Chapter - 1

Overview of Good Laboratory Practices in Pharmaceutical Industry

Introduction

GLP refers to a quality system to ensure the uniformity, consistency, reliability, reproducibility, quality and integrity of the data. GLP gives true reflection of tested results.

Good Laboratory Practices - Good laboratory practices embody a set of principles that provide framework within which laboratory work is planned, performed, monitored, recorded, reported and archived.

Good laboratory practice must be planned, reliable, accurate, recorded, reported, monitor and archive all data generated during analysis or testing.

GLP helps in providing confidence to regulatory authorities and customers that the data submitted are a true reflection of the results obtained during the testing and can therefore be relied upon when making risk/safety assessment. Below important aspects shall be taken into account to achieve GLP.

The purpose of testing items is to obtain information on their safety with respect to human health and environment. GLP is also required for registration purpose and licensing of pharmaceuticals, pesticides, food additives, veterinary drug products and some bio-products.

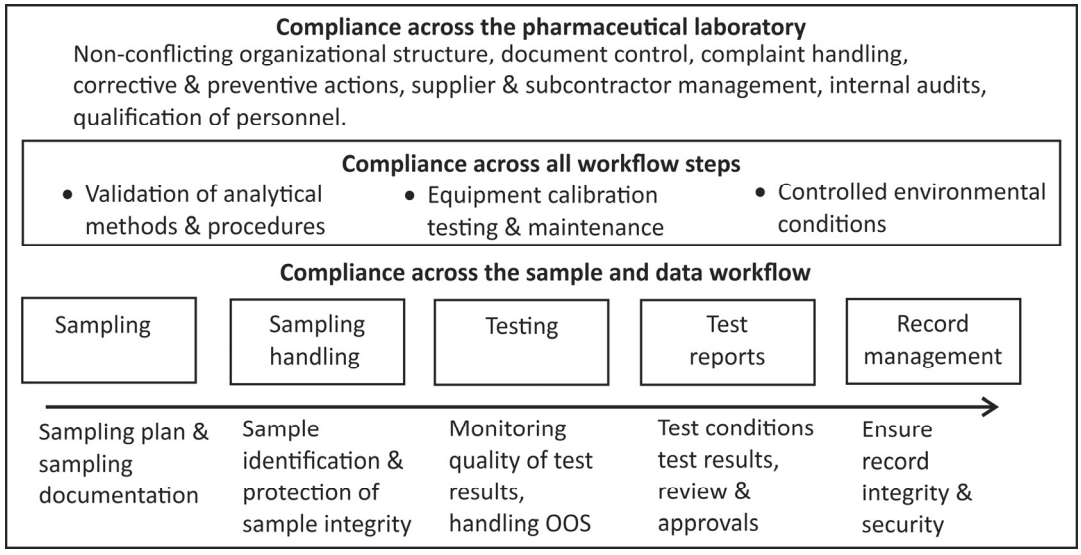
Personnel working in laboratory must have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions. Facilities must be adequate and environment control.

1.1 Fundamental of GLP

Good Laboratory Practice is defined as "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."

Fundamental of GLP depends on:

(a) Resources: Organization, personnel, facilities and equipment;
(b) Characterization: Test items and test systems;
(c) Rules: Protocols, standard operating procedures (SOPs);
(d) Results: Raw data, final report and archives;
(e) Quality Assurance: Independent monitoring of research processes
(f) Compliance across the Pharmaceutical laboratory



1.2 GLP Organisation and Personnel Management

GLP regulations require clear definitions of the structure of the research organisation and the responsibilities of the research personnel. This means that the organisational chart should reflect the reality of the institution and should be kept up to date. Organisational charts and job descriptions give an immediate idea of the way in which the laboratory functions and the relationships between the different departments and posts.

GLP also stresses that the number of personnel available must be sufficient to perform the tasks required in a timely and GLP-compliant way. The responsibilities of all personnel should be defined and recorded in job descriptions and their qualifications and competence defined in education and training records. To maintain adequate levels of

competence, GLP attaches considerable importance to the qualifications of staff, and to both internal and external training given to personnel.

