

Good Laboratory Practice (GLP)



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GLP Definition

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



Introduction

- The Good Laboratory Practice Guidelines (GLP) have been in existence for non-clinical safety studies since 1976.
- It is a quality system which intends to ensure through careful and accurate documentation , covering all aspects of study and of its environment, the quality , integrity and reliability of safety data.

History

- The FDA published proposed regulations for GLP in non-clinical laboratory studies in the Federal Register on Nov 19, 1976.
- The FDA finalised these rules and published them in the Federal Register on Dec 22, 1978 under Title 21 of the Code Of Federal Regulations as part 58 (21 CFR 58) and these regulations came into effect on June 20, 1978.
- Non-US companies that wanted to do business with the US or register their pharmacies in the US had to comply with the US GLP regulations.

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- The current document is the Organisation For Economic Co-operation and Development (OECD) principles of GLP.
- The resulting principles of Good Laboratory Practice were published and formally recommended for use in member countries by the OECD council in 1981.
- The OECD principles of GLP were revised and updated in 1997.

WHO

- WHO has published standards for Good Manufacturing Practice (GMP) covering the manufacture of drug product.

Good Clinical Practice (GCP)

covering clinical trials in humans to establish efficacy and safety

OECD members manage quality standards for non-clinical testing for the safety of potential products . (GLP)

Why have it ?

- In general terms, for companies conducting non-clinical safety studies it is a regulatory requirement and without this certificate or certification of compliance, data will not be accepted by the receiving/regulatory authorities.
- The emergence of the now familiar CRO will become ever more popular in the conduct of non-clinical safety studies.

Scope

- GLP is a requirement in regulatory non-clinical safety testing of the following test items :
 - pharmaceutical products
 - pesticide products
 - cosmetic products
 - veterinary products
 - food additives
 - feed additives
 - industrial chemicals



Purpose of GLP principles

- To promote the development of quality test data
- Obtain reliable and reproducible data
- Obtain comparable data between countries
- Achieve international confidence in study data
- Avoid repetition of studies
- Enable reconstruction of studies
- Optimise animal conditions
- Shorten the registration time of the drug



Elements of GLP

- Test facility management and personnel
- Quality assurance programme
- Facilities
- Apparatus , materials and reagents
- Test systems
- Test and reference items
- Standard operating procedures
- Performance of the study
- Reporting of study results
- Storage and retention of records and materials

GLP Principles

1) Test facility organisation and personnel

- Test facility management responsibilities
 - it should ensure that principles of GLP are complied with in its test facility.
 - ensure that the individual(s) in the test facility who fulfill the responsibilities of management are as defined by the principles of GLP
 - ensure that a sufficient no. of qualified personnel, appropriate facilities, equipment and materials are available for the timely and proper conduct of study.
 - personnel involved clearly understand the functions they have to perform and where necessary provide training for these functions.
 - appropriate and technically valid SOP are established and followed, and approve all original and revised SOPs.
 - Quality assurance programme with designated personnel and assure that quality assurance responsibility is being performed in accordance with GLP principles.

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- an individual Study Director for each study is initiated. He should have appropriate qualification, training and experience. Replacement if done should be according to the procedure and it is documented.
- in the event of multi-site study, principal investigator is designated who is appropriately trained, qualified and experienced.
- ensure document approval of study plan by the study director
- study director has made the approved study plan available to the QA personnel.
- ensure the maintenance of an historical file of all SOPs
- ensure that an individual is identified as responsible for the management of archive(s).
- ensure the maintenance of master schedule
- ensure that test facility supplies meet requirements appropriate for their use in the study
- for multi-site study, clear communication exists between study director, principal investigator, QA programme and study personnel.
- test and reference items are appropriately characterised.
- establish procedures to ensure that computerised systems are suitable for their intended purpose and are validated, operated, maintained in accordance with these principles of GLP.

When a phase of study is conducted at test site, test site management (if appointed) will have the responsibilities as defined above with few exceptions.

