SEMINAR ON

GOOD LABORATORY PRACTICES(GLP)

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Introduction to GLP

- GLP is a series of guide lines that cover the conduct and data production for non-clinical safety studies.

- They ensure quality and integrity of the data generated during the laboratory studies.

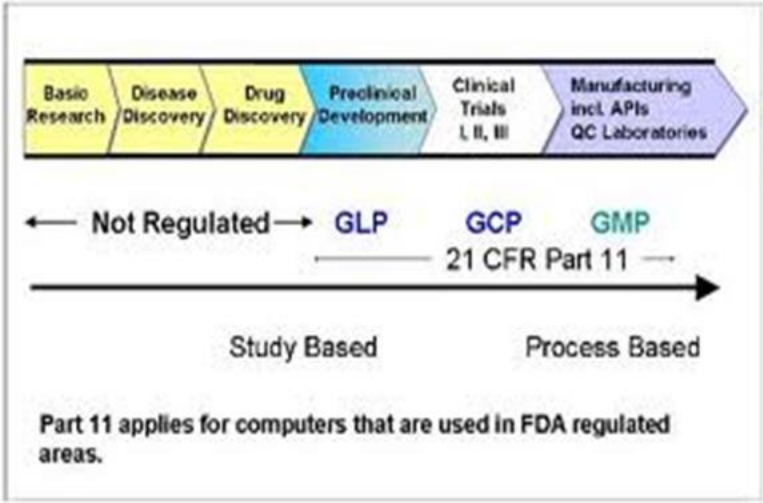
- The objective of the GLPs is to ensure that a standard approach is undertaken covering traceability and accountability and, while still allowing freedom for the scientists, to impose certain restrictions on the generation of data and the experimental work

- It must be remembered that GLP is merely common sense in a formal environment.

OECD definition of 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
- reported.



History of GLP:

- The Good Laboratory Practice Guidelines (GLP) have been in existence for non-clinical safety studies since 1976.
- In the early 1970's, the FDA investigated a number of cases of poor practice in toxicology laboratories through out the USA.
- Introduced a new regulation to cover Non clinical safety studies.
- Draft GLP in 1976.
- An enforceable US regulation in 1979.
- In 1981 OECD also published GLP principles (signed by 30 countries so far) –currently accepted as the industry standard.
- This was revised and published in 1997.

Scope of GLP:

Any company or institution performing non-clinical safety studies for the submission of data for

- a new chemical entity
- a new biological
- immunological,
- pesticide,
- veterinary or agrochemical product

or, for that matter, a similar product that will eventually appear in the marketplace and be consumed by the general public must adhere to GLP in the conduct of their non-clinical safety study experimentation.

GLP is needed for

- Non Clinical safety studies of development of drugs
- Agricultural pesticide development
- Development of toxic chemicals
- Food control (food additives)
- Test of substances with regard to explosive hazards

GLP is not needed for

- Basic research
- Studies to develop new analytical methods
- Chemical tests used to derive the specifications of a marketed food product

Purpose of GLP:

- To promote the development of quality test data.
- Comparable quality of test data to avoid duplicative testing.
- To avoid the creation of technical barriers to trade.
- Improve the protection of human health and the environment.
- Led to fewer repeated studies. This, inturn, is helping to achieve the aim of all scientists in reducing the use of animals.
- The ability to reconstruct studies proves beyond reasonable doubt that these were the values obtained and the results submitted.

Enforcement of GLP:

- In the OECD countries, for at least 14 years, an Inspectorate has been set up.
- All countries, however, have a regulatory group that, in some instances, also acts as the receiving authority for the review of data, and reports to the GLP Monitoring Authority.
- This regulatory group visits on a 2-year basis or, in Germany, a 4 year basis, those companies that have claimed compliance and will then be on a rolling program of review.
- Claim is verified in a visit from the regulatory inspector. The inspection may be performed by one or two persons for 1 to 5 days.
- At the end of the inspection, an exit meeting is held, and the company is usually given an indication of its performance.
- Noncompliance points are noted in writing and discussed, and a report is then prepared.

Primary areas covered by the GLPs:

- Responsibilities
- Training
- Quality assurance (QA)
- Facilities
- Standard operating procedures (SOPs)
- Study plans and study reports
- Data production and recording
- Equipment maintenance and calibration
- Computers and validation
- Test systems and test substances
- Archiving

Responsibilities:

The prime players in a GLP scenario would be

Test facility Management

Sponsor

Study director

Principal investigator

QA

Test facility management's responsibilities:

- In a hierarchical structure, management would be totally responsible for:
- Providing optimal environment for conducting GLP compliance of the test facility.
- Provide sufficient number of qualified personnel, appropriate facilities, equipment and materials for timely and proper conduct of studies.
- Ensure that personnel clearly understand the function they need to perform (provide training where necessary).
- Appoint study director
- It is the responsibility of management that the deviations in the test study are reported by QA and are communicated to study director.
- Ensure that SOPs are established and are being followed as required
- Ensure that computer systems are suitable for intended purpose and are validated, operated, maintained in accordance with the principles of GLP

Study director's responsibilities:

- Study director has the principal responsibility for conduct of the study as per approved study plan, coordinate the activities during the study and for final report preparation and approval.
- Design the study plan and approve
- Identify and appoint principal investigator
- Ensure that all raw data generated are fully documented and recorded
- Ensure that computerized systems in use are validated
- Should supervise all activities during the study

Principal investigator's responsibilities:

- The principal investigator is the next in line of responsibility after the study director in a multi site study.

