

Good Laboratory Practice (GLP) 101 – Regulations and Basic Studies

Zhou Chen, M.D., Ph.D.
GLP Team Lead

Division of New Drug Study Integrity (DNDSI),
Office of Study Integrity and Surveillance (OSIS)
CDER | US FDA

CDER Inspections of Good Laboratory Practice, Animal Rule, and
Bioavailability/Bioequivalence Study Sites – July 19, 2022

Disclaimer



The opinions and information in this presentation are those of the authors, and do not necessarily represent the views and/or policies of the U.S. Food and Drug Administration.



Learning Objectives

- Describe the history and scope of GLP regulations
- Describe the role of Office of Study Integrity and Surveillance with GLP
- Describe FDA's GLP program



Outline

- I. GLP Regulations: 21 CFR Part 58
- II. Role of OSIS with GLP
- III. GLP Inspection Program



21 CFR Part 58: FDA and GLP

- GLP provides a framework for conducting well-controlled studies
 - Assures quality and integrity of the data
 - Facilitates study reconstruction
 - Provides overall accountability
- New compounds are first tested for safety via nonclinical studies

Historical Perspective

- Before Good Laboratory Practice requirements were established
 - Studies conducted in the absence of published regulations
 - Inspections limited to review division requests to investigate questions about submitted studies/data
 - No systematic evaluation of laboratories conducting nonclinical laboratory studies

The Creation of GLPs



- In the early 1970's FDA became aware of cases of poor laboratory practice all over the United States.
- FDA decided to do an in-depth investigation on 40 toxicology labs.
- **Uncovered numerous fraudulent activities and poor laboratory practices.**

Historical Perspective

- After the completion of a series of hearings in 1975, 1976 and 1977, Congress proposed and then enacted the Good Laboratory Regulations for FDA
 - 21 CFR Part 58 Good Laboratory Practices For Nonclinical Studies
- The proposed regulations for Good Laboratory Practice were published in the Federal Register on November 19, 1976
- The Good Laboratory Practice Regulations, Final Rule was published in the Federal Register on December 22, 1978

Scope of GLP Regulations (21 CFR 58.1)

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 drugs, biological products, cosmetics, medical devices for human use, electronic products, food and color additives, veterinary drugs, feed additives, and tobacco products

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



OECD Principles on GLP

- Developed in 1978 and revised in 1997
 - FDA GLP Draft Rule (1976) provided the basis for OECD Principles on GLP
 - Expert group led by US
- CDER often sees compliance statements citing utilization of the OECD Principles on GLP
- Data generated in the testing of chemicals in an OECD member country in accordance with OECD Principles of GLP shall be accepted in other member countries for purpose of assessment and other uses relating to the protection of man and the environment
 - Statements of GLP compliance do not always assure compliance or good science

Outline

I. GLP Regulations: 21 CFR Part 58

II. Role of OSIS with GLP

III. GLP Inspection Program

OSIS Scientists



- Support the Pharm/Tox review process
 - Verify data quality and integrity of pivotal studies
 - Address Pharm/Tox reviewer concerns
- Surveillance oversight
 - Assess general ability to conduct GLP studies
- Investigate complaints
 - Data falsification, lack of GLP compliance



OSIS Scientists

- Development inspection assignments
 - In consult with review divisions
 - Select sites and studies
- Participate in inspections
 - Inspect sites and provide scientific expertise
- Evaluate inspection results
 - Data quality and integrity, impact on data reliability
 - Regulatory/administrative follow-up

Outline

I. GLP Regulations: 21 CFR Part 58

II. Role of OSIS with GLP

III. GLP Inspection Program

FDA GLP Inspection Program



- Verify safety data and support the Pharm/Tox review process
 - The quality and integrity of nonclinical studies used to protect human subject safety
 - nonclinical studies are critical to the drug development process
- Audit studies submitted in applications that are pivotal to review decisions
 - IND, NDA, ANDA, BLA

GLP Inspection Program



- Prioritization:
 - Animal Rule studies
 - Pivotal animal efficacy studies
 - Animal PK studies
 - Natural history studies (sometimes not inspected)
 - Directed inspections
 - Surveillance inspections

Directed GLP Inspections



- Address concerns about data integrity and study conduct
 - review divisions' concerns
 - confirm GLP compliance
 - confirm data integrity/reliability of pivotal studies
 - corrective actions since last inspection
 - OECD study audit

Directed GLP Inspections

- Complaint follow-up
 - data falsification, lack of GLP compliance
- FDA Center participation
- No pre-determined number of testing facility inspections or inspection frequency for directed inspection

GLP Surveillance Inspections

- Periodic, routine evaluation
 - Conducted mainly by ORA investigators alone
 - Assess testing facility's capability to conduct GLP-compliant studies and to comply with Part 58 regulations
 - Facility overview
 - Data audit of recently completed studies

GLP 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



Documentation typically requested at the start of an inspection includes:

- Organizational chart
- Floor plan
- Master schedule (or list) of studies
- SOP index
- Equipment index & maintenance/calibration schedules
- Study director/study personnel training files
- Pest control records

During the Inspection

- The inspector will conduct a facility tour and interview personnel
- The inspector will review many records, including:
 - Study-specific documentation and data
 - Facility and equipment records
 - Standard Operating Procedures (SOPs)
 - Training files
- Inspections typically last 5 days

Inspection Areas of Focus

- Test and control article characterization and handling
 - Storage container labeling
- Test and control article mixtures with carriers
- Reagents
- Test facility management
- Study director responsibilities
- Study personnel
- Quality assurance unit
- Study conduct
- Final study report (including contributing scientist reports)
- Archival of study records
- Facility/equipment
- Standard operating procedures (SOPs)
- Animal care
- Electronic data capture systems

At the Conclusion of the Inspection...



- Inspectors will hold a close-out meeting
- If no deficiencies are found, no Form **FDA 483** is issued
- **Form FDA 483** (Inspectional Observations) is given to management listing the deficiencies found during the inspection
- Some findings can be corrected during the inspection; however, these findings will still be listed on **Form FDA 483**

After the FDA GLP Inspection:

- If CDER/OSIS personnel participate, they write their portion of the EIR
- ORA prepares an Establishment Inspection Report (EIR) and submits it to the FDA Center for review
- OSIS reviewers will write a review of the EIR with recommendations to review divisions

EIR Classification



- **NAI (No Action Indicated)** - No objectionable conditions or practices were found during the inspection
- **VAI (Voluntary Action Indicated)** - Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action
- **OAI (Official Action Indicated)** - Regulatory and/or administrative actions will be recommended

Summary

- Valid nonclinical safety data are essential to the safety assessments for clinical trials
- GLP regulations provide the framework to ensure the quality and integrity of data from nonclinical studies
- OSIS reviewers work to provide assurance that the data supporting regulatory decisions are reliable

Challenge Question #1

Which of the following is under the scope of GLP regulations:

- A. Nonclinical PK studies
- B. Human clinical studies
- C. Nonclinical toxicology studies
- D. Pharmacology studies for efficacy and mechanism

Challenge Question #2

Which of the following statements is **NOT** true regarding OSIS scientists' work with GLP?

- A. OSIS scientists perform GLP inspections
- B. OSIS scientists review inspection reports
- C. OSIS scientists **prepare** inspection assignments
- D. OSIS GLP inspections are performed in US only

Closing Thought

Remember that GLP is a quality system that ensures the nonclinical safety studies are appropriately designed, conducted, and documented to generate reliable data.