GOOD LABORATORY PRACTICE (GLP)

Good Laboratory Practice (GLP) is a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

HISTORY

GLP was instituted in US following cases of fraud generated by toxicology labs in data submitted to the FDA by pharmaceutical companies. As a result of these findings, FDA promulgated the Good Laboratory Practice (GLP) Regulations, 21 CFR part 58.

GLP is a formal regulation that was created by the FDA. The regulations became effective June 1979.

In 1981 an organization named OECD (Organization for Economic Co-operation and Development) produced GLP principles that are international standard of the OECD Council, data generated in the testing of chemicals in one OECD Member Country, in accordance with OECD Test Guidelines and the Principles of GLP are accepted in all other OECD Member Countries.

OBJECTIVES OF GLP

- GLP makes sure that the data submitted are a true reflection of the results that are obtained during the study.
- GLP also makes sure that not to indulge in any fraud activity by labs.
- Promotes international acceptance of tests.

SCOPE OF GLP:

The Principles of Good Laboratory Practice should be applied to the non-clinical safety testing of test items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives, and industrial chemicals.

These test items are frequently synthetic chemicals, but may be of natural or biological origin and, in some circumstances, may be living organisms.

The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment

Unless specifically exempted by national legislation, these Principles of Good Laboratory Practice apply to all non-clinical health and environmental safety studies as required by regulations for the purpose of registering or licensing of:

- pharmaceuticals,

- pesticides,
- food additives
- feed additives,
- cosmetic products,
- veterinary drug products and similar products,
- biocides,
- Industrial chemicals.

GOOD LABORATORY PRACTICE – PRINCIPLES

1.Test Facility Organization and Personnel

2. Quality Assurance Programme

3. Facilities

4. Apparatus, Material, and Reagents

5. Test Systems

6. Test and Reference Items

7. Performance of the Study

8. Reporting of Study Results

9. Storage and Retention of Records and Materials

The Principles of GLP define the responsibilities of test facility management, study director, study personnel and quality assurance personnel that are operating within a GLP system, and minimum standards concerning the suitability of facilities and equipment to perform studies, the need for standard operating procedures, documentation of raw data, study reports, the archiving of records, etc.

General Provisions

- ⦿ It prescribes GLP for conducting non-clinical laboratory studies that support research and marketing permits of products regulated by FDA.
- ⦿ Applicability to studies performed under grants and contracts.
- ⦿ Inspection of the testing facility.

Test Facility Organization and Personnel

- ⦿ Study Personnel Responsibilities
- ⦿ Should have the Knowledge of the GLP principles.

- Access to the study plan and appropriate SOP's.
- Comply with the instructions of the SOP's.
- Record raw data.
- Study personnel are responsible for the quality of their data.
- Exercise health precautions to minimize risk.
- Ensure the integrity of the study.

Quality Assurance

- Quality Assurance (QA) – sometimes also known as the Quality Assurance Unit (QAU) as defined by GLP is a team of persons charged with assuring management that GLP compliance has been attained in the test facility as a whole and in each individual study.
- QA must be independent of the operational conduct of the studies, and functions as a "witness" to the whole preclinical research process.
- Program responsibilities of the QA Personnel
- Access to the updated study plans and SOP's.
- Documented verification of the compliance of study plan to the GLP principles.
- Inspections to determine compliance of the study with GLP principles.
- Three types of inspection:
  - Study-based inspections.
  - Facility-based inspections.
  - Process-based inspections.
- Inspection of the final reports for accurate and full description.
- Report the inspection results to the management statements.

Facilities

- Suitable size, construction and location.
- Adequate degree of separation of the different activities.
- Isolation of test systems and individual projects to protect from biological hazards.

- Suitable rooms for the diagnosis, treatment and control of diseases.
- Storage rooms

Apparatus, Materials and Reagents

- Apparatus of appropriate design and adequate capacity.
- Documented Inspection, cleaning, maintenance and calibration of apparatus.
- Apparatus and materials not to interfere with the test systems.
- Chemicals, reagent and solutions should be labeled to indicate identity, expiry and specific storage instructions.

Equipment

- Appropriate design and adequate capacity.
- Equipment shall be adequately inspected, cleaned and maintained.
- Equipment used for generation, measurement or assessment of data shall be adequately tested, calibrated and standardized.
- Log books for each equipment should be there.

Test Systems

- Physical, chemical and biological test systems are there.
- Records of source, date of arrival, and arrival conditions of test systems.
- Proper identification of test systems in their container or when removed.
- Cleaning and sanitization of containers.

