

TRAINING MANUAL

GOOD LABORATORY
PRACTICE (GLP)

TRAINER

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GOOD LABORATORY PRACTICE
TRAINING MANUAL

FOR THE TRAINER

A tool for training and promoting Good Laboratory Practice (GLP)
concepts in disease endemic countries



**World Health
Organization**



**For research on
diseases of poverty**
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FOREWORD

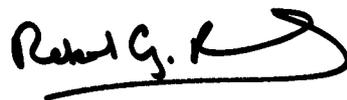
In order to assist countries in conducting non-clinical research and drug development, TDR developed a *Good Laboratory Practices (GLP)* series in 2001, comprising a *GLP Handbook* as well as *GLP Training manuals* for trainers and trainees.

The demand for this series was so great that it became one of the most frequent “hits” on the TDR website, generating interest and demand for a second edition. This second edition *GLP Training Manual for Trainers* is presented here in a revised and updated format. It supports continued technology transfer and capacity building in disease endemic countries (DECs) in line with the aims of the recent World Health Assembly Resolution (WHA 61.21) on a *Global strategy and plan of action on public health, innovation and intellectual property* (www.who.int/phi).

Since publication of the initial GLP edition, TDR-fostered GLP training efforts throughout the world (particularly in Asia, Latin America and Africa) have led to the formation of a network of GLP trainers. These trainers, acting as testers and critics, had a significant impact on the revision and expansion of this second edition GLP series.

A key aim of TDR is to empower DECs to develop and lead research activities to internationally-recognized standards of quality. This revised GLP series will support that goal, assisting DEC institutions in performing research and drug development studies. This, in turn, will also help institutions continue research initiatives into the clinical phases of development, in partnership with both the public and private sectors.

We anticipate that the use of these GLP resources will help promote cost-effective and efficient preclinical research with a long-term positive effect on the development of products for the improvement of human health. In this way, the revised GLP series contributes to TDR’s primary mission of “*fostering an effective global research effort on infectious diseases of poverty in which disease endemic countries play a pivotal role*”.



Dr R. Ridley
Director TDR

ABOUT THIS TRAINING MANUAL

This is the second edition of the WHO/TDR GLP Training Manual for Trainers. It is a support document for the WHO Good Laboratory Practice (GLP) Training Programme. The training is based on the Organization for Economic Cooperation and Development (OECD) GLP Principles which are recognized as the international standard for GLP. The training is designed to be conducted over a three-day period.

This manual for trainers is part of a suite of three documents. These are:

1. the WHO/TDR GLP Handbook (blue)
2. the GLP Training Manual for Trainers (red)
3. the GLP Training Manual for Trainees (green).

All three documents have been updated at the same time in order to maintain consistency.

Contributions to this manual have come from many sources. The first version of this manual could not have been compiled without the help of David Long, Nick Kail, David Ford, Nadya Gawadi and Phil Withers. However, this expanded second edition, initiated by the WHO/TDR Network of GLP Trainers includes contributions from all the people of the network.

In this second edition of the manual we have reorganized the contents to align them with the five fundamental points developed in the Handbook. Thus, after an introduction, the order of the five fundamental points is now:

- resources
- characterization
- rules
- results
- quality assurance.

The major difference seen in this edition is the additional material to be found in the seven appendices. This material is for optional use, depending upon the existing level of GLP knowledge of the trainees. This extra material is the result of experience from eight years of training since the publication of the first edition, and has been largely requested by the WHO/TDR GLP Trainers.

The other major advance is in the number of optional workshops at the trainers disposal. Depending upon local conditions or requirements, the trainer can select from the available workshops to suit needs. For the convenience of copying, the workshops have been removed from the training manual and are now available in the accompanying CD.

The training material is divided into two parts (1) presentation materials which are in the present volume and (2) workshop materials which are only available in the CD. There is too much material for it all to be used in a single three-day training course. As a trainer, you will have been trained under the auspices of the WHO, or you are already a recognized expert in GLP. You should, therefore, present the core material (chapters 1-6) and then select any additional presentations or workshop materials on the basis of local needs.

Presentation material

There are six chapters and seven appendices, each one dealing with a separate topic for presentation. The six chapters cover the essential core topics which you should use for all training courses. The appendices provide optional presentation material. Each of the chapters and appendices has the same format:

- **Section summary**

As the trainer you will already have this knowledge, but it is worth reading through this section before starting a presentation to fix the salient points in your mind. You should encourage the participants to read these sections between presentations for the same reason. They are included in the trainee's manual (green book).

- **Slide presentation**

The slides are for your presentations. The trainees have a copy of the same slides in their manual so they will only need to make additional personal notes. Many of the slides have instructions (in the form of "instructor's notes") to help you through the presentation. These draw attention to the "message" of the slide and occasionally suggest how you could usefully engage the group in discussion. Naturally, the trainees do not have these notes.

- **Workshop material**

The workshops are group activities. There are no hard and fast rules about the solutions to workshop issues and you will have to take each proposal from each group as a point for discussion.

Developing a good rapport with the trainees during the training session is of utmost importance. You should always be positive - never dismiss as unacceptable the group response to the workshop tasks. Find out why they have decided to make the suggestion that they put forward. The reason may be well founded, even if the response seems to be non-compliant. Finally, always try to relate what the groups have to say to the fundamental points of GLP.

ACKNOWLEDGEMENTS

The Good Laboratory Practice (GLP) Training Manual set comprises of two manuals; one for the trainer (red), one for the trainee (green). These have been designed for use as an introductory course to GLP. They are accompanied by a WHO/TDR Handbook on GLP (blue) which includes an introduction to GLP, texts concerning the salient points of the GLP Principles and suggestions on how to implement GLP in laboratories. The handbook also includes all 15 of the OECD guidance documents on GLP. WHO/TDR is particularly grateful to the OECD for permission to reproduce these documents *in extenso*.

This second edition of the Training Manual was made possible by the enthusiastic support and contributions of the WHO/TDR Network of GLP Trainers. The manuals were written by David Long, based on material which existed in the first edition and on the input from the many international GLP training sessions and workshops organized by the WHO/TDR Preclinical Coordinator since the inception of the training programme in 1999.

Particular thanks should be extended to the WHO/TDR Network of GLP Trainers who have contributed to this version and have given unflagging support to the project.

It is hoped that the training manuals will continue to provide a valuable tool for training and promoting GLP implementation in the DECs.

Comments and suggestions on all aspects of these manuals are welcome for consideration in future revisions. Please contact:

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1. INTRODUCTION TO THE OECD PRINCIPLES OF GLP

INTRODUCTION

Good Laboratory Practice (GLP) regulations became part of the regulatory landscape in the latter part of the 1970s in response to malpractice in research and development (R&D) activities by pharmaceutical companies and contract facilities used by them.

The malpractice included cases of fraud, but by far the most important aspects were the lack of proper management and organization of studies performed to generate data for regulatory dossiers. The US Food and Drug Administration (FDA) mounted a series of investigations in toxicology laboratories throughout the USA. The results of these investigations revealed a situation that could only be dealt with by imposing binding regulations. These regulations are the GLP regulations. GLP regulations were first instituted by US FDA, then by US Environmental Protection Agency (EPA); many other nations have since followed suit.

In 1981, the Organization for Economic Cooperation and Development (OECD) also published GLP Principles, and these now dominate the international arena. To date 30 countries (the member states of the OECD) have signed an agreement binding them to OECD GLP Principles. Other non-OECD member states have also adopted the OECD GLP Principles.

The intent of GLP is to regulate the practices of scientists working on the safety testing of prospective drugs (and other chemical or biochemical entities). With the obvious potential impact on patients taking medicines and on people recruited for clinical trials, the safety of drugs is a key issue and GLP is seen as a means of ensuring that scientists do not invent or manipulate safety data, and as a means of ensuring that studies are properly managed and conducted, thereby considerably increasing the chances of producing valid experimental data. GLP compliance is a guarantee that safety data are being honestly reported to the registration authorities. The results of these studies form the basis for the decision to proceed with clinical trials, prior to allowing a new drug onto the market. GLP was imposed on industry by regulatory authorities in the same manner as Good Manufacturing Practice (GMP) had been before, and Good Clinical Practice (GCP) would be later.

THE FUNDAMENTAL POINTS OF GLP

The GLP regulations set out the rules for good practice and help researchers perform their work in compliance with their own pre-established plans and standardized procedures. The regulations are not concerned with the scientific or technical content of the research programmes. Nor do they aim to evaluate the scientific value of the studies.

All GLP texts, irrespective of their origin, stress the importance on the following points five points:

1. **Resources:** organization, personnel, facilities and equipment
2. **Characterization:** test items and test systems
3. **Rules:** study plans (or protocols) and written procedures
4. **Results:** raw data, final report and archives
5. **Quality Assurance.**

The training programme of the WHO covers each of these five fundamental points and explains the requirements of GLP in each case. The major points are summarized below:

1. Resources

Organization and personnel

GLP regulations require that the structure of R&D organizations and the responsibilities of R&D personnel be clearly defined.

GLP also stresses that there should be sufficient staff to perform the tasks required. The qualifications and the training of staff must also be defined and documented.

Facilities and equipment

The regulations emphasize the need for sufficient facilities and equipment to perform the studies.

All equipment must be in working order. To ensure this, a strict programme of qualification, calibration and maintenance must be adopted.

2. Characterization

In order to perform a study correctly, it is essential to know as much as possible about the materials used during the study. For studies that evaluate the properties of pharmaceutical compounds during non-clinical studies, it is a prerequisite to have details about the test item and the test system (often an animal or plant) to which the test item is to be administered.

3. Rules

Protocols and written procedures

The **main** steps of research studies are prescribed in the study plan or protocol. Being able to repeat studies and obtain similar results is a *sine qua non* of mutual acceptance of data and, indeed, a central tenet of the scientific method, so the details of routine procedures must also be available to scientists involved in the study. However, the protocol, which provides the experimental design and timeframe for the study, does not contain all the technical **detail** necessary to conduct the study. These details are found in written standard operating procedures (SOPs). With the protocol and the SOPs it should be possible to repeat the study exactly, if necessary.

4. Results

Raw data

All studies generate raw data. These are the outcome of research and form the basis for establishing scientific interpretations and arriving at conclusions. The raw data must also reflect the procedures and conditions of the study.

Final Report

The study report contains an account of the way in which the study was performed, incorporates the study results and includes the scientific interpretation of the data. The report is provided to regulatory authorities as part of the submission for registration and marketing approval.

Archives

Storage of records must ensure safekeeping for many years and allow for prompt retrieval.

5. Quality Assurance

Quality assurance (QA), as defined by GLP, is a team of persons (often called the Quality assurance unit – QAU) charged with assuring management that GLP compliance has been attained within the laboratory. QA must be independent from scientists involved in the operational aspects of the study being performed. QA functions as a witness to the whole non-clinical research process.

For further discussion on the fundamental points of GLP, see the WHO/TDR GLP Handbook.

THE OECD GLP PRINCIPLES

GLP started when the FDA issued mandatory GLP requirements on 20 June 1979. The FDA subsequently revised these regulations a number of times but it has never altered its scope; regulations still apply to non-clinical safety studies applied to drugs. Preliminary pharmacological studies and pharmacokinetic studies not designed to test safety are still exempt from GLP requirements. A little later, the OECD introduced the OECD Principles for GLP (GLP Principles) concerning the safety testing of any chemical substance. This GLP text is binding on all 30 OECD member states. This is why these GLP Principles have been adopted as the basic rules for the training programme devised for the WHO/TDR.

The OECD recognizes that not all parts of the GLP Principles are easy to interpret. This is why the OECD has published a series of advisory documents on various aspects of the GLP Principles. In all, there are 15 OECD documents concerning GLP (including the GLP Principles). Many of these have been derived from discussions between regulators and members of industry during consensus workshops. The contents of the documents represent the current thinking of the OECD. Any member state can request that a particular subject be discussed during a consensus meeting. It is up to the OECD to decide whether the subject merits a full three-day consensus type meeting.

The OECD has established a GLP Group made up of senior members of the respective member states' GLP monitoring authorities. This group oversees the GLP activities of the OECD. The activities include the organization of training courses for GLP inspectors from all over the world and the organization of joint inspections. Together, these help to harmonize the approach of the various member states to GLP inspections.

1. Introduction to the OECD Principles of GLP



Fundamentals of OECD GLP Principles

**Introduction
and
Fundamentals of GLP**

Section 1:1

Instructor's notes

Explain

This short introduction explains why GLP is a necessary regulation.

Participants should be reminded at this point that the training course is based on the OECD Principles of GLP.

The explanation leads up to the five fundamental points of GLP which are provided at the end of the section.



Fundamentals of OECD GLP Principles

The birth of GLP

- In the early 1970s, the FDA investigated a number of cases of poor practice in toxicology laboratories throughout the USA
- Results of this investigation in about 40 laboratories revealed many cases of poorly managed studies, insufficient training of personnel, and some cases of deliberate fraud

Section 1:2

Instructor's notes

Explain

In the early and middle 1970s the FDA was alerted to cases of poor practice in certain laboratories, either by disgruntled employees or directly by FDA inspectors.

The FDA felt it necessary to perform an in-depth investigation throughout the USA. The investigation was performed in about 40 toxicology laboratories.

At the end of the investigation, the FDA published its findings, summarized in the following two slides. Some cases of fraud were detected and the laboratories concerned were strictly dealt with. One such company, Industrial Bio-Test, was closed down and the directors were imprisoned.

But most of the poor practice observed was not fraud and could be dealt with by implementing a system of quality management.

1. Introduction to the OECD Principles of GLP



Fundamentals of OECD GLP Principles

FDA Investigation findings

- Poorly-trained Study Directors and study personnel
- Poorly-designed protocols
- Protocols not followed - procedures not conducted as prescribed
- Raw data badly collected - not correctly identified - without traceability - not verified or approved by responsible persons
- Lack of standardized procedures
- Poor animal husbandry

Section 1:3

Instructor's notes

Explain

This slide and the next one list a selection of the FDA findings.

The findings of the FDA are available under the Freedom of Information Act (enacted 1966, in force 1967).

The findings listed do not include the rare cases of fraud or falsification of results.

The trainer should explain the importance of each point for the integrity and credibility of studies, with emphasis on the need to control study variables and standardize procedures.

The important point to highlight is that quality management is not primarily designed to combat fraud, but to promote a controlled and documented organization of studies.



Fundamentals of OECD GLP Principles

FDA Investigation findings

- Inadequate characterisation of test items and test systems
- Inadequate resources
- Equipment not properly calibrated or otherwise qualified
- Reports not sufficiently verified, inaccurate account of study or raw data
- Inadequate archives and retrieval processes

Section 1:4

Instructor's notes

Explain

The list on this slide is a continuation of the previous one.

1. Introduction to the OECD Principles of GLP



Fundamentals of OECD GLP Principles

FDA Decision

- Introduce a new regulation to cover NON-CLINICAL SAFETY STUDIES

- Good Laboratory Practice regulations
 - Draft USA GLP in 1976
 - An enforceable USA regulation in 1979

Section 1:5

Instructor's notes

Explain

In 1976, the FDA published a draft regulation on GLP and requested comments from interested parties.

After the consultation period, the final regulation was published in 1978.

This came into force in 1979.

Although this was a US regulation, it had a wide impact worldwide. Non-US companies wishing to register medicines in the USA now had to perform safety studies in compliance with FDA GLP.

Remind participants that at that time about 30% of the world's pharmaceutical trade occurred in the USA; it was (and still is) a market that cannot be ignored!

Many countries introduced their own GLP regulations.

The OECD produced GLP Principles in 1981. These regulations have now become the international standard in the domain and are the basis for this GLP course.



Fundamentals of OECD GLP Principles

GLP
promotes
Quality and Validity
of test data

Section 1:6

Instructor's notes

Explain

GLP is a regulation covering the quality management of non-clinical safety studies.

The aim of the regulation is to encourage scientists to organize and perform their studies in a way which promotes the quality and validity of the test data.

1. Introduction to the OECD Principles of GLP



Fundamentals of OECD GLP Principles

GLP Principles

MAIN GOAL: To help scientists obtain results that are:

- Reliable
- Repeatable
- Auditable
- Recognized by scientists worldwide

Section 1:7

Instructor's notes

Explain

GLP is a regulation covering the quality management of non-clinical safety studies.

The aim of the regulation is to encourage scientists to organize and perform their studies in a way which promotes the quality and validity of the test data.



Fundamentals of OECD GLP Principles

GLP Principles

- GLP principles are a set of organizational requirements
- The purpose is not to assess the intrinsic scientific value of a study

Section 1:8

Instructor's notes

Explain

Point out the important difference between the “science” of a study and the “organization” of a study.

GLP does not tell scientists what tests to perform, or what the scientific contents of a study plan (protocol) should be. There are other guidelines for this aspect of studies (scientific guidelines).

GLP requires that the scientists responsible for the organization of studies implement clear structures, responsibilities and procedures in compliance with GLP so that the test data are more reliable.

1. Introduction to the OECD Principles of GLP

 Fundamentals of OECD GLP Principles
<p style="text-align: center;">GLP Aim</p> <p style="text-align: center;">To make the incidence of</p> <p style="text-align: center;">False Negatives</p> <p style="text-align: center;">more obvious</p> <p style="text-align: center;">(False negative : Results demonstrate non-toxicity of a toxic substance)</p>
Section 1:9

Instructor's notes

Explain

GLP helps scientists reduce the number of false negatives arising from their studies because the studies are standardized and the variables are well documented.

A false negative for a toxicity study is a set of results that falsely reports that a test item is not toxic when in reality it is toxic.

Taken to its extreme, this could be dangerous if the test item is administered to man in clinical trials. However, such a situation rarely occurs because many preclinical studies are performed before exposing man to the test item and the chances of all these giving false negative results are slim. But all false negative results are costly, time consuming and present ethical problems (e.g. animals used to no good purpose). They should, therefore, be avoided.

 Fundamentals of OECD GLP Principles
<p style="text-align: center;">GLP Aim</p> <p style="text-align: center;">To make the incidence of</p> <p style="text-align: center;">False Positives</p> <p style="text-align: center;">more obvious</p> <p style="text-align: center;">(False positive : Results demonstrate toxicity of a non-toxic substance)</p>
Section 1:10

Instructor's notes

Explain

GLP also helps scientists reduce the incidence of false positives.

In the case of a non-clinical safety study, such results wrongly lead the scientists to believe that their test item is toxic, when really it is not.

In this case, the test item is likely to be discarded, i.e. excluded as a candidate medicine. The test item might well be a compound which could be a useful addition in the fight against disease, but because of wrong interpretation, the compound is eliminated for further research and never reaches the patients that it might have been able to help.

1. Introduction to the OECD Principles of GLP



Fundamentals of OECD GLP Principles

GLP Aim

To promote mutual recognition of study data across international frontiers

Section 1:11

Instructor's notes

Explain

GLP also promotes international recognition of study data.

When studies are performed according to OECD GLP Principles, 30 countries of the world (OECD member states), who have accepted the GLP Principles, must recognize that the data from these studies have been generated under acceptable organizational standards. Even non-OECD member states are willing to accept the reliability of data resulting from GLP compliant studies.

So, provided that the scientific aspects of the studies are reasonable, the data will be accepted as reliable and the studies as valid.

Previous to the establishment of GLP, many countries would refuse registration of drugs developed from studies conducted abroad, insisting that the trials be repeated in their won country. GLP made such policies obsolete by allowing countries to have confidence in the original data.



Fundamentals of OECD GLP Principles

GLP

- *Limit waste* of resources
- Ensure *high quality* of results
- Ensure *comparability* of results
- Promote *mutual recognition* of results

(Preamble to European Directive 87/18 EEC)

Section 1:12

Instructor's notes

Explain

In the introduction to the European Directives on GLP, the four points mentioned in this slide are cited as the reasons for GLP in the organization of safety studies.

Limiting waste of resources is particularly aimed at limiting the use of animals.

Ensuring high quality results concerns the validity of test data.

Ensuring comparability means that better information can be obtained in order to allow registration authorities to decide between candidate medicines.

Mutual recognition of results refers to the fact that GLP is an internationally accepted set of regulations for the conduct of studies.

1. Introduction to the OECD Principles of GLP



Fundamentals of OECD GLP Principles

GLP

**Managerial concept for the
organization of studies**

Section 1:13

Instructor's notes

Explain

As already emphasized, GLP stipulates the conditions for the organization of studies - not the scientific content or value of studies.

As such, GLP is a quality system for the management of non-clinical studies.



Fundamentals of OECD GLP Principles

GLP

Defines conditions under which studies are

- Planned
- Performed
- Recorded
- Reported
- Archived
- Monitored

Section 1:14

Instructor's notes

Explain

This sentence is one of the key phrases which can be located in the introductory text to the OECD GLP Principles (upon which this course is based).

GLP defines the working environment under which studies are:

PLANNED.....which is why great emphasis is placed on the study plan (protocol) and to planned changes throughout the study.

PERFORMED.....this refers to the standard operating procedures (SOPs) which are a GLP requirement.

RECORDED.....i.e. the collection of raw data and the recording of deviations, if any, during the study.

REPORTED.....one of the problems pre-GLP was that study reports did not always reflect the study data accurately. Assuring accuracy in the report has now become an essential part of GLP.

ARCHIVED.....as studies may be audited many years after their completion, it is important that the study data, specimens, samples and reports are properly archived.

MONITORED.....monitoring by study staff, quality assurance personnel and national inspectors helps to assure GLP compliance.

1. Introduction to the OECD Principles of GLP



Fundamentals of OECD GLP Principles

Five Basic Points

- 1. RESOURCES:** Personnel, Facilities & Equipment
- 2. CHARACTERIZATION :**
 - Test Article - Identification, Quality
 - Test system - Identification, Health status...
- 3. RULES :** Protocols / Study Plans, Procedures
- 4. RESULTS:** Raw data, Final Report, Archives
- 5. QUALITY ASSURANCE:** Audit/Inspection - Training - Advice

Section 1:15

Instructor's notes

Explain

This slide shows the fundamental points of GLP. They are arranged under five convenient headings.

Take time to discuss this slide with the participants, providing basic information about the meaning of each of the five points.

Explain that each of the sections is covered in the GLP Principles, but that the GLP Principles are organized under a more complicated set of chapter headings.

You will find a brief summary of the importance of the five points in the introductory text accompanying these slides and in the WHO/TDR GLP Handbook.

Each of the five points will be presented one by one during the course.

2. RESOURCES

This section on resources is divided into three parts:

1. Management
2. Personnel
3. Facilities: buildings and equipment

In addition to this section comprising general comments on the GLP requirements for management, the manual includes a separate section with more detailed information on the responsibilities of management and the study director (see appendices 2 and 3).

MANAGEMENT

Without full commitment of management, GLP systems will not function as they should and will lack credibility. Managerial aspects are therefore critical for GLP implementation in a laboratory. Laboratory management responsibilities and organisational requirements take up about 15% of the GLP text, clearly demonstrating that the regulators also consider these points as important.

Management has the overall responsibility for the implementation of both *good science* and *good organization* within their institution

Good Science

- Careful definition of experimental design and study parameters.
- Science based on known scientific principles.
- Control and documentation of experimental and environmental variables.
- Careful and complete evaluation and reporting of results.
- Results becoming part of accepted scientific knowledge.

Good Organization

- Proper planning of studies and allocation of resources.
- Provision of adequate facilities, infrastructure and qualified staff.
- Definition of staff responsibilities and provision of staff training.
- Establishment of procedures to ensure proper conduct of studies.
- Good record keeping and organized archives.
- Implementation of verification procedures for study conduct and results.

These organizational aspects of studies can be met by complying with GLP.

Management delegates a number of functions to other staff without losing the overall responsibility for the work. For each specific study, management must appoint a study director who takes on the responsibility for the planning and daily conduct of the study and also the interpretation of study results. A special section on the study director's responsibilities can be found in a later section of this manual (see appendix 3).

Planning (Master Schedule)

The need for a system of organising the allocation of resources and time for studies is self evident. GLP requires that Management ensures allocation of sufficient personnel and other resources to specific studies and support areas.

The record of planning/resource allocation required by GLP is called the master schedule. The format of the master schedule is not stipulated. However, the general rules are:

- All studies (contracted and in-house) must be included in the schedule.
- A change control procedure is in place to reflect shifts in dates and workload.
- Time-consuming activities such as protocol review and report preparation should also be included.
- The schedule is “official” (i.e. there should not be two or more competing systems for the same purpose).
- The system is described in an approved SOP.
- Responsibilities for its maintenance and updating are defined by management.
- Various versions of the master schedule are approved and maintained in the archive as data.
- Distribution is adequate and key responsibilities are identified.

