Introduction of Good Laboratory Practice

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Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily reflect the official views of the Food and Drug Administration (FDA).

Outline

- Goal, scope and approach of GLP
- FDA GLP inspection program
- Areas of concerns and case examples
- GLP inspections in China

Starting Point

- Nonclinical safety data is the first step in understanding the possible safety concerns that FDA might have to deal with.
  - for example, based on the results of toxicology testing, a human trial might be placed on clinical hold or allowed to proceed.

Intent of GLP

- Provides a framework for conducting well-controlled studies
  - assures quality and integrity of the data
  - facilitates study reconstruction
  - provides overall accountability

Role of GLP Compliance

- Ensure the consistency and reproducibility of preclinical studies included in FDA applications
- Nonclinical studies that evaluate safety must be GLP compliant

Scope of GLP Regulations (21 CFR 58.3)

This part describes **good laboratory practices** for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration…compliance with this part is intended to assure the **quality and integrity** of the **safety data**…

This includes: human and animal drugs, biological products, medical devices for human use, electronic products, food and color additives, and feed additives.

GLP: Regulatory Scope & Purpose

In vitro

In vivo

Human studies

- Nonclinical safety data is the first step in identifying possible safety concerns

Nonclinical Safety Studies

- Toxicity studies
  - general toxicity studies, genotoxicity studies, reproductive toxicity studies, carcinogenicity studies
- Safety pharmacology studies
  - cardiovascular, respiratory, CNS
- PK/TK evaluation included in GLP toxicity studies

Studies Not under GLP Scope

- Human clinical studies
- Basic research (nonclinical pharmacology studies for mechanisms of action, efficacy)
- Discovery toxicology studies
- Nonclinical PK evaluation that is not part of a GLP study
- Bioanalysis of samples for clinical trials
- Bioanalytical assays as part of a GLP study conducted in the analytical lab: GLP compliance

GLP Regulations Are **NOT:**

- Regulations that certify a facility
- Regulations that govern all animal studies
- Regulations that dictate science

GLP Goal

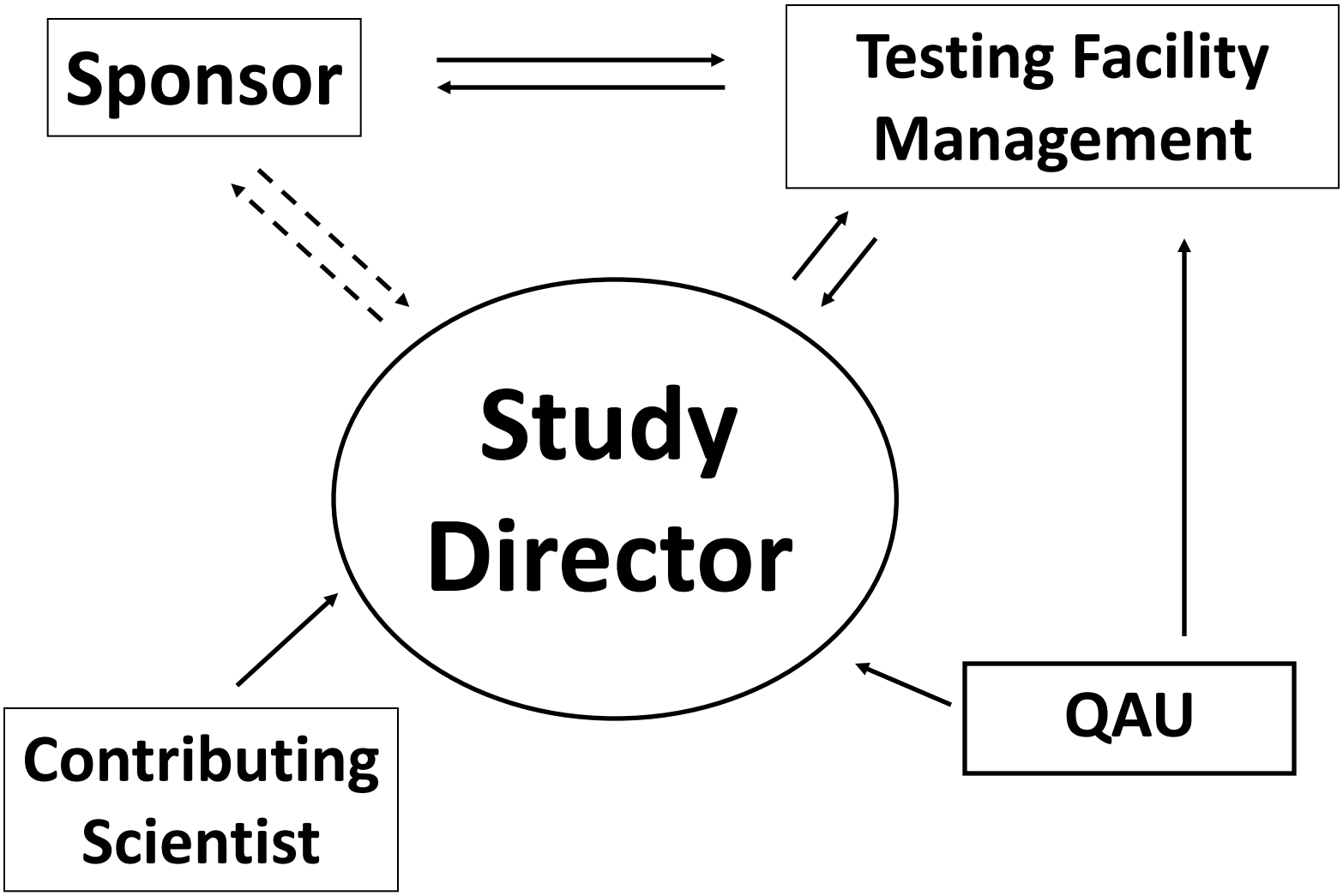
- Data quality and integrity
  - well-planned and carefully-executed studies provide the most useful information to FDA reviewers
  - compliance with GLP elements is a major step toward achieving this goal
- *All* studies used in support of FDA regulatory submissions should contain high quality data, regardless of whether Part 58 compliance is required