1.3 Organization Chart, Job Description and Specimen Signature in GLP

- The laboratory should have an organization chart depicting key positions and the names of responsible persons. The organization chart should be dated, authorized and kept up to date.
- There should be job descriptions for all personnel, including a description of their responsibilities. Every job description should be signed and dated by the staff member to whom it applies.
- There should be a list of signatures of the authorized personnel performing tasks during each study.

1.4 Personnel and Personnel Hygiene

There should be adequate number of personnel qualified in terms of education/training/ experience. All personnel must be provided training in respective working areas and training record of all the personnel should be maintained as per applicable SOP. All personnel prior to employment should be medically examined and periodic re-examination to be carried out for medical fitness. There should be written job descriptions for all persons working in Quality control.

Smoking, eating, drinking, chewing or keeping plants, food, drinks and personal medicines shall not be permitted in laboratory areas. Person suffering from any infectious disease or having any open lesions should not engage in activities which could affect the quality of analysis. All Personnel shall wear the company's uniform or aprons as applicable in the laboratory premises. Entry/exit and gowning procedure shall be followed wherever applicable.

Adhere to the procedure for personnel clothing for entering into microbiological testing laboratories. Personnel shall practice good sanitation and health habits. All personnel should follow the time schedule with respect to shift and should be punctual in attendance.

1.5 Instruments and Equipment

Laboratory should be furnished with all types of Instruments/Equipment which are necessary to carry different activities. Qualification of all instruments/equipment shall be ensured prior to routine usage. Allot identification number to all analytical instruments/ equipment. Calibrations and preventive maintenance shall be done as per schedule. Relevant SOP shall be displayed preferably near the instrument/equipment or arranged in such a way that it shall be readily available to user for reference.

The activities performed on instrument/equipment shall be updated and displayed as status board near instrument/equipment as per annexure T03. Usage Log shall be maintained for instruments/equipment as per procedure mentioned in applicable SOP. At the end of day's operation or after use, instrument/equipment shall be switched off and maintained properly.

List of 'Authorized Users' for instruments/equipment/laboratory areas shall be maintained or displayed based on requirement as per respective SOP. Temperature & humidity of stability walk in chambers or incubators shall be maintained and data shall be recorded as per requirement. Desiccant replacement from desiccator/instruments shall be done as per requirement and status shall be displayed as per annexure T04. Water from instruments/equipment shall be changed as per requirement and status shall be displayed as per annexure T05.

1.6 Laboratory Glassware

Class `A' Glassware shall be used for preparation and its certificate of compliance shall be maintained.

Clean all the laboratory glassware following applicable procedure of glassware cleaning. Cleaned and dried glassware shall be stored in dust free storage area.

Examine glassware prior to use for damage i.e. cracked, chipped or any other defective glassware.

Do not use such defective glassware and dispose it in glass bin. Do not dispose defective glassware in general waste bin. Always use clean and dry glassware for analysis. Use guard for volumetric flasks and measuring cylinder to avoid breakages.

Figure 1 Illustrative example of measuring cylinders with guard

1.7 Chemicals, Reagents and Analytical Standards

Use appropriate grade and highly purified chemicals. After receipt, label all chemicals and readymade reagents as per applicable SOP. Reagents/solutions should be prepared, standardized and stored according to respective reagents/solution specification and label appropriately.

Storage and handling of chemicals and reagent should be done in a manner considering the physicochemical properties of these substances and hazards involved in their use. In-compatibility chart/MSDS of chemicals and reagents, should be available and should be displayed preferably near the chemical storage area.

All the solutions, dispensed solvent and waste solvents collected in beaker/vessel should be covered entirely with appropriate cover by using aluminum foil or glass lid to avoid probable contamination.

Ensure the validity of the chemicals before usage and if any chemical is beyond validity period, discard the same from laboratory.

