PHARMACEUTICAL ANALYSIS (3T3)

UNIT 1 - INTRODUCTION TO GLP AND ITS APPLICATION

The formal, regulatory, concept of "Good Laboratory Practice" (GLP) originated in the USA in the 1970s because of concerns about the validity of non-clinical safety data submitted to the Food and Drug Administration (FDA) in the context of New Drug Applications (NDA). The inspection of studies and test facilities revealed instances of inadequate planning and incompetent execution of studies, insufficient documentation of methods and results, and even cases of fraud. For example, replacing animals which had died during a study with new ones (which had not been treated appropriately with the test compound) without documenting this fact; taking haematology data for control animals from control groups not connected with the study; etc. On the international level, the Organization for Economic Co-operation and Development (OECD) assembled an expert group to formulate the first **OECD Principles of GLP.** This was an attempt to avoid non-tariff barriers to trade in chemicals, to promote mutual acceptance of non-clinical safety test data, and to eliminate unnecessary duplication of experiments.

What is GLP?

Good Laboratory Practice is defined in the OECD Principles 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." The purpose of the Principles of Good Laboratory Practice is to promote the development of quality test data and provide a tool to ensure a sound approach to the management of laboratory studies, including conduct, reporting and archiving. The Principles may be considered as a set of standards for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions and the traceability of data. The Principles require institutions to assign roles and responsibilities to staff in order to ensure good operational management of each study and to focus on those aspects of study execution (planning, monitoring, recording, reporting, archiving) that are of special importance for the reconstruction of the whole study.

Since all these aspects are of equal importance for compliance with GLP Principles, it is not permissible to partially implement GLP requirements and still claim GLP compliance. No test facility may rightfully claim GLP compliance if it has not implemented, and does not comply with, the full array of the GLP rules. As far as pharmaceutical development is concerned, the GLP Principles, in their regulatory sense, apply only to studies which:

• are non-clinical, i.e. mostly studies on animals or in vitro, including the analytical aspects of such studies;

• are designed to obtain data on the properties and/or the safety of items with respect to human health and/or the environment;

• are intended to be submitted to a national registration authority with the purpose of registering or licensing the tested substance or any product derived from it.

GLP Principles are independent of the site where studies are performed. They apply to studies planned and conducted in a manufacturer's laboratory, at a contract or subcontract facility, or in a university or public sector laboratory. GLP is not directly concerned with the scientific design of studies. The scientific design may be based on test guidelines and its scientific value is judged by the (Drug) Regulatory Authority that provides marketing authorisation. However, adherence to GLP will remove many sources of error and uncertainty, adding to the overall credibility of the study. Through the application of technically valid and approved Standard Operating Procedures many sources of systematic error and artifacts may be avoided.

The requirement to formulate a study plan with a defined scientific purpose for the study will prevent false starts and diminish the incidence of incomplete or inconclusive studies. Respecting the GLP Principles will thus indirectly optimise the scientific yield of studies. When implementing GLP in a test facility, and particularly during training, it is important to clearly differentiate between the formal, regulatory use of the term Good Laboratory Practice and the general application of "good practices" in scientific investigations. Since the term "Good Laboratory Practice" is not a trade-mark protected term, any laboratory may consider that it is following good practices in its daily work. This does not comprise GLP compliance.

THE FUNDAMENTAL POINTS OF GLP

The GLP Principles set out the requirements for the appropriate management of nonclinical safety studies. This helps the researcher to perform his/her work in compliance with his/her own pre-established scientific design. GLP Principles help to define and standardise the planning, performance, recording, reporting, monitoring and archiving processes within research institutions. The regulations are not concerned with the scientific or technical content of the studies per se. The regulations do not aim to evaluate the scientific value of the studies: this task is reserved first for senior scientists working on the research programme, then for the Registration Authorities, and eventually for the international scientific community as a whole. The GLP requirements for proper planning, for controlled performance of techniques, for faithful recording of all observations, for appropriate monitoring of activities and for complete archiving of all raw data obtained, serve to eliminate many sources of error. Whatever the industry targeted, GLP stresses the importance of the following main points:

1. Resources: Organisation, personnel, facilities and equipment;

2. Characterisation: Test items and test systems;

3. Rules: Protocols, standard operating procedures (SOPs);

4. Results: Raw data, final report and archives;

5. Quality Assurance: Independent monitoring of research processes.

Standard Operating Procedures (SOPs)

A full set of good Standard Operating Procedures (SOPs) is a prerequisite for successful GLP compliance. Setting up the SOP system is often seen as the most important and most time-consuming compliance task. Even without GLP regulations, classical quality assurance techniques, indeed good management, require standardised, approved, written working procedures. Remember the following quote based on an idea from Deming & Juran: "Use standards (here: SOPs) as the liberator that relegates the problems that have already been solved to the field of routine, and leaves the creative faculties free for the problems that are still unsolved". The successful implementation of SOPs requires:

• Sustained and enthusiastic support from all levels of management, with commitment to establishing SOPs as an essential element in the organisation and culture of the laboratory.

• SOP-based education and training of personnel, so that the procedures are performed in the same way by everyone.

• A sound SOP management system to ensure that current SOPs are available in the right place.
SOP System

Purpose of GLP QA Profession:

a) Influence working practices to improve standards of quality
The main purpose of the role of the Good Laboratory Practice (GLP) Quality Assurance (QA) professional is to assure management of the compliance with the GLP regulations within their departments. GLP is the quality system applied to non-clinical safety and environmental studies during the development of new products such as medicines, industrial chemicals and pesticides. GLP gives assurance that study data submitted to government assessors is accurate, valid and of sound integrity. Monitoring for GLP compliance by the QA Professional involves conducting audits of the facilities, of ongoing work in the facilities and of various documents.
The GLP regulations require that QA conduct audits of the following types

- Facility audits – to assure the facility is fit for purpose and documents to support processes are in place
- Process and Study audits – observing personnel in the laboratory to assure they are following relevant procedures and working in compliance with GLP
- Study Plan reviews – review of the document which outlines the work to be conducted
- Study Report reviews – review of the report to check it accurately reflects the data generated during the study and contains everything required under GLP

- Computerised Systems used to generate and/or manipulate study data and facility GLP records– review of documents associated with validation of new systems plus audits of ongoing maintenance and validation status of the system

The role also involves proactive input into changes in policies and working practices within the departments. As a QA professional, you will be asked for suggestions on how to improve processes and policies within the department with a view to improving the quality of the work.

b) Work with a variety of internal and external companies

A GLP QA professional typically works with many parts of the organisation. It really is a cross departmental role. Additionally your organisation may be involved in contracting out work or in collaborations with other organizations. You may be involved in auditing quality systems within these external organizations as well as auditing other parts of your own organisation.

c) Share knowledge through consultancy and training

You may be expected to deliver training in the basic principles of GLP to new staff within your organisation as well as training for staff taking on particular GLP roles in what their responsibilities are (for example, computer system owners, Study Directors). It is also expected that all staff working in GLP areas receive periodic refresher training so you may be involved in putting together material for this as well as running training workshops. All of this training needs to be organised and documented so organisation skills are also key.

d) Provide opportunities for personal and professional development

A career as a GLP QA professional will mean that you will be constantly developing your knowledge and skills. In order to perform audits, you will need a good understanding of the science behind the work being conducted. Therefore as scientific techniques evolve and develop, you will be aware of this and learn about these exciting developments.

e) Travel

Many organisations that are involved in GLP work are large global companies that have sites on many locations. You may be required to travel to other locations in order to participate in joint audits or attend meetings. You may also be required to be involved in due diligence activities at a location of another company of which your organisation is considering a buy out or buying a drug in mid development.