GLP Approach

- Process-oriented
  - GLP can provide quality data as a result of proper utilization of and control over facilities, personnel and procedures
- In the United States, there is no certification process for laboratories or facilities conducting nonclinical regulated studies

GLP Approach

- Since each compound is different, each safety study is unique.
- Allows flexibility in laboratory operation and use of scientific judgment
  - study directors must exert this judgment.
    - overall responsibility for technical conduct, interpretation and reporting


Sponsor
Testing Facility Management
Study Director
Contributing Scientist
QAU

OECD GLP

- CDER often sees compliance statements citing utilization of the OECD Principles of GLP.
  - since there are common items to allow compliance with both, if foreign sites follow OECD GLP Principles it is likely that they are compliant with Part 58.

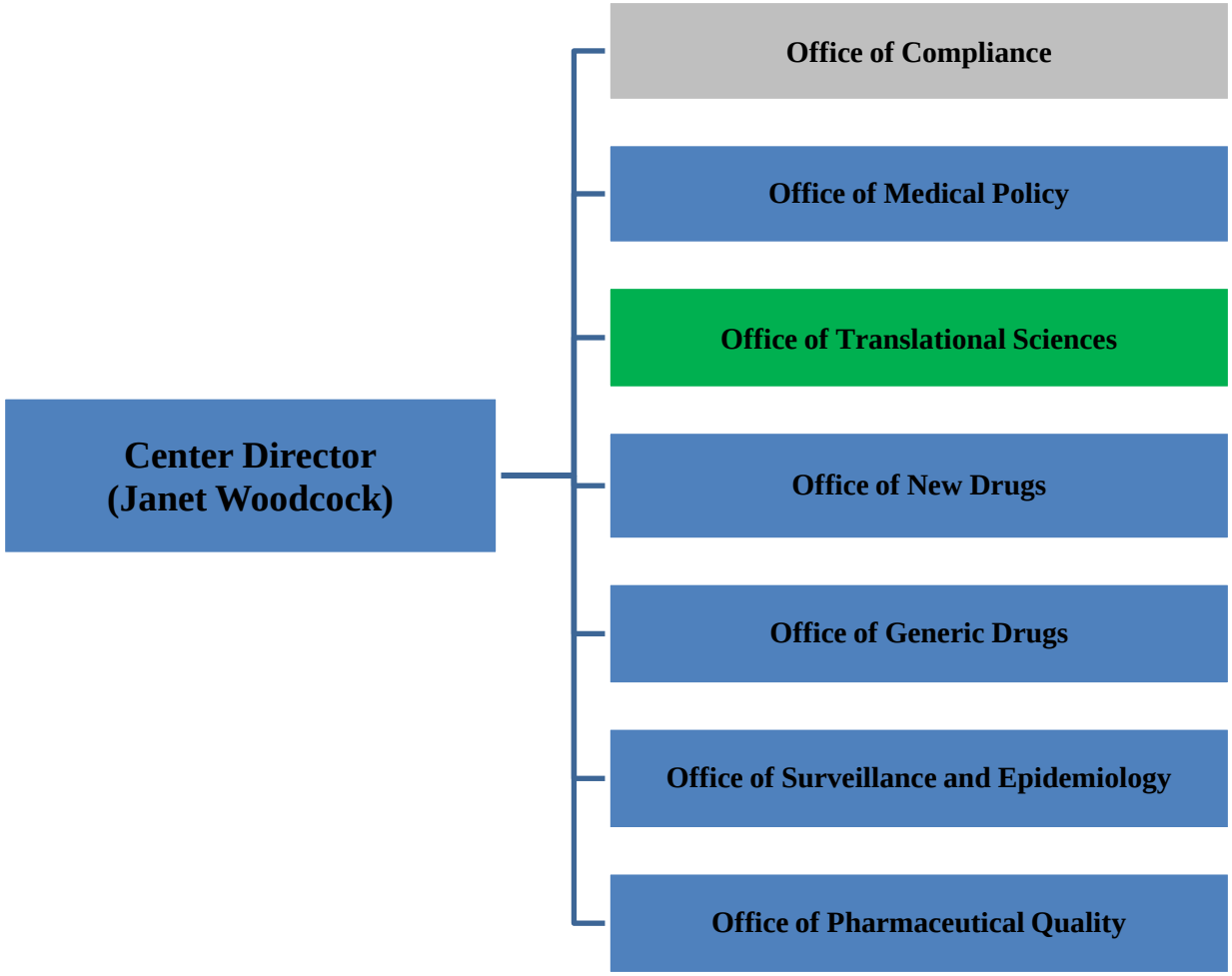
Compliance Status

- Final report statements (claims) of GLP compliance do not guarantee compliance or good science.
- Many “GLP compliant” studies fail to provide useful data and can be misleading as well.

