# CDER GCP Inspections and Outcomes

**Faranak Jamali, MD**
Compliance Reviewer, Compliance Enforcement Branch
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations/Office of Compliance
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration

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**
- **Serious** non-compliance
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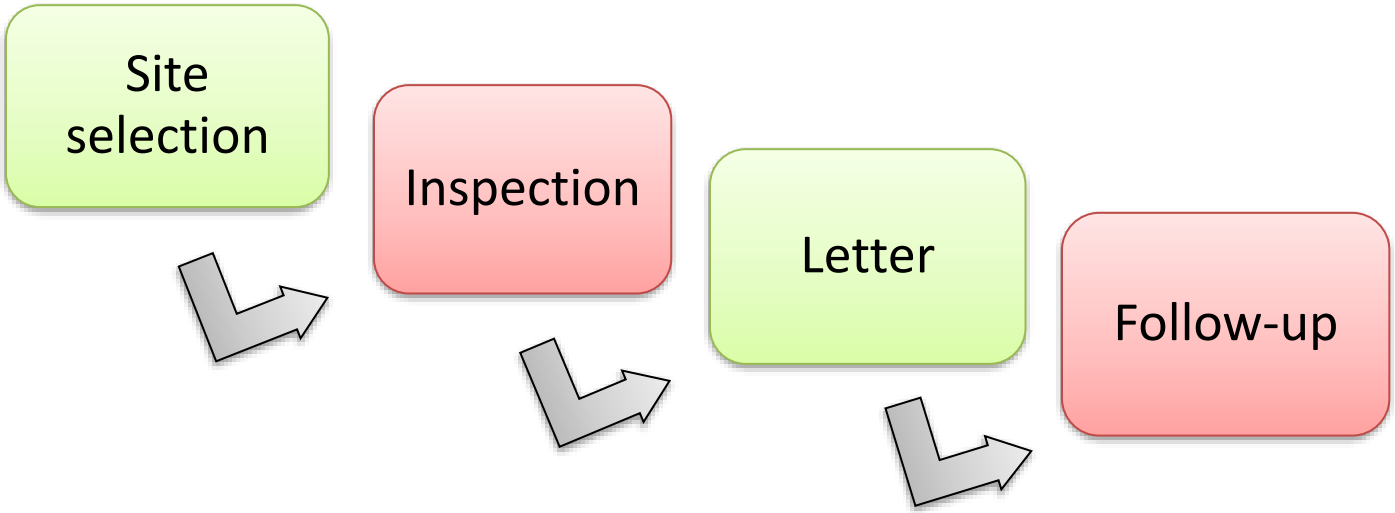
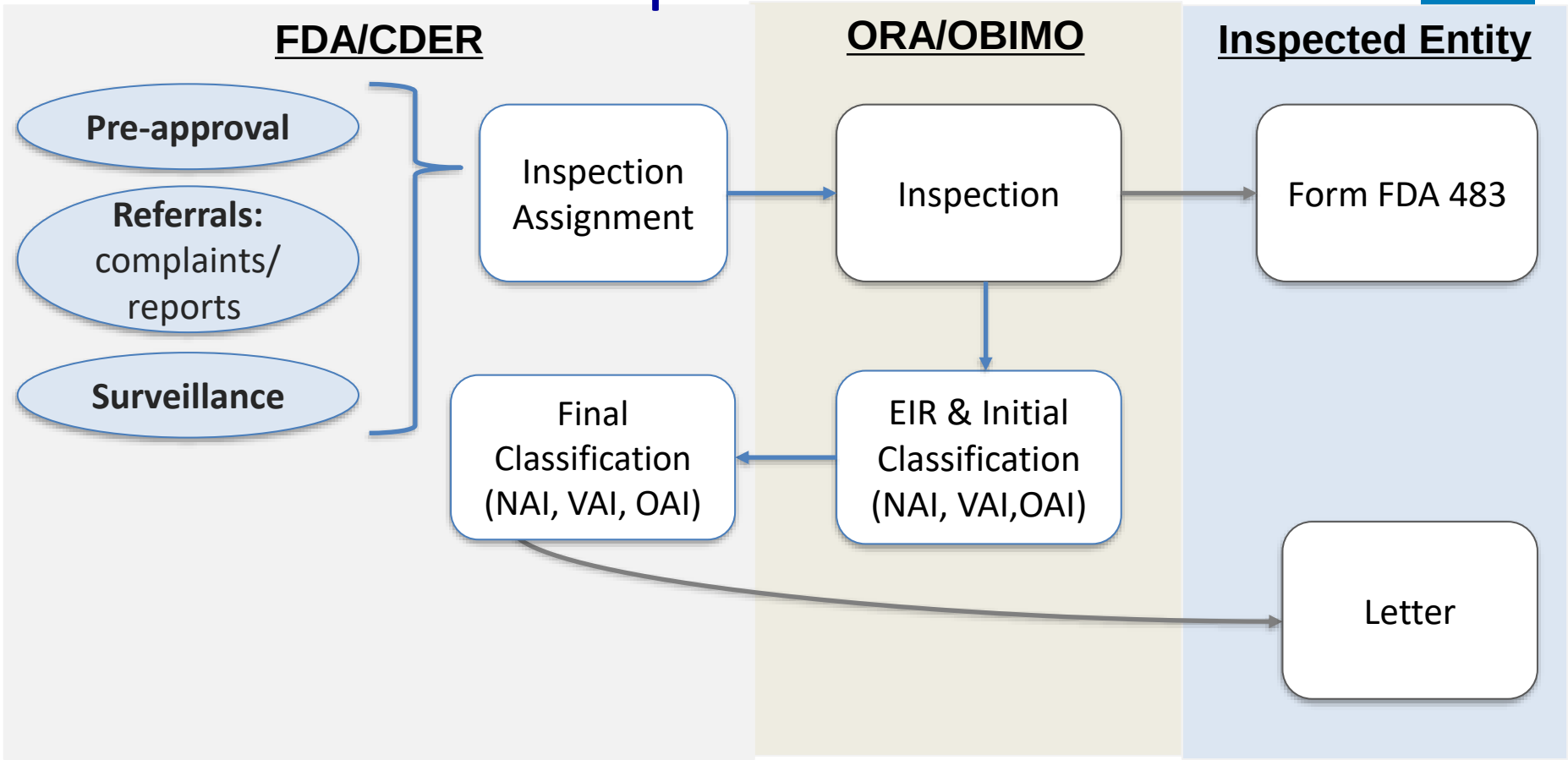
# GCP Inspection Road Map