Additionally you may be required to audit supplier companies who provide materials and/or services that are key to the work being conducted in your organisation. This is to ensure that the systems in the supplier company are adequate to ensure quality of those products that are being supplied.

f) Enjoy a variety of roles through involvement in a number of different projects, processes and locations

You could be involved in auditing a wide variety of study types ranging from animal toxicity studies designed to provide a safe dose for dosing to man to soil sediment studies looking at how an agrochemical would behave in the environment.

Additionally as you hold a unique role within the organisation that encompasses many departments, you will probably also get involved in improvement projects both in QA and in the scientific functions, as well as computer validation projects.

You may be involved in hosting inspections of your organisation from regulatory authority inspectors. This will include helping to prepare for the inspection as well as answering questions and supporting scientific staff throughout the inspection.

g) Raise your profile within your organisation

Working in QA means that you will never be stuck in an office all day not being able to meet people in other parts of your organisation. Your role means that you will be liasing with people from all parts of your organisation at all levels. You will meet people through auditing them in the laboratory and meet with management to discuss corrective actions. Working in QA is an excellent way to get to know all parts of the organisation and raise your profile.

h) Plan and organise your own workload and schedule

You will be required to plan audits and maintain schedules, which will be scrutinised by the regulatory authorities. The ability to prioritise your workload is very important, as you are likely to be involved in different projects and audits at the same time.

i) Acquire an in-depth understanding of how complex organisations work

Due to the unique position that QA hold with their 'umbrella' view, you will gain an understanding of many different areas and processes within your organisation and gain an understanding of how different parts of your organisation liase with each other.

Importance of GLP

Good Laboratory Practice (GLP) is a set of principles that guides how laboratory studies are planned, performed, monitored, recorded, reported and archived. This is different from laboratory safety standards (such as appropriate clothing). GLP helps to ensure the credibility and traceability of data submitted, thereby addressing the issue of non-reproducibility in many biopharmaceutical experiments. GLP is intended to minimise adverse drug effects and improve human health and environmental safety profiles. GLP also helps to improve accountability and precision of data through the transparent and detailed documentation of laboratory work while assigning responsibility at various steps in the experiment. In addition, the International Council

for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has mentioned GLP as a pre-requisite for the successful international registration of pharmaceuticals.

Tips to achieve GLP

1. Implement and/or adhere to Standard Operating Procedures (SOPs) in the laboratory Including SOPs relating to inspection, maintenance, calibration and testing SOPs help minimise inter-individual and inter-test variability, as well as ease reporting complicated procedures
2. Separation of different activities to minimise disturbances
3. Label all reagents and solutions with their name(s), date of opening, storage conditions and expiry date Reagents should be used and obtained in line with relevant SOPs
4. Ensure any animal studies are done on the appropriate species, this aids in proper dose selection
5. Ensure all techniques and instruments used are validated
6. All data should be linked with their sources or samples. Samples should be labeled with the particulars of the patient/subject that the sample was obtained from, as specified in SOP
7. Document all findings, not just the ones that favour the hypothesis. Ensure all documents are readily available for scrutiny. Document any pre-set inclusion and exclusion criteria Report any excluded animals or subjects
8. All analytical reports should be signed and dated by the relevant project manager Reports should be kept for at least 5 years. Archive the documents systematically such that they are readily available at any one time
9. Be familiar and up-to-date with all the procedures (and their relevant SOPs) required of you –

- If necessary, ensure you have or obtain the necessary certificate and qualifications required to perform the procedure
- Adhere to good laboratory practices and techniques

10. Be familiar with SOPs in case of an emergency and be prepared to perform them at any time. Be familiar the safety data sheet (SDS) of the chemicals used in the experiment
11. If blood and/or urine is used, keep in mind the changes in blood/urine on keeping and ensure that the blood/urine is not kept for longer than required

- ensure that the changes on keeping are either accounted for or do not affect the results of the experiment.