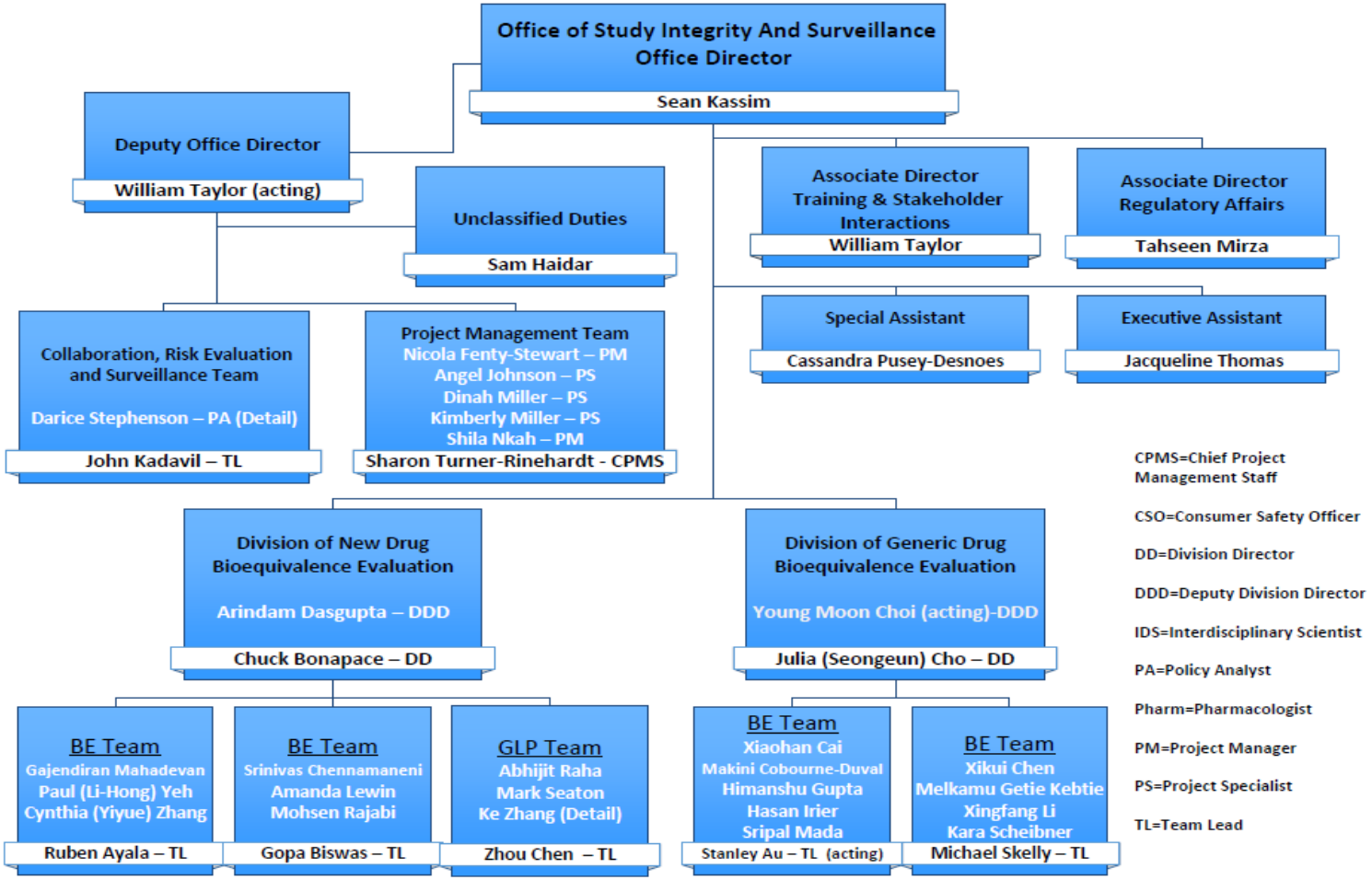
FDA's GLP Inspection Program

- Verify the GLP compliance of the testing facility
- Verify the quality and integrity of nonclinical studies used to protect human subject safety
- Audit studies pivotal to review decisions
  - IND, NDA, BLA
- All inspection expenses covered by the US government budget

CDER Organizational Chart



Office of Study Integrity and Surveillance



Directed GLP Inspections

- Address CDER concerns about data integrity and study conduct
  - nonclinical studies under review in CDER
    - verify the quality of studies pivotal to regulatory decisions
  - domestic and foreign sites
    - sponsor laboratories, contract research laboratories, academic institutions
- Complaint follow-up
  - data falsification, lack of GLP compliance

GLP Surveillance Inspections

- Periodic, routine evaluation
  - general capability to conduct GLP-compliant studies
    - facility overview
    - includes a data audit of recently completed studies
    - approximately every 2-4 years, limited to domestic facilities
  - provides industry with useful information about CDER's expectations of GLP compliance

Surveillance Inspections

- The number of testing facilities to be inspected is determined at the beginning of each fiscal year
- Studies selected from the Master Schedule or CDER database with CDER OSIS assistance
- Usually performed every 2-3 years, limited to domestic facilities

References

- FDA Regulations – 21 CFR Part 58
  - Good Laboratory Practice for Nonclinical Laboratory Studies
    - describes requirements for conducting and reporting nonclinical laboratory studies
- Compliance Program Guidance Manual
  - Good Laboratory Practice Program 7348.808
    - general inspectional focus; minimum information that must be obtained during an inspection
    - http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133765.pdf

Strategy in GLP Inspections

- Audit complex studies that entail all/most components of regulations
  - More than one QAU inspection
  - Reserve samples from studies >28 days
  - IACUC monitoring if non-rodent mammals
  - Off-site contributing scientists
  - Unforeseen circumstances
  - More likely to support clinical trials

