CDER GCP Inspections and Outcomes

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CDER BIMO Good Clinical Practices (GCP) Compliance and Enforcement – February 16, 2022

Disclaimer

The contents of this presentation are my own and do not necessarily reflect the views and/or policies of the Food and Drug Administration or its staff as per 21 CFR 10.85(k).

Outline

- **Inspection** process
- Possible **outcomes**
- **Serious** non-compliance
- **Case examples**
- **Corrective and preventive** actions

GCP Inspections

Who is Inspected?

- Clinical investigator (CI)
- Sponsor (Sp)
  - Contract Research Organization (CRO)
- Sponsor-investigator (SI)
- Institutional Review Board (IRB)

- **Purpose** of GCP inspections
- **Inspection process**
- Possible **outcomes**
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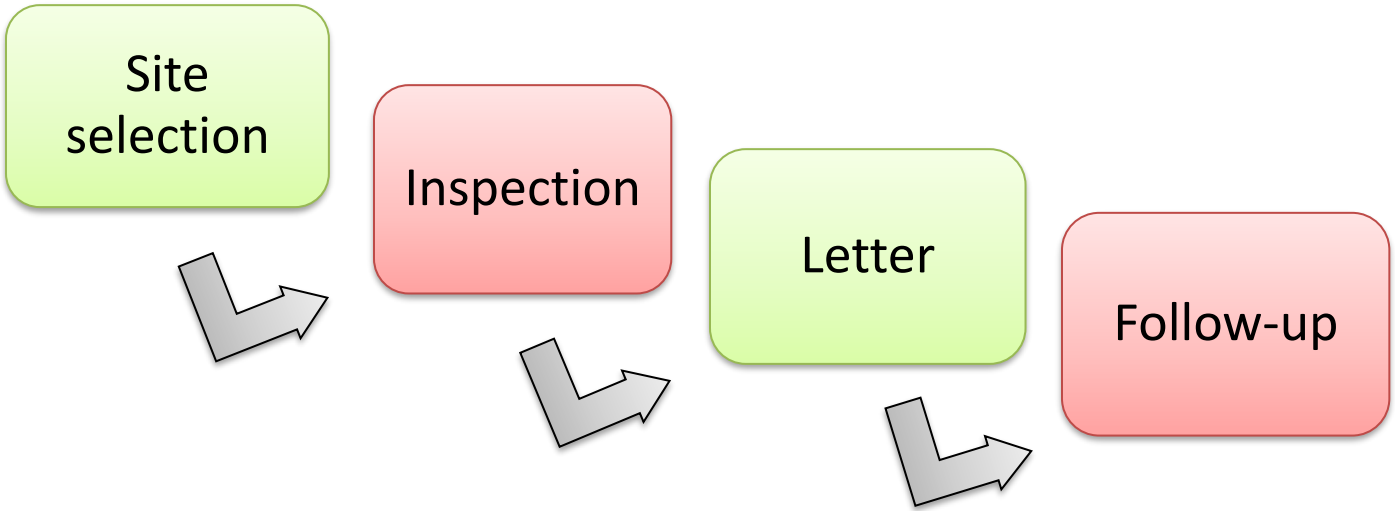
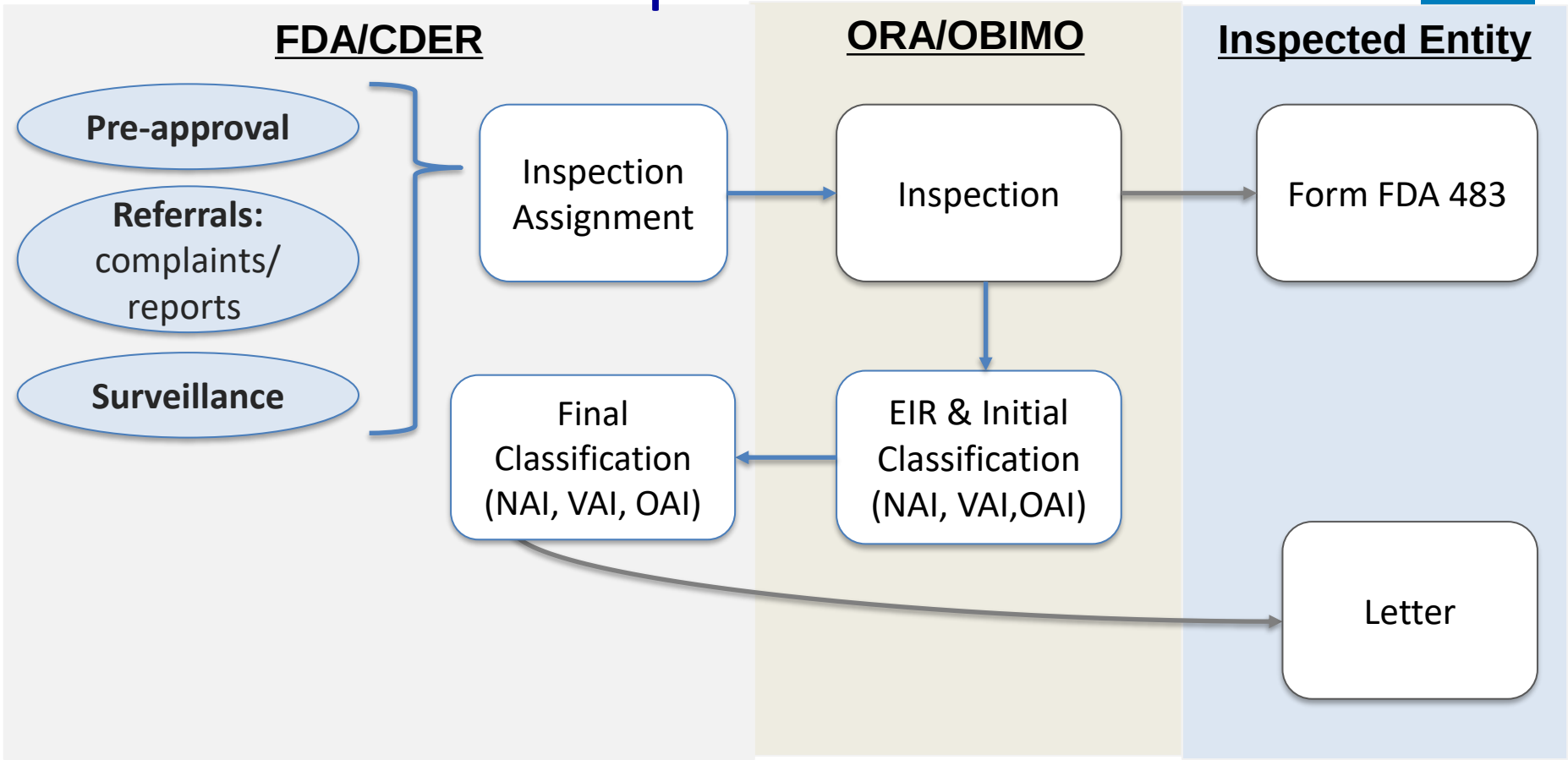
GCP Inspection Road Map