All solid and liquid chemical bottles shall be kept in the places intended for them, immediately after use. They must not be left on the work benches. Chemical stock should be checked periodically and based on the requirement if required purchase request for new chemicals should be raised. Examine chemicals for any change in appearance or nature (Colour, clarity etc.) and shall discard if any abnormalities are observed Safe disposal of chemicals shall be always ensured. Follow the appropriate chemical disposal procedure strictly.

1.8 Laboratory Reference Standards and Culture Media in Good Laboratory Practice

Qualified Reference standards must be suitable for their intended use. Qualification and certification should be clearly stated and documented. Whenever compendial reference standards from an officially recognized source exist, these should preferably be used as primary reference standards unless fully justified (the use of secondary standards is permitted once their traceability to primary standards has been demonstrated and is documented). These compendial materials should be used for the purpose described in the appropriate monograph unless otherwise authorized by the National Competent Authority.

Culture media should be prepared in accordance with the media manufacturer's requirements unless scientifically justified. The performance of all culture media should be verified prior to use.

Used microbiological media and strains should be decontaminated according to a standard procedure and disposed of in a manner to prevent the cross-contamination and

retention of residues. The in-use shelf life of microbiological media should be established, documented and scientifically justified.

Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

1.9 Good Housekeeping and Safety

The laboratory shall have adequate first aid kit and fire extinguishers located at right places and staff must be familiar and trained.

Safety data sheets must be made available to staff before testing is carried out for respective material.

All staff must wear safety apparels or other protective clothing including PPE wherever required.

While handling any chemicals, cytotoxic materials, steroids etc.; use personnel protective equipment and follow safety instructions and precaution.

Never handle any chemicals, raw materials, intermediate or bulk finished with bare hands.

Do not taste any chemical or solvents and do not touch face, mouth or eyes during analysis.

Operators carrying out sterility tests shall wear sterilized garments including headgear, face masks and shoes.

The staff must be educated in the first aid techniques and other emergency care. Water showers shall be installed at appropriate place in the laboratory. Appropriate facilities for the collection, storage and disposal of waters shall be made available. Avoid spillage of sample, chemicals and reagents, in case any spillage occurs then clean the area as quickly as possible by following appropriate safety precautions.

Staff must be aware of methods for safe disposal of corrosive/hazardous materials by using neutralization or deactivation method. Always do a visual check on electrical equipment before use looking for obvious wear or defects.

1.10 Sampling

Sampling shall be done by trained personnel in accordance with approved written procedure.

Samples shall be stored in tightly closed bags/containers at appropriate storage conditions, until their destruction. Reseal/close the sample bags/bottles immediately after

use. Sampling personnel shall have knowledge of the nature of the samples to be handled and should refer respective specification for the same.

1.11 Testing and Review

Daily work plan as per analysis requirements shall be designed by supervisor in consultation with analyst and status shall be updated as per annexure T06.

The analysis shall be done as per approved version of standard testing procedure or method of analysis.

Label all test and standard preparations for all tests with at least details such as Analytical Reference No/Batch No. Solution name and appropriate replicate preparation number wherever applicable (in a suitable short form in case of space constraint but in an identifiable manner), sign and date with legible marker pen.

A. R. No./Batch No.	:	_____
Solution Name	:	_____
Sign & Date	:	_____

Figure 2 Illustrative example of glassware label (standard and test solutions)

Use clean spatula/clean pipette/glass weighing boats/butter papers or other suitable receivers for weighing and transferring the samples.

Figure 3 Illustrative example of weighing receivers (glass weighing boats)

Balance print shall be taken for all the weighments. This print shall be stamped by using stamp for weight print as per annexure T07 and details shall be mentioned. If columns are provided to mention details on weight print itself then stamp is not required.

Wipe the tip of the burette and pipette before dispensing the withdrawn liquid. Use approved Record of analysis to enter raw data. The status of analysis preparation shall be indicated as per annexure T08.

The results shall be checked for compliance against specification. The completed ROA and analytical data shall be submitted to reviewer for review as per applicable SOP.