# CI Site Selection Factors

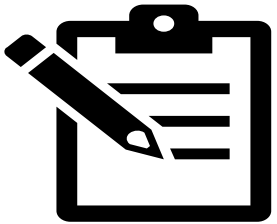
- Number of enrolled subjects
- Number of protocol violations
- Discontinuation rate
- Prior GCP history
- Prior inspections and their findings
- Number of INDs

# 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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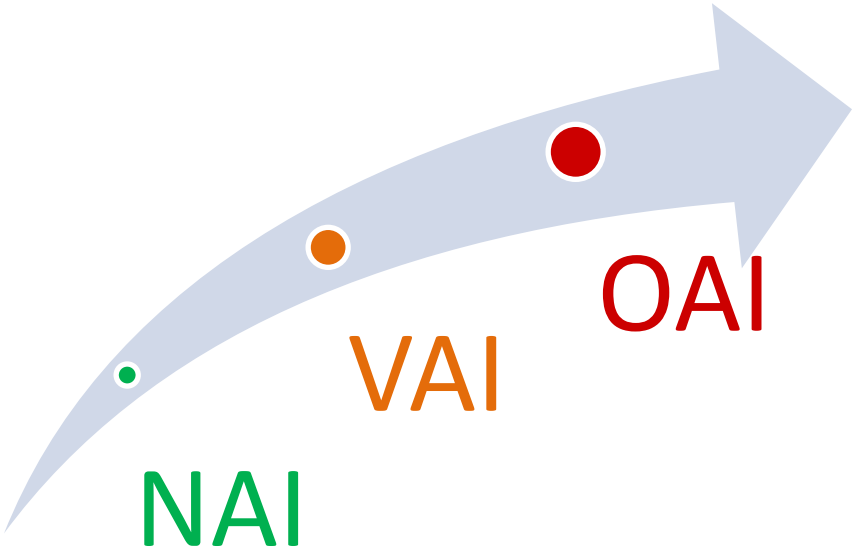
# Final Inspection Outcome




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

- **Purpose** of GCP inspections
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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

