Glisland® Training Series:

Good Laboratory Practice

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GLP Regulation History

- Problems Found in Nonclinical Laboratory Studies (pre-1979)
  1. Substantial falsification of laboratory records
  2. Animal experiments could not be repeated due to poor experimental records
  3. It was impossible to verify the results of experiments
- Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies regulation became a formal FDA requirement in 1979: 21 CFR Part 58
- FDA revised the GLP regulation in 1987 to reduce regulatory and paperwork burdens
- Purpose: to ensure quality and integrity of the data generated during the laboratory studies

21 CFR Part 58 – GLP Coverage

A. General provisions
B. Organization and personnel
C. Facilities
D. Equipments
E. Testing facilities operation
F. Test and control articles
G. Protocol and conduct of studies
H. [Reserved]
I. [Reserved]
J. Records and reports
K. Disqualification of testing facilities

Subpart A
General Provisions

- Scope
- Definitions
- Applicability to studies performed under grants and contracts
- Inspection of a testing facility

Definitions

- *Nonclinical laboratory study*
- *Application for research or marketing permit*
- *Sponsor*
- *Study director*
- *Quality assurance unit*
- *Testing facility*
- *Test system*
- *Raw data*
- *Study initiation/completion date*
- *Specimen*
- *Test and control articles*

Quiz:

- *A firm functions as a primary contractor for nonclinical laboratory studies. The actual studies are then subcontracted to nonclinical laboratories. Is the firm considered to be a "sponsor?"*

Scope

- Nonclinical (in vivo or in vitro) laboratory safety studies intended to be submitted to FDA for applications for research or marketing permit:
  - human and animal drugs
  - medical devices for human use
  - Biologics
  - electronic products
  - food and color additives
- There are 21 types of studies/data subject to GLPs
- Laboratories conducting safety studies, including contract, university, foreign and sponsor laboratories
- Exemption available: *preliminary pharmacological screening and initial pilot studies, et al.*

Exercise:
which item is subject to GLPs?

1. *The chemical procedures used to characterize the test article*
2. *The work done to develop chemical methods of analysis or to establish the specifications of a test article.*
3. *Safety studies on cosmetic products*
4. *The organoleptic evaluation of processed foods*
5. *Subcontractor laboratories conducting IEC 60601 testing for medical device Declaration of Conformity*
6. *Field trials in animals*
7. *Product acceptance testing in drug/device manufacturing process*

Applicability to studies performed under grants and contracts

- Sponsor shall notify the contract lab the requirement of GLPs for the studies
- The testing facility management designates the study director
- The sponsor is not required to approve the study director

Inspection of a testing facility

- Inspection requirements
  - Facility, records, specimens
- Record copying requirement

Quizzes:

1. *Shall the records inspection and copying requirements apply to quality assurance unit records of findings and problems, or to actions recommended and taken?*
2. *What is different between 483 and EIR?*
3. *Can FDA investigators take photographs of objectionable practices and conditions?*

Organization and Personnel

- Personnel
- Test facility management
- Study director
- Quality assurance unit (QAU)

Personnel

- Qualification
  - Education
  - Training
  - Experience
- Job description
- Sufficient number
- Sanitation and health precautions
- Clothing

Quiz:

1. *Does the QAU have to be composed of technical personnel?*

Testing Facility Management

- Designate a study director
- Quality assurance unit (QAU) requirement
- Test and control articles requirement
- Personnel, resources, facilities, equipment, materials, and methodologies requirements
- Deviation handling

Study Director

- Qualification
- Responsibilities
  - Protocol
  - Experimental data
  - Unforeseen circumstances
  - Test systems
  - GLPs
  - Archiving

Quiz:

1. *Is the study director, or sponsor, or testing facility management responsible for adherence to the GLPs?*

Quality Assurance Unit

- Independent of the personnel engaged in the direction and conduct
- Monitor study to ensure GLP compliance
- Review and approve GLP-regulated activities
- Maintain quality records
- Submit written report for each study and any findings and problems, actions recommended and taken
- Inspection and follow-up

Quizzes:

1. *Can a QAU be constituted as a single person?*
2. *Can an individual who is involved in a nonclinical laboratory study perform QAU functions for portions of the study that the individual is not involved with?*

Subpart C
Facilities

- General
- Animal care facilities
- Animal supply facilities
- Facilities for handling test and control articles
- Laboratory operation areas
- Specimen and data storage facilities