1.12 Documentation

Always follow good documentation practices. Clearly written documentation prevents errors from spoken communication. Pharmacopoeia & its supplement or addendum, technical books etc. as required, should be available in Quality Control Laboratory.

Ensure the availability of current versions of controlled documents in the laboratory.

SOPs, Specifications, Testing procedures and logbooks must be maintained securely, at the workplace where it can be easily accessed. All analytical work shall be carried out by referring to approved current version of documents such as Standard Operating Procedure, Specifications, Standard Testing Procedure, General Test Procedure etc., Analytical data shall be recorded contemporaneously. Update all relevant logbooks concurrently.

The certificates received from the vendor/manufacturer shall be reviewed with respect to its specification/standards and completeness upon receipt. As a proof of verification of tests and results (wherever applicable), the reviewer shall put a stamp as per annexure T07.

Reviewer shall sign with date as a part of review on first page and remaining pages shall be stamped as reviewed. Attach all relevant analytical raw data obtained from instrument such as analytical balance weight prints, chromatograms, spectrums, Polari meter, refractometer, particle size analyzer, potentiometer, tap density apparatus, dissolution tester etc., with sign and date to the record of analysis/after labeling the same.

The analytical raw data where it is obvious to invalid the data/results, in the event of incident (e.g. system suitability failures, instrument malfunctions/errors), OOS and OOT or data returned by the reviewer during the empower sign-off 2 process; Such data shall be stamped as invalid data.

The reason for invalidation along with sign and date shall be mentioned on first page and remaining pages shall be stamped as invalid data as per annexure T07.

The invalid data shall be attached along with the batch testing record. Protect all documents from spillage of chemicals/solutions during performing analysis.

1.13 Incident, OOS and OOT

For Quality control operation related to receipt, handling, storage, analysis, calibration, all non-conformance classified and addressed as OOS/OOT/Incidents shall be investigated, evaluated and documented according to defined procedure to identify errors like analyst

error, instrument malfunctioning, method error, improper peak shape, system suitability failure etc. according to procedure.

1.14 Self-Inspection (Internal Audits)

In order to verify compliance with the Quality control system, regular internal audits/self-inspection should be conducted in accordance with approved procedure.

1.15 Validation/Verification

Validation/Verification of analytical methods shall be followed as per applicable SOP.

1.16 Measures in Good Laboratory Practice

Establish and Follow Procedures: Develop approved procedures and inventory.

Maintain Your Proficiency: Analysts must have the education, training and experience, acquired through formal education or on-the-job training, sufficient to perform assigned analytic duties.

Validate Methods: Method should be validated before usages.

Use Traceable Standard Reference Materials (SRM): Reference material uses include validating methods that help ensure accurate data from individual test runs, calibrating instruments and assessing analyst proficiency. In the United States, a NIST standard reference material is considered the “gold standard” for that material. NIST has more than a thousand different SRMs covering diverse technologies. The results of analyses backed by NIST-traceable SRMs are widely accepted as valid.

Run in Duplicate: The purpose of duplicate (sometimes triplicate) testing is to add to the confidence that the test run has produced good data for the test object. Replicate data that is in agreement is a good measure of method reproducibility but does not prove data accuracy (validity).

Keep Original Data: Document everything and Maintain Good Records. Whether data is first recorded in electronic/digital form, in a notebook or on the closest piece of scrap paper, keep it.

Assign Instruments and Equipment to Analysts: A good practice is to formally assign that analyst the responsibility for keeping the instrument operational and for alerting management to malfunctions. When an instrument is used by multiple staff members, assign these responsibilities to a primary user, who should schedule usage time for other staff members, provide training and mentoring to new users, ensure that any instrument control charts are current and ensure that calibration and maintenance occur on schedule.

Calibrate Instruments and Equipment: Instrument should be calibrated to its working range.

Use Control Charts: Control charts are excellent tools for several uses, including those already noted. A control chart enables a laboratory to track the results of a reference material and/or control sample at the end of each test run. It gives the laboratory a snapshot of test run quality and a picture of the quality of the laboratory's results for that particular test over time.

