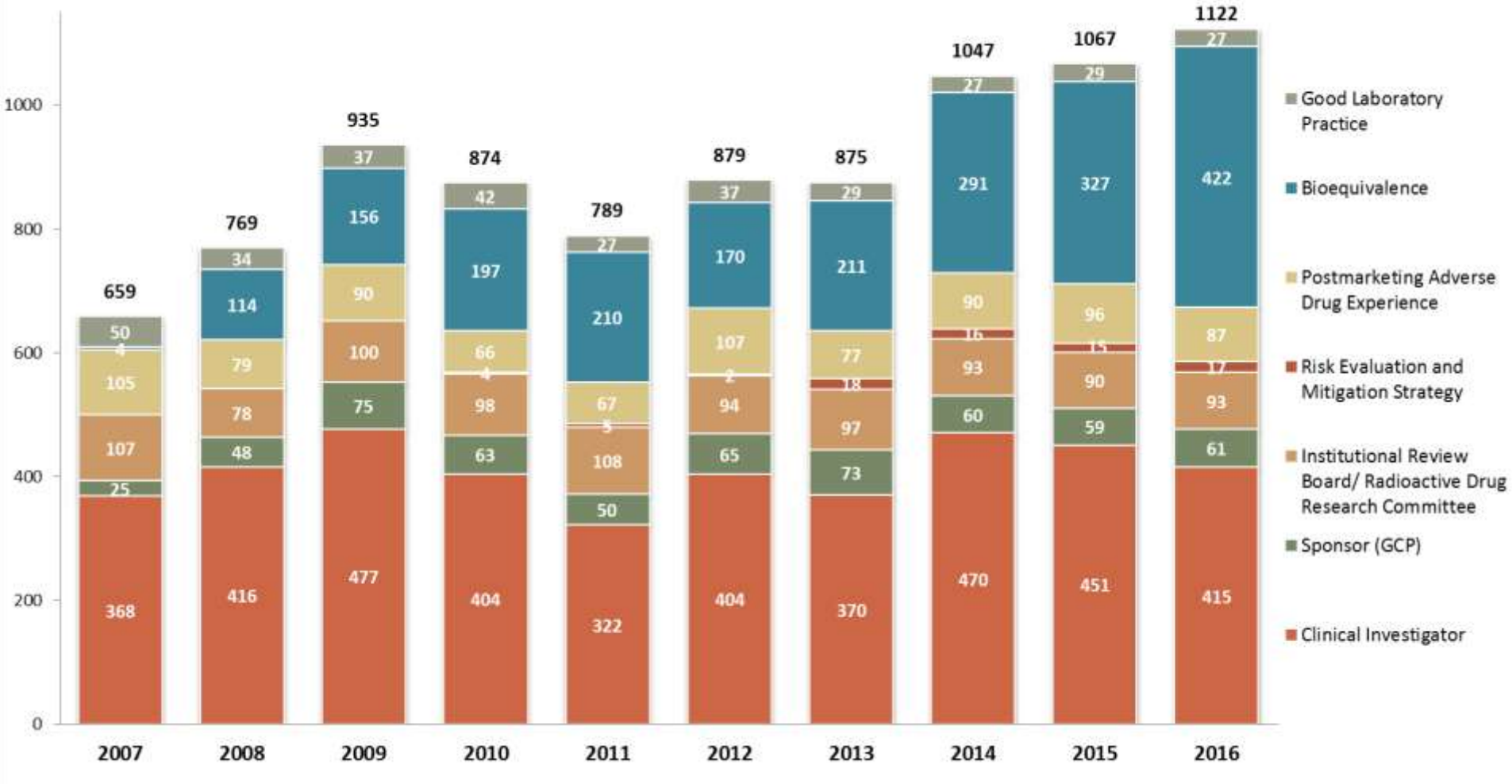
CDER Inspections

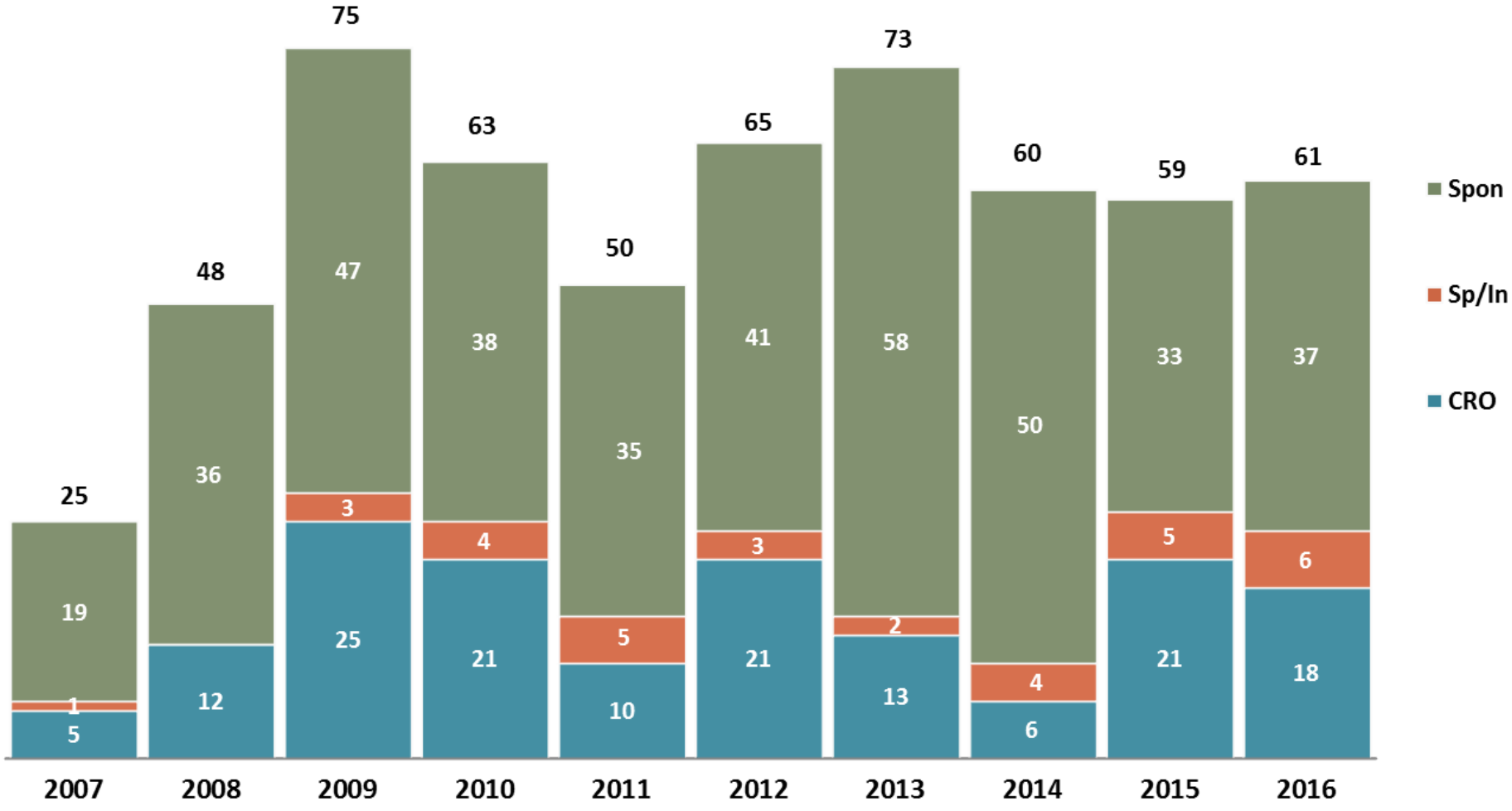


CDER, FY 2007 - FY 2016

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

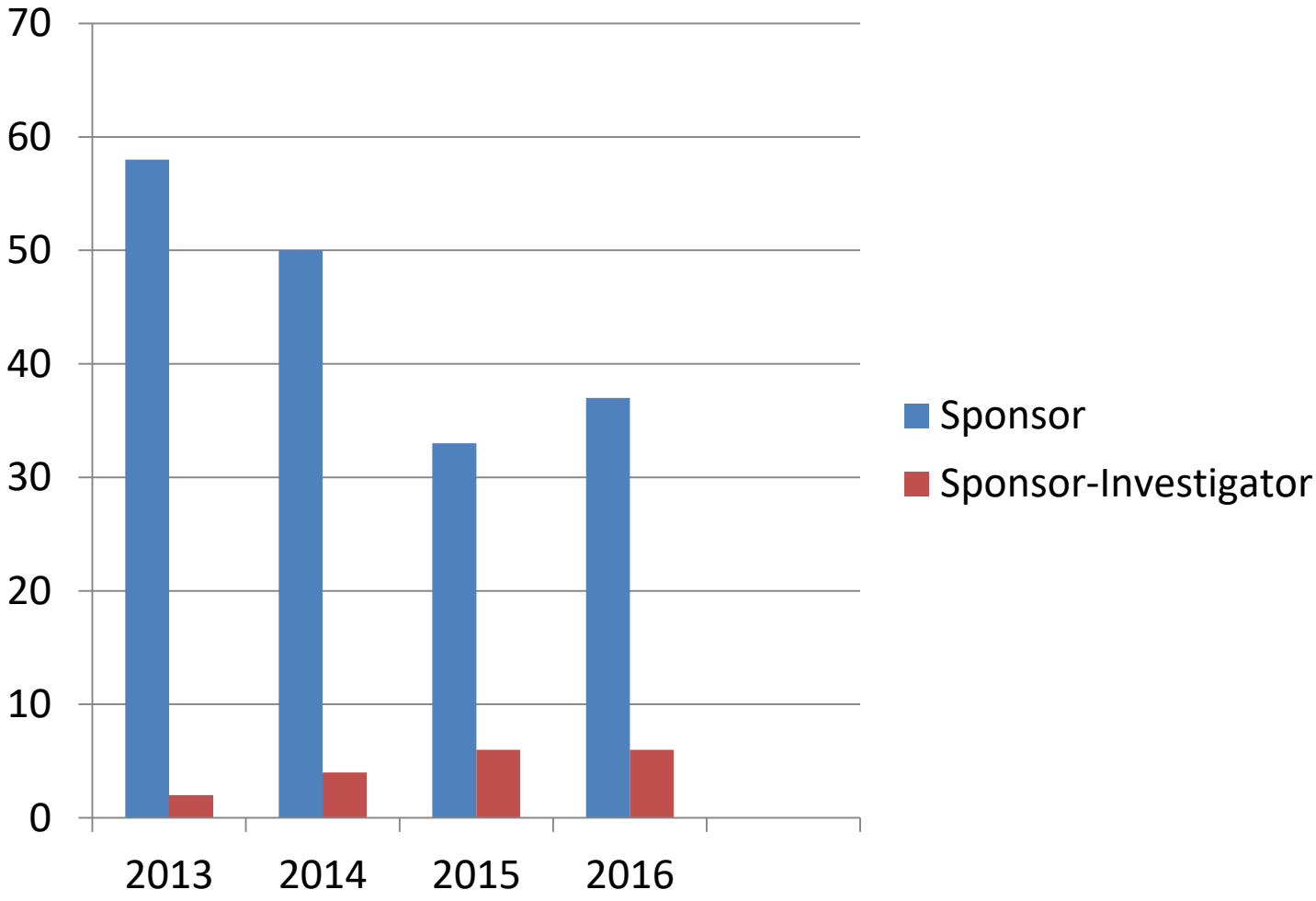
- Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
- BEQ Application-Inspections accomplished with 280 FY16 Site Visits
- Good Laboratory Practice and Bioequivalence inspection programs operated by OSIS as of January 2015

Sponsor/CRO/SI Inspections*



SI: Sponsor-Investigator
CRO: Contract Research Organization
*Based on inspection start date [Complis database as of December 20, 2016]
The Sponsor/CRO distribution shifted for FY09-12 in previous releases due to data corrections in the Complis Database.