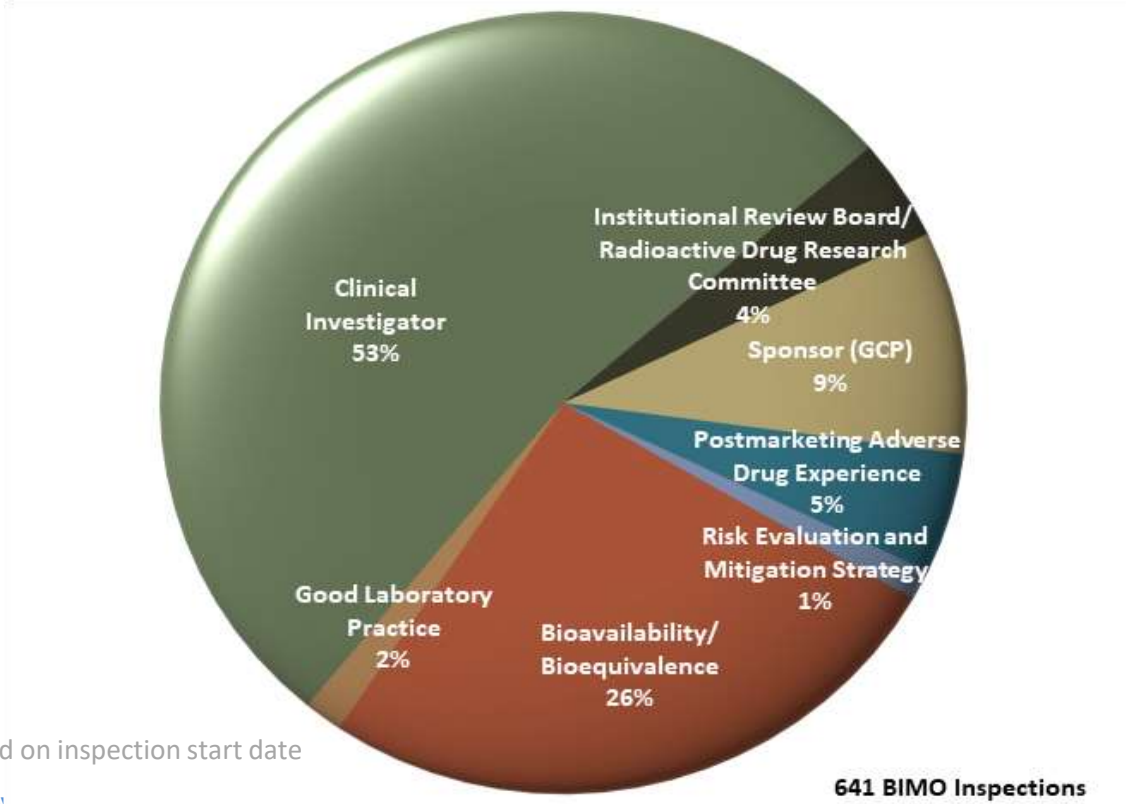
- The first step in disqualification
- For repeated or deliberate serious non-compliance
- For repeated or deliberate falsification
  - Submitted to FDA or to the sponsor
- Disqualification process initiated