Typically, once the protocol is signed and issued, the study is entered into the master schedule. Often responsibility for the master schedule rests with project management and the schedule is computerized for efficiency and ease of cross-indexing. The master schedule system is described in an SOP. Typically, QA has “read-only” and “print” access to this data file. Signed hard copies are usually archived as raw data. In contract facilities, sponsor and test item names are usually coded to provide confidentiality.

Archived master schedules are often consulted by inspectors to evaluate whether or not there were sufficient personnel available during the period of the study being inspected. The easy retrieval of historical schedules is therefore important.

PERSONNEL

GLP requires that the overall organization of the test facility be defined. This is usually done through an organization chart. This is often the first document requested by inspectors to obtain an idea of how the facility functions. Sometimes the organization chart forms part of a quality Manual or other document that describes the nature of the institution and the way in which it operates. These are high level documents. They are supplemented by more detailed information which may be incorporated into the following documents relating to each individual:

- curriculum vitae
- training records
- job description.

Together these three documents meet the GLP requirement that records are maintained to demonstrate that staff have the competence, education, experience and training necessary to perform their tasks.

The format and contents of these documents should be defined in SOPs and verified regularly in QA audits.

Curriculum Vitae (CV)

A procedure should ensure that CVs:

- exist for all personnel in a standard approved format;
- are kept up-to-date;
- exist in required languages (local and sometimes English for regulatory submissions);
- are carefully archived to ensure historical reconstruction.

In a CV it is usual to include:

- name and age of the person;
- education, including diplomas and qualifications awarded by recognized institutions;
- professional experience earned both within the institution and before joining it;
- any publications (these may be listed separately, if numerous);
- membership of associations;
- languages spoken.

All staff should have a CV. Even if some personnel do not have extensive qualifications, they will have professional experience which should be listed in their CV. It is good prac-

tice to have the CV signed and dated by the person concerned, to avoid discrepancies in the content.

Training Records

Training complements CVs. Job competence depends largely on internal and external specialized training. GLP explicitly requires that all personnel should understand the meaning of GLP, its importance, and the position of their own tasks within GLP activities. Training must be formally planned and documented. New objectives and activities always involve some training. Training systems are usually SOP based. A new SOP therefore requires fresh certification of personnel who will use it.

The training system will have elements common to all GLP management systems i.e. it is formal, approved, documented to a standard format, described in a SOP and historical reconstruction is possible through the archive. For example, the participants' attendance at this course should be documented in their training records.

Job Description

All systems of quality management are based on making people responsible for their actions.

- “Don't do something if you don't understand the reason, the context and the consequences”.
- “Each person ‘owns’ and signs his work and feels completely responsible for its correct completion”.

Having job descriptions with a clear definition of tasks and responsibilities is essential for everyone.

The contents of job descriptions should correspond to the qualifications described in the CV. In addition, they should be:

- updated at a minimum required interval (fixed by an SOP);
- signed by the person occupying the post (“n”) and at least one appropriate member of management supervising the post (“n+1”).

Rules of delegation should be defined at the test facility. Tasks can be delegated, but the final responsibility remains with the person who delegates the task.

Annual reviews of job descriptions (and reviews when major reorganizations occur) help management ensure that their organization is coherent.

FACILITIES: BUILDINGS AND EQUIPMENT

Buildings

GLP requires that test facilities be of appropriate size, construction and location to meet the requirements of the study and minimize disturbances that would interfere with the validity of the study. They should be designed to provide an adequate degree of separation between the various activities of the study.

The purpose of these requirements is to ensure that the study is not compromised because of inadequate facilities. It is important to remember that fulfilling the requirements of the study does not necessarily mean providing “state of the art” constructions, but carefully considering the objectives of the study and how to achieve them. It is up to the facility management to define what is adequate; this will depend on the kind of studies being performed.

Separation ensures that different functions or activities do not interfere with each other or affect the study.

Minimising disturbance by separation can be achieved by:

- Physical separation: this can be achieved by walls, doors or filters, or by the use of isolators. In new buildings or those under transition or renovation, separation will be part of the design.
- Separation by organization, for example by the establishment of defined work areas within a laboratory carrying out different activities in the same area at different times, allowing for cleaning and preparation between operations or maintaining separation of staff, or by the establishment of defined work areas within a laboratory.

As an illustration of the principles involved we have chosen two examples that are often found in laboratories. These are (A) The Dose Mixing Unit: the zone used for the preparation of the dosage form and (B) Animal House Facilities.

Example A: Dose Mixing Unit

The Dose Mixing Unit is a laboratory area dealing with the work flow of test items, vehicles and control items: receipt, storage, dispensing, weighing, mixing, dispatch to the animal house and waste disposal.

(Note: Most of the points which follow would equally apply to other laboratory areas such as analytical or histopathology areas.)

A.1 - Size

The laboratory must be big enough to accommodate the number of staff working in it

and allow them to carry on their own work without risk of interfering in each other's work or mixing up different materials.

Each operator should have a workstation sufficiently large to be able to carry out the operation efficiently. There should be sufficient physical separation between the workstations to reduce the chance of mix up of materials or cross contamination. The dose mixing area is a sensitive zone and access to it should be restricted so as to limit the possibility of people becoming vectors of pollution or contamination between studies or test items.

A.2 - Construction

The laboratory should be built of materials that allow easy cleaning and do not allow any test items to accumulate in corners or cracks and cross contaminate others. There should be a proper ventilation system with filters that serve to protect personnel and prevent cross contamination. Many modern dose mixing areas are designed in a "box" fashion, each box having an independent air handling system.

A.3 - Arrangement

Ideally there should be separate areas for:

- storage of test items under different conditions
- storage of control items
- storage of vehicles
- handling of volatile materials
- weighing operations
- mixing of different dose forms e.g. diet and liquid
- storage of prepared doses
- cleaning equipment
- offices and refreshment rooms
- changing rooms.

Example B: Animal House Facility

To minimize the effects of environmental variables on the animal, the facility should be designed and operated to control selected parameters (such as temperature, humidity and light). In addition, the facility should be organized in a way that prevents the animals from coming into contact with disease, or with a test item other than the one under investigation.

Requirements will be different depending upon the nature and duration of the studies being performed in the facility.

Risks of contamination can be reduced by a “barrier” system, where all supplies, staff and services cross the barrier in a controlled way.

A typical animal house should have separations maintained by provision of areas for:

- different species
- different studies
- quarantine
- changing rooms
- receipt of materials
- storage of materials
 - bedding and diet
 - test doses
 - cages
 - cleaning equipment
- necropsy
- waste disposal.

The building and rooms should provide sufficient space for animals and studies, allowing the operators to work efficiently.

The environment control system should maintain the temperature, humidity and air-flow constantly at the defined levels for the species concerned.

Design should allow easy and thorough cleaning of surfaces of walls, doors, floors and ceilings. There should be no gaps or ledges where dirt and dust can accumulate. Water should not accumulate on uneven floors i.e. floors should be smooth and even and without crevices.

Whatever the capabilities or needs of the laboratory, sensible working procedures can reduce the damage from outside influences.

Such procedures may include:

- minimising the number of staff allowed to enter the building;
- restricting entry into animal rooms;
- organising work flow so that clean and dirty materials are moved around the facility at different times of the day and ensuring that corridors are cleaned between these times;
- requiring staff to put on different clothing for different zones within the animal facility;
- ensuring that rooms are cleaned between studies.

Equipment

Suitability and Calibration

To perform a study properly, adequate equipment must be available. All equipment should be suitable for its intended use. The equipment that is suitable for a given study depends on the type of the study and the study objectives. Suitability can only be assessed by consideration of the performance of the equipment. For example, there is no need to have a balance capable of weighing to decimals of a milligram to obtain the weekly weight of a rat; however a balance with this precision may be required in the analytical laboratory. Defining the suitability of equipment is a scientific problem to be judged by the study director.

For some equipment it is necessary to conduct formal tests or even formal qualification to demonstrate that it is fit for its intended use. This is often the case for analytical equipment.

Whether formally qualified or not, all equipment must be calibrated and maintained to ensure accurate performance. Most frequently, the calibration depends on the use of standards used. For example, in the case of a balance, the standards are the weights that have been certified by a national or international standards authority as being within specified limits. Frequently the laboratory will have a set of certified weights. These “primary standards” are only used to qualify “secondary standards”, which are then used on a routine basis.

Another example is standard chemicals which are used to test/calibrate equipment, like pH meters, to ensure accurate performance. Standards may also be compound samples of known concentration used to ensure that analytical equipment is functioning as expected and providing a basis for the calculation of the final result.

The laboratory must decide the acceptable frequency for calibration; this will depend on the type of equipment and its use. The calibration programme should be included in the SOPs of the institution.

Proof that equipment is performing to specifications is essential, whether generating data (e.g. analytical equipment or balances) or maintaining standard conditions (e.g. refrigerators or air conditioning equipment). This can be done by periodic checking at a frequency that allows action to be taken in time to prevent any adverse effect on the study should the equipment be faulty. Logbooks are often used to record these regular verifications.

Full documentation of all tests for suitability and for all calibration must be kept within the laboratory to allow scientists to assess the accuracy of measurements taken during studies. These data should be archived so that they are readily available should it become

necessary to investigate the results of a study, or during regulatory inspections. Records of repairs and routine maintenance, and any non-routine work should be kept.

The purpose of these GLP requirements is to ensure the reliability of data generated and to ensure that data are not lost as a result of inaccurate, inadequate or faulty equipment.

Maintenance

Facilities - Buildings and Equipment

GLP requirements that equipment should be maintained are based on the assumption that this reduces the likelihood of an unexpected breakdown and consequent loss of data.

Maintenance may be carried out in two distinct ways:

- preventive or planned, whereby a regular check is made irrespective of the performance of the equipment;
- curative or reparative, when the piece of equipment is not functioning according to specification or when the equipment or system has broken down.

Planned routine maintenance is a useful precaution for equipment that does not have a suitable backup or alternative. However, some pieces of equipment, such as modern-computer driven analysers or electronic balances, do not lend themselves to routine maintenance. A better approach may be to check them regularly and ensure that suitable contingencies are available if any problem occurs. The contingencies may include having duplicate equipment, having immediate access to an engineer, or having immediate access to a contract laboratory with equivalent equipment.

Back-up for vital equipment as well as back-up for power failure should be available whenever possible. A laboratory should have the ability to continue with essential services to prevent the loss of animals or data. For example, a laboratory carrying out animal studies may need a stand-by generator capable of maintaining at least the animal room environment to prevent the loss of the animals that would irretrievably affect the study. Meanwhile, samples could be stored for a period until power is restored.

Early warning that equipment is malfunctioning is important. Periodic checks will help detect malfunction, but this may also be achieved with alarms, particularly if the problem occurs at a time when staff are not present in the laboratory.

Routine maintenance requires planning and this should be indicated in a service plan. There are no specific rules concerning the format of the plan. Like all planned events the service plan should clearly indicate what is to be done and when. The related SOP should indicate tolerances for the targeted dates, how the actions are to be recorded and, of course, who is responsible for maintaining the plan.

When equipment is serviced, this should be recorded so that tracing back to this service

(even many months or years after the event) is possible. It is a good idea to label serviced equipment to indicate when it was last serviced and when the next service is due. This makes it easy for staff using the equipment to assess whether or not the service is overdue. Equipment should not be used without maintenance cover.

There should also be documents recounting the breakdown or problems encountered with equipment. Each time a service, check or repair action is undertaken this should be recorded, identifying the person performing the work, the type and nature of work done and the date. Such documentation is frequently called a “fault action report”. The history of the fault and how it has been handled, including the outcome of repair work etc., should be clearly indicated. This applies equally whether the action is taken by an in-house person or by someone who is brought in for a specific task (e.g. a contractor for calibration, repair or qualification).

Documentation

Facilities – Buildings and Equipment

Staff must be sure that the equipment they use is suitable for use, has been adequately calibrated and maintained and is not outside its service interval.

Records of equipment suitability, calibration, checking and maintenance demonstrate that the laboratory SOPs have been followed and that the equipment used in any study is adequate for the job and performing to its specification. Records should also demonstrate that required actions have been taken as a result of the checks made. Documents and records should also show that staff are well instructed in the use of equipment and are able to take appropriate action when problems arise.

The following section lists documents that should be present in a GLP compliant institution.

SOP:	<p>SOPs for instructions in the routine use, cleaning, calibration etc. of the facility or equipment.</p> <p>SOP for the regular verifications or services performed on buildings or equipment.</p>
Qualification documents:	<p>When formal qualification is required, each phase of the qualification process should be documented. Each phase should have a protocol defining the tests to be conducted, data resulting from these tests, a report including the test results and a conclusion.</p> <p>When no formal qualification is required, the study director or the management of the institution should define, usually in an SOP, the purpose of the equipment. For example, a balance with a precision to the nearest gram will be suitable for weighing in an animal house but not in the analytical laboratory.</p>
Logbook:	<p>Logbooks are kept to record the use of equipment (e.g. HPLC column used for product “x” – with dates, then for product “y” – with dates). They are also used for recording regular checks (e.g. regular use of check-weight for balances, temperature record for refrigerator, etc.).</p>
Service report:	<p>Service reports and equipment labels indicate which instrument was serviced, when and by whom. The date of the next service is usually recorded on the equipment label. In the case of routine servicing the actual service procedure would be included in the SOP concerning the apparatus or facility.</p>
Fault action report:	<p>These reports are made when something goes wrong. This is not routine work and an SOP may not be available for the person who deals with this problem. Therefore the fault action report should include the work performed on the equipment, the date of the work and the person who carried out the job. It is important that the person signs off with a statement indicating whether the equipment is fit or unfit for use.</p>

2. Resources

Resources

RESOURCES

Management Personnel Buildings & Equipment

Section 2:1

Instructor's notes

This section on resources has been divided into several parts.

Human resources: This section first briefly examines management responsibilities and then the responsibilities of other personnel.

Physical resources: This section has been divided into buildings and equipment, and includes a sub section on computerized systems as these are more and more often used when performing GLP studies.

Explain

Any scientific enquiry requires proper resources.

GLP regulations state that management must provide proper resources – both human and physical resources/infrastructure such as buildings and equipment.

GLP requires that all resources be adequate for the task at hand. Management must be able to demonstrate this.

Resources

MANAGEMENT

Overall responsibility for GLP implementation

Section 2:2

Instructor's notes

Explain

GLP requires that each test site or test facility retains a document identifying individuals with management responsibilities.

Top management must commit themselves to the pursuit of good science and the implementation of GLP.

2. Resources



Resources

Management is responsible for providing resources and demonstrating that these are suitable for the task

- **Personnel**
 - **Study Director** → single point of study control
 - **Quality Assurance** → ensures management of GLP compliance
 - **Archivist** → manages archives
 - **Study personnel** → perform study according to instructions
- **Facilities / Equipment**

Section 2:3

Instructor's notes

Explain

Management must demonstrate, in whatever way deemed fit, that the resources provided are appropriate.

With respect to personnel, management must appoint trained persons to perform the work of the study director, quality assurance and archivist.

We shall return to these specific responsibilities later on in the course.



Resources

MANAGEMENT

- **Has responsibility for promoting:**
 - Good science
 - Good organisation

Section 2:4

Instructor's notes

Explain

Management must take overall responsibility for both the conduct and interpretation of the study, including all scientific and organizational aspects.

Activity

Ask participants to list the points that fall under good science versus good organization (about 10-15 minutes).

2. Resources



Resources

Good Science

- Experimental design
- Based on known scientific principles
- Knowledge of experimental variables / bias
- Interpretation of results
- Results become part of accepted scientific knowledge

Section 2.5

Instructor's notes

Explain

Discuss the lists that the participants have made and compare with the points on this slide. They are likely to have good points not included here.

Good science is about the thought process behind the experimental design. This underscores the validity of the study.



Resources

Good Organisation

- Planning of studies and resource allocation
- Adequate physical facilities
- Sufficient qualified staff - recruitment
- Definition of staff responsibilities

Section 2.6

Instructor's notes

Explain

Discuss the lists that the participants have made and compare with the points on this slide and the next one.

Good organization is about (but may not be limited to) the items listed in this slide and the next one.

2. Resources

 Resources
<p style="text-align: center;">Good Organisation</p> <ul style="list-style-type: none">• Staff training• Ensuring proper conduct of studies• Good record keeping & organized archives• Implementation of verification procedures for study conduct and results
Section 2:7

Instructor's notes

Explain

Discuss the lists that the participants have made and compare with the points on this slide and the previous one.

 Resources
<p style="text-align: center;">Good Organisation</p> <ul style="list-style-type: none">• All these organisational aspects are covered by GLP• GLP is about ensuring good organisation of studies
Section 2:8

2. Resources



Resources

Planning / Resource Allocation

- Management responsibility
- Sufficient physical resources and personnel

↓

MASTER SCHEDULE

Section 2:9

Instructor's notes

Explain

Some specific organizational requirements are presented in the next few slides.

The master schedule is a document that records the planning of the studies performed at a site or in a department.

It may be used to demonstrate that sufficient resources are (were) available to perform studies compliant with GLP.



Resources

Master Schedule

- All studies should be included
- Keep up-dated & have a change control procedure
- Include actions such as protocol review and report preparation
- Have only one official schedule

Section 2:10

Instructor's notes

Explain

The master schedule should contain information which is useful for the planning aspects of studies performed by the institution. There are no hard and fast rules about the form of the schedule. The information included should be used by management to ensure appropriate use of resources and to demonstrate that sufficient resources are (were) available at all times.

The schedule can be a tabulated document or may be drafted by using a database or project management tool.

Management is responsible for approving the master schedule, but the task of authorship is often delegated to a specialist group such as project management.

The quality assurance team must be provided with a current copy of the schedule.

Other GLP points are listed in this and the next slide.

2. Resources

Resources

Master Schedule

- Define the system in an SOP
- Decide who should maintain this document
- Archive - as necessary
- Distribute to those who need it

Section 2:11

Instructor's notes

Explain

See previous slide.

Resources

Master Schedule

Test item :

STUDY INFORMATION				DATES						...
Study N°	Study Director	Title	Location	Protocol Review	Start Date	End In-Vivo	Draft Report Audit	Final Report Review	Archive	Comments

Section 2:12

Instructor's notes

Explain

In this example studies concerning a particular test item are listed with reference to dates for certain phases and other useful details. However, the master schedule could be organized by type of study or even by test system used.

2. Resources



Resources

PERSONNEL

Organisation shown in standard documents

- Organisation charts, reporting relationships
- Curriculum vitae
- Training records
- Job descriptions

Section 2:13

Instructor's notes

Explain

To document the way in which the resource “personnel” is organized, management must implement the 4 types of standard documents mentioned in the slide.



Resources

Organisation Chart

- Should give a good idea of how the organisation operates
- Keep it simple
- Add functional responsibilities only if this helps to explain the organisation

Section 2:14

Instructor's notes

Explain

Management must provide an up-to-date organizational chart.

This is used to explain quickly the way in which the organization is structured and who reports to whom.

Many facilities add the number of staff present in each department or service unit to illustrate the size of the organization.

In very small organizations it is common to find the names of all staff on the organizational chart. In larger organizations the job title is often used instead of actual names.

There are no specific rules about how an organizational chart is drawn up.

2. Resources

**Resources**

Curriculum Vitae

- For all personnel
- In standard format
- Up-to-date / archived
- Contains :
 - qualifications/education/diplomas
 - professional experience

Section 2:15

Instructor's notes

Activity

On a flip chart, draw a list of the things you would expect to see in a CV.

It is usual to put the following information in CVs:

- name, age and sex of the person;
- education, including all diplomas and qualifications awarded by recognized institutions;
- professional experience both within the institution and before joining it;
- any publications;
- membership of associations;
- languages spoken.

Even members of staff without formal qualifications need to have CVs. These will contain details of the professional experience which qualifies them for their task.

Training that does not lead to a diploma is not normally included in a CV but should be included in the person's training records.

Once again there are no hard and fast rules about the contents of a CV in GLP, but the institution should provide a common format so as to ensure that relevant information has not been left out.

**Resources**

Training Records

- **Past**
 - Induction to the job
 - Competence of personnel regarding SOPs
 - External courses / internal courses
 - Attendance at congresses/seminars may be included
- **Future**
 - Training plans for each member of staff
- **Up-to-date and archived**

Section 2:16

Instructor's notes

Explain

Training records should include information of all training not included in the CV. There is no need to repeat here the formal education and qualifications of personnel.

Include training that qualifies the person for the assigned job. This should be based on the laboratory SOPs and on practice.

Include all courses attended both internally and outside the institution. (Include this course!)

You may also include attendance to seminars and symposia/conferences.

2. Resources



Resources

Job Descriptions

- Clearly define day-to-day responsibilities and tasks
- Make it clear who reports to whom
- Describe delegation of tasks
- Must be up-to-date
- Standard format
- Best signed by "n" and "n + 1"

Section 2:17

Instructor's notes

Explain

Everyone needs a job description.

The job description details the day-to-day tasks of the person concerned.

Many laboratories include the relevant part of the organizational chart.

It is best if management fixes the format of job descriptions for the entire institution.

It is recommended that the job description be signed both by the person concerned (n) and by the person's immediate superior (n+1). This is not a GLP requirement, but it is a good way of ensuring that both parties understand their respective responsibilities which is a GLP requirement.



Resources

Job Descriptions

- Department / group
- Name, position, level
- Name, position of the direct supervisor
- Position summary
- Tasks and responsibilities
- Work relationships
- Approval signatures and dates

Section 2:18

Instructor's notes

Explain

These are the sections that are often seen in job descriptions, but the actual presentation of contents is left to the discretion of management.

2. Resources

 Resources
<p style="text-align: center;">FACILITIES BUILDINGS & EQUIPMENT</p>
Section 2:19

Instructor's notes

Explain

Facilities have been divided into two parts:

1. buildings
2. equipment.

 Resources
<p style="text-align: center;">BUILDINGS</p> <ul style="list-style-type: none">• Suitability / Adequate for the study• Maintenance• Documentation including site plans
Section 2:20

Instructor's notes

Explain

The GLP regulations do not stipulate exactly how buildings should be constructed. It is up to management and study staff to satisfy authorities that the buildings are of adequate size and design and that they function properly.

The exact type of structure depends upon the kind of work to be performed in the building.

The important issue is to be able to prove that studies are free from interference, disturbance, pollution and cross contamination.

2. Resources



Resources

BUILDINGS : Factors to consider

- **Experimental**
 - Test systems
 - Study types
 - Number of studies
- **Staff**
 - Safety & comfort of staff
 - Possible impact on study from staff
- **Operational**
 - Access / security
 - Cleaning
 - Storage
 - Utilities & maintenance
 - Waste disposal

Section 2.21

Instructor's notes

Explain

The factors listed here should be taken into consideration when assessing whether a particular building is adequate for the job, or when designing a new building.



Resources

BUILDINGS : Suitable / Adequate for the study

- **Size, Construction, Location**
- **Minimize disturbances**
- **Separation between activities**

Section 2.22

Instructor's notes

Explain

Use the key words on this slide to structure a discussion on what participants consider to be adequate with respect to the different kinds of studies they perform.

2. Resources



Resources

BUILDINGS : Adequate Separation

- **Physical separation**
 - Rooms
 - Cabinets / isolators
 - Air systems and filters

- **Separation by organisation**
 - Defined work areas
 - One-way systems
 - Different activities in same areas at different times
 - Cleaning between activities
 - Separate staff

Section 2:23

Instructor's notes

Explain

Sometimes it is necessary to physically separate studies from one another. This may mean providing separate rooms for studies, or holding test systems in cabinets or even isolators, or assuring that areas are separated by efficient air systems with filters.

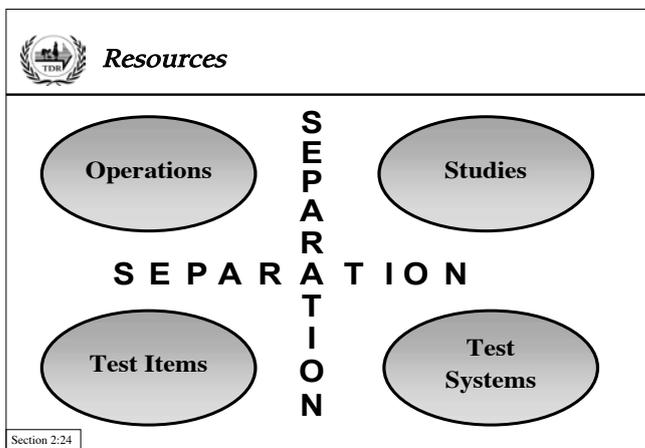
Physical separation is not always necessary. There are other ways of preventing interference between studies. Some are mentioned under the heading "separation by organization".