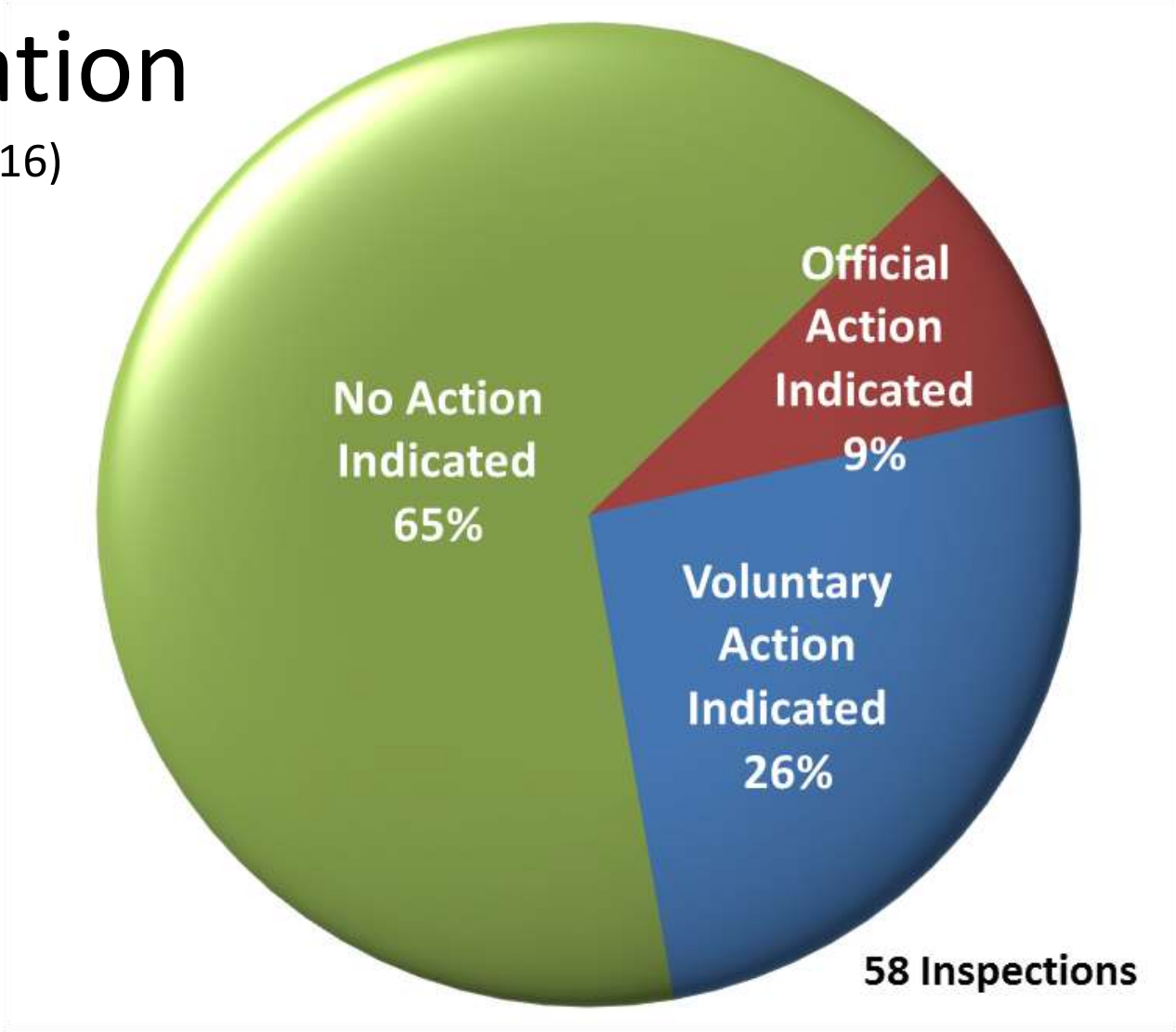
Sponsor & SI Inspections



FY 2013 – 2016 (as of 11/18/16)
Data searched by Inspection Start Date

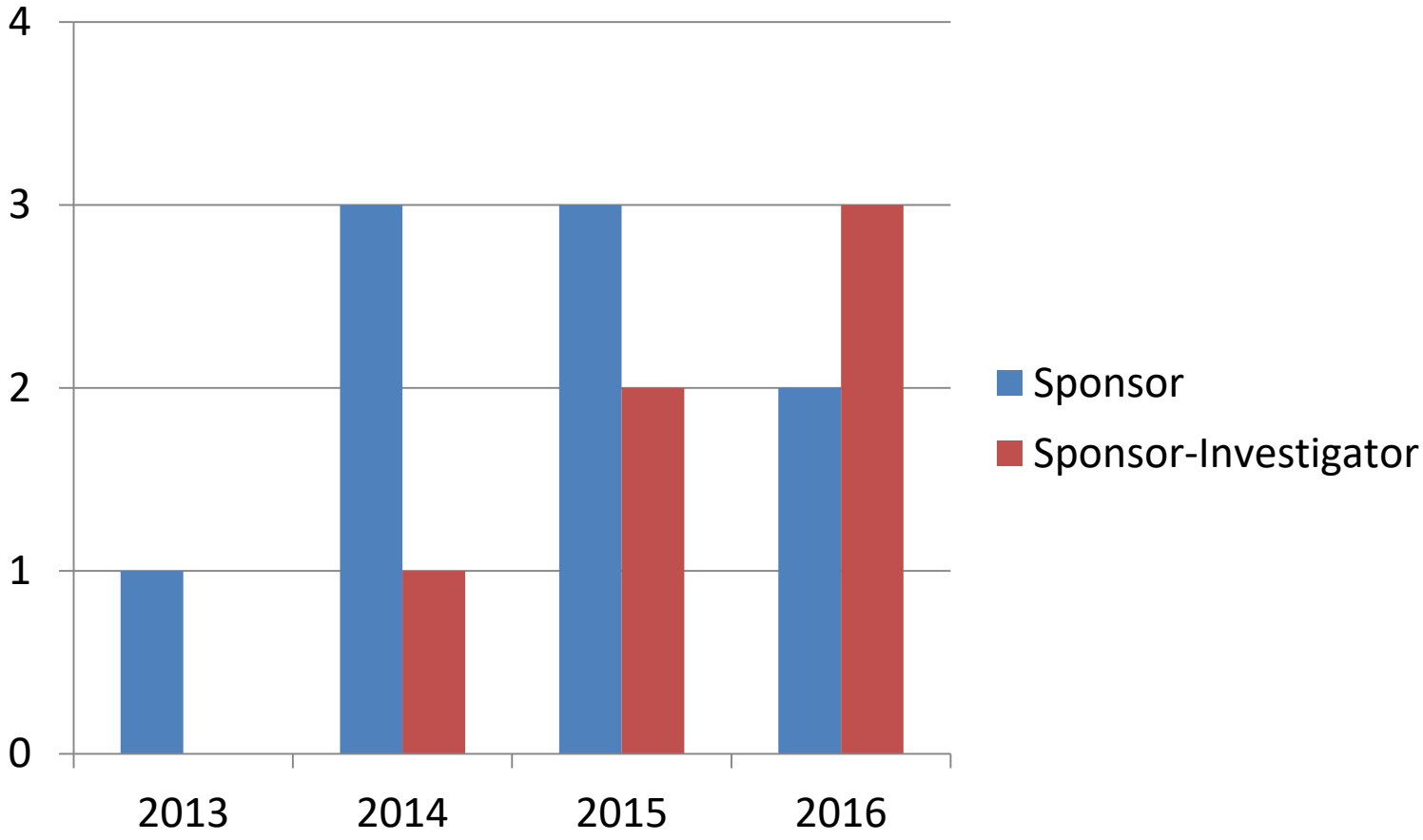
Sponsor/SI/CRO Classification

(CDER, FY 2016)



*Based on letter issue date [Complis database as of December 20, 2016]
Includes Sponsor-Investigator Inspections

GCP Sponsor & SI OAI Classification



FY2013-2016, as of 11/18/16

www.fda.gov

Most Common Sponsor Violations OAI letters

- Failure to ensure proper monitoring (2/3 of OAIs)
- Failure to submit an IND (1/3 of OAIs)
- Failure to ensure study is conducted according to investigational plan (1/3 of OAIs)

(FY 2013-2016*)

By a show of hands:

Regarding the sponsor-investigators, which violations do you think were more common in our 2013-2016 OAI letters ?

- Violations related to clinical investigator responsibilities
- Violations related to sponsor responsibilities

Most Common Sponsor-Investigator Violations-OAI Letters

- Failure to follow the protocol (2/3 of OAIs), as a CI
- Failure to submit an IND (1/2 of OAIs), as a sponsor