- The principal investigator should ensure that delegated phases of the study are conducted in accordance with the applicable GLP.

Study personnel responsibilities:

- The personnel involved in the study team should be knowledgeable especially in GLP and SOPs.
- Document any deviations in study plan and communicate these deviations to study director
- Responsible for quality of raw data recorded
- Should take utmost precautions to maintain sound health and in the event of any abnormality in health condition, should report to study director.

Sponsor's responsibilities:

Sponsor should be:

- Aware of the concerned regulatory authority requirements
- Knowledgeable with the requirements of the GLP principles
- Should evaluate the test facility,facility management,study director and the scope of the study
- The final report should be thoroughly reviewed for compliance with the current GLP principles before submission of the dossier to the regulatory authority.

Quality Assurance Unit(QAU)

- Independent group-Does not become involved in the conduct of the study
- Responsibilities

  review of the study plan

  review of the study in the in-life phase

  data audits

  final study report audit.

- The **aim of QA** is to assure the management that compliance with GLP is maintained throughout the entire study, that the data integrity is maintained, and that compliance with the SOPs and the study plan is adhered to by all experimental study staff
- to ensure that all critical aspects of this process are reviewed through different studies over a period of time.

- Various **audits** performed by QAU

  study audit

  systems audit

  process audit

- After every audit, a report is produced that is then discussed with the study director and circulated to the management with the overall agreement from the study director relating to the audit findings and their explanation of the resolution.

Facilities:

General:

1. The test facility should be of suitable size, construction and location to meet the requirements of the study and to minimize disturbance that would interfere with the validity of the study.

2. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study.

Test System Facilities:

1. The test facility should have a sufficient number of rooms or areas to assure the isolation of test systems and the isolation of individual projects, involving substances or organisms known to be or suspected of being biohazardous.
2. Suitable rooms or areas should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems.
3. There should be storage rooms or areas as needed for supplies and equipment. Storage rooms or areas should be separated from rooms or areas housing the test systems and should provide adequate protection against infestation, contamination, and/or deterioration.

Facilities for Handling Test and Reference Items:

1. To prevent contamination or mix-ups, there should be separate rooms or areas for receipt and storage of the test and reference items, and mixing of the test items with a vehicle.
2. Storage rooms or areas for the test items should be separate from rooms or areas containing the test systems. They should be adequate to preserve identity, concentration, purity, and stability, and ensure safe storage for hazardous substances.

Archive Facilities:

- Archive facilities should be provided for the secure storage and retrieval of study plans, raw data, final reports, samples of test items and specimens. Archive design and archive conditions should protect contents from untimely deterioration.
- Material retained in the archives should be indexed so as to facilitate orderly storage and retrieval.
- Only personnel authorized by management should have access to the archives. Movement of material in and out of the archives should be properly recorded.
- If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archives of the sponsor(s) of the study(s).

Waste Disposal:

- Handling and disposal of wastes should be carried out in such a way as not to jeopardize the integrity of studies.

- This includes provision for appropriate collection, storage and disposal facilities, and decontamination and transportation procedures.

Apparatus, Material, and Reagents:

1. Apparatus, including validated computerized systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.
2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement.
3. Apparatus and materials used in a study should not interfere adversely with the test systems.
4. Chemicals, reagents, and solutions should be labeled to indicate identity (with concentration if appropriate), expiry date and specific storage instructions. Information concerning source, preparation date and stability should be available. The expiry date may be extended on the basis of documented evaluation or analysis.

Standard operating procedures:

- Standard operating procedures (SOPs) are written procedures for a laboratories program. They define how to carry out protocol-specified activities.
- SOPs must be reviewed on a regular basis, (approximately every 2 years).
- Revisions to SOPs should be approved by test facility management.
- Each separate test facility unit or area should have immediately available current Standard Operating Procedures relevant to the activities being performed therein.
- Deviations from Standard Operating Procedures related to the study should be documented and should be acknowledged by the Study Director and the Principal Investigator(s), as applicable.

Standard Operating Procedures should be available for the following categories of test facility activities:

1. Test and Reference Items

Receipt, identification, labeling, handling, sampling and storage.

2. Apparatus, Materials and Reagents

a) Apparatus

Use, maintenance, cleaning and calibration.

b) Computerized Systems

Validation, operation, maintenance, security, change control and back-up

c) Materials, Reagents and Solutions

Preparation and labeling.

3. Record Keeping, Reporting, Storage, and Retrieval

Coding of studies, data collection, preparation of reports, indexing systems, handling of data, including the use of computerized systems.