# Follow-up Inspection

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

# CDER BIMO Inspections

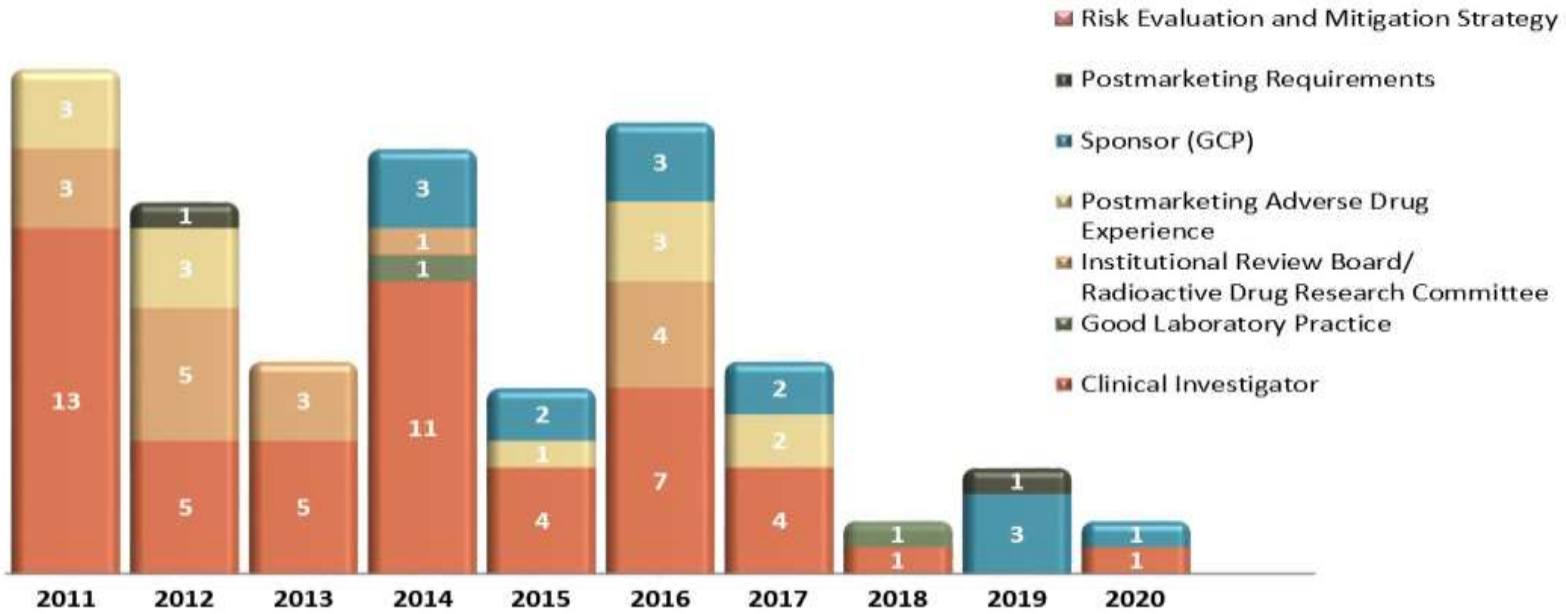
CDER BIMO FY 2020




Based on inspection start date

# Warning Letters – BIMO

(CDER, FY 2011 - FY 2020)



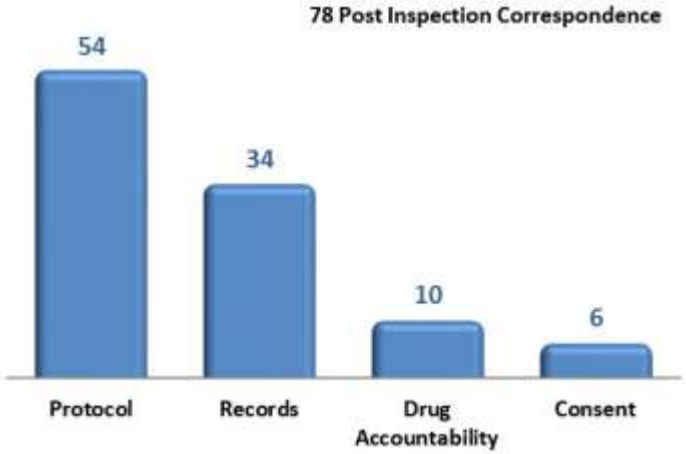

*Based on letter issue date [Complis database as of Feb 9, 2021].