Study Director Responsibilities

- He is the one who has the responsibility for the overall conduct of the study and for its final report.
- He should – approve the study plan and any amendment to the study plan by the dated signature
- Ensure the QA personnel have a copy of the study plan and any amendments in a timely manner and communicate effectively with the QA personnel as required during the conduct of the study
- Ensure that study plan ,amendments and SOPs are available to the study personnel.
- Ensure that the study plan and its final report for a multi-site study identify and define the role of principal investigator and test facilities and test sites involved in the conduct of the study.
- Ensure that all the raw data generated are fully documented and recorded.
- Ensure that computerised systems used in the study have been validated.
- Sign and date the final report to indicate acceptance of responsibility for the validity of the data and to indicate the extent to which the study complies with these principles of GLP.
- Ensure that after completion of the study , the study plan , the final report, raw data and supporting material are archived.

Principal investigator(s) responsibilities

- He will ensure that the delegated phases of the study are conducted in accordance with the applicable principles of GLP.

Study personnel(s) responsibilities

- All the personnel who are involved in the study must be knowledgeable in those parts of the principles of GLP which are applicable to their involvement in the study.
- They will have access to the study plan and appropriate SOPs applicable to their involvement in the study. It is their responsibility to comply with the instructions in these documents. Any deviation from these instructions should be documented and communicated directly to the study director , and/or if appropriate, the principal investigator(s)
- All the study personnel are responsible for recording raw data promptly and accurately in compliance with these principles of GLP, and are responsible for their data.
- They should exercise health precautions to minimise risk to themselves and to ensure the integrity of the study. They should communicate to the appropriate person any relevant known health or medical condition in order that they can be excluded from operations that may affect the study.

Quality Assurance Programme

- The test facility should have a documented QA programme.
- It should be carried out by an individual designated by and directly responsible to management and who are familiar with the test procedures.
- This individuals should not be involved in the conduct of the study being assured.

- Responsibilities of Quality Assurance Programme
- They should
 - maintain copies of all approved study plan and SOPs in use in the test facility and have access to an up-to-date copy of the master schedule.
 - verify the study plan and the verification should be documented.
 - conduct inspections to determine if all studies are conducted in accordance with the principles of GLP. Inspections should also determine the study plans and SOPs have been made available to study personnel and are being followed.

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- Inspections are 3 types –study based, facility based and process based.
- Final reports are inspected to confirm that the methods, procedures and observations are accurately and completely described and that the reported results accurately reflect the raw data of the studies.
- Promptly report any inspection results in writing to management and to the study director and to the principal investigator and the respective management, when applicable.
- Prepare and sign a statement, to be included with the final report, which specifies types of inspections, their dates, including the phase(s) of the study inspected and the dates inspection results were reported to management and the study director and principal investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

3)Facilities

- 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.
- The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of the study.
- Test System Facilities
 - The test facility should have sufficient no. of rooms/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.
 - Suitable rooms or areas should be available for the diagnosis , treatment and control of diseases to ensure that there is no unacceptable degree of deterioration of test systems.
 - There should be storage rooms / areas as needed for supplies and equipment. Storage rooms /areas should be separated from rooms/areas housing the test systems and should provide adequate protection against infestation , contamination or deterioration.

Facilities for handling test and reference items

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

Archives facilities

-these 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 from untimely deterioration.

Waste disposal

-handling and disposal of waste should be carried out in such a way as not to jeopardise the integrity of studies. This includes provision for appropriate collection, storage and disposal facilities and decontamination and transportation procedures.

4) Apparatus, Materials and Reagents

- Computerised systems should be validated. They should be suitably located with appropriate design and adequate capacity.
- Apparatus used in the study is periodically inspected, cleaned, maintained and calibrated according to SOPs. Records of these activities should be maintained.
- Apparatus and materials should not interfere with the test systems.
- chemicals, reagents and solutions should be labelled to indicate identity, expiry date and storage instructions. Information concerning source, preparation date and stability should be available. The expiry date may be extended on the basis of documented evaluation/analysis.

5) Test systems

- Physical/chemical: -

- ~ apparatus used for the generation of physical/chemical data should be suitably located and of appropriate design and adequate capacity.

- ~ the integrity of the physical/chemical test system should be ensured.