Activity

Lead a discussion with the participants on the ways in which pollution/contamination may occur between studies (10 minutes maximum).

Think about cleaning materials, pathogens brought in by staff, storage conditions of test items, feed, equipment, etc.

35



Instructor's notes

Explain

The way to protect studies from contamination, disturbance or interference is to ensure separation between studies, test systems, operations and test items.

2. Resources

**Resources**

BUILDINGS : Examples

Two examples :

- Dose mixing unit
- Animal facilities

Section 2:25

Instructor's notes

Explain

Two different examples will be used to stimulate discussion on important factors in the design of buildings. The first concerns a dose mixing unit, the second an animal facility.

**Resources**

Dose Mixing Unit

Deals with test and control items and their :

- Receipt
- Storage
- Dispensing
- Weighing
- Mixing
- Dispatch

Section 2:26

Instructor's notes

Activity

Ask the participants to list the major functions carried out in a dose mixing unit.

Compare items listed to the list on this slide.

Now ask the participants to write down the important points to be considered when evaluating the physical adequacy of a Dose Mixing Unit.

Get the participants to group their thoughts under the headings:

1. Size
2. Construction
3. Location / separation

The participants' thoughts can be compared with the suggestions in the next two slides (about 15 min).

2. Resources

 Resources
<p style="text-align: center;">Dose Mixing Unit</p> <ul style="list-style-type: none">• Size<ul style="list-style-type: none">• Accommodates all activities (including paperwork) without risk of mix-ups or cross contamination• Sufficient working area, separate storage and waste disposal• Construction<ul style="list-style-type: none">• Materials allow for easy cleaning• Air flow / filters protect test items & personnel
Section 2:27

Instructor's notes

Explain

These are typical ideas which are likely to have been brought out during the discussion.

 Resources
<p style="text-align: center;">Dose Mixing Unit</p> <p>LOCATION - Separate areas for :</p> <ul style="list-style-type: none">• Storage of test materials under different conditions• Storage of control materials• Handling volatile materials• Weighing areas• Mixing different dose forms (e.g. diet & liquid)• Storage of prepared dose• Cleaning equipment• Offices - rest rooms / changing rooms
Section 2:28

Instructor's notes

Explain

These are typical ideas which are likely to have been brought out during the discussion.

2. Resources



Resources

Animal House Facilities

- Design should :
 - Reduce risk of test system :
 - being affected by environmental variables
 - encountering disease
 - encountering other test articles
- Separate activities where possible, use barriers

Section 2:29

Instructor's notes

Explain

Facilities for animals must also be designed to separate activities so that there is a very low incidence of interference between studies.

Systems with some barriers are often promoted to ensure minimal disturbance. But this state-of-the-art design is very costly and not always necessary.

Activity

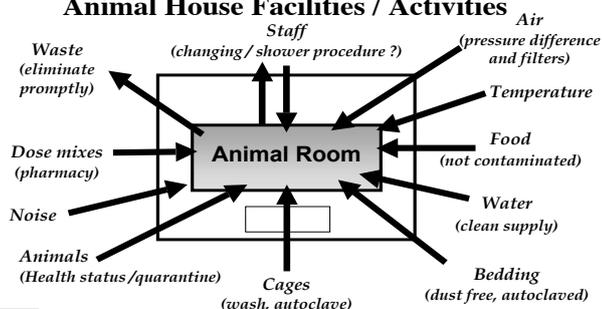
Participants should be asked to list the important variables which need to be controlled to prevent disturbance in studies or contamination/pollution between studies.

Their thoughts should be compared with the diagrammatic representation shown on the next slide, and the ideas represented in the next three slides of this section (about 5 min).



Resources

Animal House Facilities / Activities



Section 2:30

2. Resources

**Resources**

Animal House Facilities

- ***Separation***
 - *Species*
 - *Studies*
 - *Quarantine*
 - *Changing rooms*
 - *Receipt of material*

Section 2:31

Instructor's notes

Explain

This slide and the next one list the way in which separation of entities will help safeguard the studies from cross contamination/pollution, disturbance and the influence of uncontrolled variables.

**Resources**

Animal House Facilities

- ***Separation***
 - ***Storage***
 - *bedding*
 - *diet*
 - *dose mixes*
 - *cages*
 - *Necropsy*
 - *Laboratory techniques*
 - *Waste disposal*

Section 2:32

Instructor's notes

Explain

See previous slide.

2. Resources



Resources

Animal House Facilities

- ***Environmental factors controlled and/or measured***
 - Temperature / humidity
 - Air flow
 - Light (intensity and duration)
 - Noise
- ***Cleaning***
 - Smooth flat surfaces, walls, doors, ceilings
 - No gaps, cracks, holes

Section 2:33

Instructor's notes

Explain

Important environmental factors and factors relevant to cleaning are listed in this slide.



Resources

Animal House Facilities

- Even if facilities are not "State of the Art" :
 - Minimize staff entry into building
 - Restrict entry into animal rooms
 - Organise work flow (e.g. use of corridors clean / dirty at different times)
 - Require staff to adopt dress procedures
 - Clean between studies

Section 2:34

Instructor's notes

Explain

There are a number of procedures that can be implemented to help keep contamination and other interferences at a minimum even, if a barrier system is not available.

Some of these procedures are indicated in this slide.

2. Resources

 Resources
<p style="text-align: center;">EQUIPMENT</p> <ul style="list-style-type: none">• Suitability• Calibration
Section 2:35

Instructor's notes

Explain

This second part of the section on facilities concerns the equipment used during the GLP studies.

GLP regulations require you to make certain that the equipment used in studies :

- is suitable for the task in hand;
- is properly calibrated and maintained.

All these points have to be well documented, as will be seen later.

 Resources
<p style="text-align: center;">EQUIPMENT : Suitability</p> <ul style="list-style-type: none">• The scientist's responsibility• Sometimes requires proof of suitability• May need formal equipment qualification
Section 2:36

Instructor's notes

Explain

The question, "Is your equipment suitable for the job?" is directed to the person responsible for the science of the study – the study director.

Study staff must be able to justify the use of their equipment and demonstrate that it is suitable for the work being performed.

Some equipment, when used in certain methods, will require proof of suitability by formal testing or even formal qualification. This may be the case in the analytical or clinical pathology laboratory. Only the study staff can decide whether there is a need for formal commissioning and qualification.

2. Resources



Resources

EQUIPMENT : Calibration

- Need proof of standard working conditions
- Calibration usually requires use of standards
- If feasible, link :
 - "secondary - working" standards to...
 - ..."primary" standards to...
 - ..."national / international" standards
- Fix frequency of calibration in SOP
- Respect calibration frequency

Section 2:37

Instructor's notes

Explain

All equipment used must be calibrated to demonstrate that it is working within the limits fixed by the manufacturer and the scientist, and is producing reliable data.

It is advisable to maintain a link between the working standard of the laboratory and a certified standard kept at an international or national level e.g. a standard weight used to check balances. This is usually achieved by purchasing a primary standard, which has a certificate, from the national weights and measures authority. This in turn is used to calibrate a secondary standard for routine use in the laboratory.

The scientist must decide the appropriate frequency of calibration for each instrument. This frequency should be documented in an SOP and respected.



Resources

BUILDINGS and EQUIPMENT

- Maintenance
- Documentation

Section 2:38

Instructor's notes

Explain

The GLP regulations require you to make certain that the buildings and equipment are well maintained.

Maintenance must be documented.

2. Resources

Resources

BUILDINGS / EQUIPMENT : Maintenance

- Preventive maintenance
- Curative maintenance (fix it when it breaks)
- Back-up equipment / procedures
- Contracts with external service organizations
- Alarms

Section 2:39

Instructor's notes

Explain

Maintenance is usually divided into preventive maintenance (e.g. changing ultra-violet bulbs in some equipment as output is known to decline over time) and curative maintenance which consists of repair work on broken equipment.

In the case of equipment that breaks, it is necessary to either have back-up equipment or a back-up procedure so that the work can continue. The latter is the case when a computer system goes down.

Most institutions also have maintenance contracts with external service companies (often the vendor supplies this "after-sales service" for its equipment). Maintenance work should be described in detail and should be traceable (contract, date, equipment number, technician, etc.).

If your building/equipment has an alarm, make sure that it is in working order, that it is regularly checked (part of the maintenance plan) and that, when the alarm goes off, there is an response procedure in place.

Resources

BUILDINGS / EQUIPMENT : Service Plan

Plan title												
YEAR	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
Check Airflow alarms	D	D	D	D	d	d	d	d	d	d	d	d
Check Air Intakes	D	D	D	D	d	d	d	d	d	d	d	d
Check lane working	D	D	D	D	d	d	d	d	d	d	d	d
Check drive belts	M	M	M	m	m	m	m	m	m	m	m	m
Lubricate fans			X			x			x			x
Record Air Flows					x						x	
Strip lane		X										

Section 2:40

Instructor's notes

Explain

This table is an example of the kind of service plan the maintenance department should keep.

It displays the planned interventions on an air conditioning system.

Letters in lower case represent actions (d = daily, m = monthly, x = periodic) which are planned throughout the year.

Letters change to UPPER CASE (D, M, X) when the actions have been completed.

Each completed action would be accompanied by a record of the action, signed and dated by the responsible person.

2. Resources

 Resources
MAINTENANCE : Service /Report / Label
INSTRUMENT NO. _____
DATE OF LAST SERVICE _____
NEXT SERVICE DUE _____
NAME OF SERVICE PROVIDER _____
Signature / date _____
Section 2:41

Instructor's notes

Explain

This information shows that the equipment has been properly serviced. Often the information is on a label attached to the equipment.

It is important not to use equipment that is no longer covered by the service. Hence, the information "Next service due" on the label is important.

 Resources
MAINTENANCE : Fault Action Report
BUILDING NO./DEPARTMENT/ROOM _____ EQUIPMENT I.D. _____
DESCRIPTION OF FAULT _____ Signature _____ Date _____
IMMEDIATE ACTION TAKEN _____ Signature _____ Date _____
ACTION BY SERVICE PROVIDER _____ Signature _____ Date _____
INSTRUMENT OK FOR USE _____ Signature _____ Date _____
Section 2:42

Instructor's notes

Explain

When equipment needs servicing or repairing, records must be kept regarding who did the repair work, what was done, when and what the outcome was.

This is called a "fault action report".

After repair, a responsible person should sign to attest that the equipment is ready for use.

2. Resources

**Resources**

BUILDINGS / EQUIPMENT: Documentation

- Have SOPs for :
 - Use of building / equipment
 - All maintenance actions including outside contractors
- Keep records of :
 - Use - logbook
 - Qualification calibration / checks
 - Maintenance service plan
 - Fault action reports

Section 2:43

Instructor's notes

Explain

This slide reminds us of the need for SOPs for all equipment.

Logbooks should be kept to record the use of equipment.

Records must be kept for all acts of maintenance involving buildings/equipment.

**Resources**

COMPUTERISED SYSTEMS

Should be:

- Developed
- Validated
- Operated
- Maintained

In compliance with the Principles of GLP

Section 2:44

Instructor's notes

Explain

Computerized systems may be used for the generation, collection, measurement or assessment of data intended for regulatory submission.

Computerized systems may vary from simple programmable analytical instruments to a Laboratory Information Management System (LIMS).

2. Resources



Resources

COMPUTERISED SYSTEMS : Responsibilities

- Management – must ensure suitability for intended purposes
- Study Director – must be aware of the involvement of such systems in studies and ensure that they are GLP compliant
- Personnel – must ensure that they use the systems following instructions
- QAU – must monitor use and GLP compliance

Section 2:45

Instructor's notes

Explain

Management must ensure that computerized systems are suitable for their intended use within the research institution. They should ensure that policies regarding personnel, their use of computers and how the data are to be handled are in place and are followed.

The study director must be aware of the extent to which computerized systems will be used during his/her study. The study director's responsibilities for electronic data are the same as for data recorded on paper and only systems that have been validated should be used.

Personnel should develop, validate, operate and maintain computerized systems in accordance with GLP Principles and recognized technical standards.

QA personnel should monitor GLP compliance with regard to computer use and validation. They should have direct read-only access to data stored in computerized systems so that they can conduct reviews.



Resources

COMPUTERISED SYSTEMS

- Training : documented on the job / external
- Facilities : Physical location, back up
- Equipment : Hardware & software , their communications
- Maintenance & Disaster recovery :
- Security – physical, software
- Validation to ensure that systems are suitable for their intended use
- Documentation should cover policies, description of systems, source code and SOPs

Section 2:46

Instructor's notes

Explain

All personnel involved with computerized systems should have appropriate training which could be on-the-job or external. All training must be documented.

The physical location of computerized systems should ensure that there is no exposure to extreme temperatures, humidity, dust electromagnetic interference and proximity to high voltage cables. The electrical supply should be regarded as important.

GLP Principles that apply to equipment also apply to computerized systems; hardware & software. Communication may be between computers or between computers and peripheral components. These are potential sources of problems of non-compliance.

Documented procedures should include routine preventative maintenance, fault repair and disaster recovery with details of roles and responsibilities.

Security should ensure data integrity (which is a primary objective of GLP).

Validation processes should address formal acceptance of systems and assessment of suitability for use. Change control procedures should be in place, respected and documented.

2. Resources

**Resources**

COMPUTERISED SYSTEMS

- Data
 - Raw data should be defined
 - System design should provide an audit trail capability
 - There should be provision for long term retention of data

- Maintenance logs and calibration records are required to verify the validity of raw data or to permit study reconstruction. These should be archived

- Electronic data should be stored with the same level of access control, indexing and expedient retrieval as for other types of data.

Section 2:47

Instructor's notes

Explain

Data generated as direct computer inputs should be identified at time of input by the individual responsible for the data entries.

System design should allow for retention of full audit trails to show changes to the data without deleting the original data. It should be possible to identify who made changes and when they were made. Reasons for all changes should also be kept as part of the audit trail.

The GLP Principles for archiving data must be applied consistently to all types of data, including electronic data.

**Resources**

Documentation for Buildings / Equipment



The diagram illustrates the documentation requirements for buildings and equipment. It features a central coffee machine icon with arrows pointing to various documents: SOPs (Standard Operating Procedures), Qualification report, Logbook, Service reports, and Fault action report. Each document is represented by a corresponding icon: a book for SOPs, a folder for Qualification report, a binder for Logbook, a clipboard for Service reports, and a clipboard for Fault action report.

Section 2:48

Instructor's notes

Explain

This slide summarizes diagrammatically the different sorts of documents that you are expected to have if you wish to claim GLP compliance for the buildings/equipment at a test site.

3. CHARACTERIZATION

To perform good scientific studies, it is best to know as much as possible about the materials used in the experiments. Characterization is about accumulating this knowledge. In non-clinical studies, characterization principally concerns the test item (often a chemical compound) and the test system (often a live animal). GLP requires characterization of at least these two entities.

The **test item** might be an active ingredient for a medicine, a pesticide, a food additive, a vaccine, a chemical compound used industrially, a biomass, an extraction from plant tissue, etc. The test item is most frequently characterized by its analytical profile e.g. chemical identity, impurity, solubility, stability, etc. In order not to confuse issues and provide false results, it is very important that the test item be protected from cross contamination from other chemicals (or even the same chemical of a different batch) and from pollution by external factors such as bacteria, dust, water, etc. The GLP Principles therefore require that proper conditions for the receipt and storage of the test item are in place.

Frequently, the test item is formulated before administering it to the test system. Thus, GLP also requires that the test facility implements exact procedures for formulation so that the same method is used, leading to the same concentrations each time. Once again, precautions must be taken to prevent mix-ups between formulations, cross contamination and pollution. A description of the GLP requirements for test items is given below.

The **test system** could be an animal, a plant, a bacterium, an isolated organ, a field or other ecosystem or even analytical equipment, etc. Since the characterization of the test system can vary widely, the GLP requirements are less precise than for the test item. The classical situation of an animal as test system is used as an example in the discussion below.

THE TEST ITEM

The identity, activity and bioavailability of the test item are key factors in the study. Interpretation of the study results is often based on the proof that the test system has received the correct amount of test item at the correct points in time. This is achieved by proper control and documentation at each stage of preparation. In addition, you must be

able to demonstrate the constant nature and quality of the test item and in particular that it does not degrade over the course of the study. Hence, GLP attaches great importance to the chain of custody of test items and the efforts made to minimize their potential cross contamination or pollution.

A GLP quality assurance programme should systematically minimize the possibility of contamination or pollution of the test item, and prevent wrong level or wrong test item administration to the test system.

Test item Control Before Formulation

Receipt

The test item is supplied by the “manufacturer” or the “sponsor”. The test item may come from a sector within the same company as the test facility or from an outside organization. In either case, and irrespective of the size of the test facility or number of studies being conducted, a formal procedure must exist for receipt, storage and control. Staff must be designated for the responsibilities of receipt and handling of the test item. In a large laboratory, the designated staff log the arrival, identity and issue of test items, but in small facilities these duties may fall in the study director or an authorized technician. Designation of responsibility should be documented in an SOP.

The responsible person should know in advance when a test item will arrive so that he/she can ensure proper storage conditions and necessary handling requirements. In the case of a contract study, the sponsor should provide this information to the CRO in a standard form. During the development of the protocol, the sponsor should provide essential information to the test facility for the safe handling of the test item and for the preparation of the formulation.

The sponsor will either provide, or indicate that he has obtained, results on the chemical characterization of the test material. The manufacturer will already have archived his records concerning the manufacture of the test item.

Packaging of the test material is very important. The test item container should be strong enough to withstand transfer between sites. The sponsor should consider the method and duration of transport. This is particularly true when the material is packed in fragile containers, such as glass bottles, or when the test item must be transported in a frozen or cooled state over long distances using public transport. Unexpected situations, such as airport delays, strikes or bad weather, should always be factored in.

The test item should be clearly labeled with sufficient information for identification. A delivery form should ideally contain the following information:

- manufacturer's name or sponsor's name

- date of dispatch
- number of containers or items, type of contents and quantity
- identity of the test item
- batch numbers
- identity of the person responsible for the dispatch
- name of the transporter and type of carrier.

Each container should be clearly labelled with sufficient information so that the test facility is able to confirm the test item identity. Ideally labels should contain the following information:

- test item name
- batch number
- expiry date
- storage conditions
- container number
- total weight
- initial gross weight.

On arrival at the test facility the the test item should be handled and received according to procedure. It is most important that the compound is logged in as soon as possible after arrival to ensure a complete audit trail and to demonstrate that it has not been held under conditions which might compromise its chemical activity. The receipt procedure should include instructions for handling it in the event of the designated person being absent or the container being damaged. The study director should be informed of the arrival of the test item.

The information supplied by the manufacturer or the sponsor should be cross checked by the test facility and records should be kept of each delivery. All deficiencies or problems relating to the receipt of test items should be noted.

Storage

Test items should be stored under closely controlled conditions, particularly with respect to access and environment. The stores manager should ensure that only designated staff have access to the material. The stores are kept locked when not in use. Separate areas should be available for storage at different temperatures.

The storage of test items is arranged to minimize the risk of any cross contamination between compounds and containers. Where possible, the test items are housed in special containers to prevent breakage or spillage within the store.

On arrival at the test facility, a sample of the batch of test item is taken and stored in a separate container. This “reserve sample” is ideally held in a separate compound archive under the same conditions as the bulk of the test material. It carries the following information on its label:

- test material identification (name or code number)
- batch number
- storage conditions
- net weight
- date on which sample was taken.

This will be retained by the test facility in the compound archive for the same duration as the study raw data and specimens. Normally this sample will not be used unless it is needed for confirmatory analysis.

Use

A record of the use of the test item is kept on a form allowing a running check. This will provide a complete trail of the items (and quantities) used and is therefore useful for monitoring actual use against expected use. The type of information recorded includes:

- date of use;
- study number. This is important if the same batch of test item is being used for more than one study. (Some laboratories divide the material into separate containers for each study);
- gross weight before use. The container and contents are weighed prior to each use (the initials of the person carrying out this weighing are also recorded);
- gross weight after use. The container and contents are weighed after use;
- weight of material used. This is the amount of material disappearing from the container on each occasion;
- weight from dose-preparation records. This is the amount of material recorded as used in the preparation of the dose form. Comparison between this record and the amount that has been removed from the container provides a useful double check on the amounts weighed out;
- discrepancy. This allows for explanation of any accidents, such as spillage;
- stock remaining. This gives an idea of the total quantity of material left in the container and provides a warning to place orders for additional material as stock decrease.

Disposal

Following the completion of a study, surplus amounts of test item should be disposed of in an environmentally acceptable way. This final event should be recorded so that all of the material can be totally accounted for.

Preparation of the Dose Formulation

If the test system receives an incorrect dose, or if there is a doubt about the dose level administered, the experiment is almost certainly compromised. The following well specified procedures and clear documentation at every stage of the process is therefore vital.

Initial Preparation and Planning

Before the study begins, a number of points must be defined and communicated to the staff by the study director.

- Dose levels, number of animals and dose volume: This information in the protocol allows the study director to estimate how much test item is required and to ensure that a sufficient amount is available throughout the course of the study. As part of this consideration he/she should also check on the purity of the test item. In most cases, the test item is assumed to be 100% active ingredient, but if significantly less than this, it may be necessary to adjust the amounts to be weighed for use (and to investigate the impact of the impurities on the validity of the study).
- Concentration of the dose, amount or volume required: The volume required will vary throughout the study with the animals' weight. The study director will keep this under review. To ensure that this is done regularly the study director is required to produce a request form on a regular basis (for instance, every two weeks).
- SOPs must exist to cover the preparation of the formulation, the analysis, the documentation and data required, and for the use of all equipment.
- The method of preparation of the dose form should be tested prior to the start of the study. This entails a trial preparation of at least the highest dose level to confirm that the various standard procedures described in the SOPs produce a homogeneous dose of the correct concentration.
- This trial preparation may indicate the need for further development of the method and experimentation with other vehicles or different mixing techniques.
- The stability of the dose form must also be assessed with the vehicle used.

Following this trial, the procedure for the preparation of the formulation may need to be modified.

Formulating the Test Item

In many test facilities an independent group formulates the test item. It is important to record clearly what is planned and what is actually done. Even if the study director carries out the whole process, the formulation plan is an important element of traceability to be documented.

Before the container of material is opened, the persons carrying out the procedure should ensure that:

- there is a dedicated workstation of adequate size for the procedure;
- the surface where the preparation will be made is clean. This is often best achieved by covering it with a clean sheet of paper or plastic, which is disposed of after each test item preparation;
- there are adequate clean containers, spatulas and other small equipment at hand;
- labels have been made out and are available;
- no other compound is being handled at the same time. This minimizes the possibility of confusion or cross contamination.

The test item is obtained from the store. The identity is checked against the protocol and the instructions for preparation are followed.

The control mixes are usually prepared first. Then the test item is mixed with the vehicle exactly following the method of the procedure. In most cases this involves making up each concentration from a separately weighed amount of test item, mixing it first with a small volume of vehicle and gradually increasing the amount of vehicle before finally adding the required total volume. In some cases where the material forms a solution in the vehicle or where the diet is the vehicle, it may be preferable to formulate the highest concentration and dilute samples of that for the lower levels.

Following preparation, the dosing material is placed in suitable containers before being passed to the animal room for dosing. The suitability of the containers should be considered carefully in order to preserve the integrity of the dose form, including:

- **Composition:** The container must not react with either test material or vehicle.
- **Size:** If the formulation needs to be mixed using a magnetic stirrer in the animal house to keep it in homogenous suspension, the container must be big enough to develop a vortex, but not so big, in relation to the volume, to prevent the mixer from functioning correctly.

The final container (and any intermediate containers) should be labelled to allow iden-

tification. The container sent to the animal house should carry at least the following information:

- study number
- group number (and if relevant, cage number)
- weight of the container and contents
- date formulated
- storage conditions.

In many laboratories, the label on each dose is colour coded to match the label on the corresponding cage.

Sampling and Quality Control of Dose Formulation

Analysis of the formulation is usually included in the study. This is to ensure that the concentration, stability and homogeneity of the test item/vehicle mixtures is properly assessed. This information may be generated after the start of the study. In practical terms, however, it may be advantageous to conduct some of these analyses before the study starts, as doing so could save time and resources in the event of a problem

As indicated above, the measurement of stability and homogeneity of the test item/vehicle formulation is best performed as a trial preparation. Samples are often taken at different levels in the dosing vessel (or at different times during actual administration) to ensure that there is no variation between the concentration given to the first animals and that given to the last animals. For long-term studies, where stock preparations are made throughout the study, aliquots will also be taken and analysed periodically to assess the shelf-life of the formulation.