- 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

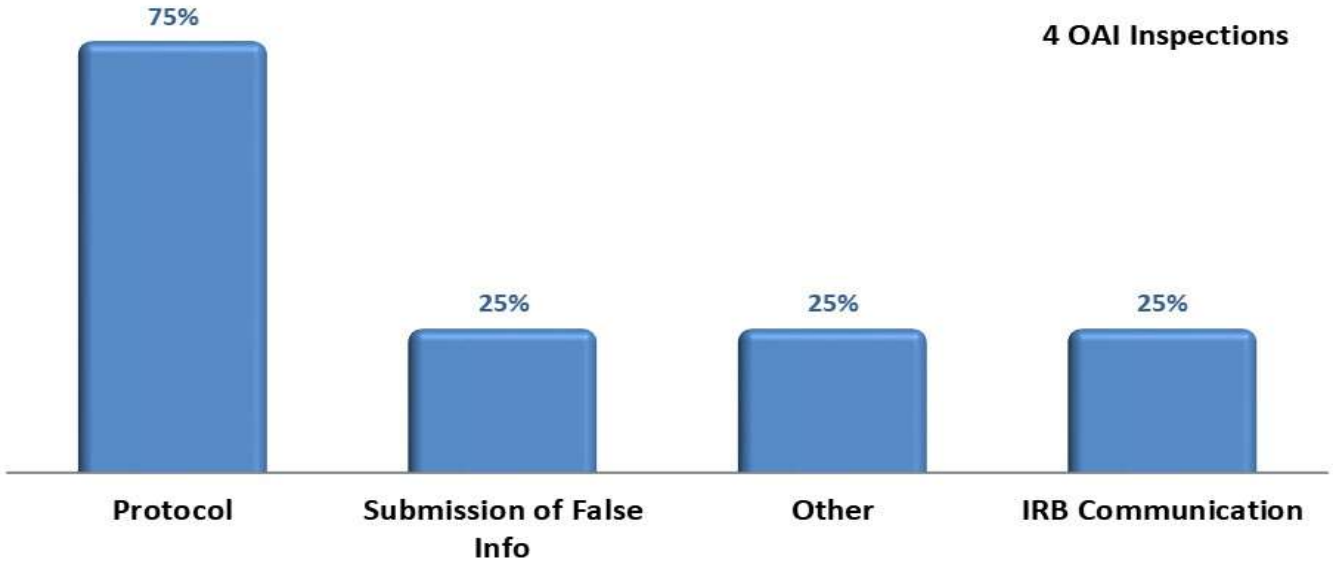

*Based on LogOut Date and Classification. [Complis database as of Feb 9, 2021]. Log out date: Final completion date

** 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)

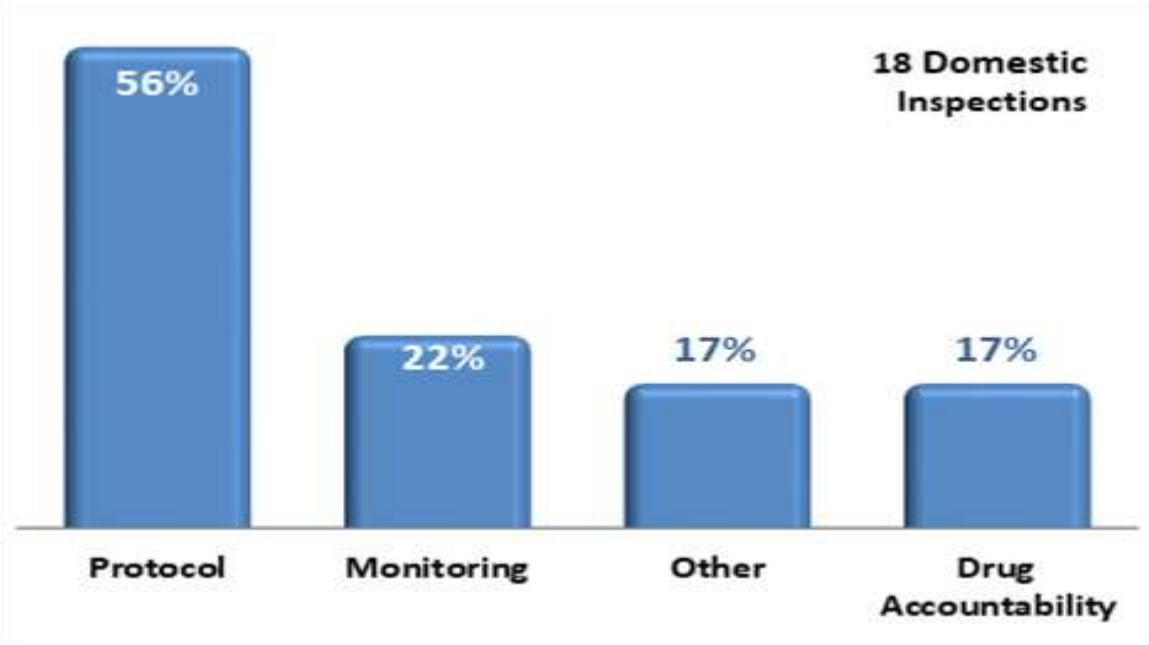



*Based on letter issue date. [Complis database as of Feb 9, 2021].