- Biological: -

- ~ proper conditions should be established for storage ,housing, and care of biological products in order to assure the quality.

- ~ when a new plant or animal system is received it is isolated until its health status is evaluated.

- ~ if any morbidity/mortality arises ,the lot is discard from the study.

- ~ at the experiment starting date, the test system should be free from disease/condition that may interfere the study.

- ~ test system if gets injured/diseased during the course of study should be isolated and treated to maintain the integrity of the study.

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- Any diagnosis or treatment of disease before or during the study should be documented.
- Records of source , date of arrival , arrival condition of test are maintained.
- Biological test systems should be acclimatised to the test environment for an adequate period before the first administration of the test/reference item.
- During use, housing and containers of the test systems should be cleaned and sanitised.
- Any material that comes in contact with the test system should be free of contaminants at a level that interfere the study.
- Use of pest control agents should be documented.

6) Test and Reference Items

- Receipt, Handling, Sampling and Storage
 - * records including test item and reference item characterisation, date of receipt, expiry date, quantities received and used in the studies are maintained.
 - * handling, sampling and storage procedures should be identified in order that the homogeneity and stability are assured to the degree possible and contamination or mix-up are precluded.
 - * storage containers should carry identification information, expiry date and specific storage instructions.

Characterisation

- * each test and reference item should be appropriately identified (e.g., code, CAS number, name, biological parameters etc)
- * for each study, the identity, including batch number, purity, composition, concentrations or other characteristics to appropriately define each batch of the test or reference items should be known.

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- If the test item is supplied by the sponsor it is necessary to verify the test item subject to the study.
- The stability of the test and reference items under storage and test conditions should be known for all the studies.
- If the test item is administered or applied in a vehicle , the homogeneity, concentration and stability of the test item in that vehicle is to be determined. For test items used in the field studies (e.g., tank mixers) , these may be determined through separate laboratory experiments.
- A sample for analytical purposes from each batch of test item should be retained for all studies except short - term studies.

7) Standard Operating Procedures

- A test facility should have written standard operating procedures approved by the test facility management that are intended for the quality and integrity of the data generated by the test facility.
- Revisions to SOPs should be approved by test facility management.
- Each separate test facility unit area should have immediately available current SOPs relevant to the activities being performed therein.
- Deviations from SOPs related to the study should be documented and should be acknowledged by the study director and the principal investigator(s) as applicable.
- The following are the examples for which SOPs are available
 - test and reference items
receipt, identification, labelling, handling, sampling and storage

Contd....

- Apparatus, materials and reagents

- apparatus ----- use, maintenance, cleaning and calibration
- computerised systems ----- validation, operation, maintenance, security, change control and back-up.
- materials, reagents and solutions ----- preparation and labelling

Record keeping, reporting, storage and retrieval

- Coding of studies, data collection, preparation of reports, indexing systems , handling of data, including the use of computerised systems

Test system (where appropriate)

- room preparation and environmental room conditions for the test system.
- procedures for receipt, transfer, proper placement, characterisation, identification and care of test systems.
- test system preparation, observations and examinations, before ,during and at the conclusion of the study.
- collection , identification and handling of specimens including necroscopy and histopathology.
- siting and placements of test systems in test plots.

Quality Assurance Procedures

- operation of QA personnel in planning, scheduling, performing, documenting and reporting inspections.

8) Performance of the study

- Study plan

a written plan should exist prior to the initiation of the study. It should be approved by dated signature of the study director and verified for GLP compliance by QA personnel. It should also be approved by management and the sponsor, if required by national regulation or legislation in the country where the study is being conducted.

any amendments to the study plan should be justified and approved by the dated signature of the study director and maintained with the study plan.

deviations from the study plan should be described, explained, acknowledged and dated in a timely fashion by the study director and/or principal investigator(s) and maintained with the study of raw data.

for short-term studies a general study plan accompanied by a study specific supplement may be used.