Test and Reference Items

- Receipt, handling, sampling and storage
- Characterization of items.
- Known stability of test and reference items.
- Stability of the test item in its vehicle (container).
- Experiments to determine stability in tank mixers used in the field studies.
- Samples for analytical purposes for each batch.

Standard Operating Procedures (SOP)

- Written **procedures** for a laboratories program.
- They define how to carry out protocol- specified activities.

- Most often written in a chronological listing of action steps.
- They are written to explain how the procedures are supposed to work
- Routine inspection, cleaning, maintenance, testing and calibration.
- Actions to be taken in response to equipment failure.
- Keeping records, reporting, storage, mixing, and retrieval of data.
- Definition of raw data.
- Analytical methods.

Performance of the Study

- Prepare the study plan.
- Content of the study plan.
  - › Identification of the study.
  - › Records.
  - › Dates.
  - › Reference to test methods.
  - › Information concerning the sponsor and facility.
- Conduct of the study.

Reporting of Study Results

- Information on sponsor and test facility.
- Experimental starting and completion dates.
- A Quality Assurance Program Statement.
- Description of materials and test methods.
- Results.
- Storage (samples, reference items, raw data, final reports) etc.

Storage and Retention of Records and Materials

- Store study plan, raw data, samples (except wet samples like blood, body fluids, etc.).
- Inspection data and master schedules.

- SOPs.
- Maintenance and calibration data.
- If any study material is disposed of before expiry the reason to be justified and documented.
- Index of materials retained.

PROTOCOL

Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain, as applicable, the following information:

- A descriptive title and statement of the purpose of the study.
- Identification of the test and control articles by name, chemical abstract number, or code number.
- The name of the sponsor and the name and address of the testing facility at which the study is being conducted.
- The number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system.
- The procedure for identification of the test system.
- A description of the experimental design, including the methods for the control of bias.
- A description and/or identification of the diet used in the study as well as solvents, emulsifiers, and/or other materials used to solubilize or suspend the test or control articles before mixing with the carrier.
- The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.
- Each dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control article to be administered and the method and frequency of administration.
- The type and frequency of tests, analyses, and measurements to be made.
- The records to be maintained.

- ⦿ The date of approval of the protocol by the sponsor and the dated signature of the study director.
- ⦿ A statement of the proposed statistical methods to be used.
- ⦿ All changes in or revisions of an approved protocol and the reasons therefore shall be documented, signed by the study director, dated, and maintained with the protocol.

CONDUCT OF A NONCLINICAL LABORATORY STUDY.

- ⦿ The nonclinical laboratory study shall be conducted in accordance with the protocol.
- ⦿ The test systems shall be monitored in conformity with the protocol.
- ⦿ Specimens shall be identified by test system, study, nature, and date of collection.
- ⦿ This information shall be located on the specimen container or shall accompany the specimen in a manner that precludes error in the recording and storage of data.
- ⦿ All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink.
- ⦿ All data entries shall be dated on the date of entry and signed or initialed by the person entering the data.
- ⦿ Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change.

HANDLING OF ANIMALS

- ⦿ GLP for animal facilities is intended to assure qualities maintenance and safety of animal used in laboratory studies while conducting biomedical and behavioral research and testing of products
- ⦿ CPCSEA (Committee for the Purpose of Control and Supervision on Experiment on Animal)
- ⦿ The most commonly used animals: -

Frog, Guinea Pig, Mouse, Rat, Rabbit, Monkey, Cat, Dog, Sheep.

VETERINARY CARE

- Animals should be observed regularly and problems of animal health and behavior recorded & addressed

- Personnel hygiene & Training of staff.
- Appropriate & protective gears (gloves, masks, head cover, shoes)
- Personnel should have periodic medical checkups to ensure their health status
- All newly received animals from outside sources shall be isolated and their health status shall be evaluated
- If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary
- These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study.
- The diagnosis, authorization of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.
- Animals of different species shall be housed in separate rooms when necessary.
- Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals.
- Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with study and reasonably expected to be present in such feed or water are not present in levels above those specified in the protocol.
- Documentation of such analyses shall be maintained as raw data.
- If any pest control materials are used, the use shall be documented.
- Cleaning and pest control materials that interfere with the study shall not be used.
- Standard operating procedures shall be established for
    - Animal room preparation
    - Animal care
    - Receipt
    - identification, storage, handling, mixing, and method of sampling of the test and control articles
    - Test system observations
    - Laboratory tests.
- Handling of animals found moribund or dead during study.