1.17 Technical Transfer of Testing Methods in Good Laboratory Practice

Prior to transferring a test method, the transferring site should verify that the test method(s) comply with those as described in the Marketing Authorization or the relevant technical dossier. The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a detailed protocol. The transfer protocol should include, but not be limited to the following parameters:

- Identification of the testing to be performed and the relevant test method(s) undergoing transfer;
- Identification of the additional training requirements;
- Identification of standards and samples to be tested;
- Identification of any special transport and storage conditions of test items;
- The acceptance criteria which should be based upon the current validation study.
- Deviations from the protocol should be investigated prior to closure of the technical transfer process;
- The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation, if applicable

1.18 On-going Stability Programme in Good Laboratory Practice

The on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions. The on-going stability programme should be described in a written protocol and should include, but not be limited to the following parameters:

- Number of batch(es) per strength and different batch sizes, if applicable;
- Relevant physical, chemical, microbiological and biological test methods;
- Acceptance criteria;
- Reference to test methods;

- Description of the container closure system(s);
- Testing intervals (time points);
- Description of the conditions of storage (standardised ICH/VICH conditions for long term testing, consistent with the product labelling, should be used);
- Other applicable parameters specific to the medicinal product.

The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol. In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

1.19 Documentation in Good Laboratory Practice

- Specifications;
- Procedures describing sampling, testing, records (including test worksheets and/or laboratory notebooks), recording and verifying;
- Procedures for and records of the calibration/qualification of instruments and maintenance of equipment;
- A procedure for the investigation of Out of Specification and Out Of Trend results;
- Testing reports and/or certificates of analysis;
- Data from environmental (air, water and other utilities) monitoring, where required;
- Validation records of test methods, where applicable;
- Trend analysis for test results and environment controls;
- All raw data such as laboratory notebooks and/or records should be retained and readily available.

1.20 Sampling in Good Laboratory Practice

Sampling may be required for different purposes, such as prequalification; acceptance of consignments; batch release testing in-process control; special controls; inspection for

customs clearance, deterioration or adulteration; or for obtaining a retention sample. Sampling shall consist following contents:

- Approved procedure sampling plans and methods must be written and defined;
- Samples must be representative of the population;
- Samples or sampling plans must be based on appropriate statistical criteria, and;
- Representative of batch;
- Sample should be Samples must be properly identified and handled;
- Equipment to be used the amount of the sample to be taken;
- Instructions for any required sub-division of the sample;
- The type and condition of the sample container to be used;
- Identification of containers sampled;
- Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials; storage conditions;
- Instructions for the cleaning and storage of sampling equipment.

A. Approaches for sampling plans will be discussed for:

- Incoming Packaging Components
- Incoming Raw Materials
- Labeling Materials
- Non-sterile Liquid Products
- Sterile Products
- Creams, Suspensions, and Emulsions
- Powder Blends
- Tablets, Capsules, and Other Solid Dosage Forms

1.21 Testing in Good Laboratory Practice

Testing methods should be validated. A laboratory that is using a testing method and which are defined in the marketing authorization or technical dossier. The results obtained should be recorded. The tests performed should be recorded and the records should include at least the following data:

- Name of the material or product and, where applicable, dosage form;
- Batch number and, where appropriate, the manufacturer and/or supplier;
- References to the relevant specifications and testing procedures;
- Test results, including observations and calculations, and reference to any certificates of analysis;
- Dates of testing;

- Initials of the persons who performed the testing;
- Initials of the persons who verified the testing and the calculations, where appropriate;
- A clear statement of approval or rejection (or other status decision) and the dated signature of the designated responsible person;
- Reference to the equipment used.