The samples analysed should demonstrate the effectiveness of the dose preparation process. However periodic checks are often required to confirm that the process is being carried out correctly throughout the study, even if the doses are made up fresh each time. Only the chemist who takes the samples (not the persons making up the mixture or performing the dosing) should know the day they will be taken. It is preferable to take the sample in the animal room, as this gives information not only on the concentration administered to the animals but also evidence of the homogeneity and stability of the test article.

Records

The following dated records should be kept for the formulation process:

- confirmation of test item identity
- identity of formulation instruction (request)

- weight of empty container
- weight of container + test item
- weight of added vehicle
- final weight of mixture
- signature/initials of all staff carrying out procedures.

Dosing

The purpose of this procedure is to deliver the required amount of test formulation to the animal accurately and consistently. Therefore, the procedure must be carried out very carefully and the records should confirm that all the animals were dosed with the correct volume and concentration.

Detailed records with built in cross-references can help to support the fact that the dosing has been conducted correctly.

Staff must be well trained, both to ensure that the exact amount is delivered and to assure the well being of the animals. In many countries the staff dosing the animals must be licensed or formally qualified in some way under animal welfare laws.

On arrival in the animal area it should be confirmed that the dose amount and identity are the same as that issued by the formulation department. Staff should make sure that the container is still intact. Usually, to confirm this, the arrival weight is checked against the weight reported on issue from the formulation department. The containers are then kept appropriately (e.g. on a magnetic stirrer) until dosing commences.

The dosing procedure is conducted in a fixed order so as to minimize the possibility of cross contamination and confusion between animals, dose groups and different formulations.

When dosing animals orally, most laboratories observe the following precautions:

- The animals are dosed group by group, in ascending dose levels.
Ensure that only one dose container is open at a time and that each dose level has its own catheter and syringe.
All cages of one group should be identified before the group is dosed, using the group number and label colour code.
- A new catheter and syringe is used for each dose level.
- The used container, catheter and syringe are removed from the dosing station before the new group is dosed.
- The outside of the catheter is wiped with a clean tissue before each animal is dosed. This prevents the possibility of test material being drawn into the lungs.

- Only one cage of animals is opened at a time. If the animals are individually housed, they should be returned to the same cage following the dosing. If housed in groups, the animals should be placed in another container until all animals from the cage have been dosed and then returned to their original cage.
- Each animal is identified (e.g. by a tail tattoo), as well as its cage number.

The dose volume is calculated from the body weight using a list of volumes for each weight to avoid the risk of calculation error.

Records identify:

- the staff involved in dosing;
- the dose given to each animal. This record acts both as a confirmation of dosing to each individual and as a record that can be cross-checked against the expected weight;
- the date and time dosing took place;
- the weight of each dose level container before and after dosing. This allows expected use to be checked against actual use of the formulation.

THE TEST SYSTEM

The term “test system” covers a range of possibilities. Very often test systems are animals, but they can also be plants, bacteria, organs, cells or indeed analytical equipment. This section describes the situation where the test system is an animal.

Conditions and processes must satisfy the scientific requirements of the study and must also abide by **National Animal Welfare Legislation**. Although this training course is not intended to cover these aspects, some references are included as the laws may affect your laboratory and your procedures.

Facilities

For any study, the study director and/or the animal care manager must ensure that personnel, procedures, equipment and design features are in place to sufficiently meet the needs of the study and its procedures. In particular, it is important to buy in healthy animals and to prevent the spread of disease and to use the separation techniques mentioned in the resources section.

Choice of Test System

The scientist must match the quality and quantity of animals to the requirements of the

research.

The study director and management therefore define the animal (phenotype/genotype, number, sex, age, supplier, etc.) for any study by considering the following points:

- appropriateness of the model
- study and project objectives
- availability of historical background data and past experience.

The choice of test system should be justified in the protocol.

Suppliers, Ordering, Transport and Receipt

Compared to preclinical testing, the cost of test systems is not significant. Therefore always insist that the best quality be available. Effort spent on facilities, environmental control and equipment cannot reverse the impact of poor quality animals on a study.

The quality of animals, animal feed and bedding should be assessed by audit. Usually the QA group and the person responsible for animal care do this together. Purchasers should make sure that they get what they pay for and that no variables (e.g. pesticide contamination, colony renewal, veterinary treatments, transport problems, etc.) compromise quality. Suppliers should be treated as partners in the research. They usually appreciate constructive criticism and will voluntarily provide useful information and valuable suggestions to improve study quality. A documented dialogue should be established and maintained with principal suppliers. The suppliers should provide certificates of animal health, freedom from parasites, etc.

Animal order forms, transport certificates and suppliers' invoices are part of the raw data. On arrival, the animals are inspected following an SOP; they are also counted, sexed, and evaluated for general health and transport induced stress. Paperwork (including a check to verify that animals comply with age and weight specifications as defined in the protocol) are completed and put in the data file. The animals are then transported to the study room and housed in clean cages with food and water according to general SOPs.

Acclimatization

For most studies the protocol and SOPs require that animals have a period of acclimatization to laboratory conditions during which time their health status is confirmed and unsuitable individuals are identified/eliminated. The length of this acclimatization period depends upon the species, the supplier and the type of study.

Documentation of room preparation, animal receipt, husbandry, observations, measurements, environmental conditions and any other activities during this period should be maintained.

Animal Identification

Identification of animals must be consistent throughout the study. Most laboratories use a system of cage cards (temporarily before group assignment and permanently afterwards), as described in the protocol. The animal management department uses the consecutive temporary numbers to ensure animal accountability. As for dosing materials, permanent cage cards often follow a standard colour coding scheme. Numbers are unique within the study and appear on all data and specimens pertaining to the animal throughout all phases of the study. When groups are assigned, individual animals are identified to prevent mix-ups. Each time animals are removed from their cages, SOPs require an identity check. In many laboratories, the means of identification (e.g. tail tattoo) is archived.

Assignment to Groups

According to the protocol, animals must be assigned to groups before the dosing period starts. If animals are randomized, a copy of the statistical or random tables used is maintained as raw data. Rack and cage locations are documented from this point onwards. Special care is taken to fully document any disqualification of animals during the acclimatization period. These data may indicate systematic problems with the supplier or the animal type. Unexpected findings should be brought to the supplier's attention. Such findings should be investigated and their impact evaluated.

Husbandry

Routine (e.g. room, rack and cage cleaning/changing, feeding, watering, environmental checks) and special (e.g. fasting) husbandry operations are carried out as per SOP and documented in the log book or appropriate system. Observations that may be pertinent to the study (e.g. empty feeder, blood in litter, etc.) should be documented and the study director notified, as necessary.

Control and Monitoring of Environmental Variables

Fundamental to the concern about animal care is the requirement that the study report include a description of all circumstances that may have affected the quality or integrity of the data. Awareness of such circumstances depends largely on knowledge of the animals' physiological and behavioural needs, the programme defined in SOPs and, of course, the training of technical, quality assurance and scientific staff. The diversity of factors that may interfere with a study is such that only major variables may be covered here. There is, however, substantial literature on this subject.

Once SOPs are defined and approved for each situation (length and type of study, species, etc.), data are collected and evaluated regularly by the professional staff. Deviations from the norm or alarming circumstances are documented and evaluated for corrective action and for any possible effect on the study. Such events have to be given due consideration in the final report.

In general, each variable is evaluated regarding:

Source

Examples: Temperature/humidity is often related to the heating ventilation and air conditioning system (HVAC) system and the presence and efficiency of a back-up generator. Bedding contaminants are usually related to the manufacturer's source of raw material. Soap or detergent residue contamination depends on the rinsing efficacy of the cage washer. Air quality may depend on the proximity of hood exhausts within the laboratory.

Risk

Example: Barrier procedures against incoming microbiological contamination are more important for lifetime studies than for acute studies. Bedding/litter characteristics and noise can be critical for teratology or blood pressure studies – less so for other study types. Light timer failure can be more critical for albino strains than for others. Water quality concerns can be much greater with automatic watering systems than with bottles. Most of the risk evaluation is study, species or project specific. For example, feed characteristics (particle size) can affect diet-admix quality. Basal dietary Vitamin A level may be critical in retinoid testing but not for other families of test molecules. Likewise, bedding characteristics can affect studies in many different ways because of physical and chemical factors.

Monitoring

Examples: Cage rinse analyses, certificates of analysis for feed, water and bedding, environmental recorders, manometers, air turnover measurement, insect pheromone traps, etc.

Control

Example: Light timers, barrier procedures, water and air filters, etc.

All systematic or fortuitous detection of abnormal situations is documented and the effect on the study results evaluated. By following this approach, systematic monitoring and control should protect against many undetected influences on the test system.

Finally, a historical database of species-specific normal control values (age/weight, mortality, haematology and biochemistry, selected histopathological signs, teratology, spontaneous tumour type and incidence, etc.) should be compiled and compared against control group parameters. Meaningful deviations from the norm should trigger review of animal care and environmental control procedures.

3. Characterization



Characterization

CHARACTERIZATION

Part I

TEST ITEM

Section 3:1

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Characterization

TEST ITEM

- **Test Item**
- **Preparation of dose formulation**
 - *i.e. Formulation of test item*
- **Chemical analysis**
 - *i.e. Analysis of both test item & formulation*

Section 3:2

Instructor's notes

Explain

The test items that are used in preclinical safety studies can be very different.

The trainer should ask the participants to suggest items other than chemical substances that might be tested. However, the majority are chemical compounds; chemical substances are used as examples of test items throughout this training course.

The GLP regulations deal with the three points in the slide:

- Test item
- Preparation of dose formulation – this is the test item formulated ready to be administered to the test system
- Chemical analysis – of both the test item and the formulation of the test item

3. Characterization

 Characterization
TEST ITEM
<ul style="list-style-type: none">• GMP is not required for the manufacture of batches used in preclinical (GLP) studies• Regulatory authorities require testing to ensure test items are suitable for preclinical testing/studies• Use single lot throughout the study, if possible• Protect the test item from cross contamination or pollution• Ensure that there are traceable records for all test items
Section 3:3

Instructor's notes

Explain

There is often confusion about whether or not Good Manufacturing Practice (GMP) is needed for the production of batches used in GLP studies.

GMP is required for the manufacture of actual medicines and for the preparation of clinical trial materials used in clinical studies performed in man. GMP is not required for test items used in GLP studies.

However, authorities do require that you demonstrate that test items are suitable for use. This means you must be certain of the identity of the test item, and protect it from accidental cross contamination or pollution.

Using a single batch of compound throughout a study reduces variability and makes it easier to interpret the results of the study.

It is a requirement to be able to track the receipt and use of the test item during the period that the item is at the test facility.

The test item quality should be as similar as possible to the compound that is to be used in clinical trials.

 Characterization
TEST ITEM
<ul style="list-style-type: none">• Characterization is essential to ensure no major quality problems• Chemical production changes can lead to physico-chemical variability• Physico-chemical variables affect bioavailability<ul style="list-style-type: none">• Impurity profile• Particle size
Section 3:4

Instructor's notes

Activity

Discuss with the participants the points they consider important for their studies with regard to the quality of the test item.

3. Characterization



Characterization

PREPARATION OF DOSE FORMULATION

- **Has the dose-form :**
 - **The right test item?**
 - **The right concentration?**
 - **Always been prepared in the same way?**
- **Have you got procedures for :**
 - **Receipt?**
 - **Storage?**
 - **Preparation?**
 - **Delivery to point of use?**
 - **Disposal?**

Section 3:5

Instructor's notes

Explain

GLP requires that procedures guarantee that the dose formulation administered is made with the right test item, at the right concentration and in the same way each time.

You must also be able to show that you have complete traceability of the custody, preparation, use of test item and the dose formulation.



Characterization

ANALYSIS

- **Analytical results are used to evaluate the quality of the test item and the dose formulation**
- **The Study Director should have this information as soon as possible**
- **The data from the analyses must be reliable, hence should be generated under GLP conditions**

Section 3:6

Instructor's notes

Explain

The analytical laboratory provides results that are used to demonstrate that the correct dose of the correct test item has been made prior to administration to the test systems.

Unless these results are reliable, the entire study may be seriously compromised.

GLP regulations require these data to be generated in compliance with GLP Principles.

3. Characterization

**Characterization**

CHARACTERIZATION

Part II

TEST SYSTEMS

Section 3:7

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**Characterization**

What are Test Systems ?

- **Animals**
- **Bacteria**
- **Cells**
- **Organs**
- **Plants**

can also be

- **Analytical equipment**

Section 3:8

Instructor's notes

Explain

Test systems are not necessarily animals, though this is frequently the case in preclinical studies.

Activity

The slide lists various test systems. Ask the participants to add more to the list from their own studies.

3. Characterization



Characterization

TEST SYSTEMS : Animals

- **GLP compliance**
- **Compliance with animal welfare legislation**

Section 3:9

Instructor's notes

Explain

Test systems are commonly animals, hence such systems are used as the example throughout this section.

The way test systems are handled must comply both with GLP regulations and with national animal welfare law.

You could be asked during a GLP inspection to prove that you respect animal welfare legislation.



Characterization

ANIMALS

- **Scientist must match quantity and quality of animals to research requirements**
- **Study Director defines**
 - **phenotype / genotype**
 - **sex, age**
 - **supplier**
 - **number**
- **Reasons for selecting the test system should be in the Study plan**

Section 3:10

Instructor's notes

Explain

It is the responsibility of the study director to select the right type of animal for the study.

There are many reasons for choosing specific types or strains.

GLP requires you to explain in the protocol why a particular test system has been chosen for a particular study.

The number of animals used in a study is also a decision that the study director must make.

The number of animals used in a study involves ethical considerations. Using too many animals means waste of lives while using too few could result in insufficient data for statistical analysis; this is also a waste of animal lives as the study may well have to be repeated.

3. Characterization



Characterization

ANIMALS

- **Species / Strain**
- **Health status**
- **Supplier**
- **Background data**
- **Separation**

Section 3:11



Characterization

ANIMALS - Husbandry

- **Follow National regulations**
- **Routine checks on :**
 - **rooms : cleaning**
 - **cages / racks : cleaning, changes**
 - **feed / water**
 - **environmental parameters :**
temperature, humidity, light, air renewal
- **Document checks**
- **Document deviations from SOPs**

Section 3:12

Instructor's notes

Explain

You will need to keep a careful check on the status of the animals you use, the way in which they are handled and the conditions under which they are housed, both during the experimental phase and during the pre-study phases (including acclimatization).

Many organizations have dedicated personnel to keep track of environmental factors in the animal house. Data from these checks should be supplied to the study director so that he/she can evaluate the impact of these factors on the outcome of the study.

Regular checks should be made on the documents filled in by the animal care staff (e.g. cage changes, washing of racks, treatment of diseased animals, etc.), by responsible staff and by the QAU during audits.

When there is a deviation from normal procedure, this should be noted. The study director must be informed as he/she will need to assess the impact of the deviation and comment on this in the final study report.

3. Characterization



Characterization

ANIMALS - Assignment to Groups

- **Procedure for assignment to groups is in the protocol**
- **Keep data used for assigning groups**
- **Log locations of rack / cage, if applicable**
- **Document all cases of "disqualification"**

Section 3:13

Instructor's notes

Explain

Keep all the documents showing how the animals were assigned to groups. It is important to be able to demonstrate that no bias was introduced in the study from the way the animals were grouped and caged (including their location in the animal room).

Any animal eliminated from the groups, for whatever reason, must be accounted for and the reason for elimination recorded.

It should be remembered that one of the reasons why GLP came into existence was the malpractice of replacing diseased animals with healthy ones during the course of an experiment. Inspectors are, therefore, very sensitive to this issue.



Characterization

ANIMALS / Identification

- **Must be identified during :**
 - acclimatization
 - study
- **Large animals - individual marks throughout**
- **Small animals - cage labels for acclimatization**
 - - individual unique i.d. for study
- **Animal i.d. on all data**
- **Regular i.d. check**

Section 3:14

Instructor's notes

Activity

Discuss with participants the different ways in which animals can be identified, based on their own experience.

During the discussion draw attention to the fact that some SOPs can help reduce the possibility of mistaking one animal for another and jeopardizing the study (e.g. "never have two cages open at the same time in an animal room").

Explain

All data referring to animals should include full animal identity.

It is always necessary to identify animals at the moment of dosing.

It is good practice to perform regular identity checks on the animals in a given room to make sure that there are no identification problems.

3. Characterization

 Characterization
<p style="text-align: center;">ANIMALS - Acclimatization</p> <ul style="list-style-type: none">• Length depends on species / protocol• Health check at specified times• Document preparation / approval of study room
Section 3:15

Instructor's notes

Explain

The acclimatization period obviously depends on the species and type of study being performed.

During the acclimatization keep full documentation on the procedures performed (health checks, treatment, etc.) and the animals identified.

When the animals are ready for the study, the study room is cleaned, disinfected, supplied with feed etc. These and other preparations should be recorded.

 Characterization
<p style="text-align: center;">ANIMALS - Receipt</p> <ul style="list-style-type: none">• Inspect upon arrival - SOP<ul style="list-style-type: none">• health / sex• number delivered / number ordered• weight / age• Record receipt and any deviations from specifications• Check against protocol requirements• Stock in clean room
Section 3:16

Instructor's notes

Activity

Receipt of animals is an important phase in the activity of the laboratory. It should be fully documented.

Organizations must have SOPs covering this part of the laboratory activity.

3. Characterization



Characterization

ANIMALS - Supply

- **Assess quality by "Supplier qualification"**
 - usually by scientist + QA
- **Apply same to bedding and animal feed**
- **Keep order form, supplier's invoice, transport certificate, etc. as raw data**

Section 3:17

Instructor's notes

Explain

It is important to establish a "partnership" with the animal supplier.

Most organizations audit the suppliers of animals, feed and bedding materials. It is also important to review the conditions under which the animals are transported. Transport stress can introduce important variables into the study and have a significant effect on the health of the animals.

Keep letters, invoices, supply and delivery notes from the suppliers as raw data.



Characterization

ANIMALS - Environment

- **GLP says study report must contain**
"...a description of all circumstances that may have affected the quality or integrity of the data"
- **Environmental conditions belong to these "circumstances"**

Section 3:18

Instructor's notes

Explain

When the study director writes the final report he/she must take into account the environmental conditions under which the animals have been kept. He /she will be particularly interested in any deviations from target values for temperature, humidity etc.

Deviations from specifications should be reported and their impact evaluated and commented on in the study report.

4. RULES

The institute's rules for organizing and conducting GLP studies must be defined in documents approved by management. Rules defining who does what, how, when and where, are called **PRESCRIPTIVE** documents.

There are two main types of prescriptive documents:

- the protocol (or study plan) which describes how the study is designed and how it is to be conducted, including the expected timeframe of the study;
- the standard operating procedures (SOP) which provide detailed instructions about how to actually perform each technical procedure, and how to ensure sound organization of the study, its environment and data.

THE PROTOCOL OR STUDY PLAN

The laboratory should have prescriptive documents that support and regulate the conduct of the scientific studies. The purpose of these documents is to:

- describe general policies, decisions and principles governing the way in which the research centre operates;
- define the experimental design for particular studies;
- instruct staff about how to carry out routine operations;
- provide support retrospectively when investigating what was actually done.

The types of documents that the laboratory will have range from the general **policy statements** through job descriptions for individuals to **standard operating procedures** detailing how a procedure should be conducted on any study. However, the pivotal document for the conduct of any individual study is the **protocol or study plan**. This document explains in detail why the study is being performed, how the work will be organized, what data will be collected during the experiment and who is responsible for the various aspects of the study.

The protocol is the central document through which the study director communicates the objectives and conduct of the study to the study staff and to third parties (such as the quality assurance unit [QAU] or the study sponsor). In the case of a study performed by a contract research organization (CRO), the protocol may also be contractual. The pro-

protocol contains the overall experiment plan with timeframe, a description of the study design with methods and materials and the responsibilities of the scientific staff concerned.

Since the protocol is the principal means of communication with study staff it should be designed and written with clarity so that it can be readily understood by everyone.

Content of the protocol

The content of the protocol is designed to meet the scientific requirements of the study and also to comply with GLP.

Identification:

The study identification number, or the number attributed to the protocol, must provide a means of uniquely identifying the study in the records of the laboratory and of confirming the identity of all data generated during the study. For example, the number may contain an element that identifies the test compound, the department, or the study. There are no set rules for the system to use for identification.

Title and Statement of Purpose:

It is important to state why a study is being performed. A study must be planned and designed in advance. This can be done adequately only if the designer has a clear understanding of the purpose of the work.

Identification of Test (and Control) Items

This includes not only the chemical name and/or code number of the test item but also its specifications or characterizations or details about how these will be determined if they are not yet available. The protocol must also detail any control materials to be used in addition to the vehicle.

Name of Sponsor and Address of Test Facility:

The sponsor and the test facility may or may not be the same company. The protocol should indicate where the test is to be carried out and also include the address of any consultants involved. The name of the sponsor should also be included.

Name of Study Director and Other Responsible personnel:

The name of the study director must be included in the protocol. It is good practice to identify any other responsible scientists who are going to contribute significantly to the

study. Most laboratories include the names of scientists who will be responsible for the interpretation of the data generated under their responsibility (e.g. pathologists, clinical pathologists). For contracted studies, it is usual to include the name of the monitor or contact person for the sponsor.

Proposed Dates:

The proposed dates for the study are the start and finish dates (corresponding to the date when the protocol is signed and the date when the report is signed by the study director) and the experimental dates. These correspond to the dates when the first and last experimental data are collected.

To help study personnel perform their work, the protocol may include a more detailed time plan. This may be produced separately.

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Justification for Selection of the Test System:

When animals are the test system being used in an experiment, the species and possibly the strain may be defined in scientific test guidelines. However, even if working to test guidelines, it is still important to state in the protocol why the test system has been chosen. Often the choice is based on the background (historical) data available at the test facility (or site).

Description of the Test System:

For animal experiments, this will include the proposed species, strain, age, weight and source of animals and how they are to be identified. It will also contain details of the animal husbandry including environmental conditions, diet and its source.

Experimental Design:

- Dosing details:
 - Dose levels
 - Frequency of dosing
 - Vehicles used
 - Method of preparation
 - Quality control.
- Method of assigning animals to their experimental groups.
- Parameters to be measured and examined:

This section identifies the measurements to be made and the frequency of measurement. If certain procedures are not routine and not covered by SOPs complete details of the non standard procedures, or references to them, would be required.

Note: Details of analytical methods are not usually included in protocols but are available as SOPs or “Methods” documents which are kept, and referenced, in the analytical laboratory together with the study data.

- Statistical methods

Other information

- Data retained after the study and the period for which they will be retained.
- Quality Assurance:

Frequently, the protocol outlines the proposed QA programme.

Approval of the Protocol

Approval of the protocol is vital before starting the study. The sponsor and the study director will agree on the design of the study before it begins, allowing time for all staff to be made aware of their involvement in the study. However, the signature of the study director is the only mandatory signature. This marks the date of study initiation and represents his/her agreement to take full responsibility for the study.

It is critical therefore that the protocol is produced in time to allow for adjustments before the experimental work begins. Too little time between submission of the protocol and the start of the study may lead to serious problems later on.

Sufficient time must be allowed to:

- produce the protocol,
- discuss its implications with staff concerned
- circulate the protocol for QA review
- circulate the protocol for scientific approval
- circulate the approved version to all staff involved in the study.

Only then should the study be initiated. In many laboratories a critical step in the study, such as ordering of the animals, may not be taken until a signed protocol is in hand.

Distribution of the Protocol

All staff involved in the study should have easy access to a copy of the protocol. In order to confirm that this is so, it is worth obtaining a signature from each recipient. It is good practice, but not a GLP requirement, to hold briefings/meetings before the study begins to ensure that everyone is aware of their role in the study.

Protocol Amendments

The protocol is the document that regulates the conduct of the study, but it should never be thought of as immutable. It can be changed to allow the study director to react to results or to other factors during the course of the work. If, however, a change to the study design is made, this should be documented and explained. In such cases the study director writes a protocol amendment.

A protocol amendment is only issued to document a prospective change in the study design or conduct. If a change in a procedure needs to be instituted before a formal protocol amendment can be generated, a file note is produced and signed by the study director and (except in rare circumstances) the sponsor's approval/consent is obtained by phone, fax, or e-mail. This is then followed by a protocol amendment as soon as possible.

Unplanned changes, omissions, errors in study conduct or any other cases where the protocol has not been followed cannot be covered by protocol amendments. This is not acceptable practice. In most laboratories such unplanned "one off" occurrences are documented in a file note attached to the relevant raw data. These constitute deviations from study design and are not amendments to the study. They must not be "covered" by an amendment produced after the event.