CI Site Selection Factors

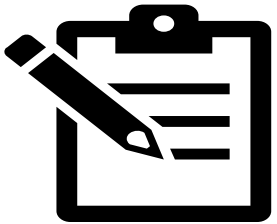
- Number of enrolled subjects
- Number of protocol violations
- Discontinuation rate
- Prior GCP history
- Prior inspections and their findings
- Number of INDs

GCP Inspection Process



What is reviewed?

- Human subject protection:
  - Informed consent adequacy, IRB approval
- Adherence to the protocol:
  - Eligibility criteria, randomization
  - Blinding, study visits
- Documentation practices; data verification:
  - Key: Primary endpoints, transfer of data into Case Report Forms (CRFs)
- Reporting compliance:
  - To IRB: unanticipated events, change in investigational plan
  - To sponsor: AE's and SAE's, …



3 Key Elements to Review

Study participants

- Safety, rights, and welfare come first!

Protocol adherence

- Protocol is the blueprint
- All sections of the protocol matter

Data verification

- Data: a clear reflection of study conduct?
  - Traceable records
  - Interpretable data

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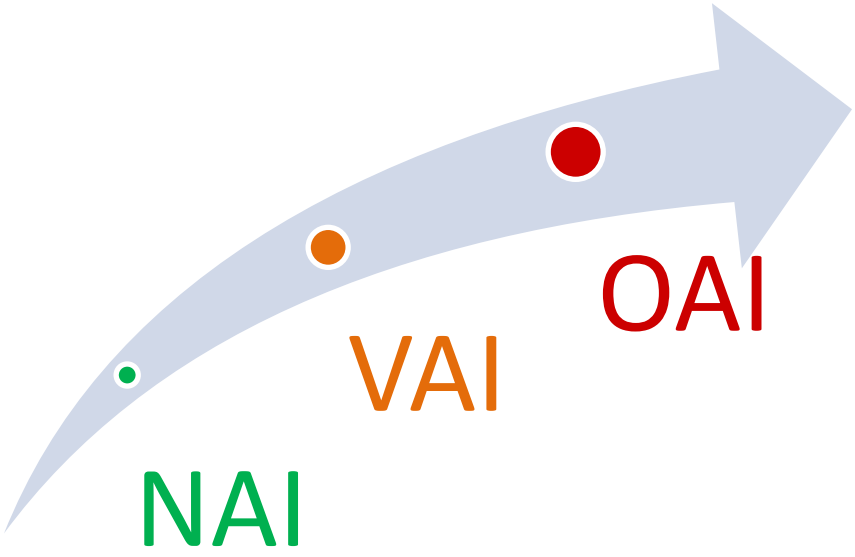
Final Inspection Outcome



NAI: no violations identified

VAI: violations identified but do not meet the threshold for OAI

OAI: serious noncompliance, repeated or deliberate failure to comply with the regulations

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

Why should we submit a 483 response?

15 business days

Form
FDA 483

+

Your
Written
Response

May

- Mitigate
- Disprove
- Clarify

Supporting documentation
Your acknowledgement
Your commitment

What to consider in your 483 response?

- Submit timely response
- Include a commitment
- Address each observation
- Note: if agree or disagree
- Provide corrective or preventive actions
- Provide timeline
- Provide method
- Submit documentation

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Official Action Indicated – OAI

- Significant and serious, and/or numerous regulatory violations
  - Repeated, deliberate
  - Falsified or fabricated data submitted to sponsor or FDA
- Scope, severity, or pattern of violations
  - Unreasonable and significant risk to subjects
  - Subjects' rights seriously compromised
  - Data integrity or reliability compromised

OAI – Warning Letter (WL)

- Available to the public (redacted)
- Informal and advisory
- An opportunity to improve compliance
- Follow-up inspection