- 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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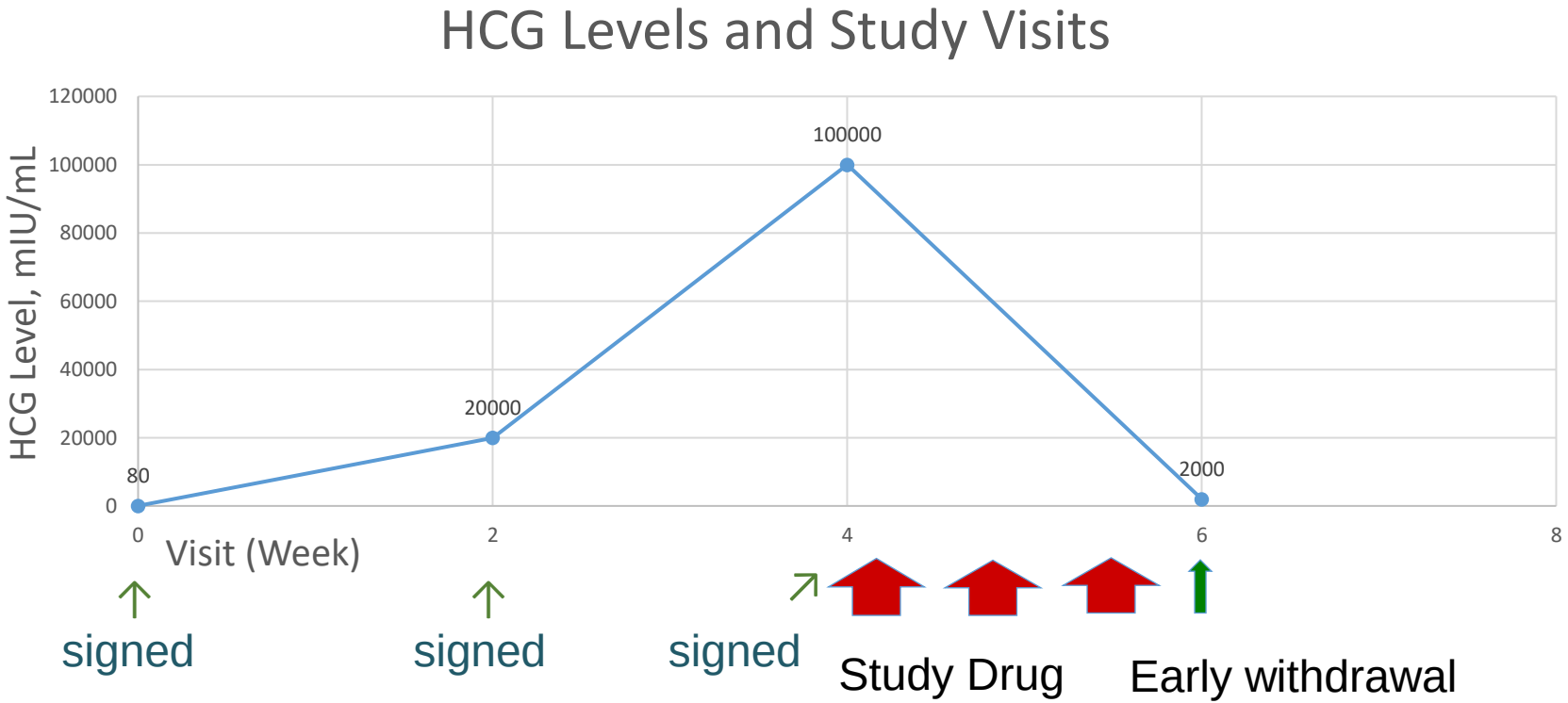
# CI – WL: Failure to Retain Records

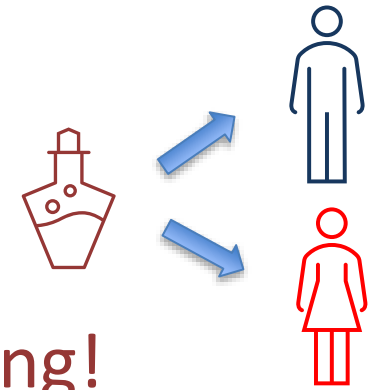
- 22 subjects were enrolled and completed the study.
- After study completion, all records were packed into boxes, and placed in archiving room.
- FDA inspection found missing records:
  - All 22 signed/dated consent forms and all case report forms
  - For 16 of 22 randomized: Medical histories, eligibility, 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?