Some Facts for CDER GLP Inspection

- Number of GLP inspectors in CDER: 4
- Number of ORA BIMO investigators: 90
- Number of testing facilities: No complete list, but more than 300 facilities
- Testing facilities audited each year: about 30
- Fees charged for inspections: $0
- Certification: FDA does not certify GLP labs
- How to get FDA inspection: GLP studies submitted to CDER with drug applications

GLP Problem Areas and Case Examples

Problem Area: Test Articles

- Study directors don't always know if the intended dose was the actual dose administered.
  - test article purity, stability not provided to study director; thus not available for final report
  - GLP violation: 21 CFR 58.185(a)(4)
  - Results of concentration, uniformity, stability not available for discussion as possibly affecting quality/integrity
  - GLP violation: 21 CFR 58.113

Inspectional Example 1

- GLP surveillance inspection
- Dosing formulations not tested for strength, stability, and uniformity
- Post-inspection assay results found sub-potent concentrations

Why this might be happening…

- Test article characterization and dosing formulation analyses are sometimes thought of as “sponsor responsibilities.”
  - sponsor can test but study directors need the results.
- Study directors, testing facility management don’t necessarily follow-up and require the data.

Problem Area: Study Director

- Single point of study control
- Overall responsibility for technical conduct of study, interpretation, analysis, documentation, reporting of results

Inspectional Example 2: Incomplete Final Report

- Test article detected in control group dosing formulations
- Study director
  - signed the final report before receiving the results
  - failed to address the impact of contamination on study outcome in the final report
- A circumstance that may have affected the quality or integrity of the data!

Inspectional Example 3: Reproducibility Issue?

- Safety study with concomitant TK
- Drug in control and placebo plasma samples
  - levels as great as 36 times the LLOQ
- Accuracy of reported TK concentrations not reliable
  - large difference between original and repeat results (25-525%)

Test Article in Controls

- Increased reports of significant drug levels in untreated animals
  - concentrations measured in plasma/serum greatly exceed the limit of quantitation for the assay.
- Source
  - Dosing error?
  - Sample contamination?
  - Analytical error?

Inspectional Example 4: Observational Sensitivity

- Reprotoxicity studies found unusually low incidence of spontaneous variations, malformations.
- In both control and treated animals
- Concern regarding observational sensitivity
  - Abnormality rate reported to FDA 0.15%
  - Published, spontaneous abnormality rate 4.3-7.2%

OSIS found…

- Study personnel with less training than counterparts at other facilities
- No explanation for low rate of thoracic and abdominal abnormalities reported

- Impact: More than 100 studies unreliable for review purposes
  - If no inspection, having accepted numerous flawed studies, how are the safety assessments valid in preparing for human exposure?
  - What could be done to assure appropriate controls and prevent multiple applications from being rejected?

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA GLP Inspections in China

GLP Inspections – Beijing, China

- September 9-20, 2013
- Contract Research Laboratory (CRO) A
  - 3 IND submissions
  - 5-item FDA 483
- Contract Research Laboratory B
  - 2 IND submissions
  - 4-item FDA 483

GLP Inspections – Shanghai, China

- June 2-13, 2014
- Contract Research Laboratory C
  - 3 IND submissions
  - 7-item FDA 483
- Contract Research Laboratory D
  - 2 IND submissions
  - 4-item FDA 483