OAI – NIDPOE

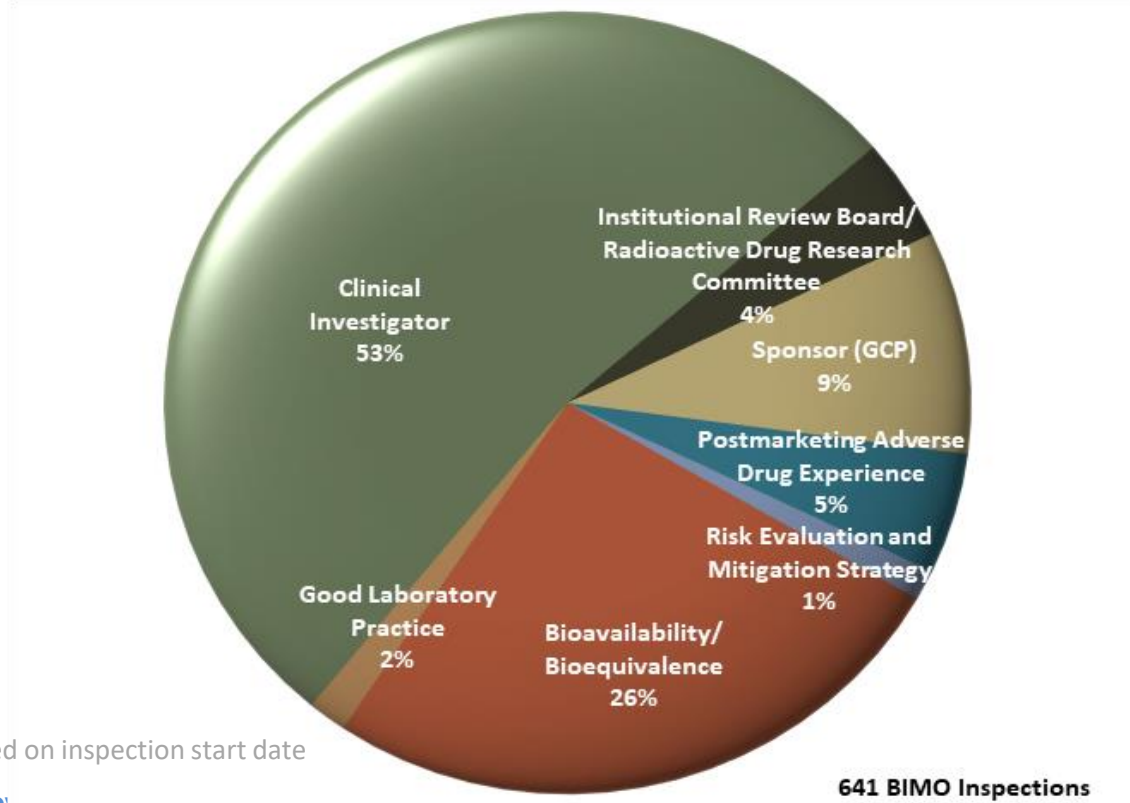
- The first step in disqualification
- For repeated or deliberate serious non-compliance
- For repeated or deliberate falsification
  - Submitted to FDA or to the sponsor
- Disqualification process initiated

Follow-up Inspection

- ✓To ensure violations are not repeated
- ✓To verify implementation of corrective/preventive actions
- ✓To ensure compliance is sustained