- Necropsy of animals or post mortem examination of animals.
- Collection and identification of specimens.
- Histopathology.
- Data handling, storage, and retrieval.
- Maintenance and calibration of equipment.
- Transfer, proper placement, and identification of animals.

CONTROL OF ANIMAL HOUSE:

Location of the animal house:

- It should be separate building
- it should be clean and hygienic
- it should be protected from insects
- Animal house should have maximum number of rooms
- it should have quarantine area, so that new animals can be held for observation
- it should have extra space for office, surgery, stores, washing and sterilizing.
- Good ventilation should be provided by air conditioner
- Should have exhaust fans to remove the odors
- Heating arrangements should be provided during winter climate
- in the simplest form of animal house should have four departments normal animals, experimental animals, clean store for food and feeding washing, cleaning and incinerating.

Maintenance of the animals:

- Animals should live in comfort and psychologically acceptable habitat
- Small animals like rat, mice should be kept in cages which are built of plastic, galvanized iron or aluminum etc.
- Anodized aluminum cages are suitable as it is light weight and corrosion resistance
- Size of cages should have adequate space for animals to move freely
- Cages should have removable closures to place food and water
- Cages should be cleaned and frequently sterilized
- the bedding should be clean in order to prevent infections.

Diet:

- Must be sufficient in quantity to cover energy required
- It should be correct quality to satisfy biological need

- It should be appetizing
- A balance diet should be given regularly

Cleanliness:

- Animals will not live under dirty condition. They should be kept clean, otherwise there is a risk of epidermal disease
- Weekly once animals should be transferred to clean cages
- The dirty cages washed with soap water and sterilized in hot air oven
- Breeding animals should not be changed frequently, because they may lose the weight.

Litters:

- A layer of absorbent material should be spread to a depth of ½ - 1 inch on the bottom of cage
- Fine soft wood, wood shavings, sugar cane pith can be used for absorbent
- Pregnant animals must be supplied with nesting materials

Cages:

- Each species of animals requires its own type of cage
- it should have enough room for free movement and space for resting
- cage should have holder for small card on which the name of experiment identifying mark of the animal's data and relevant matter is written
- card must not be removed before conclusion of experiment
- the card must be placed in such a way that it cannot be detached by the animals
- breeding cages should be labeled to easy identification

Ventilation:

- Ideally the entire animal house should be air conditioned, if not adequate ventilation from windows should be ensured
- Animals kept in badly ventilated room are more liable to respiratory disease
- the exhaust air should be discharged in a manner where it cannot reenter buildings.

Temperature and humidity:

- the animal house temperature must be maintained sudden fluctuation in temperature must be avoided
- the humidity of the animal house must be moderate depending on the animal habitat. For example: rabbit - 45 % ; mice - 65 %.

Prevention of disease:

- the new animal should be kept in a special quarantine room and kept for observation 10 – 14 days during this period, any animal sick (or) dead, the stock should be held in quarantine.

Bedding:

Two types

1. Absorbent types of bedding

2. Bedding used for nesting

- Bedding should be stored in a dry and ventilated building
- Wood, wool and straw to be kept on racks of the floor to avoid contamination

Hygiene:

- Sterilization: it is the process of removing all living pathogenic organism
- Methods: heat, chemical, irradiation.
- Disinfection: it is the killing of organisms by the application of chemicals, physical agents to contaminated objects.

REPORT PREPARATION AND DOCUMENTATION:

Generally, report headings include a Summary, an Introduction, a Narrative, a Summary of the Exit Discussion, and Annexes.

All of the information presented under these headings should portray an accurate picture of the adherence of the testing facility to the principles of GLP and the quality of any study report that may have been audited.

The narrative headings may contain information as follows:

1. Summary:

The summary section of the report should be presented first and should provide background information on the test facility, the type of inspection that was conducted, the deviations from the GLP Principles that were noted, and the responses of the test facility to the presented deviations.

2. Introduction:

- The purpose and general description of the inspection, including the legal authority of the inspectors and the quality standards serving as the basis for the inspection.
- An identification of the inspectors and the dates of inspection.
- A description of the type of inspection (facility, study audit, etc.)
- An identification of the test facility, including corporate identity, postal address, and contact person(s) [with telephone and telefax number(s)]
- A description of the test facility identifying the categories of test substances and testing that is done and presenting information on the physical layout and the personnel.
- The date of the previous GLP inspection, resulting GLP compliance status, and any relevant changes made by the test facility since that inspection.