4. Test System (where appropriate)

a) Room preparation and environmental room conditions for the test system.

b) Procedures for receipt, transfer, proper placement, characterization, identification and care of the test system.

c) Test system preparation, observations and examinations, before, during and at the conclusion of the study.

d) Handling of test system individuals found moribund or dead during the study.

e) Collection, identification and handling of specimens including necropsy and histopathology.

f) Siting and placement of test systems in test plots.

5. Quality Assurance Procedures

Operation of Quality Assurance personnel in planning, scheduling, performing, documenting and reporting inspections.

Study plan & Reports:

- The study plan is merely an indication of all of the activities that will take place, resources required, time frames, and objectives.
- It can be likened to a road map that allow participants to start at the beginning and to proceed through the various mazes to the final completion point indicated by the study report.
- The one golden rule in GLP is one study plan, one study director, and one report.
- The study report itself is a mirror image of all the headings in the study plan
- Both the study plan and the report are audited by QA, and each study plan and report are generally determined by the company's format.

Content of the Study Plan:

1. Identification of the Study, the Test Item and Reference Item

a) A descriptive title;

b) A statement which reveals the nature and purpose of the study;

c) Identification of the test item by code or name (IUPAC; CAS number, biological parameters, etc.);

d) The reference item to be used.

2. Information Concerning the Sponsor and the Test Facility

a) Name and address of the sponsor;

b) Name and address of any test facilities and test sites involved;

c) Name and address of the Study Director;

d) Name and address of the Principal Investigator(s), and the phase(s) of the study delegated by the Study Director and under the responsibility of the Principal Investigator(s).

3. Dates

a) The date of approval of the study plan by signature of the Study Director. The date of approval of the study plan by signature of the test facility management and sponsor if required by national regulation or legislation in the country where the study is being performed.

b) The proposed experimental starting and completion dates.

4. Test Methods

Reference to the OECD Test Guideline or other test guideline or method to be used.

5. Issues (where applicable)

a) The justification for selection of the test system;

b) Characterization of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age and other pertinent information;

c) The method of administration and the reason for its choice;

d) The dose levels and/or concentration(s), frequency, and duration of administration/ application;

e) Detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed, and statistical methods to be used (if any).

6. Records

A list of records to be retained.

Conduct of the study:

- A unique identification should be given to each study. All items concerning this study should carry this identification.
- The study should be conducted in accordance with the study plan.
- All data generated during the conduct of the study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialed and dated.
- Any change in the raw data should be made so as not to obscure the previous entry, should indicate the reason for change and should be dated and signed or initialed by the individual making the change.

Content of the Final Report:

1. Identification of the Study, the Test Item and Reference Item

a) A descriptive title

b) Identification of the test item by code or name (IUPAC,CAS number, biological parameters, etc.);

c) Identification of the reference item by name;

d) Characterization of the test item including purity, stability and homogeneity.

2. Information Concerning the Sponsor and the Test Facility

a) Name and address of the sponsor;

b) Name and address of any test facilities and test sites involved;

c) Name and address of the Study Director;

d) Name and address of the Principal Investigator(s) and the phase(s) of the study delegated, if applicable;

e) Name and address of scientists having contributed reports to the final report.

3. Dates

Experimental starting and completion dates.

4. Statement

A Quality Assurance Programme statement listing the types of inspections made and their dates, including the phase(s) inspected, and the dates any inspection results were reported to management and to the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

5. Description of Materials and Test Methods

a) Description of methods and materials used;

b) Reference to OECD Test Guideline or other test guideline or method.

6. Results

a) A summary of results;

b) All information and data required by the study plan;

c) A presentation of the results, including calculations and determinations of statistical significance;

d) An evaluation and discussion of the results and, where appropriate, conclusions.

7. Storage

The location(s) where the study plan, samples of test and reference items, specimens, raw data and the final report are to be stored.

Pitfalls:

- A pitfall could be seen as a restriction on the scientist against performing free research.
- It could also be seen as an intrusion by an independent body looking at why problems occur and at the sorts of problems that occur and carrying out regular reviews with senior management about these problems.
- Costs will increase because of time pressures and the necessity of involving third-party reviews.
- The recording of data will now be subject to more QC, more required approvals, extra costs, and, generally, more data presented.
- Time must be taken to write and review SOPs. This in itself can be a very costly exercise.

Benefits:

- GLP system allows for a better standard of research, less repeated work, the ability to have full accountability and traceability of everything within the experimental phase, and the knowledge that all documentation produced at the end of the study is now safe and secure in the archive and can be readily accessed for regulatory review or inspection.
- Fewer studies are being repeated, and, therefore, the immediate benefit is the lowering of subject usage.
- Data, when generated with a certificate or a compliance statement, will now be accepted by all OECD member countries means that once the study is completed and the regulatory submission made, the time for acceptance several countries (if submissions are made in a multistate procedure) will be reduced dramatically.

Conclusion:

- All non-clinical safety studies, when conducted according to the principles of GLP and adequately addressing science as well as compliance, can achieve a very high success rate both in the outcome of the science and in the acceptance of data for a regulatory submission.

References:

- OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, ENV/MC/CHEM (98)17, As revised in 1997. http:\\www.oecd.org/ehs/ehsmono/index.htm#GLP

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THANK YOU