General

- Suitable size
- Suitable construction
- Suitable design

Animal care facilities

- Sufficient number of animal rooms or areas to meet separation requirements
- Separate areas for or the diagnosis, treatment, and control of laboratory animal diseases
- Collection and disposal of all animal waste and refuse

Quizzes:

1. *Do the GLPs require clean/dirty separation for the animal care areas?*
2. *Do the GLPs require that separate animal rooms be used to house test systems and conduct different studies?*
3. *Do the GLPs require that access to animal rooms be limited only to authorized individuals?*

Animal supply facilities

- Storage areas for
  - feed
  - Bedding
  - Supplies
  - Equipment
- Special control for feed and bedding
- Perishable supplies preservation

Facilities for handling test and control articles

- Separate areas for:
  - Receipt and storage of the test and control articles
  - Mixing of the test and control articles with a carrier, e.g., feed
  - Storage of the test and control article mixtures
- separate from areas housing the test systems
- adequate to preserve the identity, strength, purity, and stability of the articles and mixtures

Quiz:

1. *Do test and control articles have to be maintained in locked storage units?*

Laboratory operation areas

- Separate laboratory space for routine and specialized procedures

Specimen and data storage facilities

- Space for
  - storage and retrieval
  - archive
  - limited access
- Storage conditions for
  - minimizing deterioration of documents and specimens

Subpart D
Equipment

- Equipment design
- Maintenance and calibration of equipment

Equipment design

- Equipment types
  - equipment used in the generation, measurement, or assessment of data
  - equipment used for facility environmental control
- Appropriate design
- Adequate capacity to function according to the protocol
- Suitably located for operation, inspection, cleaning, and maintenance

Maintenance and calibration of equipment

- Inspection, cleaning, maintenance
- Testing, calibration, standardization
- SOP requirements
- Written records requirements
- Remedial actions

Quizzes:

1. *Do GLPs require qualification of equipment?*
2. *Do GLPs require validation of computerized system?*

Good Practice

1. Equipment validation for the purpose of study
2. Procedures for equipment operation, calibration and maintenance
3. Equipment logbook
4. Computerized system in compliance with 21 CFR 11

Subpart E
Testing Facilities Operation

- Standard operating procedures
- Reagents and solutions
- Animal care

Standard operating procedures

- Adequate to insure the quality and integrity of the data
- Deviations from standard operating procedures shall be authorized by the study director and shall be documented in the raw data
- Significant changes in established standard operating procedures shall be properly authorized in writing by management
- Change history and revision maintenance

Quiz:

1. *Can the study director authorize changes in the SOPS?*

Typical SOPs for Nonclinical Labs

1. SOP policy
2. Quality assurance function
3. Data handling, storage, and retrieval
4. Equipment qualification, routine inspection, cleaning, maintenance, testing, calibration
5. Analytical methods development and validation
6. Health and safety precautions
7. Receipt, identification, storage, mixing, and sampling of test and control articles
8. Record keeping and change controls
9. 21 CFR 11 compliance
10. Animal care

Reagents and solutions

- Labeling requirements
  - Identity
  - titer or concentration
  - storage requirements
  - expiration date
- Prevent the use of deteriorated or outdated reagents and solutions

Animal care

- SOPs for
  - Housing
  - Feeding
  - Handling
  - Care
- Health status check for animals
- Handling of sick animals
- Identification
- Housing separation
- Cleaning and sanitization
- Analysis of feed and water
- Bedding selection and changes
- The use of pest control materials

Subpart F
Test and Control Articles

- Test and control article characterization
- Test and control article handling
- Mixtures of articles with carriers

Test and control article characterization

- Documentation of methods
  - Synthesis, fabrication, or derivation of the test and control articles
- Batch records
  - The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article
- Stability analysis
- Sample reservation and retention

Quiz:

1. *What expiration date should be on the label of test articles whose stability is being assessed concurrently with the conduct of the study?*

Test and control article handling

- Proper storage
- Distribution procedures
- Identification
- Documentation
  - Receipt and distribution
  - Date and quantity of each batch distributed or returned

Quiz:

1. *With regard to safety studies in large animals (cattle, horses, etc.), must test article accountability be maintained and can the animals be used-for food purposes?*

Mixtures of articles with carriers

- Testing requirements
  - determine the uniformity of the mixture
  - determine, periodically, the concentration of the test or control article in the mixture
  - determine the stability of the test and control articles in the mixture
- Expiration date labeling