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- Content of the study plan

It should contain -----

item # identification of the study, the test item and reference

a) a descriptive title

the study b) a statement which reveals the nature and purpose of

c) identification of the test item by code or name

d) the reference item to be used

information concerning the sponsor and the test facility

a) name and address of the sponsor

involved b) name and address of the test facilities and test sites

c) name and address of the study director

the phase delegated by the study director and under the
responsibility of the principal investigator

d) name and address of the principal investigator and

Dates

the date of approval of the study director and by the
management and sponsor and if required by national regulation
/legislation in the country where the study is being performed.

the proposed experimental starting and completion dates.

Contd....

- Test methods

reference to the OECD test guidelines or other guideline or method to be used.

Issues

the justification for the selection of test system

characterisation of the test systems

the method of administration and the reason for its choice:

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

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

Records

a list of records is retained.

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- Conduct of the study

- ' a unique identification should be given to each study. Such identification should enable traceability, as appropriate for the specimen and study

- ' the study should be conducted in accordance to the study plan.

- ' the data generate during the conduct of the study should be recorded. These entries should be signed or intialled 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 intialled by the individual making the change.

- ' data generated as a direct computer input should be identified at the time of data input by the individual(s) responsible for direct data entries.

- ' computerised system design should provide for the retention of full audit trails to show the changes in the data without obscuring the original data.

- ' these systems should have the possibility of having the details of those persons who made the changes with the timed and dated.

- ' reasons for the changes should be given.

9) Reporting of Study Results

- A final report should be prepared for each single study. for short-term studies a standardised final report accompanied by a study specific extension may be prepared.
- Reports are signed and dated by the principal investigator or scientist involved in the study.
- The final report is signed and dated by the study director taking the responsibility for the validity of the data. The extent of compliance with these principles of GLP should be indicated.
- corrections or additions to the final report are made into the form of amendments. These should clearly mention the reasons for changes and should be signed and dated by the study director.
- Reformatting of the final report to comply with the submission requirements of a national registration or Regulatory authority does not constitute a correction, addition or amendment to the final report.

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- Content of the final report

The final report should include

- 1) identification of the study, Test Item and Reference Item
 - a) a descriptive title
 - b) identification of the test item by the code or name
 - c) identification of the reference item by the name
 - d) characterisation of the test item including the 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 the test facilities and test sites involved
 - c) name and address of the study director
 - d) name and address of the principal investigator and the phase(s) of the study delegated, if applicable
 - e) name and address of the scientist having contributed reports to the final report.

Dates

experiment starting and completion dates.

Contd....

- Statement

a QA 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 to principal investigator(s) if applicable. This also serve to confirm that the final report reflects the raw data.

Description of materials and test methods

description of materials and methods used

reference to OECD Test Guideline or other test guideline or method

Results

a summary of results

all information and data required by the study plan

a presentation of the results, including calculations and determinations of statistical significance

an evaluation and discussion of the results and, where appropriate, conclusions.

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- 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.

10) Storage and Retention of Records and Materials

the following should be retained to the archives for the period specified by the appropriate authorities

- the study plan, raw data, samples of test and reference items, specimens and the final report of each study.
- records of all inspections performed by the QA programme as well as master schedule.
- records of qualification, training, experience and job descriptions of personnel
- records and reports of the maintenance and calibration of apparatus
- validation documentation for computerised systems
- the historical life of SOPs
- environmental monitoring records

In the absence of a required retention period, the final disposition of any study materials should be documented. When samples of test and reference items and specimens are disposed of before the expiry of the required retention period for any reason, this should be justified and documented. Samples of test and reference items and specimens should be retained only as long as the quality of the preparation permits evaluation.

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- Material retained in the archives should be indexed so as to facilitate storage and retrieval.
- Only personnel authorised 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).

Weakness and Strength

- Weaknesses in GLP
 - does not take regard for scientific content
 - does not consider further steps along the reporting chain
 - tends to over-elaborate technical detail
 - focus on testing chemicals
- Strengths in GLP
 - insists on verifiability (audit)
 - insists on documented actions
 - same standards world wide

CONCLUSION

- Following GLP will help us obtain quality and reliable data and also remind us to minimize hazardous waste in the laboratory.
- It is clearly understood that the issue of GLP is obviously so crucial to modern laboratory operations.
- The Good Laboratory Practices have become as an essential ingredient for any professional scientist.

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