1.22 Annexure

Table 1 Format for Quality Control Laboratory closedown checklist

Quality Control Laboratory Closedown Checklist			
Date :			**Page No.**
S. No.	**Check Points**	**√/ X / NA**	**Remarks**
	All water taps are closed.		
	All the glassware kept in designated place.		
	Exhaust fan of Titration room is switched OFF.		
	All acids and reagents kept in designated place.		
	Exhaust fan of Fume Hood is switched OFF & panel door is closed.		
	All the chemicals /Reagents/ Standards kept in designated place.		
	Sink is clean and clear.		
	Glassware drying oven switched off.		
	Area is tidy and samples kept on designated place.		
	All SOPs/Working documents are kept on designated place.		
	All instruments/equipment's/computers are in standby mode/switched OFF.		
	All columns and other accessories are kept in designated place.		
	GC gas lines are turned OFF (If GC is not running)		
	All lights are switched OFF.		
	GC gas line connection from cylinders located at Gas Bank shall be off or dismantle. (If GC is not running).		
Checked by:		Verified By:	
Date:		Date	

Table 2 Format for Microbiology Laboratory closedown checklist

Microbiology Laboratory Closedown Checklist			
Date :			**Page No.**
S. No.	**Check Points**	**√ /X/NA**	**Remarks**
	Media placed at designated place.		
	Instruments/Equipment are switched OFF.		
	Computers are shut down.		
	SOP and all other documents placed at designated place.		
	Unloaded articles placed at designated place.		
	LAF working bench cleaned.		
	LAF motor, UV light, Visible light switched OFF.		
	Cultures placed at designated place.		
	Observed plates removed.		
	BOD incubators working properly.		
	Pass Boxes are empty, cleaned and their door closed from both side.		
	Clean and dried Glassware kept in their respected place.		
	Doors of Autoclave are closed.		
	Area clean and tidy.		
	Lights switched OFF.		
Checked by:		Verified By:	
Date:		Date	

Table 3 Format for Instrument/Equipment status board

Logo
INSTRUMENT /EQUIPMENT STATUS BOARD
Instrument/Equipment Id. No. : _____
Product Name : _____
Batch No. /A.R. No. : _____
Test : _____
Under Analysis/Awaited for Results
Analyst Name/Sign : _____
Date : _____
Date : _____
XXXX-00

Table 4 Format for desiccant replacement status label

Logo
DESICCANT REPLACEMENT STATUS
Item Name : _____
Replaced on : _____
Next Due Date : _____
Sign / Date : _____
XXXX-00

Table 5 Format for water replacement status label

Logo
WATER REPLACEMENT STATUS
Instrument/Equipment ID : _____
Replaced on : _____
Next Due Date : _____
Sign/Date : _____
XXXX-00

Table 6 Format for daily work allotment and status report

Daily Work allotment and status report **Page No.**					
Analyst Name/Employee Code: **Group/Section:** **Work Allotted by :** **Date:**					
Shift	**Work Allotted for the day/Previous day Carry over (AR No. / Batch No/Other details)**	**Test**	**Activity started (Hr.)**	**Analyst Sign/Date**	**Status (Remarks, if any)**
Details of Incident, OOT or OOS, if any:					
Reviewed By (Sign & Date):					

Table 7 Format for stamps

1. Stamp for weight print

A.R. No. : _____
Test. : _____
Signature : _____
Date : _____

2. Stamp for Invalid Data

INVALID DATA
Reason : _____
Sign/Date : _____

3. Stamp for Reviewed

REVIEWED
Sign/Date : _____

Table 8 Format for analysis status board

Logo
ANALYSIS STATUS BOARD Product Name : _____ Batch No./A.R. No. : _____ Test : _____ Under Analysis/Awaited for Results Analyst Name/Sign : _____ Date : _____
XXXX-00

Table 9 Change History format

Change History	
Department :	Page No.:
Document Type	SOP
Document No	TAP029-00
Title	Good Laboratory Practices

Table 9 *Contd…*

Document No. & Version No.	Effective Date	Change Control No. & brief details of changes
TAP029-00	12-12-2017	Change Control No. 20172915 New SOP prepared.

Document No. Version No.	Effective Date	Change Control No. & brief details of changes
TAP029-00		Change Control No. 20172915 New SOP prepared.