The important elements of a protocol amendment are that the:

- study being amended is clearly identified;
- amendment is uniquely numbered;
- reason for the amendment is clear and complete;
- section of the original protocol being amended is clearly identified;
- new instruction is clear;
- distribution is the same as that of the original protocol. *This is particularly important to avoid confusion. For example, suppose that a first amendment is only circulated to the toxicologist, but a second amendment is then produced relating to animal husbandry which is issued to the animal care staff only. The animal care staff will have no way of knowing whether the first amendment involved them.*

In practice, there are many adequate ways of amending a protocol. For example, the amended section of the protocol may be included in full in the amendment. Alternatively, the amendment may only comprise a description of how the protocol section has been changed. As with the original protocol, the most important factor is that all the staff responsible for performing the amended procedure are instructed clearly. Once again, they must have adequate notice and it is vital that they receive the amendment; otherwise the instructions in the original protocol may still be followed.

As with the original protocol, the study director approves the amendment and is responsible for issuing it. He/she is also responsible for ensuring that the new instruction is performed correctly. It is essential to review amendments for GLP compliance. This is a QA function but because amendments are invariably urgently required by study staff, the review is often performed retrospectively.

STANDARD OPERATING PROCEDURES (SOPs)

Implementing a good SOP system is a prerequisite for successful GLP compliance. It is also often seen as the most important and most time-consuming compliance task.

Even without GLP regulations, classical quality assurance techniques and good management require standardized, approved written working procedures.

Remember the quotation based on ideas from W. Edwards Deming and Joseph Juran:

“Use standards (i.e. 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 organization and culture of the laboratory;
- SOP-based education and training of personnel so that the procedures are performed in the same way by all personnel;
- a sound SOP management system to ensure that **current** SOPs are available in the right place.

SOP system overview

Care should be taken when designing and setting up the SOP system to meet the above requirements.

The system should include the following characteristics:

- **Total integration** into the laboratory’s system of master documentation (i.e. not a separate system in potential conflict with memos or other official means of conveying directives to laboratory personnel).
- **Comprehensive coverage of:**
 - all critical phases of study design, management, conduct and reporting;
 - “scientific” administrative policy and procedures (e.g. formats, safety and hygiene, security, personnel management systems, etc.);

- standard scientific techniques.
- **Readability.** A standard format should be adopted (one standard format is presented in the WHO/TDR document “Handbook for Quality in Basic Biomedical Research”). The procedures should be written in clear, uncomplicated sentences and with appropriate vocabulary so that all personnel can understand the instructions unambiguously. All personnel should be encouraged to constructively discuss procedures. Ideally, SOPs should be written by the people who perform the work, thus making them responsible for the work they do.
- **Usability and traceability.** For reasons of traceability and easy use, a two-tier system of SOPs is often the preferred approach. The first tier reflects general policies and procedures; the second covers operational instructions. It is advisable to use a method for binding and/or protecting procedures (SOP manuals) with an up-to-date table of contents, logical chapter divisions and selective distribution. In some laboratories SOPs are available directly from a computer screen, but in such cases special rules about printing SOPs (expiry dates, etc.) and rules about electronic signatures must be implemented.
- **Procedures should be fully understood and adhered to.** If deviations occur, easy communication routes with the study director and management is essential to ensure GLP requirements are met and to conserve the credibility of the system.
- **A responsible person should be identified for each SOP** to ensure that queries are dealt with and that each procedure is kept up to date. Periodic review of each SOP should be conducted.
- A **formal change control** system that ensures historical reconstruction. A working SOP system appears to be perpetually incomplete because of additions, deletions and modifications reflecting the normal rate of improvements or changes. Ease and rapidity of updating should be ensured.
- **Centralized organization** of formatting, numbering, issuance, modification and destruction is necessary in order to avoid duplication of effort, incoherence, delays, lack of traceability and incomplete distribution.
- Procedures should be **immediately available** to the people performing the work.

If properly designed to ensure the above characteristics, the SOPs will provide the following benefits to the laboratory:

- Standardized, consistent procedures (person-to-person, test-to-test variability reduced).
- A means of study reconstruction, if needed.

- Optimum efficiency.
- Capture of technical and administrative improvements.
- Demonstration of management commitment to quality as part of the SOP approval process.
- Ease of documenting complicated techniques (a simple reference to the procedure should often suffice).
- Continuity in case of personnel turnover.
- Training manual.
- Means of communication in case of audit, visits, technology transfer, etc.

In fact, the simple act of formally writing down instruction and obtaining management approval helps to promote process improvement.

In summary, most laboratories incorporate the necessary characteristics into the following approach:

- A two tier system.
- A defined format.
- Drafts reviewed by all concerned people, with a formal review of the final draft by QA.
- SOPs usually approved and signed by (at least) two people:
 - a designated author
 - an appropriate member of management.
- A formal change control system, co-ordinated by a designated person/group.

During the course of the study, a general SOP (tier 1) requires that all modifications to operational SOPs should be approved in advance by the study director, or another appropriate level of management. If this is impossible he/she should be informed in writing of all changes/deviations. This record, along with the technical person's and/or the study director's assessment of the deviations are maintained as raw data in the study file for audit and consideration when writing the final report.

4. Rules



Rules

RULES

- 1. Protocol or Study Plan**
- 2. Standard Operating Procedures (SOPs)**

Section 4:1

Instructor's notes

Explain

The two document types presented in this section are the Study protocol and the Standard Operating Procedure



Rules

RULES

- **Protocol / Study Plan – overall plan of experiment**
- **Standard Operating Procedures (SOPs) – detailed instructions for all routine processes**
- **These are *PRESCRIPTIVE* documents.**
- **These tell us *who* is going to do *what, when, where* and *how* (and sometimes *why*)**

Section 4:2

Instructor's notes

Explain

Both the Study Protocol and the Standard Operating Procedure are formal documents which aim to instruct study staff about their assigned tasks during the study and how to perform certain procedures.

This means that these documents are prescriptive and must be scrupulously followed.

The protocol is a high level document which defines the study design. As such it provides the overall plan of the study and its experimental design.

SOPs are instructions on how to perform the routine procedures that make up a good part of the study.

Combined, these prescriptive documents should enable another researcher to perform the same study in the same way.

4. Rules

**Rules**

1. Protocol or Study Plan

Section 4:3

**Rules**

Protocol or Study Plan

- **Approved by the Study Director**
- **May follow scientific guidelines**
- **Information on major events of the study**
- **Provides overall timeframe**

"MASTER PLAN"

Section 4:4

Instructor's notes

Explain

The protocol is the pivotal scientific document for GLP studies. It should provide enough information to the reader (who may be a member of a receiving authority or a member of the study staff) about the methods used to perform the study.

The protocol often follows international guidelines, but not necessarily.

The protocol is a master plan for the study that provides information on the study design and the timeframe.

The protocol must be approved by the study director, even if the study is sponsored by another organization.

4. Rules



Rules

Protocol or Study Plan

CONTENT

- **Scientific**
- **Organizational and GLP**

Section 4:5

Instructor's notes

Explain

The protocol covers both the scientific and the organizational aspects of the study.

Only the organizational / GLP aspects are covered in these slides.

The study director is responsible for the science and the organization of his/her study.

Activity

Ask a few of the participants which scientific aspects they would include in protocols for their own studies.



Rules

Protocol or Study Plan

- **Pivotal document for**
 - **communication to study staff**
 - **fixing study objectives**
 - **contractual reasons**
(e.g. between contract laboratory and sponsor)
 - **providing basic dates**
(particularly study start and finish dates)
 - **indicating study methods**

Section 4:6

Instructor's notes

Explain

The importance of the protocol as a formal document for communication or for contractual reasons should be emphasized.

Activity

Ask the participants how they formalize their study instructions in their respective institutions.

4. Rules

 Rules
Protocol or Study Plan
FUNCTIONS
<ul style="list-style-type: none">• Specification for study activities<ul style="list-style-type: none">• which activities, when, where• non-standard practice• Defines responsibilities and resource needs• Communication / instructions• Basis for contracts• Basis for regulatory discussions
Section 4:7

Instructor's notes

Explain

The protocol is a multi-purpose document. Some of its functions are outlined here.

Activity

Ask the participants to list other possible functions of the protocol.

 Rules
Protocol or Study Plan
GLP REQUIREMENTS
<ul style="list-style-type: none">• Identification<ul style="list-style-type: none">• must be unique to each study• used to identify study data• may identify test compound• may identify department concerned• can be cross-referenced to other studies
Section 4:8

Instructor's notes

Explain

Each study must have its own, individually and uniquely identifiable protocol so that it is never confused with another.

From the protocol number, it is usually possible to trace all the study data and other items of interest (as shown in the slide).

4. Rules



Rules

Protocol or Study Plan

GLP REQUIREMENTS

- **Title and statement of purpose**
 - **Why the study is being performed**
 - **Regulatory considerations (if any)**
 - **Reference to scientific guidelines (if any)**
 - **Title usually contains information on at least: species, test item, route of administration & duration**

Section 4:9

Instructor's notes

Explain

GLP requires each study to have a clear statement of purpose. This is expressed in the protocol. The points usually addressed in the purpose section are outlined in this slide.

Sometimes a good study title is sufficient to explain the purpose of the study (e.g. study of the short-term toxicity of compound X when administered orally to the rat as a single dose, followed by a two-week observation period).



Rules

Protocol or Study Plan

GLP REQUIREMENTS

- **Test and control item description typically includes:**
 - **Chemical name**
 - **Batch identification**
 - **Specifications**

Section 4:10

Instructor's notes

Explain

GLP requires that the test, control and any reference items all be identified. Usually, test items are identified by the points characteristics listed on the slide.

The test item may only be identified by a code number or name. This is often the case when a CRO is performing the studies on behalf of a sponsor.

It is preferable to use a single batch throughout the study so as to eliminate possible batch-to-batch variability.

Specifications of test items may not be known for items in the early stages of development.

4. Rules

 Rules
Protocol or Study Plan
GLP REQUIREMENTS
<ul style="list-style-type: none">• Test facility / sponsor information<ul style="list-style-type: none">• Addresses / Location (s) of study (could be a multi-site study)• Identity of consultants• Identity of sub-contractors
Section 4:11

Instructor's notes

Explain

GLP requires all the partners participating in the study to be identified. In some multi-site studies there can be many such partners.

There is a section devoted to multi-site studies in the appendix of this training manual.

 Rules
Protocol or Study Plan
GLP REQUIREMENTS
<ul style="list-style-type: none">• Study Director and responsible personnel<ul style="list-style-type: none">• must identify the Study Director• must identify the Principal Investigators for multi-site studies• may identify other Responsible Scientists• may identify the Study Monitor
Section 4:12

Instructor's notes

Explain

Although GLP only requires identification of the study director in a protocol (and principal investigators if it is a multi-site study) it is strongly recommended that other significant personnel are also identified. The protocol may also be used to clarify responsibilities and to ensure good communication.

The study monitor is the person who will follow the study on behalf of the sponsor, especially when a study is preformed by a contract research organization (CRO).

4. Rules

**Rules**

Protocol or Study Plan

GLP REQUIREMENTS

- **Dates**
 - **Proposed dates for the start and the finish of the experimental period**
 - **Date protocol approved by Study Director**
 - **Date signed by management, if necessary**
 - **Date signed by sponsor, if necessary**

Section 4:13

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Instructor's notes

Explain

The four following dates must be included in the study plan / protocol to meet GLP requirements:

1. Study initiation date = date the study director signs the study plan / protocol (this date is added to the protocol when it is signed).
2. Experimental starting date = date on which the first study specific data are collected (this date is a planned date in the protocol).
3. Experimental completion date = the last date on which data are collected for the study (this date is a planned date in the protocol).
4. Study completion date = the date the study director signs the final report (this date is a proposed date in the protocol).

Activity

Explain to the participants that a good protocol will include a more extensive plan for the study than just the minimum GLP requirements outline above. It is useful to include all dates (in the protocol or in a separate planning document) that will help scientists working in different areas to coordinate their activities.

Stress the importance of using a draft protocol as a planning document so that all scientists involved in the study can agree to the overall timeframe. For example, it is important that the study director agrees with the clinical pathologist concerning the dates that blood samples will be dispatched to his/her laboratory for analysis.

**Rules**

Protocol or Study Plan

GLP REQUIREMENTS

- **Test System**
 - **Description**
 - species, strain, health status
 - age, weight, sex, source
 - environmental conditions, animal husbandry
 - diet, source and possible contaminants
 - **Justification of choice**
 - could be based on scientific guidelines, regulations
 - could be based on background data

Section 4:14

Instructor's notes

Explain

Each type of test system has its peculiarities. In this slide the example of a mammal has been used to illustrate a test system.

Activity

Ask the participants how they would describe the test systems they use. These may be plants, bacteria, cell lines, isolated organs or even analytical apparatus etc.

4. Rules

**Rules**

Protocol or Study Plan

GLP REQUIREMENTS

- **Experimental design** (depending on study)
 - **Dosing details**
 - dose levels and frequency
 - vehicles
 - preparation
 - Quality Control (QC)
 - **Assignment of animals to experimental groups**
 - pre-test
 - during study / cages / racks

Section 4:15

Instructor's notes

Explain

This slide and the next one indicate the points that are likely to be important in the experimental design for a typical animal toxicity study.

This is only an example, the participants will be faced with real protocols in the workshop activities.

Points to be highlighted are:

- The routine method of preparation of the dose would be covered in detail in SOPs or in a preparation method document. Therefore, details of dose mixing procedures would not be required in the protocol.
- It is usual in long-term animal studies to perform quality control (QC) analytical work at the start of the study, often during the first week, to confirm that the correct concentrations of dose mixes are being prepared. It is good practice to repeat these QC analyses periodically throughout the study to ensure that there are no deviations from procedure throughout the study.
- The method of group assignment of animals is important since it reduces group-to-group variability. Animals should also be distributed in cages and racks in a manner that reduces the possible effects of environmental variables.

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**Rules**

Protocol or Study Plan

APPROVAL / REVIEW

- **Approved and dated by the Study Director before study starts**
- **Allow time for protocol review by QA**
- **Allow time for corrections**
- **Allow time for distribution to study staff**
- **Allow time for pre-study meeting**

Section 4:16

Instructor's notes

Explain

Further items covered in the protocol are given here as examples.

The statistical methods that will be used at the end of the study should be mentioned. Additional tests can, of course, be performed as necessary.

Mention where the archives of the study will be kept.

Most GLP protocols also indicate the extent to which QA will cover the study in its programme of inspections/audits

Activity

After this slide, the participants should read sections 8.1 and 8.2 of the OECD GLP Principles where they will find the full list of protocol requirements.

If the trainer prefers, this reading can be done immediately prior to the workshop on protocols.

4. Rules

**Rules**

Protocol or Study Plan

GLP REQUIREMENTS

- **Experimental design**
 - Parameters evaluated during study
 - body weights
 - clinical signs
 - bio-analysis / haematology
 - necropsies / pathology
 - Statistical methods
 - Archives post-study
 - Quality Assurance

Section 4:17

Instructor's notes

Explain

As stated earlier, the study director signs and dates the protocol to approve it. The protocol may be signed by management. It is also usual for the sponsor to sign the protocol to indicate his/her approval.

Usually the draft protocol is reviewed by QA before the final signature by the study director. This should be done before the signature is provided in order to avoid having to write an amendment if QA finds something wrong.

The most frequent criticism regarding the writing of protocols is that the study director does not allow enough time before the start of the study for everyone to read and comment on the protocol.

**Rules**

Protocol or Study Plan

AMENDMENTS

- **Planned study changes**
- **Approved by Study Director (may require sponsor agreement)**
- **Must be seen by all study staff**
- **Must go through review process**
- **Must not be used to "correct" protocol deviations**

Section 4:18

Instructor's notes

Explain

Amendments are only used for planned changes to the study. This may include extending the study period, changing the study staff mentioned in the protocol, adding experimental parameters, etc.

The amendment must be signed by the study director. The amendment must also be reviewed by QA, but as some of the changes may be urgent, the review may be retrospective.

Under no circumstances should amendments be issued for "unplanned changes". Deviations should be noted in the study file, brought to the attention of the study director and reported in the final report.

4. Rules

**Rules**

Protocol or Study Plan

AMENDMENTS

- **Main elements:**
 - **Study / protocol identification and unique issue number**
 - **Clear description of change and identification of section changed**
 - **Reason for change**
 - **Approval by Study Director / Sponsor**
 - **Review process**
 - **Circulated to all staff who received the protocol**

Section 4:19

Instructor's notes

Explain

Amendments must have all the attributes of traceability needed to identify the study concerned, the change planned (i.e. the part of the protocol affected), and the reasons for the change.

All personnel that received the original protocol should also receive all the amendments (even if they are not directly concerned).

**Rules**

Protocol or Study Plan

AMENDMENTS versus DEVIATIONS

- **Amendments are planned changes to the protocol**
 - **Formalised in document called "Protocol Amendment" signed by the Study Director before the change is made**
- **Deviations are unplanned events**
 - **Recorded in study file & brought to the attention of the Study Director**
 - **Impact evaluated & discussed in final report**

Section 4:20

Instructor's notes

Explain

The difference between an amendment and a deviation is fundamental.

Amendments are planned changes, documented in a protocol amendment and signed and approved by the study director before implementation.

Deviations are unplanned events, where the protocol has not been followed by mistake, by accident or because of unforeseen circumstances. They therefore cannot be covered by a protocol amendment. However they must be recorded, the study director must be informed about what happened, he/she must evaluate the possible impact on the study and the deviation must be reported in the final report of the study.

4. Rules

*Rules*

2. Standard Operating Procedures (SOP)

Section 4:23

*Rules*

Standard Operating Procedures

- **Written detailed instructions**
- **Cover all laboratory activities**
- **Provides in-depth instructions : who does what, when, where and how**

Section 4:24

Instructor's notes

Explain

Standard operating procedures (SOPs) are routine instructions for laboratory operations. They are a necessary addition to the protocol if a study is to be repeated exactly.

In most cases SOPs provide answers to the following questions:

- What is the operation being performed?
- Who performs the operation?
- When and where is the operation being performed?
- How is the operation actually conducted?

4. Rules



Rules

Standard Operating Procedures

“Use standards (*i.e.* 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”

Based on an idea from W. Edwards Deming & Joseph Juran

Section 4:25

Instructor’s notes

Explain

This famous quote from the gurus of the “Total Quality Movement” may be applied to SOPs; it indicates the importance of the concept that SOPs standardize routine procedures.

SOPs only apply when there is a standard practice which will be repeated. If the work being performed is not routine, there is no need to write an SOP. The instructions will be included in another document, the protocol or the laboratory notebook.



Rules

Standard Operating Procedures

For successful SOP implementation:

- **Management support-company culture**
- **Training to SOPs**
- **SOP management system**

Section 4:26

Instructor’s notes

Explain

It is not worth trying to implement GLP if top management does not support it. As SOPs are an integral part of GLP, they too must have full management support. Management must be convinced of the advantages that a good SOP system can confer on the institution.

SOPs should be used as a tool for educating and training staff. Those who perform a technique for a GLP study must do so in compliance with the SOP. There must be an exact correspondence between what the SOP instructs and how the procedure is actually done.

Up-to-date SOPs need to be available for consultation at all times, otherwise operations will be performed which are not in compliance with SOPs and standardization will be lost; as a result the experiment will be vulnerable to false positives and false negatives. This is why a good SOP management system is essential.

4. Rules

 Rules
Standard Operating Procedures
SYSTEM CHARACTERISTICS
<ul style="list-style-type: none">• Part of laboratory master documentation system• Cover all activities<ul style="list-style-type: none">• Administration / personnel management• Safety / hygiene• Technical• Readable, clear, precise, practical• Fully understood and followed
Section 4:27

Instructor's notes

Explain

With management support, SOPs become an integral part of the documentation of the organization.

SOPs need to be written to cover all the technical aspects of studies. These are probably the most important SOPs.

SOPs should also cover the administrative aspects of activities, especially where the activity impinges on the conduct of the study (e.g. the transfer of data to the archives, or the management of documents), as well as safety and hygiene (e.g. the handling of dangerous chemicals, the elimination of waste, the protective clothing needed for entry into an animal room etc.).

In general, SOPs are needed for all sectors that ensure the GLP environment in addition to those needed for specific studies.

SOPs must be easy to read and understand. An independent, but informed, person from quality assurance should review the SOP before it is issued in order to ensure clarity.

The SOP must be followed exactly, otherwise there is increased test-to-test variability, no traceability and no auditability. Quality assurance will inspect certain activities within a study to ensure that SOPs are being respected.

 Rules
Standard Operating Procedures
SYSTEM CHARACTERISTICS
<ul style="list-style-type: none">• Responsible person for each SOP• Immediately available• Formal change control• Central organization
Section 4:28

Instructor's notes

Explain

To facilitate the management of SOPs, particularly for updating, someone should be identified as responsible person for each SOP. This person ensures that the SOP corresponds to the needs of the laboratory, is kept up to date, and that the persons using it are trained to use it.

Any changes to SOPs must be made following a standard method, described in an SOP. This is called change control.

A central organization dealing with the management of SOPs is helpful, but not mandatory (each department or unit can control its own SOPs). This ensures that the SOPs used on a site are harmonized. In some laboratories, the QAU undertakes this responsibility.

4. Rules



Rules

Standard Operating Procedures

Centralized organisation - Roles

- Set standard format
- Single point for i.d. / numbers / issuance
- Change control (versions) : traceability
- Ensure distribution / destruction
- Ensure cross-departmental coherence of SOPs
- Ensure review by QAU

Section 4:29

Instructor's notes

Explain

In this slide some of the roles of a centrally organized management system for SOPs are mentioned.

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Rules

Standard Operating Procedures

Benefits from good SOP system

- Standardized, consistent procedures, reduce test-to-test variability
- Means of study reconstruction
- Optimizes the way things are done
- Record technical and administrative improvements

Section 4:30

Instructor's notes

Activity

Ask the participants to draw up a list of the advantages they would expect to accrue from a well-managed SOP system.

Compare with the points in this slide & the next one.

4. Rules



Rules

Standard Operating Procedures

Benefits from good SOP system

- Approval by management formalizes their commitment to quality
- Ease of documenting complicated techniques
- Continuity in case of personnel turnover
- Forms training manual
- Means of communication (e.g. during audits, visits, technology transfers)

Section 4:31

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Rules

Standard Operating Procedures

DEPARTMENT:		GROUP:	
TITLE: STANDARD OPERATING PROCEDURES <i>(Writing, Reviewing, Approval, Distribution, Use and Modifications)</i>			
N°: ABC/123/001		PAGE 1 OF 5	
Approval / Date:			
Author/Responsible Name	Management Name	Quality Name	
Signature	Signature	Signature	
Date applicable:		Revision period:	
The following SOPs are cited in the text of this SOP ABC/110, CDE/420, ABC/224			

Section 4:32

Instructor's notes

Activity

There is no oneway to format SOPs.

This is an example of the type of header you often see on SOPs. Other formats will be provided during workshops. (You can also find a format in the WHO/TDR guideline on Quality Practices for Basic Biomedical research – QPBR.)

It is important to stipulate the date when the SOP came into force. This is necessary for traceability of operations.

There is no need for the QAU to sign SOPs. But this is frequently done in Europe to signify that the SOP has been reviewed. It is not a way of underwriting or approving the technical aspects of the SOP

If possible, avoid referring to other SOPs in the SOP concerned - otherwise, when you change the number of one you will have to change the reference in all others.

4. Rules



Rules

Standard Operating Procedures

Sections in SOPs should be standardised e.g.

- **Title**
- **Purpose**
- **General**
 - highlights principal features
 - gives background information
- **Procedure**
 - instructions in logical / chronological order
- **References and "Help"**
 - contact person in case of problems

Section 4.33

Instructor's notes

Explain

Most organizations have a standard set of sections required in their SOPs. This is one example.

5. RESULTS

The experimental phases of the study generate data. The study director reports these data in the discussion and conclusion sections of a study report. The report and its associated data are the outcome of the experiment. This information becomes part of the scientific base of knowledge as soon as the results reach the public domain, often through publication. Given the potential importance of the knowledge derived from the study, it is important that the data are complete, have integrity and are kept safe.

This section describes the GLP Principles relating to data collection, reporting and archiving.

RAW DATA AND DATA COLLECTION

Carrying out procedures and making observations

Before any procedure is conducted, the study director will have ensured that :

- sufficient numbers of adequately trained and experienced staff are available;
- staff have read and understood the protocol and a copy of it is available wherever each procedure is to be carried out;
- SOPs have all been written and are available in the work areas. *If SOPs are not available for any reason (e.g. a non standard method is to be used) this should be documented in the protocol or other study records and the document should be available to staff;*
- necessary equipment and supplies are available;
- data recording forms are available in the work area, ready for use.