Quiz:

1. *Do test or control article concentration assays have to be performed on each batch of test or control article carrier mixture?*

Subpart G
Protocol for and Conduct of a Nonclinical Laboratory Study

- Protocol for a nonclinical laboratory study
- Conduct of a nonclinical laboratory study

Protocol

- Approval of written protocol
- Content of the protocol
  1. The purpose of the study
  2. The test and control articles
  3. Sponsor and testing facility
  4. The animals
  5. Identification procedure
  6. Experimental design
  7. Diet, carriers, specifications
  8. Dosage level and administration
  9. Tests, analyses, measurements
  10. Records
  11. Approval date by sponsor and study director
  12. Statistical methods
- Change controls

Conduct of a Nonclinical Laboratory Study

- Be conducted in accordance with the protocol
- Be monitored in conformity with the protocol
- Specification identification
- Records of gross findings
- Data recording and changes

Quizzes:

1. *What are the GLP requirements that are applicable to computerized data - acquisition systems?*
2. *In some countries, employees do not sign raw data records but rather they use an official seal, which is unique to the employee. Is this an acceptable procedure?*

Subpart J
Records and Reports

- Reporting of nonclinical laboratory study results
- Storage and retrieval of records and data
- Retention of records

Raw Data

1. Laboratory worksheets
2. Records
3. Memoranda
4. Notes
5. The result of original observations and activities of a nonclinical laboratory study
6. Necessary for the reconstruction and evaluation of the report of that study

Records & Reports

1. Raw data
2. Specimens
3. Study protocols
4. Study reports
5. QA inspections
6. Personnel training & qualifications
7. Equipment calibration & maintenance records

Data Recording and Documentation

- Recording Raw Data
  1. Legibility, permanence, & accountability
  2. What was done
  3. How it was done
  4. When the work was performed
  5. Who performed the work
  6. Signature and date
- Changing / Correcting Raw Data
  1. Not to obscure the previous entry
  2. Indicate reason for change if necessary
  3. Sign and date

Reporting of Nonclinical Laboratory Study Results

- Final report
  1. Facility information and the study dates
  2. Objectives and procedures
  3. Statistical methods
  4. Test and control articles
  5. Stability data
  6. Methods
  7. Test system
  8. Dosage and administration
- Signature and date of the study director
- Amendments

Storage and retrieval of records and data

- What to be retained:
  - Raw data
  - Documentation
  - Protocols
  - Reports
  - Specimens*
- Archive
  - Expedient retrieval
  - Storage conditions
  - Access controls

Retention of records

- Retention time
  - 2 years rule
  - 5 years rule
- Special specimens and samples
- Master schedule sheet, copies of protocols, and records of quality assurance inspections
- Summaries of training, experience and job descriptions
- Equipment records
- Original records or true copies
- Record transfer

Quiz:

1. *At the termination of a nonclinical laboratory study, can a contractor send all of the raw data, study records, and specimens to the sponsor of the study?*

Disqualification of Testing Facilities

- Purpose
- Grounds for disqualification
- Notice of and opportunity for hearing on proposed disqualification
- Final order on disqualification
- Actions upon disqualification
- Public disclosure of information regarding disqualification
- Alternative or additional actions to disqualification
- Suspension or termination of a testing facility by a sponsor
- Reinstatement of a disqualified testing facility

GLP Requirements for Contract Labs

"Consulting laboratories, contractors, and grantees are covered by the GLPs to the degree that they provide data for a nonclinical laboratory study. The sponsor or person contracting the service must notify them that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part. The consulting laboratory, contractor, or grantee is only required to comply with those parts of the GLPs that are appropriate to the nature of their contributions to a study. " (FDA CP 7348.808)

Key GLP Implementation Elements

1. Management responsibilities
2. Standard Operation Procedures (SOPs) to ensure complete coverage and consistent operation
3. Quality assurance unit (QAU) to ensure the procedures and protocols are properly followed and data are accurate
4. Personnel qualification and training to ensure the competency
5. Facility and equipment qualification and maintenance
6. Study director and study protocol
7. Test methods, reagents, solutions and control articles
8. Animal cares
9. Statistical methods for data analysis
10. Document controls, record and specimen controls and retention time

Glisland GLP Services

1. GLP training
2. GLP audit
3. Qualification and validation of equipments
4. Compliance gap analysis and improvement
5. Response to 483 and Warning Letter