CDER BIMO Inspections

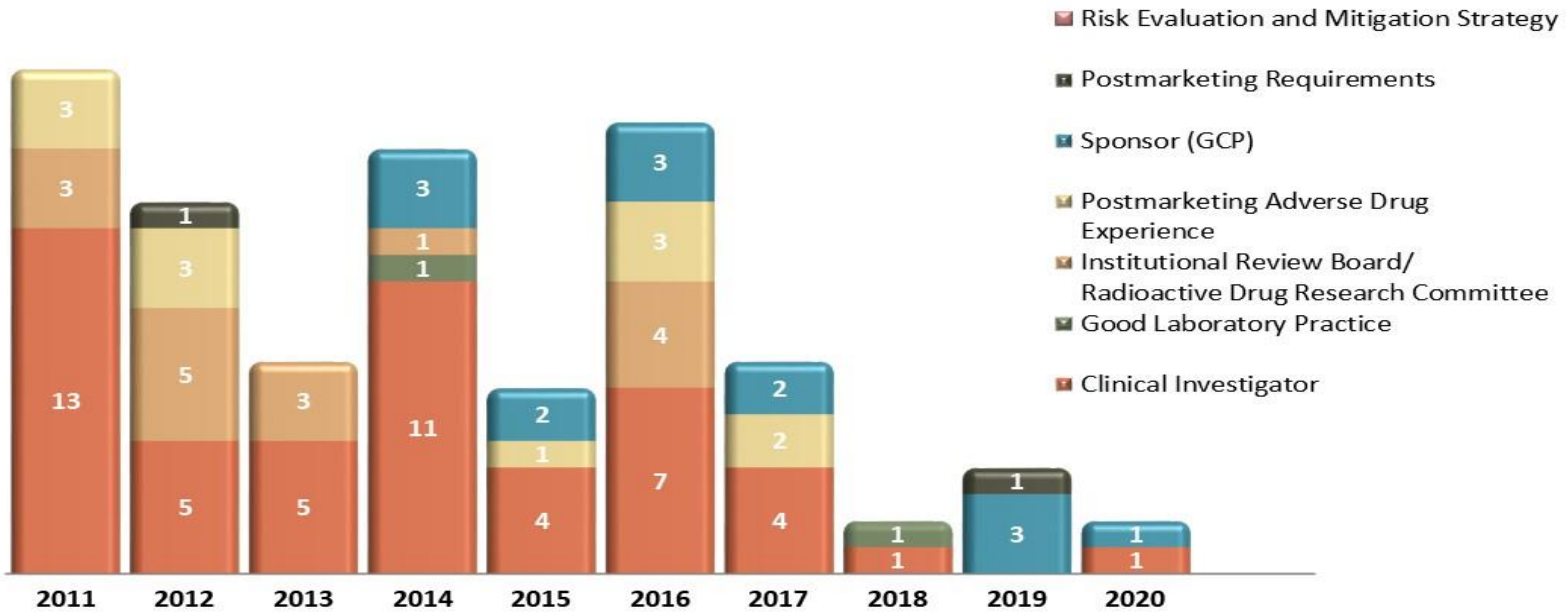
CDER BIMO FY 2020



Based on inspection start date

Warning Letters – BIMO

(CDER, FY 2011 - FY 2020)



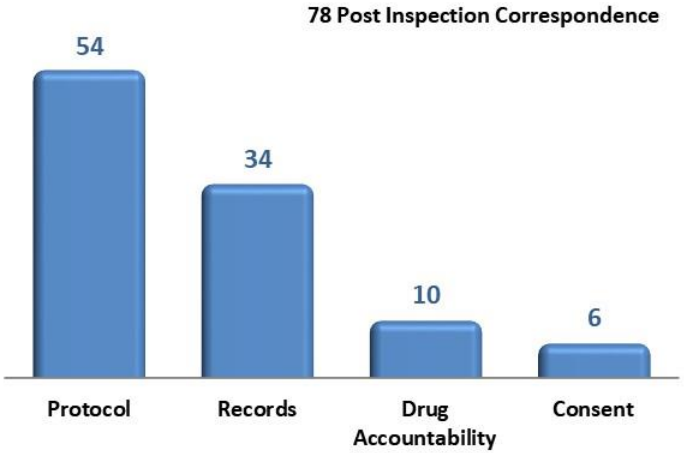
*Based on letter issue date [Complis database as of Feb 9, 2021].

- PMR includes: Accelerated Approval PMR (21 CFR part 314, subpart H); Pediatric Research and Equity Act PMR; Animal Efficacy PMR (21 CFR part 314, subpart I), and FDA Amendments Act PMRs (section 505(o)(3) of the Federal Food Drug & Cosmetic Act).
- Sponsor metrics include both Sponsor and Sponsor-Investigator.

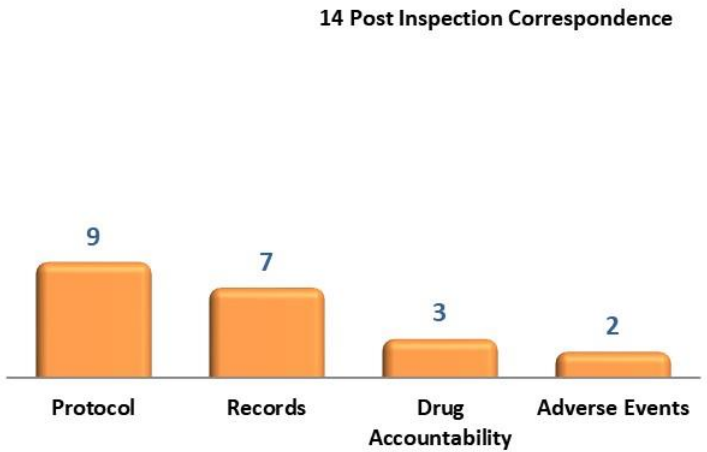
Inspectional Findings – CI

(CDER, FY 2020)