3. Narrative:

The Narrative portion of the report should contain a complete and factual description of the observations made and activities undertaken during the course of the inspection. Generally, the information recorded in this section should be reflected under the headings in the GLP Principles, as listed below:

- Organization and Personnel
- Quality Assurance Programme
- Facilities
- Apparatus, Materials, Reagents and Specimens
- Test Systems
- Test and Reference Substances
- Standard Operating Procedures
- Performance of the Study
- Reporting of Study Results
- Storage and Retention of Records

When a study has been selected for audit, the inspection report should describe the procedure for conducting the audit, including a description of the portion of the data or study that was actually examined. Any findings during the audit should be described in the Narrative and documented in the Annexes.

4. Exit Discussion:

- At the end of an inspection/ study audit, an Exit Conference should be held between the inspection team and the responsible management of the test facility, at which GLP deviations found during the inspection/ study audit may be discussed.
- The exit discussion should be summarized in this section.

- The report should note the date and time of the Exit Conference; the names of attendees (inspection team, facility and others), with their affiliations.
- Responses of facility representatives to the inspection team's remarks should also be described.
- In the case where a written list of observations has been made available, the test facility should acknowledge the inspectors' findings and make a commitment to take corrective action.
- If a receipt of documents taken by the inspection team was prepared and signed by facility management, the person to whom the receipt for documents was provided should be identified.
- A copy of the receipt should be included in the Annexes.

5. Annexes:

The Annexes should contain copies of documents that have been referenced in the report.

Such documents may include:

- Organizational charts of the facility

- The agenda for the inspection

- A listing of SOPs that have been demonstrated during the inspection

- A listing of deviations that have been observed

- Photocopies that document observed deviations.

REPORTING OF NONCLINICAL LABORATORY STUDY RESULTS

Final report shall contain:

1) Information on sponsor and test facility.

2) Experimental starting and completion dates.

3) Objectives and procedures stated in protocol (including the changes in protocol).

4) Description of materials and test methods.

5) A Quality Assurance Program statement.

6) Storage (specimens, reference items, raw data and final report).

STORAGE, RETRIEVAL AND RETENTION OF RECORDS & DATA

- Archives should be there for orderly storage and expedient of all raw data, documentation, protocols, specimens and final reports.
- Index of materials retained.
- Master schedule sheet, copies of protocols and records of Quality Assurance inspections shall be maintained by QAU.
- Wet specimens and samples of test and control articles shall be retained until the quality of preparation affords evaluation.
- If any study plan is disposed of before expiry the reason to be justified and documented.

DISQUALIFICATION OF A FACILITY

- Before a workplace can experience the consequences of noncompliance, an explanation of disqualification is needed.
- The FDA states the purpose of disqualification as the exclusion of a testing facility from completing laboratory studies or starting any new studies due to not following the standards of compliance set by the Good Laboratory Practice manual.

Grounds for Disqualification:

- The testing facility failed to comply with one or more regulations implemented by the GLP manual
- The failure to comply led to adverse outcomes in the data; in other words, it affected the validity of the study.
- Warnings or rejection of previous studies have not been adequate to improve the facility's compliance.

Consequences of Noncompliance:

The FDA states the following consequences of noncompliance:

- The commissioner will send a written proposal of disqualification to the testing facility.
- A regulatory hearing on the disqualification will be scheduled.
- If the commissioner finds that after the hearing, the facility has complied, then a written statement with an explanation of termination of disqualification will be sent to the facility.
- Thus, if it can be shown that such disqualifications did not affect the integrity and outcome of the study itself, or did not occur at all, then the study may be reinstated at the will of the commissioner.

Upon Disqualification:

If the commissioner finds that the facility was noncompliant on any of the grounds after the hearing, then a final order of noncompliance will be sent to the facility with explanations:

1. If a testing facility has been disqualified, any studies done before or after the disqualification will need to be determined as essential to a decision (acceptable or not)

2. If the study is determined unacceptable, then the facility itself may need to show that the study was not affected by the noncompliance that led to the disqualification

3. Once finally disqualified, the facility may not receive or be considered for a research or marketing permit and the study is rejected.

FDA may turn it over to the federal, state or local law enforcement.

Disqualification by Sponsor:

The facility's sponsor may terminate or suspend the facility from doing any non- clinical study for a permit.

The sponsor is required to notify the FDA in writing within 15 working days that the facility is to be suspended or terminated.

Reinstatement of a Disqualified Facility:

The disqualified facility will be required to put in writing to the commissioner reasons why it should be reinstated and any actions the facility will take or have taken to assure any disqualification problems will not happen again.

1. The commissioner will inspect the facility and determine if it shall be reinstated

2. If it is reinstated, the commissioner is required to notify all persons that were notified of the disqualification including the facility itself.