Before starting any procedure using a particular piece of equipment, the operator should ensure that it is functioning correctly and has undergone the required checks. (In the case of a balance, for instance, this may involve use of check weights before every sequence of weighing - although the balance check is done less frequently in many laboratories unless the machine is moved.) The operator should ensure that this equipment has been checked by reference to the appropriate log book or an equipment label.

In summary, data collection requires:

- adequate numbers of well-trained staff
- appropriate equipment
- good preparation with planning records available
- complete instructions.

Records and recording

Good record keeping is essential for complete reconstruction and accurate reporting of a study. If data are lost or a record is incomplete, the study and its results may be seriously compromised.

Raw data are defined as original results recorded made during the course of the study. These data are necessary for the reconstruction of the study (for example, by a senior scientist or an inspector) after the study completion date.

The raw data should include :

- “WHAT was done”

Describing procedures carried out and demonstrating that the instructions in the protocol were carried out, that relevant SOPs were followed and that the results of the observation or measurement were included.

- “HOW it was done”

Indicating that data were collected and recorded in accordance with the methods set out in the SOPs and protocol. There should be indications of any deviations from the instructions.

- “WHEN the work was performed”

Demonstrating that the timeline in the protocol was followed. This should be done by recording the date, and, if necessary, the time at which procedures were carried out. For certain procedures very exact timing is necessary and the data must demonstrate that the schedule has been followed. Examples of this may be procedures required at definite times after dosing (as in the case of toxicokinetic studies).

- “WHO performed the work”

The data should clearly identify who was responsible for carrying out the procedure and recording the data. Where more than one person was involved in a procedure this should be recorded in the data and the responsibilities of each described..

The records are therefore a great deal more than a list of figures. All data generated during the conduct of a study should be **identified** and **recorded directly, promptly, accurately, legibly** and **indelibly** by the person **entering the data**, and be **signed or initialled**,

and ***dated***. Any changes should be made so that ***the previous entry*** is not obscured and if necessary ***should indicate the reasons for corrections***. Such changes should be ***accompanied by date and signature*** of the ***person making the change***.

Identified

Study number, animal number, etc. should be recorded with the data in order to guard against mix-ups.

Directly

Records should not be made on scraps of paper and then transcribed into a final form. The first written records constitute the ***raw data*** and must be retained. When data are recorded directly by computer the raw data are either considered to be the magnetic medium or an immediate, direct print-out. Similarly, equipment-derived raw data may be in the form of a direct printout or in the form of digital files.

Promptly

Data must be recorded immediately after the operation is performed. It is not acceptable to make the record some time after the job has been finished.

Accurately

This is most important as the integrity of the study rests on it.

Legibly

Data that cannot be read are of no use and records that are difficult to decipher raise doubts about their credibility.

Indelibly

One of the original problems that gave rise to GLP was that data had been recorded in pencil and were subject to subsequent changes. Indelibility of data increases its authenticity and credibility.

Signed

Accountability is one of the basic tenets of GLP, hence the need for a record of who did every job on a study. Documenting the fact that the person was adequately trained for the procedure performed increases the credibility of the results obtained.

Dated

The date of each signature demonstrates that the procedure was conducted and recorded at the correct point in the study.

Reasons for corrections

Records may require alteration from time to time, but a clear *audit trail* showing why a change was made, by whom and when, is needed.

Data should be gathered in a way that facilitates both recording and subsequent data management (e.g. data entry, reporting, audit, archiving).

Data should be recorded in a logical way. Duplication should be avoided wherever possible.

Proforma documents assist the process by encouraging staff to record all the necessary data.

FINAL REPORT

The final study report is the responsibility of the study director and must include the following contents:

- name and address of test facility
- dates of start and finish of the study
- name of study director
- objectives of the study
- details of test items and vehicles
- description of the test system
- details of dosing, route and duration
- summary of findings
- discussion
- conclusion
- references
- GLP compliance statement from the study director
- QA statement of inspections/audits
- signed/dated reports from contributing scientists.

The study director is responsible for the entire study, including the report. He/she must make sure that the study report describes the study accurately. The study director is also

responsible for the scientific interpretation of study results.

Finally, the study director must indicate in the study director's GLP compliance statement whether the study was performed in compliance with GLP Principles. If the study was not fully compliant, those parts that were not compliant must be identified in the report.

Accurate Reporting and Deviations

“The report should fully and accurately reflect the raw data.”

This quote from the GLP Principles means that everything that happened during the study should be reported, but does not necessarily mean that every piece of raw data should be included in the report. The report should allow the reader to follow the course of the experiment and the interpretation without the need to refer to outside material. In practice, a good deal of the original data are included. More importantly, the report should not be a selection of “highlights” of the study, leaving out the part that did not work or overlooking restarts that were needed for some reason.

The report should always cover all aspects of the study that deviated from the original intention as laid down in the protocol or the SOPs, whether this is considered to have impacted the study integrity or not.

The report may include input from scientists other than the study director, such as specialists within the test facility or from outside consultants or the sponsor. These may form parts of the report, signed and dated by the contributing scientist. Data from outside the test facility should have been derived in compliance with GLP. If this is not the case, the study director should indicate this in his/her GLP compliance statement.

GLP requires the study director to include a statement in the report accepting responsibility for the validity of all data in the report, even that of contributing scientists, and confirming that the study was performed in compliance with GLP.

Report Review

After the report has been drafted, it will pass through a review stage and a quality assurance audit. During this period modifications may be made to the report, but it is important that all modifications are approved by the study director. The process of approval prior to finalization may involve both peer review by other scientists and a review by the

sponsor. It is important that all accepted changes be incorporated before finalization of the report as the report cannot be modified once the study director has approved and signed it. After finalization, modifications can only be made by a formal amendment, which is a separate document appended to the unmodified final report. Such amendments must be signed and approved by the study director who identifies the change and the reason for amending the report.

ARCHIVING

The archives should not be considered as simply a place for the collection and storage of *old material*. It is a safe depository of invaluable information. It is also a centre for the compilation and distribution of summary documents and a major tool for the reconstruction of studies performed in the past.

Function of Archives

The archives and the archivist provide :

- a centralized, secure repository for the storage and retrieval of original scientific data, master copies of document and of study reports;
- a means of controlling and documenting the distribution and modification of archived material;
- an efficient organizational tool for preparing project summary documents - drug master files (DMF); investigation new drug dossiers (IND); new drug application dossiers (NDA); and investigator's brochures etc. - made possible by a formal filing system and cross indexation;
- a unique repository for all project-related work facilitating the quick and complete retrieval needed for historical reconstruction;
- an organization for updating official documents in circulation and for storage of all document versions, including those no longer in force.

What is Archived?

- Study data.
- Personnel data.
- Systems data.
- Quality assurance files.

For most studies, what constitutes the core study file is based on the information found

in the protocol. It is important that study files are pre-collated in envelopes, boxes, files etc. before submission. Specimens and samples are inventoried, labelled and packaged according to SOPs.

System-generated data or personnel files (e.g. training records, animal ordering forms, HVAC maintenance, computer validation records etc.) should be submitted to the archives periodically. These files are usually kept separate from study files as they are relevant to several studies at any one time. Quality assurance files are also kept separate from study files. Notebooks and loose leaf files usually have tables of contents in order to facilitate indexing.

When is Material Submitted and by Whom?

For a given study, it is the responsibility of the study director, or his/her delegate, to submit verified and complete data for the study to the archivist at the end of the study. For long term studies the submission of data is done periodically throughout the trial.

For systems data, personnel files and quality assurance documents, the manager responsible for the section must submit files for archiving at appropriate intervals.

Term of Storage

The OECD GLP Principles require organizations to respect national regulations for the period of archiving. As many organizations register compounds internationally files may need to be archived indefinitely. This policy reflects the varying retention times required by different GLP/GCP/GMP regulations and the possible internal need to consult old data for product improvement/liability or scientific reasons.

Thus, research facilities impose strict rules on the destruction of archived materials. When a space problem arises, very old holdings and abandoned projects belonging to chemical families of no current interest may be destroyed upon justification and written authorization from upper management. If a company goes out of business, product licence holders at that time should be notified and archival responsibility transferred.

How are Archives Submitted?

All records and materials transferred to the archives should be transported there personally by designated personnel. The original of all required documents should be submitted. A record should be made of all material submitted to the archive on a submission form.

How are Archives Stored?

Securely :

- Only authorized persons are allowed access to the archives.
- Storage units should protect against hazards such as flooding, fire, vandalism.

Under conditions which minimize deterioration :

- Usually a ventilated general environment.
- Copies made of data recorded on heat-sensitive paper.
- Refrigeration where necessary.
- General warehousing procedures defined.
- Paraffin blocks sealed, tissues wrapped in preservative, cover slips on slides etc.
- Computer back-ups maintained in a security cabinet.

INDEXING

Indexing is often computerized and allows complete and rapid retrieval starting from any one of the indexing parameters.

All studies or lots of specific materials are given unique holding numbers that are cross referenced to their location in the archives. Systems and personnel documents are usually kept chronologically according to the type of material.

Indexing parameters that are often used include :

- Project or study number
- Protocol number (often the same as study number)
- Test item or reference item identification number
- Test facility identifier
- Test site identifier
- Key word retrieval from study title (route, species...)
- Key word retrieval from comments section of master schedule (regulatory information, dates..)
- Department

Retrieval from Archives

Once an item has been officially deposited in the archives, access to the original should be restricted. It should be examined in situ within the archive area and in the presence of the archivist. Photocopies may be made on request.

Any removal of items from the archives should only be allowed in exceptional circum-

stances . This removal should be authorized in writing by senior management. The history of each holding is recorded and signed by the archivist and the person taking responsibility for the material removed.

5. Results

**Results**

RESULTS

Section 5:1

**Results**

- **Results include:**
 - **Raw data**
 - **Study files**
 - **Data on environmental conditions**
 - **etc.**
- **These are *DESCRIPTIVE* documents.**
- **They give us the result of the experiment**
- **Thy tell us *who did what, when, where and how***

Section 5:2

Instructor's notes

Explain

The results of a study come in various forms. They may be numerical values, or handwritten observations. They may concern the test system directly, information on the test item, or environmental parameters of the study etc.

As these results describe the study outcome and what happened during the study, they are termed DESCRIPTIVE DOCUMENTS.

5. Results

**Results**

RESULTS

- **Raw data and data collection**
- **Study report**
- **Archives**

Section 5:3

Instructor's notes

Explain

This section deals with how results are collected, reported and archived.

Stress the importance of data as being "WHAT IS LEFT AT THE END OF THE STUDY". In a sense it is the only tangible result of the scientific inquiry.

The data will be reported in the FINAL REPORT.

The FINAL REPORT and the DATA will be stored in the archives for safekeeping at the end of the study. (For some long-term studies it is wise to archive bit-by-bit throughout the course of the study).

**Results**

RAW DATA AND DATA COLLECTION

Raw Data : Definition

- **Original (first, on-the-spot) record**
- **Needed for study reconstruction**

Section 5:4

Instructor's notes

Explain

The GLP definition of RAW DATA is two-fold. It may be useful to illustrate the way in which raw data are defined by using a flip chart to demonstrate the relationship between, for example, a set of individual values recorded from a series of weights, and the mean value.

- Each individual weight is a raw datum, needed to reconstruct the weighing series.
- The mean can be calculated from the raw data.

5. Results



Results

RAW DATA AND DATA COLLECTION

BEFORE the study starts :

Study Director assures that:

- **There are sufficient trained personnel**
- **The protocol is understood & available**
- **That SOPs are immediately available**
- **That equipment / supplies are at hand**
- **That the data collection forms are in the data file**

Section 5:5

Instructor's notes

Explain

This slide discusses the preparation that is needed before an experiment starts.

The process is ultimately the responsibility of the study director but he/she may delegate this to a senior technician.

Draw attention to the important last line, that when the study is on-going, data are generated and it is important to be ready to collect them in an organized way. This is why most laboratories prepare data collection forms prior to beginning the study.



Results

RAW DATA AND DATA COLLECTION

DURING the study:

- **Remember lost / inaccurate data may invalidate the study**
- **Collect data on prepared forms / notebooks so that they indicate:**
 - **"WHAT" was done**
 - **"HOW" it was done**
 - **"WHEN" it was done**

and

 - **"WHO" collected the data**

Section 5:6

Instructor's notes

Activity

Some raw data are so vital that losing any of them would invalidate the whole study. Discuss with the participants what they consider to be the most important data for their studies.

You can use the analogy of the series of weights (and the mean value) to highlight the fact that one piece of lost data (a weight) can never be replaced.

Explain

The collection of data must be done in such a way as to allow another person afterwards to find out who did what, when, where and how.

This is called auditability.

Data that can be audited gives the study credibility. The reputation of an organization depends in great part on the auditability of the data.

5. Results

 Results
RAW DATA AND DATA COLLECTION <i>DURING the study:</i> “WHAT” Data should show : <ul style="list-style-type: none">• that the protocol was followed• that the process complied with SOP instructions• the results of observations
Section 5:7

Instructor's notes

Explain

Recorded data should clearly identify the process by which it was generated and should confirm this process was performed according to protocol and SOPs.

 Results
RAW DATA AND DATA COLLECTION <i>DURING the study:</i> “HOW” Data should show that methods were carried out: <ul style="list-style-type: none">• as indicated in the protocol and SOP• or that any <u>deviations</u> from protocol/ SOPs were recorded
Section 5:8

Instructor's notes

Explain

Not all procedures will go according to plan. All deviations from the planned method should be recorded carefully in the raw data. The impact of deviations must be assessed by the study director and will be commented on in the study report.

5. Results



Results

RAW DATA AND DATA COLLECTION

DURING the study:

“WHEN”

Data should show:

- **Timing as per protocol - data / time**
- **Any deviations from protocol schedule were recorded**

Section 5:9

Instructor's notes

Explain

The requirements with respect to recording the times that operations occurred depend upon the type of experiment performed.

In some studies, timing must be recorded to the nearest minute (or less). In others it is sufficient to say for example that “the clinical observations were carried out twice, in the morning and again in the afternoon”.



Results

RAW DATA AND DATA COLLECTION

DURING the study:

“WHO”

Data should show:

- **Identity of operator**
- **Identity of data recorder – if different from operator**
- **Identity of verifiers / correctors**

Section 5:10

Instructor's notes

Explain

Everyone who is concerned with the collection, recording or verification of the data should be identified. There should be a record of what they did and when they did it.

5. Results

 Results
RAW DATA AND DATA COLLECTION <i>DURING the study:</i> Data should be recorded: <ul style="list-style-type: none">• Directly / not transcribed from a rough copy• Promptly• Accurately• Legibly Then: <ul style="list-style-type: none">• Sign & date• Explain corrections
Section 5:11

Instructor's notes

Explain

These are the general rules for data collection.

Never use pencil, never use "white out", never correct data if you do not explain why, and sign and date every change. The spirit of this policy also applies to computerized data.

When done correctly, this is what is meant by leaving an AUDIT TRAIL.

 Results
RAW DATA AND DATA COLLECTION <i>AFTER the study:</i> Data should be : <ul style="list-style-type: none">• Collected together in one place – organized in logical order• Verified for completeness• Handed over to the Study Director• Kept in a safe place
Section 5:12

Instructor's notes

Explain

The study director uses the data to write his/ her report.

Assembling the data, checking for missing data, and organizing it into coherent groups will facilitate the report-writing phase.

5. Results

**Results**

FINAL REPORT

Section 5:13

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**Results**

FINAL REPORT

GLP Requirements for Contents

- **Name & address of test facility/site**
- **Dates of study (start and finish)**
- **Name of Study Director**
- **Study objectives**
- **Test article details**
- **Test system details**

Section 5:14

Instructor's notes

Explain

Ask the participants to look at the GLP regulations concerning the requirements for final reports (see section 9.2 of the OECD GLP Principles).

They will note that the requirements include a list of contents for the final report. Most of these are mentioned in this slide and the next.

Ask if there are any questions or comments relating to these requirements.

Discuss what should be considered the experimental start and completion dates.

5. Results

**Results**

FINAL REPORT

GLP Requirements for Contents

- Dosing details - route, duration
- Results/statistics
- Summary of findings
- Discussion
- References
- Study Director GLP compliance statement
- Signed/dated reports from scientists
- QA statement

Section 5:15

Instructor's notes

Activity

Activity as above.

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**Results**

FINAL REPORT

Once signed ...

... modifications by amendments only

(QA audit of amendments)

Section 5:16

Instructor's notes

Explain

Once a final report has been signed by the study director, it cannot be changed. If there is a need to correct, modify or amplify the report, this has to be done by issuing a separate amendment to the report must be issued.

The amendment must indicate what is being changed or added to the report. The amendment should indicate why the modification is being made. The amendment must be signed by the study director and must be audited by the QAU.

Activity

This approach to the recording of report amendments is explained in section 9.1.5 of the OECD GLP Principles. Ask the participants to read this section.

5. Results

**Results**

ARCHIVES

Section 5:17

**Results**

ARCHIVES

This is what is left when the study is over

- **Study plan**
- **Raw data**
- **Specimens**
- **Final report**
- **QA documents**
- **Personnel records**
- **Facilities/equipment qualification records**
- **Historical SOP file**
- **Etc.**

Section 5:18

Instructor's notes

Explain

What is left at the end of the study is used to demonstrate the validity and traceability of the scientific results. This is why the archives are so important.

Listed here are the documents etc. that you would find in the archives. There may be other items to archive, depending on the type of study performed.

These items may not all be archived together in the same place. It is not usual, for example, to archive paper and specimens in the same place because they often need different storage conditions.

QA documents should be stored separately (can be in the same room) from the study archives.

5. Results

**Results**

ARCHIVES : Function

- Long-term, secure storage and fast retrieval of data
- Contains all original scientific data, master documents and reports, etc.
- Endpoint for regulated work

Section 5:19

Instructor's notes

Explain

The archive securely stores important items over a long period of time.

**Results**

ARCHIVES : Submission form

DEPT./GROUP : Holding number :

PROJECT :

STUDY N° :

QUANTITY	DESCRIPTION	COMMENTS
Date	Signature of submitter	Signature of archivist

Section 5:20

Instructor's notes

Explain

When the study director or other staff submit a document to the archives, it should be carefully logged in. At this point responsibility for the integrity of the data is transferred from the study director to the archivist. It is important to guarantee that all the data are transferred and that there is a record of what is transferred.

Most organizations use a transfer form like the one in this slide. It is completed at the time of transfer and is signed by the study director and the archivist, who both attest to the material being handed over to the safekeeping of the archivist.

5. Results

 Results		
ARCHIVES : History / Events Form		
DATE	EVENT	AUTHORIZATIONS

Section 5:21

Instructor's notes

Explain

Whenever documents are taken out of the archives, split up or otherwise interfered with, full records of these events must be made. This is usually done by using an events form like the one in this slide.

In this way a complete history of the movement of archived material is established. This will help to limit the loss of material.

 Results	
ARCHIVES: Security	
<ul style="list-style-type: none">• Only authorized entry permitted - per SOP• Examination <i>in-situ</i> of documents is preferred• Photocopies made in place, if possible• Protection against fire, flood and vandalism if possible	

Section 5:22

Instructor's notes

Explain

Archived materials must be protected from interference (particularly unauthorized removal) and from disasters such as fire, flood and deliberate vandalism.

Access to the archives should be restricted. There should be a SOP to describe the conditions of entry into the archive (e.g. by signing in and out) and a list of persons who are allowed access.

If possible, no one should be allowed to remove articles from the archives. Instead, people may be able to consult the documents in the archive zone and, if necessary, make a photocopy of the data.

5. Results

*Results*

ARCHIVES

Storage conditions should minimize deterioration

- **Fire, flooding precautions ?**
- **Air conditioned general environment ?**
- **Copies made of heat sensitive papers ?**
- **Refrigeration used where necessary ?**
- **Blocks sealed in bags, tissues in preservative, slides ?**
- **Computer back-ups maintained in security cabinet ?**

Section 5:23

Instructor's notes

Explain

GLP regulations require you to store archives under conditions that minimize possible damage and loss. Many institutions have poor archiving facilities. This slide is a list of questions that should come to mind when considering potential storage locations.

Activity

Discuss with the participants other possible archival conditions applicable to their studies.

*Results*

ARCHIVES

Indexing parameters

- **Project**
- **Test article/reference article and lot numbers for test item and formulated material if appropriate**
- **Protocol/study number**
- **Testing facility**
- **Key word retrieval from comments section of master schedule (e.g. regulatory information, dates)**
- **Department**

Section 5:24

Instructor's notes

Explain

In order to be able to rapidly retrieve archived material, it is essential to set criteria for the indexing of the material.

Most organizations use a combination of the criteria listed in this slide, but any criteria that ensure rapid retrieval are acceptable.

6. QUALITY ASSURANCE

GLP defines the minimum quality assurance requirements necessary to ensure the validity of experimental results. The quality assurance unit (QAU), a group of persons with a set of defined duties that ensures management that all the quality processes implemented in an institution are functioning correctly. Most organizations use the abbreviation QA (quality assurance), rather than QAU, and this is the term adopted here.

According to GLP, QA acts as an “independent” quality control service. However, QA may also serve as a facilitator and “consultant” in the establishment of quality systems.

In summary, the fundamental mission of QA is that of an independent witness to the whole preclinical research process and its organizational framework.

To respect GLP Principles, QA must review all phases of preclinical research - from planning to reporting and archiving of the documentation.

To be effective, QA must have access to staff documents and procedures at all levels of the organization, and be supported by a motivated top management.

QA audit files should be accessible to facility management, but not to regulatory authorities or other external legal persons.

PROTOCOL (OR STUDY PLAN) REVIEW

QA reviews the protocol for completeness and clarity. At some laboratories QA also signs the protocol – however, this signature is not mandatory. Often, the original signed protocol is archived right away. This ensures against loss, controls distribution of any subsequent amendments, opens the archive file and avoids misplacing the original. QA receives and maintains a copy of all protocols together with any subsequent amendments.

SOP REVIEW

Management has the responsibility of assuring that SOPs are generated, approved, distributed and archived. Management is responsible for both the scientific content of SOPs and for their compliance with GLP.

QA has the responsibility of reviewing SOPs. In those laboratories where QA signs the SOPs, this is done to indicate that the SOP is GLP-compliant, complete, clear and not in conflict with other SOPs that exist on the research site. This is not a mandatory duty. The QA signature does not approve the technical content of an SOP.

PLANNING (MASTER SCHEDULE, INSPECTION PLAN)

The study is entered into the master schedule sheet (MSS), which is a list of all studies at the facility, before the study starts and often before the protocol is written. (The MSS is part of the project management system. In small institutes the maintenance of the MSS is sometimes a QA function. It is part of the responsibility of a project management team in larger laboratories. Regardless, QA must be aware of all planned studies and must have a copy of, or direct access to, the MSS no matter who is responsible for maintaining it).

QA staff plan their inspections and audits considered necessary to support the study with input from the study director, if necessary. QA maintains its own inspection and audit plans study by study. These study-specific inspection targets are entered onto a planning system in the QA department along with facility/system and process inspections. This allows overall planning and the efficient allocation of QA resources.

AUDITS AND INSPECTIONS

An audit or an inspection is a methodical evaluation that should be performed in cooperation with the people whose operations are being audited. An internal audit is not an inquisition or a punitive exercise. There are arguments for and against performing unannounced QA inspections but usually inspections and audits are planned with the study director or his representative.

In addition to the QA review of planning activities, QA performs three types of audits/inspections:

- Study-based inspections/audits.
- Facility/Systems-based inspections/audits.
- Process-based inspections/audits.

QA may also audit contractors and suppliers.

Inspections are performed as planned with additional or follow-up inspections if necessary. There are many useful guides available on inspection and audit techniques.

Some general points:

- SOPs for inspections and for audit reports should be prepared in dialogue with staff.
- The inspector/auditor should prepare for the inspection/audit. Usually this means reviewing the protocol, applicable SOPs and past inspection findings beforehand.
- The inspector/auditor must follow all rules of access, safety and hygiene and must not disrupt the work.
- The inspector/auditor must allow sufficient time for the inspection.
- Checklists may be used, as necessary. Adherence to a checklist is no guarantee of completeness but it is useful for training and as a guide. Also, checklists enable management to approve QA methods and coverage, and provide technical staff with a means of self-checking. Checklists are usually established formally and updated over time. However, a checklist raises the risk of missing an unexpected finding.
- At the end of the inspection, or at least before a report is issued, the inspector should discuss all problems with the persons inspected. Any error (e.g. dosing error, animal ID) should be pointed out immediately,
- Findings/comments should be clear, specific and constructive. Sometimes solutions to problems can be suggested by QA.
- Comments should be constructive. One way of ensuring this is to propose a solution to each problem reported in the inspection report.
- The report circulated to management (with or without a separate summary) should include comments and responses. Rules for the writing, approval, distribution, and archiving of inspection/audit reports as well as arbitration procedures should be included in the SOPs.
- As a general rule, internal QA inspections and audits target events and organization, not people. The more problems uncovered and resolved the better the level of quality.