Domestic CI Deficiencies



Foreign CI Deficiencies



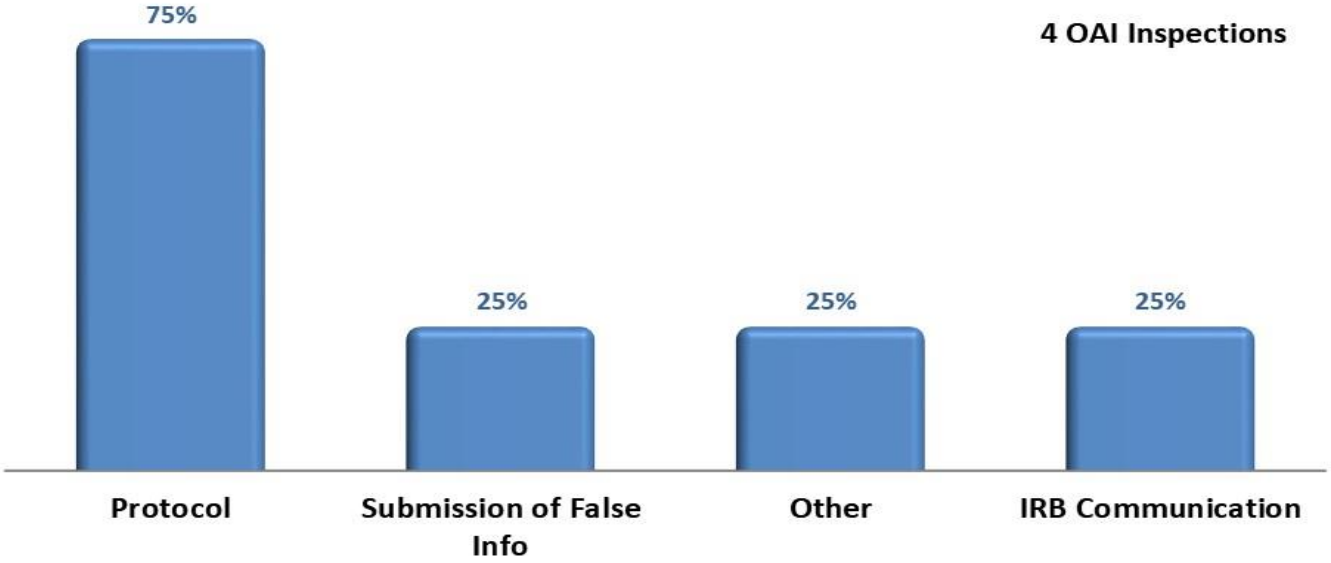
*Based on LogOut Date and Classification. [Complis database as of Feb 9, 2021]. Log out date: Final completion date

** Inspection Activity with Voluntary Action Indicated (VAI) and Official Action Indicated (OAI) Classifications.

- Note: this does not denote number of inspection activities completed, but rather number of inspection reports evaluated and closed. *Inspection activity may have multiple deficiencies.*

Frequency of Inspectional Findings: CI – OAI

(CDER, FY 2020)