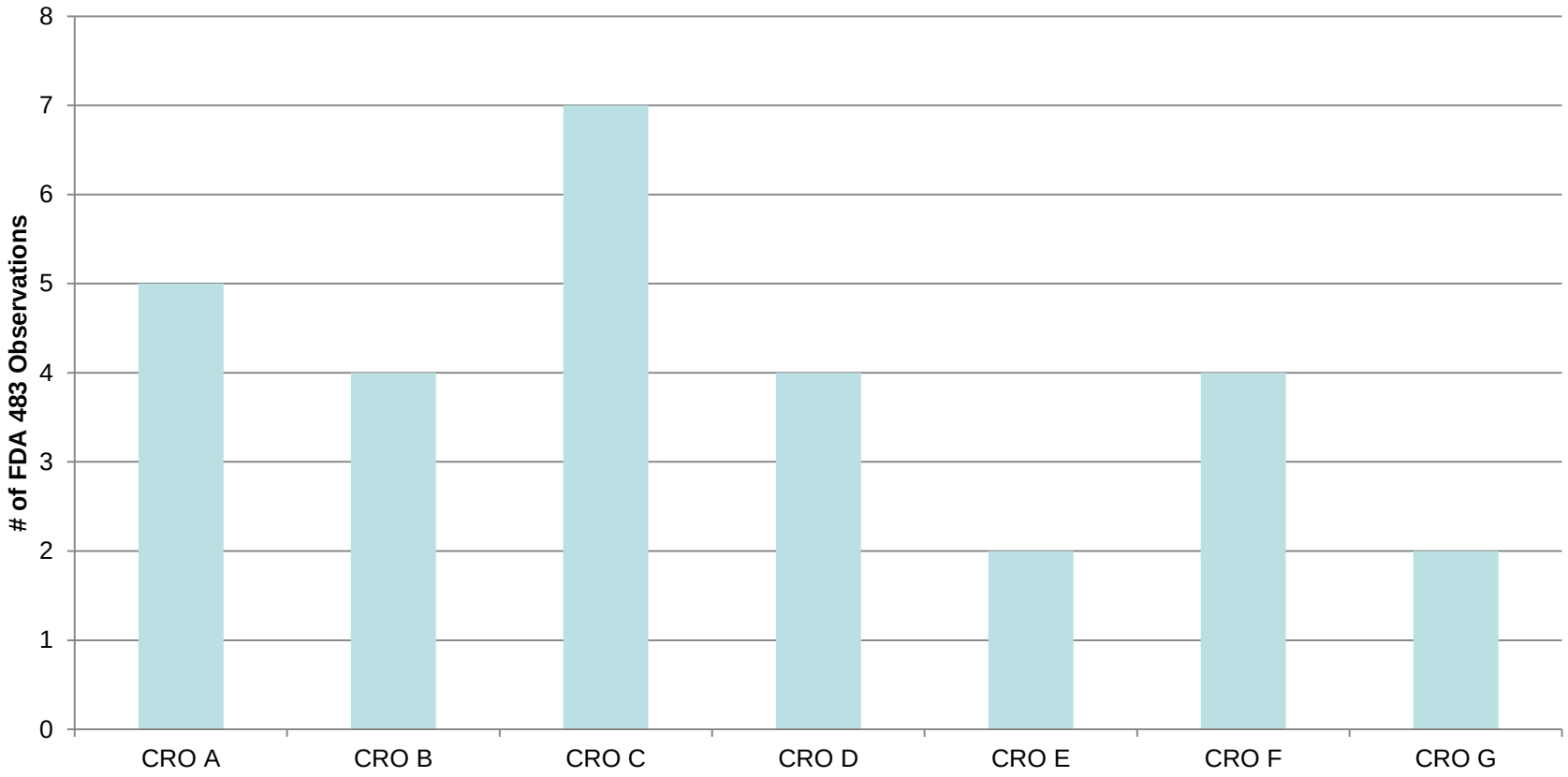
GLP Inspections – Shanghai, China

- July 20-25, 2015
- Contract Research Laboratory E
  - 3 IND submissions
  - 2-item FDA 483