Study-based inspections/audits

Study based inspections target specific critical phases of the study. Determining what is critical to a study is an important part of QA work. It can seldom be done person and usually requires input from scientific specialists, such as the study director for example. Many QA groups use risk analysis techniques to assist them in identifying the critical phases. All techniques used by QA should be explained in their SOPs.

Study-based inspections/audits are reported to the study director who responds to each finding with an action plan to correct or improve the study's compliance.

System or facility-based inspections/audits

These are performed independently of studies. Frequency should be justified in terms of impact. This may be achieved by use of a risk analysis approach. The results of a system/facility inspection are reported to the appropriate manager of the test facility rather than to a study director. The follow-up procedure will, however, be exactly the same as for a study specific inspection.

Systems/Facility-based inspections typically cover areas such as:

- personnel records
- archives
- animal receipt, acclimatization and disposal
- cleaning
- computer operations and security
- access and security
- SOP management
- water supply.
- metrology

Process-based inspections

Process-based inspections are also performed independently of specific studies. They are conducted to monitor procedures or processes of a repetitive nature. Again, the frequency of process-based inspections may be justified by a risk analysis approach. These process-based inspections are performed because it is considered inefficient or inappropriate to conduct study-based inspections on repetitive phases. The OECD recognizes “that the performance of process-based inspections covering phases which occur with a very high frequency may result in some studies not being inspected on an individual basis during their experimental phases”. Other useful process-based inspections are those that focus on cross-organizational processes – for example, the transfer of test samples from the animal facilities to the bio-analysis laboratory.

Final Report/Raw Data Audit

QA should audit all reports from GLP studies with reference to the protocol, SOPs and raw data. An audit does not necessarily mean a 100% check of all data contained in the report. Enough data should be audited to convince QA that the report gives a complete and truthful account of the way in which the study was performed and provides an accurate representation of the data. QA is also looking for evidence of authenticity and GLP

compliance in the data i.e. signatures, dates, handling of corrections and deviations, consistency, etc.

Typically, QA may cover the following during the report audit :

- contents
- data completeness
- protocol compliance
- animal environment records
- test item QC/accountability
- dose preparation/dosing/QC records
- individual tables versus raw data (sample basis)
- summary tables
- appendices
- conclusions.

Whatever the audit plan, it should exist in writing as part of the audit file. QA should keep a trace of what was audited for any specific report.

QUALITY ASSURANCE STATEMENT

The QA statement that is placed in the report provides the dates on which the study was inspected and the findings reported to the study director and management. QA also reports the study phases inspected, along with the dates (as recommended by OECD).

The QA statement is not a GLP compliance statement. The study director provides this. However the following OECD recommendations with regard to the QA statement should be kept in mind :

“It is recommended that the QA statement only be completed if the study director’s claim to GLP compliance can be supported. The QA statement should indicate that the study report accurately reflects the study data. It remains the study director’s responsibility to ensure that any areas of non-compliance with the GLP principles are identified in the final report”.

In this way, the signed QA statement becomes a “release” document assuring that :

- the study report is complete and accurately reflects the conduct and data of the study;
- the study was performed in compliance with GLP;
- that all audit comments have been satisfactorily resolved.

QA INSPECTIONS OF SUPPLIERS AND CONTRACTORS

Most QA organizations also inspect/audit suppliers of major materials (animals, feed, etc.). In the same manner, QA may also inspect contract facilities before work is contracted out (and subsequently on a regular basis if the contract site is used often). This applies whether the work contracted out is a whole study or as part of a study (e.g. analytical work).

For pivotal studies, QA may schedule periodic visits to the contract site to ensure that the contractor is in compliance throughout the duration of the study and may review the final report independently.

ISSUING AND ARCHIVING OF QA FILES AND REPORTS

QA serves both as:

- an internal control function;
- a guarantee to the public at large that preclinical studies are performed in a way that will result in valid data.

QA reports issued to the study director and to management should be strictly regarded as internal working documents. They are particularly valuable if important findings are picked up during the QA activities, reported accurately, discussed and acted upon. Therefore, the QA audit reports are not normally available to regulatory authorities. The intention of this restriction is to encourage QA to report findings honestly, without fearing that the facility will be damaged in the event of adverse findings.

It follows that the QA reports are not for general distribution, and should be handled with discretion. It is best to archive reports separately from the study files so that regulatory authorities or external auditors do not access them inadvertently during inspections.

6. Quality assurance unit



Quality Assurance Unit

**QUALITY ASSURANCE
UNIT**

Section 6:1

Instructor's notes

Explain

This is the last of the five fundamental points of GLP.

The quality assurance unit (QAU) is the subject of an important chapter of GLP Regulations. To help with interpretation of the QA-section, the OECD has published a consensus document*.

You will need to have this consensus document to hand because it will be referred to often during this presentation.

Remind the participants that the abbreviation "QA" is much more frequently used than "QAU".

*OECD Series on Principles of GLP Compliance Monitoring Number 4 (revised). Consensus Document "Quality Assurance and GLP".



Quality Assurance Unit

GLP :
**A quality standard and concept
for the organization of studies**

Section 6:2

Instructor's notes

Explain

To understand the work of QA it should be remembered that GLP is a standard for the organization of studies.

Remember that GLP is not a set of rules that judges the scientific value of studies.

QA works in the area of compliance with GLP and in the area of study organization.

6. Quality assurance unit


Quality Assurance Unit

GLP :
Defines conditions under which studies are:

- **planned**
- **performed**
- **recorded**
- **reported**
- **archived**
- **monitored**

Section 6.3

Instructor's notes

Explain

GLP is concerned with the organization of studies and, in particular, the way in which they are: PLANNEDThis is why the protocol is important.

PERFORMEDThis is why respecting SOPs is important.

RECORDED.....This is why GLP gives such importance to raw data.

REPORTEDThis is why the study director is requested to make a final report including his scientific judgement.

ARCHIVED.....It is important to ensure the protection of raw data and full traceability after the end of the study.

MONITORED.....Continuous monitoring of the study is done by the study director and his/her team, by management and also by QA.


Quality Assurance Unit

QA PROGRAMME / PERSONNEL

GLP requires:

- **Documented QA programme**
- **Personnel who are familiar with studies**
- **QAU independent from study staff**
- **QAU reports to management**
- **That the Master Schedule be supplied to QAU**

Section 6.4

Instructor's notes

Activity

Read with the participants the section on "Qualifications of QA personnel" from the OECD consensus document "Quality Assurance and GLP" page 7. Discuss with the group.

Explain

The GLP regulations require that QA has a documented programme. This means that QA must have its own SOPs on how it operates, and must record what it does.

QA personnel must be familiar with the studies they are auditing. Note that the GLP regulations do not require QA personnel to be scientific experts in these studies; the expert is the study director. QA personnel should, however, be experts in GLP, quality systems and organizational issues.

QA personnel must be independent of the study personnel. They report directly to the facility management, never to the study staff. This allows them to be as objective as possible during audits and inspections. There are, therefore, no conflicts of interest with the study itself.

QA must have a copy of the master schedule. They need this to plan their own inspection / audit programmes.

6. Quality assurance unit

 Quality Assurance Unit	Instructor's notes
<p style="text-align: center;">QA RESPONSIBILITIES (from GLP)</p> <ul style="list-style-type: none">• Assure study plan & SOPs are available• Ensure study plan & SOPs are followed by<ul style="list-style-type: none">• inspection• audit <p>Section 6:5</p>	<p>Activity</p> <p>Ask all the participants to read section 2 of the OECD GLP Principles.</p> <p>What follows highlights some of the aspects that are detailed in that section.</p> <p>Explain</p> <p>The GLP Principles require QA to check that all personnel have protocols and SOPs available for their work and that these documents are followed during the performance of their work.</p> <p>This is achieved by audit or inspection. This programme of audits / inspection should be defined in the QA SOPs.</p>

 Quality Assurance Unit	Instructor's notes
<p style="text-align: center;">QA RESPONSIBILITIES (from GLP)</p> <ul style="list-style-type: none">• Record findings in writing• Review final reports• Prepare/sign QA statement <p>Section 6:6</p>	<p>Explain</p> <p>When QA performs an audit / inspection it must be recorded in writing.</p> <p>Any findings resulting from the investigation must be reported to the appropriate person in management and the study director if the finding is about a specific study.</p> <p>QA audits and makes sure that the results in the final report accurately represent the raw data.</p> <p>QA will add a statement to the study report detailing the dates and the nature of the investigations performed during the study.</p>

6. Quality assurance unit

 Quality Assurance Unit	Instructor's notes <i>Explain</i>
<p style="text-align: center;">QA RESPONSIBILITIES (from GLP)</p> <ul style="list-style-type: none">• Review study plan / protocol (an obligation)• Review SOPs (a recommendation) <p>Section 6:7</p>	<p>Although the OECD GLP Principles clearly state that QA must verify (review) the protocol, the same is not clearly stated for SOPs. However, the OECD consensus document on QA responsibilities recommends this.</p>

 Quality Assurance Unit	Instructor's notes <i>Explain</i>
<p style="text-align: center;">QA INSPECTION / AUDIT</p> <p>3 Types:</p> <ul style="list-style-type: none">• Study-based• Facility / system-based• Process-based <p>Section 6:8</p>	<p>The OECD GLP Principles recommend that QA performs three types of inspections / audit. These are explained in the following slides.</p>

6. Quality assurance unit

 Quality Assurance Unit	Instructor's notes Explain
<p style="text-align: center;">QA INSPECTION / AUDIT</p> <p>Study-based</p> <ul style="list-style-type: none">• Protocol / Study plan• On-going (usually critical phases)• Report (with respect to raw data) <p>Section 6:9</p>	<p>Study-based inspections are those that investigate specific studies.</p> <p>They are performed on the protocol, the phases of the study that are on-going, and on the final report.</p> <p>Typically, QA identifies important study phases, which are then inspected during the actual performance of operations.</p>

 Quality Assurance Unit	Instructor's notes Explain
<p style="text-align: center;">QA INSPECTIONS / AUDITS</p> <p>Facility / Systems-based</p> <ul style="list-style-type: none">• buildings / equipment / metrology• support services• computer systems• personnel training / documentation• others <p>Section 6:10</p>	<p>Facility-based inspections cover wider aspects of the laboratory's operations than those relating to a single study.</p> <p>The slide shows some examples of the type of facility inspections that QA could conduct within a laboratory.</p> <p>Activity</p> <p>Read the definition of facility inspections in the OECD consensus document "Quality Assurance and GLP": Section on QA inspections, page 8.</p>

6. Quality assurance unit

 Quality Assurance Unit	Instructor's notes <i>Activity</i>
<p style="text-align: center;">QA INSPECTIONS / AUDITS</p> <p>Process-based</p> <ul style="list-style-type: none">• Inspections of processes which occur frequently, e.g.<ul style="list-style-type: none">• slide preparation• reading Ames tests• measuring food consumption	<p>Read to participants the paragraph in the OECD consensus document “Quality Assurance and GLP” relating to process inspections, and explain what it means. Section “QA inspections” page 8.</p> <p>Examples of process-based inspections are given in this slide.</p>
Section 6:11	

 Quality Assurance Unit	Instructor's notes <i>Explain</i>
<p style="text-align: center;">QA INSPECTIONS / AUDIT</p> <ul style="list-style-type: none">• Suppliers• Sub-contractors	<p>QA also performs inspections of important suppliers (such as suppliers of animals) and work contracted out to third parties.</p>
Section 6:12	

6. Quality assurance unit

Quality Assurance Unit

QA INSPECTION REPORT

Header			
Phase audited	QA comments	Responses/corrective action planned	
	Signature Date	Signature	Date

Section 6:1

Instructor's notes

Explain

This is an example of the format of a QA report that is written up and submitted to management and the study director.

It is important that QA clearly explains the finding recorded during the inspection/audit and that the study director (or other responsible manager) responds with a plan of action for correcting the problem.

If the study director does not agree with the QA finding, in which case, he/she should say so here.

Quality Assurance Unit

QUALITY ASSURANCE STATEMENT

- **Dates of inspections**
- **Dates of findings to Study Director & Management**
- **Phases audited**
- **Confirmation that report reflects methods used and data generated – report exceptions**
- **Sign only if GLP compliance statement from Study Director is considered justifiable and all corrective actions have been completed**

Section 6:2

Instructor's notes

Activity

Read the section on “audits of data and final reports” in the consensus document and the section on “The QA statement”.

Discuss the points raised in these sections.

This slide summarizes the requirements with respect to the QA statement.

It is a good idea here to reiterate the difference between:

1. The QA statement and the QAU
2. The GLP compliance statement and the study director.

Both of these appear in the final report.

APPENDICES

The following seven appendices are optional sections to be used at the discretion of the trainer, depending on the level of GLP knowledge of the trainees and their specific needs.

The sections cover the most important guidance documents published by the OECD that are not already incorporated into the first 6 chapters.

These are:

1. The International GLP of the OECD
2. Management: Roles and Responsibilities
3. The Study Director: Roles and Responsibilities
4. Multi-Site Studies
5. Short Term Studies
6. GLP and Computerized Systems
7. GLP and in vitro studies

APPENDIX 1: THE OECD AND ITS GLP ACTIVITIES

WHAT IS THE OECD?

- The acronym OECD stands for: Organisation for Economic Cooperation and Development.
- This OECD comprises a group of 30 member countries. In alphabetical order the member states are:

AUSTRALIA
AUSTRIA
BELGIUM
CANADA
CZECH REPUBLIC
DENMARK
FINLAND
FRANCE
GERMANY
GREECE
HUNGARY
ICELAND
IRELAND
ITALY
JAPAN

KOREA
LUXEMBOURG
MEXICO
NETHERLANDS
NEW ZEALAND
NORWAY
POLAND
PORTUGAL
SLOVAK REPUBLIC
SPAIN
SWEDEN
SWITZERLAND
TURKEY
UNITED KINGDOM
UNITED STATES

- There are also active relationships with 70 other non-member countries, NGOs etc.
- All OECD member states have a commitment to democratic government.
- They all subscribe to the principles of the market economy.
- The OECD is perhaps best known by most people for its regular publications on the economic affairs of the OECD member states.

- But its work does not only cover economics and market problems, it also deals with social, scientific and environmental issues.
- The OECD helps governments to respond to key social, economic and scientific issues.
- Help is not given by financial means, but rather by identifying policies that work promoting certain policies.
- The OECD produces international recommendations and agreements with the view to promoting rules of the game in areas where multilateral agreement is necessary.
- It is in this capacity that the OECD developed an interest in Good Laboratory Practice which was finalized in the “OECD Principles of Good Laboratory Practice” in 1981.

HOW GLP WORKS THROUGH THE OECD

- The OECD has a Governing body made up of Representatives from each member country.
- It functions as an international agency, state representatives have ambassador status.
- The Governing body provides guidance for the work of the OECD committees.
- One of the committees is the OECD Working Group on GLP.
- The GLP activities of the OECD are promoted and supervised by the Working Group on GLP.
- Dialogue, consensus & peer review are at the heart of the OECD and certainly apply to the way in which the Working Group on GLP try to organize their international activities.
- The Working Group on GLP comprises the Heads of all national GLP monitoring authorities.
- The group meets regularly to plan OECD GLP activities.
- The group verifies the implementation of GLP in member states.
- The group promotes training courses for GLP inspectors and future inspectors.
- The group promotes harmonization of inspections in member states through joint inspections.

WHY WERE THE OECD PRINCIPLES ON GLP DEVELOPED?

- In its role of promoting the exchange of chemicals between member states, the OECD developed a series of Test Guidelines for assessing the safety of chemicals and a companion recommendation on GLP, known as “the Principles of Good Laboratory Practice”.
- The work of the OECD related to chemical safety is carried out in the Environmental Health and Safety Division.
- The Environmental Health and Safety Division publishes free-of-charge documents in six different series: Testing and Assessment; Principles on Good Laboratory Practice and Compliance Monitoring; Pesticides; Risk Management; Chemical Accidents and Harmonization of Regulatory Oversight in Biotechnology.
- More information about the Environmental Health and Safety Programme and EHS publications is available on OECD’s World Wide Web site
- The aim of the OECD GLP Principles was to create a level “regulatory” playing field for member states involved in the import and export of chemicals, thus minimising the effects of non-tariff barriers between these states.

WHAT IS THE MAD DECISION?

- The implementation of GLP was accompanied by an OECD Decision on MUTUAL ACCEPTANCE of DATA (known as the MAD agreement) in 1981.
- In the introduction to the OECD GLP Principles we can find the following statement “[The] Principles of GLP were formally recommended for use in Member countries by the OECD Council in 1981. They were set out (in Annex II) as an integral part of the Council Decision on Mutual Acceptance of Data in the Assessment of Chemicals, which states that “data generated in the testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment”.
- The MAD decision has been signed by all of the OECD member states.
- The MAD decision facilitated the international harmonization of GLP and monitoring compliance.

- Thus, from the moment of signing the decision on MAD, all of the OECD members agreed to apply the Principles of GLP to their regulated non-clinical studies.
- In this sense, the OECD Principles of Good Laboratory Practice have become an international standard for GLP.
- Following their acceptance of the OECD GLP Principles, some countries have simply integrated the Principles into national law. This is the case for the European Union which adopted the OECD GLP Principles in a European directive.

HOW DOES OECD SEE THE PURPOSE OF PRINCIPLES ON GLP?

- All governments are concerned about the quality of non-clinical health studies, because it is with data from such studies that assessments are made concerning the safety of the test item and particularly whether or not it is safe to proceed to clinical trials in human beings.
- The OECD GLP Principles were implemented to establish criteria for the performance of these studies.
- The major objective of Good Laboratory Practice is to promote high quality test data.
- Confidence in the quality of test data forms the core for the credibility of the study and the basis for the mutual acceptance of data among countries.
- The OECD document goes on to say: “If individual countries can confidently rely on test data developed in other countries, duplicative testing can be avoided, thereby saving time and resources. The application of these Principles should help to avoid the creation of technical barriers to trade, and further improve the protection of human health and the environment.” Thus we can also see the OECD interest in GLP in terms of economic development and cooperation between member states.

WHAT IS THE SCOPE OF OECD GLP PRINCIPLES?

- All regulatory non-clinical health and environmental safety studies are subject to the OECD Principles on GLP
- Principally, such studies concern safety studies necessary for the registration of:
 - Pharmaceuticals
 - Pesticides

- Food additives
- Cosmetic products
- Veterinary drugs
- Industrial chemicals
- Typically these tests may be performed in the laboratory, in greenhouses in the field....
- The reason for performing these tests is to obtain data on the properties and/or the safety of the test item with respect to human health and/or the environment

THE OECD PRINCIPLES ON GOOD LABORATORY PRACTICE

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What are the aims of the OECD GLP Principles?

- The MAIN GOAL is to help scientists obtain results which are:
 - Reliable
 - Repeatable
 - Auditable
 - Recognized by scientists worldwide.
- The purpose is not to assess the intrinsic scientific value of a study.
- The GLP Principles are a set of organizational requirements.
- The GLP Principles aim to make the incidence of False Negatives (e.g. results demonstrating non-toxicity of a toxic substance) more obvious.
- Equally, under GLP, False Positives (e.g. results demonstrating toxicity of a non-toxic substance) become more obvious.
- GLP also assists in:
 - Limiting the waste of resources
 - Ensuring high quality of results
 - Ensuring comparability of results
 - Promoting mutual recognition of results
- GLP is a managerial concept for the organization of studies.
- GLP defines the conditions under which studies are
 - Planned
 - Performed
 - Recorded
 - Reported

- Archived
- Monitored
- The importance of Traceability and Auditability of studies is also underlined in the OECD GLP Principles.

THE OECD GUIDANCE DOCUMENTS

- The OECD has produced a number of documents concerning GLP.
- The first and the BASIC document is the “OECD PRINCIPLES OF GOOD LABORATORY PRACTICE” This is the document which provides the “regulatory standard”.
- However, the GLP group, conscious of the fact that regulatory texts often require further explanation to render them pragmatic, has promoted the publication of a number of explanatory texts to assist in the implementation of GLP Principles. The following table provides the names of the 15 publications with a brief summary of the intent of each.

#	Title	Summary
1.	OECD Principles on Good Laboratory Practice	<p>The basic regulatory text. The Principles of GLP as agreed by the member states through the MAD.</p> <p>Defines the conditions under which studies are</p> <ul style="list-style-type: none">– Planned– Performed– Recorded– Reported– Archived– Monitored <p>Provides the responsibilities of all the actors in a GLP study.</p>
2.	Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice	<p>To facilitate the mutual acceptance of test data generated for submission to Regulatory Authorities of OECD Member countries, harmonization of the procedures adopted to monitor good laboratory practice compliance, as well as comparability of their quality and rigour, are essential. The aim of this document is to provide detailed practical guidance to OECD Member countries on the structure, mechanisms and procedures they should adopt when establishing national Good Laboratory Practice compliance monitoring programmes so that these programmes may be internationally acceptable.</p> <p>It is recognized that Member countries will adopt GLP Principles and establish compliance monitoring procedures according to national legal and administrative practices, and according to priorities they give to, e.g., the scope of initial and subsequent coverage concerning categories of chemicals and types of testing. Since Member countries may establish more than one Good Laboratory Practice Monitoring Authority due to their legal framework for chemicals control, more than one Good Laboratory Practice Compliance Programme may be established.</p>

- 3. Revised Guidance for the Conduct of Laboratory Inspections and Study Audit**

The purpose of this document is to provide guidance for the conduct of Test Facility Inspections and Study Audits which would be mutually acceptable to OECD Member countries. It is principally concerned with Test Facility Inspections, an activity which occupies much of the time of GLP Inspectors. A Test Facility Inspection will usually include a Study Audit or “review” as a part of the inspection, but Study Audits will also have to be conducted from time to time at the request, for example, of a Regulatory Authority.

Test Facility Inspections are conducted to determine the degree of conformity of test facilities and studies with GLP Principles and to determine the integrity of data to assure that resulting data are of adequate quality for assessment and decision-making by national Regulatory Authorities. They result in reports which describe the degree of adherence of a test facility to the GLP Principles. Test Facility Inspections should be conducted on a regular, routine basis to establish and maintain records of the GLP compliance status of test facilities.
- 4. Quality Assurance and GLP (revised 1999)**

The OECD Principles of GLP have been in force for over fifteen years (see No.1 in this OECD Series on Good Laboratory Practice and Compliance Monitoring, as revised in 1997). Valuable experience has been gained at test facilities where these principles have been applied, as well as by governmental bodies monitoring for compliance. In light of this experience, some additional guidance can be given on the role and operation of quality assurance programmes in test facilities.
- 5. Compliance of Laboratory Suppliers with GLP Principles (revised 1999)**

Provides guidance about the requirements of GLP with respect to suppliers of resources used during GLP studies.

6. The Application of the GLP Principles to Field Studies (revised 1999)

The GLP Principles are intended to cover a broad range of commercial chemical products including pesticides, pharmaceuticals, cosmetics, veterinary drugs as well as food additives, feed additives and industrial chemicals. Most experience in GLP compliance monitoring by the national monitoring authorities in OECD Member countries has been gained in areas related to (non-clinical) toxicological testing. This is because these studies were traditionally deemed of greatest importance from a human health standpoint, and early identified laboratory problems primarily involved toxicological testing. Many established compliance monitoring procedures of the OECD Member countries were thus developed from experience gained in the inspection of toxicology laboratories.

Compliance monitoring procedures for laboratories performing ecotoxicological studies are also relatively well developed. The area of field studies with pesticides or veterinary drugs, such as residue, metabolism, and ecological studies, presents a substantial challenge to GLP monitoring authorities and experimental testing facilities in that study plans, conditions, methods, techniques, and findings differ significantly from those traditionally associated with toxicological testing, as well as most laboratory-based ecotoxicological testing.

7. The Application of the GLP Principles to Short-Term Studies (revised 1999)

The OECD Principles of GLP are general and not specific to any particular type of test or testing discipline. The initial experience in OECD Member countries in compliance monitoring has been primarily in long-term toxicity studies. Although subject to the OECD Principles of GLP, short-term studies present special concerns to management and compliance monitoring authorities based upon the existence of particular procedures and techniques.