- Failure to maintain adequate records of disposition of drug (1/3 of OAIs)

(FY 2013-2016*)

A Case with Top 2 Sponsor Violations

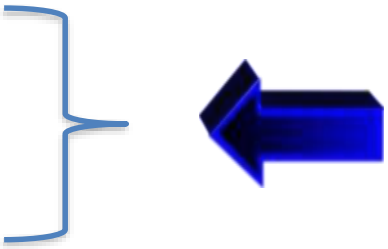
- Sponsor submitted an IND and provided data from Protocol 1 (ongoing)
- Protocol 1: Enrolled subjects before IND submission
- Herbal product: Administered to subjects for therapeutic effect
- Indication: To treat an infectious disease in a high risk patient population

Inspectional Findings

- ½ subjects randomized (50 screened)
- Product: Plant extract
- Study drug: unapproved
- No IND submitted prior to the study initiation
- No monitoring of the study (CI inspection)

What Did We Do?

- IND on hold!
- Inspection classified as OAI



Why?

  - Study initiated without IND submission
  - Lack of monitoring

All IND Exemption Criteria Met?

- A lawfully marketed drug in U.S. 
- Not intended to support a new indication or significant change in labeling, or advertising 
- Route of administration, dosage, patient population,… does not increase risk
- …

312.2(b)

Was The Plant Extract A “Drug”?

- “Articles intended for use in a diagnosis, cure, mitigation, treatment, or prevention of disease” and
- Articles (other than food) intended to affect the structure or any function of the body of man or animals

Was The Monitoring Adequate?

- Only verbal discussions with the CI!
- Non-compliant CI: no data collected on CRFs as required by Protocol 1
- Sponsor did not identify and/or correct the site's noncompliance

Prevention Is Better Than Treatment

- Use a well-designed, well-written, articulated protocol
- Train the CI and site staff
- Monitor, monitor, monitor
- Communicate efficiently on updates and revisions of the investigational plan

Useful FDA Guidance

- Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

- Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Summary

- BIMO program coverage and process
- Regulatory requirements for sponsors
- Metrics: sponsor and SI inspections
- Inspection classifications and actions
- Common violations
- Example

Questions

Please complete the session survey:

surveymonkey.com/r/DRG-D2S04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