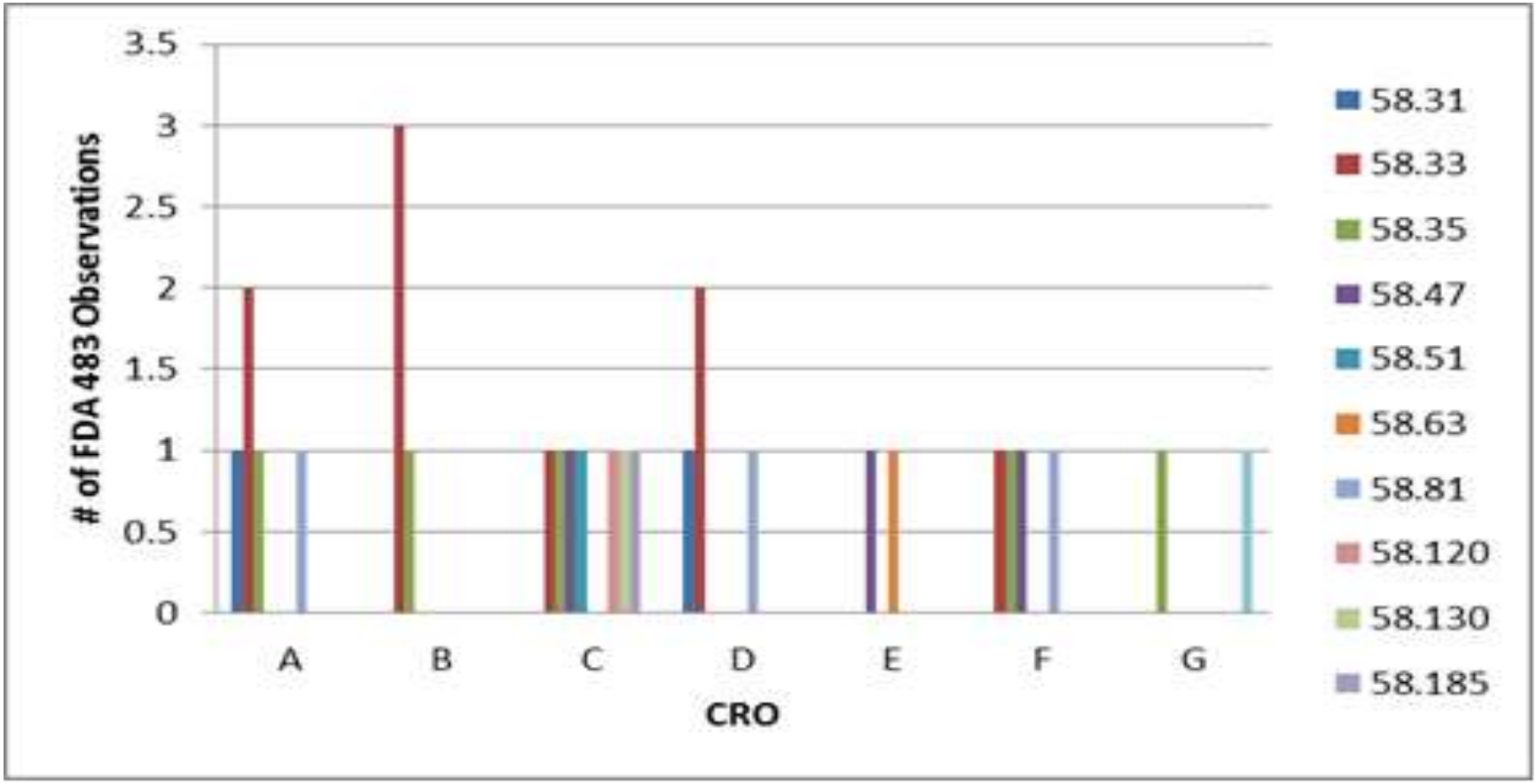
GLP Inspections – Shanghai, China

- August 8-19, 2016
- Contract Research Laboratory F
  - 2 IND submissions
  - 4-item FDA 483
- Contract Research Laboratory G
  - 2 IND submissions
  - 2-item FDA 483

483 Observations to Inspected CROs



Inspectional Observations



Impression of Chinese Firms

- Pre-announced inspections (serious, prepared, “better than actual state?”)
- Some data too good (e.g., TK sample collection)
- US trained scientists/staff from US firms
  - QA Directors from US, but knowledge may not be up-to-date
- Quality of English translation variable (study report, SOPs)

Impression of Chinese Firms

- Equipment varies between firms (e.g., Provantis system)
- Technicians appear to be skilled
- Eager to learn and accept FDA recommendations/suggestions
- Made corrective actions immediately

Impression of Chinese Firms

- Not all CROs in China perform the same quality work (similar to the US)
- GLP as a quality system is newer to China (approximately 2000) compared to the US (1978) and OECD (1979)
- Significant improvement in the quality of newer (2013) vs. older studies (e.g., 2007-2008)
- International/China GLP inspections are necessary and beneficial to both CROs and FDA

Summary

- Nonclinical studies that produce data in support of applications for research or marketing permits for products regulated by FDA, are conducted in compliance with GLP regulations (21 CFR Part 58)
- The intent of the GLP regulations is to assure the quality and integrity of the data
- Study documentation should allow for study reconstruction

Questions?