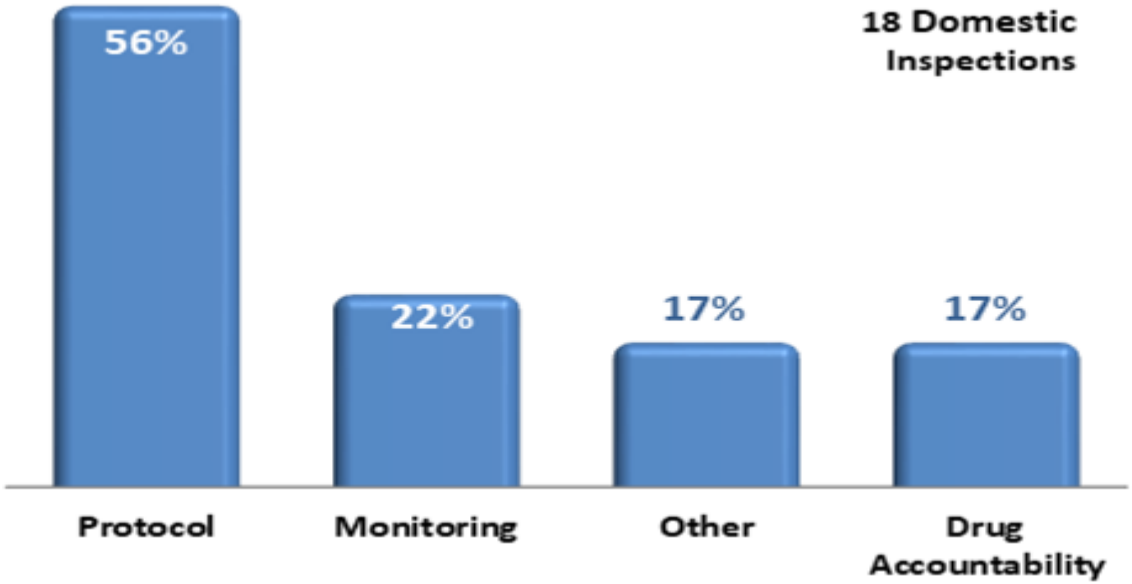


*Based on letter issue date. [Complis database as of Feb 9, 2021].

- Note: this represents the number of inspection reports evaluated and closed which differs from the number of inspection activities performed. *Inspection activity may have multiple deficiencies.*

Inspectional findings – Sponsors

(CDER, FY 2020)



Based on final inspection classifications and letter date.

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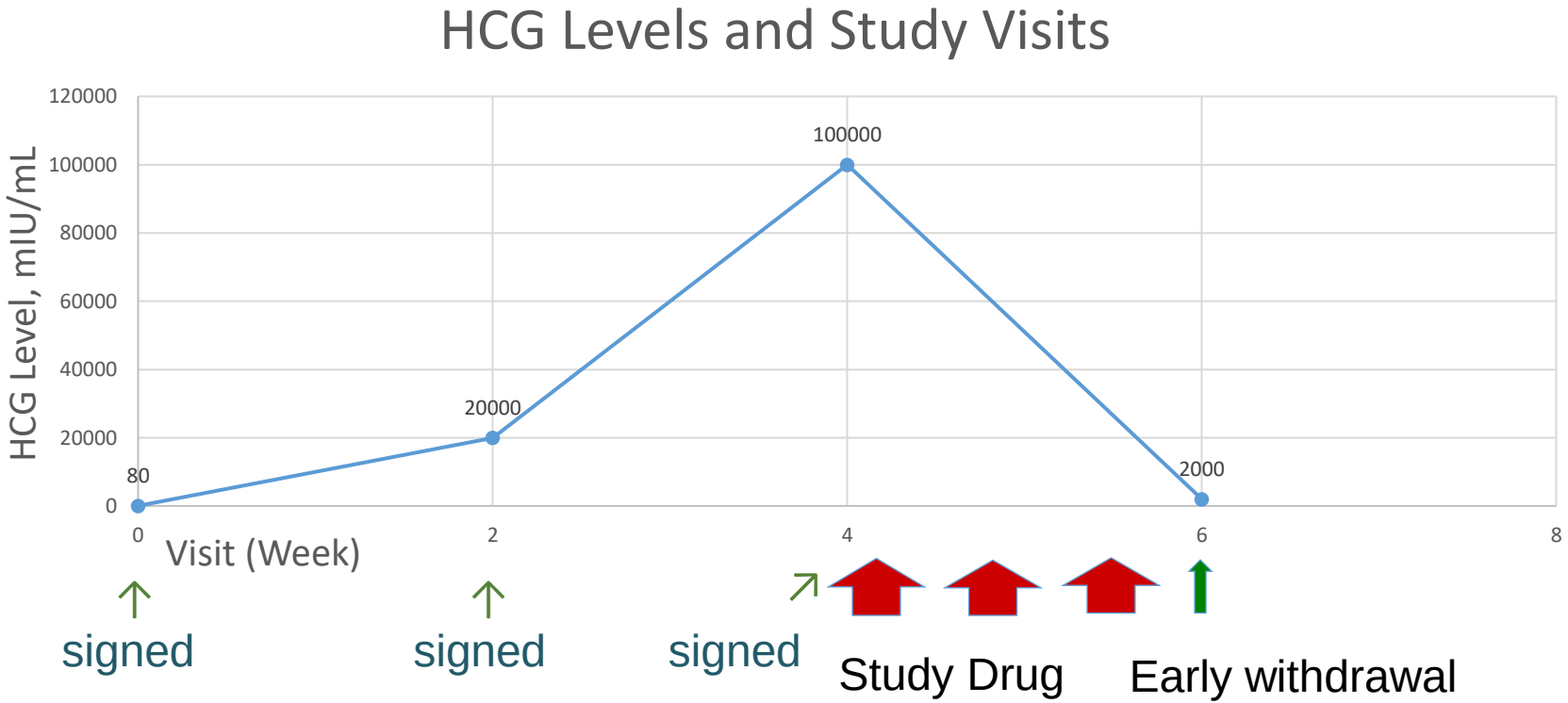
CI – WL: Failure to Retain Records

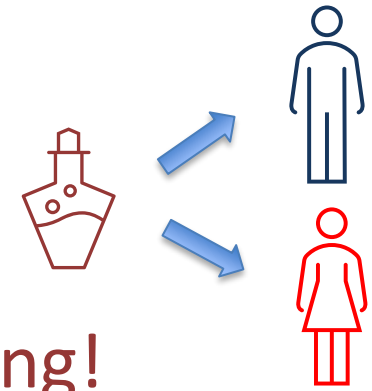
- 22 subjects were enrolled and completed the study.
- After study completion, all records were packed into boxes, and placed in archiving room.
- FDA inspection found missing records:
  - All 22 signed/dated consent forms and all case report forms
  - For 16 of 22 randomized: Medical histories, eligibility, adverse events, concomitant meds, progress notes, visit assessments
- 483 Response: Department reorganization contributed to the loss of records.
- WL was issued for failure to retain records.

CI WL – Protocol Violation



Sponsor WL – Failure to Submit IND

- Sponsor did not submit an IND!
  - An unapproved antiviral drug
  - To subjects with HCV-HIV co-infection
- Sponsor did not ensure proper monitoring!
- 483 response:
  - Sponsor's judgment:
    - The product was not a drug; but a dietary/food supplement.



HCV: hepatitis C virus
HIV: Human Immunodeficiency syndrome

21 CFR 312.2(a) [21 CFR 312.20(a) and 312.40(a)

IND Exemption Criteria

- 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 significantly increase risk
- For lawfully marketed drugs, not intended to support a significant change in advertisement for the drug

312.2(b)

…IND Exemption Criteria

- In compliance with IRB requirements for informed consent
- In compliance with requirements for promotion of the study drug
- A bioavailability or bioequivalence study of an unapproved version of an approved drug product

21 CFR 312. 50 and 56
21 CFR 312.7
21 CFR 320.31 and 21 CFR 312.2(c))

CI NIDPOE – Data Falsification

- Data falsification after subject's death:
  - Study records falsely documented efficacy endpoint assessments
  - Physical exams, AE assessments, concomitant meds
  - Telephone visits related to primary endpoint
  - False data (primary endpoint) submitted to the sponsor

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Some Tips for CAPA

Focus on violations in original OAI

Establish all GCP aspects

Hire Qualified staff

Improve Documentation: SOP, work instructions, study worksheets

Train: CI and study team

Strengthen Site Infrastructure

Design study-specific CAPA

Implement and Sustain CAPA

Summary

- Inspection procedures
- Inspected entities: CI/Sp/SI
- Inspection outcome: NAI/VAI/OAI
- Examples of OAI letters

Closing Thought…

- Build high standards for GCP compliance:
  - Proactive compliance
  - Well-articulated protocol
  - Risk identification

Challenge Question

What is usually the most common type of regulatory violation found in clinical investigator inspections?

A. Record keeping violations

B. Informed consent violations

C. Protocol violations

D. Failure to report unanticipated events to the IRB

References

- U.S. Food and Drug Administration, Investigations Operations Manual 2021
  - https://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM607759.pdf
- U.S. Food and Drug Administration Bioresearch Monitoring Program (BIMO) Compliance Programs
  - https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs
- U.S. Food and Drug Administration, Regulatory Procedures Manual Chapter 4 Advisory Actions
  - https://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074330.pdf

Thank you!

Questions?