The Revised Principles of GLP define a short-term study as “a study of short duration with widely used, routine techniques”. Short-term biological studies include acute toxicity studies, some mutagenicity studies, and acute ecotoxicological studies. Physical-chemical studies are those studies, tests or measurements which are of a short duration (typically not more than one working week), employ widely-used techniques (e.g. OECD Test Guidelines) and yield easily repeatable results, often expressed by simple numerical values or verbal expressions.

Typical physical-chemical studies include but are not limited to chemical characterization studies, melting point, vapour pressure, partition coefficient, explosive properties and other similar studies for which test guidelines exist. However, the regulatory agencies/receiving authorities in Member countries will specify which of these tests should be submitted to them and which should be conducted under the Principles of GLP.

8. The Role and Responsibilities of the Study Director in GLP Studies (revised 1999)

The study director represents the single point of study control with ultimate responsibility for the overall scientific conduct of the study. This is the prime role of the study director, and all duties and responsibilities as outlined in the GLP Principles stem from it. Experience has shown that unless responsibility for the proper conduct of a study is assigned to one person, there is a potential for personnel to receive conflicting instructions, which can result in poor implementation of the study plan. There can be only one study director for a study at any given time. Although some of the duties of the study director can be delegated, as in the case of a subcontracted study, the ultimate responsibility of the study director as the single central point of control cannot.

9. Guidance for the Preparation of GLP Inspection Reports

One of the goals of the work of the OECD Panel on Good Laboratory Practice is to facilitate the sharing of information from GLP compliance monitoring programmes conducted by Member countries. This goal requires more than the promulgation of enforceable principles of GLP and the conduct of an inspection programme by the national monitoring authority. It is also necessary to have the reports of the inspections prepared in a useful and consistent manner. The Guidance for the Preparation of GLP Inspection Reports developed by the Panel on GLP set forth below suggests elements and/or concepts that can contribute to a useful report of a GLP inspection and study audit. It may be used by Member countries as a component of their compliance monitoring programme.

10. **The Application of the Principles of GLP to Computerized Systems (1995)** Throughout recent years there has been an increase in the use of computerized systems by test facilities undertaking health and environmental safety testing. These computerized systems may be involved with the direct or indirect capture of data, processing, reporting and storage of data, and increasingly as an integral part of automated equipment. Where these computerized systems are associated with the conduct of studies intended for regulatory purposes, it is essential that they are developed, validated, operated and maintained in accordance with the OECD Principles of Good Laboratory Practice (GLP).
11. **The Role and Responsibility of the Sponsor in the Application of the Principles of GLP** Although the revised Principles of Good Laboratory Practice only explicitly assign a few responsibilities to the sponsor of a study, the sponsor has other implicit responsibilities. These arise from the fact that the sponsor is often the party who initiates one or more studies and directly submits the results thereof to regulatory authorities. The sponsor must therefore assume an active role in confirming that all non-clinical health and environmental safety studies were conducted in compliance with GLP. Sponsors cannot rely solely on the assurances of test facilities they may have contracted to arrange or perform such studies. The guidance given in this document attempts to outline both the explicit and implicit responsibilities of a sponsor necessary to fulfil his obligations
12. **Requesting and Carrying Out Inspections and Study Audits in Another Country** In the 1989 Council Decision-Recommendation on Compliance with the Principles of Good Laboratory Practice (C(89)87/Final), Member countries decided that, for purposes of the recognition of the assurance by another Member country that test data have been generated in accordance with GLP Principles countries “shall implement procedures whereby, where good reason exists, information concerning GLP compliance of a test facility (including information focusing on a particular study) within their jurisdiction can be sought by another Member country.” It is understood that such procedures should only be applied in exceptional circumstances.
- The Working Group on Good Laboratory Practices proposed clarification of this decision based on the Revised OECD Principles of GLP and recommended the procedures set out in this document. This clarification was considered necessary, since it was recognized that some test facilities have test sites located under the jurisdiction of another country.

These facilities or sites may not necessarily be part of the GLP compliance monitoring programme of the country of location, although many Member countries consider this desirable and useful. The Working Group agreed, that the use of the term “test facility” in the 1989 Council Act encompassed both “test facility” and “test site” as defined in the Revised OECD Principles of GLP. Therefore any Member country can request an inspection/study audit from both test facilities and test sites located in another country. This request could concern any organisation associated with regulated GLP studies, whether these be main test facilities or test sites (dependent or independent of the test facility) which carry out phases of a study such as chemical analysis, histopathology or field studies.

- 13. The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies** Provides guidance relative to the responsibilities of personnel running GLP studies when activities are conducted at two or more sites. In particular it describes the responsibilities and the relationships between the Study Director at the test facility and the Principal Investigators at the different test sites. It also discusses the role of Quality Assurance personnel at the different facility/sites. Recommendations are provided relating to the reporting structure between the various actors
- 14. The Application of the Principles of GLP to *in vitro* Studies** This Advisory Document of the Working Group on Good Laboratory Practice was developed in 2003 and 2004 with the assistance of experts in *in vitro* testing. This area of non-clinical safety testing is especially important in light of animal welfare concerns. The document should be considered together with the OECD Principles of GLP (No. 1 in the series) and the Consensus Document on the Application of the Principles of GLP to Short-Term Studies (No. 7 in the series.)
- 15. Establishment and Control of Archives that Operate in Compliance with the Principles of GLP** The archiving of records and materials generated during the course of a non-clinical health or environmental safety study is an important aspect of compliance with the Principles of Good Laboratory Practice (GLP). The maintenance of the raw data associated with a specific study and the specimens generated from that study are the only means that can be used to reconstruct the study, enabling the information produced in the final report to be verified and the compliance with GLP of a specific study to be confirmed. The purpose of the guidance contained in this document is to assist in conforming to the requirements of the OECD Principles of Good Laboratory Practice as they relate to archiving.



OECD & GLP Activities

“International”

GLP of the OECD

Appendix 1:1

Instructor’s notes

The acronym OECD means : Organisation for Economic Cooperation & Development.

The OECD has 30 members, including most of the major economic countries of the world.



OECD & GLP Activities

Key Dates

- 1979 : FDA GLP Regulations (revised 1987)
- 1981 : OECD GLP Principles (revised 1998)
- 1983 : EPA GLP Regulations
- 1986 : EU GLP Directive (the OECD Principles)

- At least 6 different Japanese GLP Regulations
- Etc.....

Appendix 1:2

Instructor’s notes

In 1976 the FDA published a draft regulation on GLP and requested comment from interested parties.

After the consultation period, the final regulation was published in 1978.

This came into force in 1979.

It is an American regulation, but had a wide impact world-wide because non-US companies wishing to register medicines in the USA now had to perform safety studies in compliance with FDA GLP.

Remind participants that at that time, about 30% of the world’s pharmaceutical trade occurred in the USA; it was (and still is) a market that cannot be ignored!

Subsequently, many countries introduced their own GLP regulations.

The OECD produced GLP Principles in 1981. These regulations have now become the international standard in the domain.

The OECD GLP Principles are the basis for this GLP course.



OECD & GLP Activities

What is the OECD?

- A group of 30 member countries committed to democratic governance and market economy
- Active relationships with 70 other non-member countries and with NGOs
- Produces internationally agreed instruments, decisions and agreements in areas where multilateral agreements are needed
- Dialogue, consensus & peer review are at the heart of the OECD

Appendix 1:3



OECD & GLP Activities

How does the OECD work?

- Governing body made up of Representatives of member countries
- It functions as an international agency, state representatives have ambassador status
- The Governing body provides guidance for the work of the OECD committees
- In the case of GLP, the activities are promoted and supervised by the OECD Working Group on GLP

Appendix 1:4



OECD & GLP Activities

The OECD GLP Principles

- Are approved by all 30 member states
- This is the *only* GLP guidance document that has achieved international agreement
- The OECD GLP Principles are, *ipso facto*, international regulations
- Member states have signed an accord – *the Mutual Acceptance of Data* (MAD) agreement – to accept the validity of study data generated in compliance with OECD GLP Principles
- OECD GLP promotes the acceptance of data across international frontiers

Appendix 1:5

Instructor's notes

Some countries (for example all European Union countries) have incorporated the OECD GLP Principles into their own National legislation. So the GLP Principles become legally binding.



OECD & GLP Activities

The OECD Working Group on GLP

- Comprises the Heads of all national / monitoring authorities
- Meets regularly to plan OECD GLP activities
- Verifies the implementation of GLP in member states
- Promotes training courses for GLP inspectors and future inspectors
- Promotes harmonisation of inspections in member states through joint inspections

Appendix 1:6

Instructor's notes

The GLP group of the OECD promotes the GLP activities of the OECD across national frontiers.



OECD & GLP Activities

The OECD GLP Publications

- The OECD has published 15 GLP documents covering:
 - The Principles of GLP
 - Guidance documents for inspectors on how to perform their tasks
 - Guidance on reporting inspection results between OECD members
 - Guidance documents on how to interpret the GLP Principles

Appendix 1:7

Instructor's notes

The OECD has produced a number of documents concerning GLP.

The first and the BASIC document is the "OECD PRINCIPLES OF GOOD LABORATORY PRACTICE" This is the document which provides the "regulations".

However, the GLP group, conscious of the fact that regulatory texts often require further explanation to render them pragmatic, has promoted the publication of a number of explanatory texts to assist in the implementation of GLP Principles. The list in the next 3 slides provides the names of the 15 publications. In the text accompanying this presentation you can find a brief summary of each.

In red on these slides are the publications that figure in this training course.



OECD & GLP Activities

The OECD GLP Publications

The full 15 OECD GLP publications are:

1. OECD Principles on Good Laboratory Practice
2. Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice
3. Revised Guidance for the Conduct of Laboratory Inspections and Study Audit
4. Quality Assurance and GLP

Appendix 1:8

***OECD & GLP Activities*****The OECD GLP Publications**

5. Compliance of Laboratory Suppliers with GLP Principles
6. The Application of GLP Principles to Field Studies
7. The Application of GLP to Short-Term Studies
8. The Role and Responsibilities of the Study Director in GLP Studies

Appendix 1:9

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***OECD & GLP Activities*****The OECD GLP Publications**

9. Guidance for the Preparation of GLP Inspection Reports
10. The Application of the Principles of GLP to Computerised Systems
11. The Role and Responsibility of the Sponsor in the Application of the Principles of GLP
12. Requesting and Carrying Out Inspections and Study Audits in Another Country

Appendix 1:10

***OECD & GLP Activities*****The OECD GLP Publications**

13. The Application of GLP to the Organisation and Management of Multi-Site Studies
14. The Application of the Principles of GLP to in-vitro Studies
15. Establishment and Control of Archives that Operate in Compliance with the Principles of GLP

Appendix 1:11

***OECD & GLP Activities***

GLP
promotes
Quality and Validity
of test data

Appendix 1:12

Instructor's notes

GLP is a regulation covering the quality management of non-clinical safety studies.

The aim of the regulation is to encourage scientists to organize and perform their studies in a way which promotes the quality and validity of the test data.

 OECD & GLP Activities
GLP Principles
<p>MAIN GOAL: To help scientists obtain results which are:</p> <ul style="list-style-type: none"> • Reliable • Repeatable • Auditable • Recognized by scientists worldwide
<small>Appendix 1:13</small>

Instructor's notes

Studies that are GLP compliant promote reliability of test data because the study staff must carefully document any deviations from fixed plans and because the GLP organization encourages the scientist to document all experimental variables.

GLP studies must be fully documented (methods, procedures, deviations), which means that they can be accurately repeated at any time in the future.

The full documentation of the studies, from planning activities right through to the production of reports, means that all the activities of the study are traceable and therefore the study may be audited by third parties.

Complete documentation gives the study full traceability and solid credibility.

Since GLP is an internationally accepted standard for the organization of studies, performing such experiments to GLP promotes the acceptance and recognition of the study results world-wide.

 OECD & GLP Activities
GLP Principles
<ul style="list-style-type: none"> • The purpose is not to assess the intrinsic scientific value of a study • GLP principles are a set of organizational requirements
<small>Appendix 1:14</small>

Instructor's notes

Repeat the important difference between the "science" of a study and the "organization" of a study.

GLP does not tell scientists what tests to perform, or what the scientific contents of a study plan (protocol) should be. For some studies, there are other guidelines for this aspect of research (scientific guidelines).

What GLP requires is that the scientists responsible for the organization of studies implement clear structures, responsibilities and procedures in compliance with GLP so that the test data are more reliable.

 OECD & GLP Activities
<p>GLP Aim</p> <p>To make the incidence of</p> <p>False Negatives</p> <p>more obvious</p> <p>(e.g. Results demonstrating the non-toxicity of a toxic substance)</p>
<small>Appendix 1:15</small>

Instructor's notes

GLP helps scientists reduce the number of false negatives from their studies because the studies are standardized where they can be and because the variables are well documented.

A false negative for a toxicity study is a set of results that falsely makes the scientist believe that a test item is not toxic when in reality it is toxic.

Taken to its extreme, this could be dangerous if the test item (believed wrongly to be inoffensive) is administered to man in a clinical trial. However, such a situation rarely occurs because there are many studies to perform before getting to man and the chances of them all turning in false negative results is not great. BUT all false negative results are costly, time consuming and present ethical problems (animals used to no good purpose) and should, therefore, be avoided.

 OECD & GLP Activities
<p>GLP Aim</p> <p>To make the incidence of</p> <p>False Positives</p> <p>more obvious</p> <p>(e.g. Results demonstrating the toxicity of a non-toxic substance)</p>
<small>Appendix 1:16</small>

Instructor's notes

In the same way that GLP helps reduce the incidence of false negatives, GLP also helps scientists avoid false positives.

In the case of a non-clinical safety study, these are results which wrongly lead the scientists to believe that their test item is toxic, when it really is not.

In this case, the test item is likely to be discarded, i.e. excluded as a candidate medicine. The test item might well be a compound which could be a useful addition in the fight against disease, but because of wrong interpretation, the compound is eliminated and never reaches the patients that it might have been able to help.

 OECD & GLP Activities
<p>GLP Aim</p> <p>Promote mutual recognition of study data across international frontiers</p>
<small>Appendix 1:17</small>

Instructor's notes

GLP also promotes international recognition of study data.

When studies are performed to OECD GLP Principles, 30 countries of the world must recognize that the data have been generated under acceptable organizational standards. Even non-OECD member states are willing to accept the reliability of data resulting from GLP compliant studies.

So, provided that the scientific aspects of the studies are reasonable, the data will be accepted as reliable and the studies as valid.

For the purposes of the registration of studies in foreign countries, this is a fundamental advance over the time prior to GLP where many countries insisted that the studies from a foreign state be repeated in their own country because the confidence in the original data was very limited.

 OECD & GLP Activities
<p>GLP</p> <ul style="list-style-type: none"> • Limit waste of resources • Ensure high quality of results • Ensure comparability of results • Promote mutual recognition of results <p>(Preamble to European Directive 87/18 EEC)</p>
<small>Appendix 1:18</small>

Instructor's notes

In the introduction to the European Directives on GLP, the four points mentioned in this slide are cited as the reasons for requiring GLP for the organization of safety studies.

Limiting waste of resources is particularly aimed at limiting the number of animals used in experiments.

Ensuring high quality of results concerns the validity of test data described above.

Ensuring comparability means that better information can be obtained in order to allow registration authorities to decide between candidate medicines.

International recognition of results refers to the fact that GLP is an internationally accepted set of regulations for the conduct of studies.



OECD & GLP Activities

GLP

**Managerial concept for the
organization of studies**

Appendix 1:19

Instructor's notes

As outlined already, GLP stipulates the conditions for the organization of studies, not the scientific content or value of studies.

As such, GLP is a quality system for the management of non-clinical studies.



OECD & GLP Activities

GLP

Defines conditions under which studies are

- Planned
- Performed
- Recorded
- Reported
- Archived
- Monitored

Appendix 1:20

Instructor's notes

This sentence is one of the key phrases which can be located in the introductory text to the OECD GLP Principles (upon which this course is based).

GLP defines the working environment under which studies are:

PLANNED.....which is why great emphasis is given to the study plan (protocol) and to possible planned changes throughout the study.

PERFORMED.....this refers to the Standard Operating Procedures (SOPs) which are a GLP requirement.

RECORDED.....the collection of raw data and the recording of deviations during the study are concerned here.

REPORTED.....one of the problems pre-GLP was that study reports did not always accurately reflect the study data, so assuring accuracy in the report has become an essential part of GLP.

ARCHIVED.....as studies may be audited many years after their completion, it is important that the study data, specimens, samples and reports are correctly stored after the study.

MONITORED.....monitoring by study staff, quality assurance personnel and national inspectors helps assure GLP compliance.

 OECD & GLP Activities
<p style="text-align: center;">Five Basic Points</p> <p>1. RESOURCES: Personnel, Facilities & Equipment</p> <p>2. CHARACTERIZATION : Test Article, Identification, Quality etc. Test System</p> <p>3. RULES : Protocols / Study Plans, Procedures</p> <p>4. RESULTS: Raw data, Final Report, Archives</p> <p>5. QUALITY ASSURANCE: Audit/Inspection - Training - Advice</p>
Appendix 1:21

Instructor's notes

This slide shows the fundamental points of GLP. They are arranged under five convenient headings.

Take time to discuss this slide with the participants, providing basic information about the meaning of each of the five items.

Explain that each of the sections is dealt with in the GLP Principles, but that the Principles are organized under a more complicated set of chapter headings.

You will find a brief summary of the importance of the 5 points in the introductory text in this training manual.

Each of the five points is presented in turn during the main part of the course.

APPENDIX 2: GLP AND MANAGEMENT

WHAT IS MANAGEMENT?

- The OECD has a definition for test facility management: “..the person(s) who has the authority and formal responsibility for the organization and functioning of the test facility according to these Principles of Good Laboratory Practice.” *In fine*, the test facility management is, therefore, responsible for the implementation and the maintenance of GLP within the laboratory for which he/she is responsible.
- However, it is understood that the test facility management is the “top” management and that some of the GLP obligations will be formally delegated to other senior managers. But it is also clear that the delegated GLP responsibilities or roles must be clearly identified and that the delegation must be formal and well documented.
- Documentation may be in the form of job descriptions (or other formal documents) signed by management. Some responsibilities and line functions will also be clear from the organizational chart. All these documents must be updated regularly to reflect the real situation within the laboratory.

MANAGEMENT RESPONSIBILITIES

The Following Responsibilities (in italics) are those identified in the OECD GLP Principles. Each quoted item is followed by a commentary

Each test facility management should ensure that these Principles of Good Laboratory Practice are complied with, in its test facility.

At a minimum it should:

- a) ensure that a statement exists which identifies the individual(s) within a test facility who fulfil the responsibilities of management as defined by these Principles of Good Laboratory Practice;*

A high level facility document must identify who is the Test Facility Manager. This is often done in a Quality Manual or other document that summarizes the policies of the laboratory.

As mentioned above, management will delegate responsibilities to senior personnel. All delegations must be documented. In particular, management must appoint study directors, QA personnel, Archivists etc. The documentation of such appointments may be global in the form of management policies and memos or even in SOPs. They may also be individual in the form of responsibilities for a defined time period. The documentation will also include job descriptions signed by management (and the person concerned).

Top management may delegate responsibilities to senior managers who will in turn delegate some responsibilities to lower level managers. In all cases delegation must be traceable through the facility's documents.

b) ensure that a sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the study;

It is difficult to judge whether or not sufficient personnel and resources are available, but management should be able to tell from the success rate of studies, the number of problems arising during research and the time required to complete tasks. During an inspection by the authorities this aspect of the facility's organization will be examined by the inspectors. Often they will start by examining the master schedule and the workload of key personnel such as the study director. They will also look at maintenance and calibration issues regarding facilities and equipment to see whether or not a GLP environment is truly in place.

c) ensure the maintenance of a record of the qualifications, training, experience and job description for each professional and technical individual;

This requirement concerns the systems that must be in place for the documentation of competencies, qualification and training of each person working to GLP. This is usually implemented by setting up systems to ensure the recording of CVs, job descriptions and training to technical and important administrative procedures. Top

management will delegate the maintenance of such systems to other senior staff once the system has been established. Maintenance of the systems, including the possibility of reconstructing specific historical situations, is essential as often the credibility and integrity of studies depends on these vital support documents.

d) ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions;

The function of each individual member of staff is provided in the job description. Training to very technical procedures is usually delegated to the discipline expert within the facility, though it may also be achieved by training provided by outside organizations. Whatever the situation it is important to record the training in detail and to provide information on the level of competency that the trainee has acquired. This may be achieved by providing a test at the end of the training period which evaluates the trainee's performance.

e) ensure that appropriate and technically valid standard operating procedures are established and followed, and approve all original and revised standard operating procedures;

Implementing a compliant management system for the standard operating procedures (SOPs) for a facility is an important task. (The section on SOPs in this training manual recounts the requirements of GLP in this area). Facility management will usually delegate this responsibility to a senior person often by creating a specialized document management group which may also include responsibility for the archives. The approval of SOPs by management may also be delegated to an appropriate level, as long as this delegation is formally documented. However, facility management will often maintain the role of signing the high level procedures.

f) ensure that there is a Quality Assurance Programme with designated personnel and assure that the quality assurance responsibility is being performed in accordance with these Principles of Good Laboratory Practice;

Facility management must appoint someone to be in charge of the facility's quality assurance programme (QAP – often simply called QA). The Head of QA will then fix GLP compliant procedures for his/her group with the approval of management.

The QA processes, including the types of inspections performed (with their specific frequencies), the way in which QA reports to study directors and management, and the involvement of QA in other activities like training and corrective/preventive actions will be stipulated in the QA SOPs. These SOPs are usually signed by test facility management to indicate agreement with the practices therein prescribed.

g) ensure that for each study an individual with the appropriate qualifications, training, and experience is designated by the management as the study director before the study is initiated. Replacement of a study director should be done according to established procedures, and should be documented.

The study director job is a key post. Management should choose people who have the required technical skills of course, but the study director also needs good organizational skills, good communication skills and often diplomacy too. All the non-technical components are particularly important in the multi-site situation where a complex network of study participants exists. The multi-site situation is explained in detail in another appendix to this manual. Sometimes the study director will need replacing. This could be because of extended leave or for unforeseen reasons. In either case management should document the replacement and keep the details in the facility records. Some organizations have a procedure for the automatic replacement of a study director in case of absence; this can be an SOP based procedure.

h) ensure, in the event of a multi-site study, that, if needed, a principal investigator is designated, who is appropriately trained, qualified and experienced to supervise the delegated phase(s) of the study. Replacement of a Principal Investigator should be done according to established procedures, and should be documented.

The Principal Investigator (PI) is responsible for a study phase (or more) on a separate test site. He/she reports to the study director for the study concerned and to site management otherwise. Again, because replacement is sometimes inevitable it is good practice to decide before the replacement how this will be achieved and documented. That is the sense behind this GLP requirement.

i) ensure documented approval of the study plan by the study director;

Management implements a system for the writing of experimental study plan, or protocol, which should be SOP-based and must include a step where the study director approves the study plan by signing and dating the document. The date represents the initiation of the study. The study director's signature signifies that he/she is willing to take on full responsibility for the conduct and the reporting of the study. The study director becomes the single point of control of the study from that point on.

j) ensure that the study director has made the approved study plan available to the quality assurance personnel;

Management implements an SOP-based system which requires the study director to provide the study plan to quality assurance. This act should be documented. QA uses the study plan to finalize their inspection and audit task during the study.

k) ensure the maintenance of an historical file of all Standard Operating Procedures;

Management must implement an SOP management system. This is often integrated into a wider system for the management of all documents. SOPs must be kept up to date and this may mean retiring some from use. Whenever retirement happens, and at each revision, the original versions must be kept; they are normally archived. The group of SOPs in use, all modified and retired SOPs is referred to as the historical file. With the historical file, usually comprising the archived originals, it should be possible to reconstruct completely the life cycle of each SOP, including when it came into use, when it was revised and when it was retired.

l) ensure that an individual is identified as responsible for the management of the archive(s);

An archivist must be named for each Test Facility/Site. In small laboratories, this person may not be employed full time for archive administration, he/she may perform some other tasks, like document or SOP management, but a person must be formally appointed by management, is habitually designated on the organization chart and must have a job description which includes the responsibility for the archives.

m) ensure the maintenance of a master schedule;

The master schedule is a document that compiles information necessary for tracking studies at a facility. It may also be used for assessing workload. There must be a single official master schedule and management frequently delegates the responsibility for maintaining this to a project management group (in large laboratories) or to an administrative department (in smaller laboratories). There is no rule as to who should be appointed for this task; it is up to management to choose a suitable unit.

n) ensure that test facility supplies meet requirements appropriate to their use in a study;

As part of ensuring adequate resources for the experimental work to be performed, management must ensure the proper provision of supplies. Supplies are very different depending upon the study concerned. In most facilities, major suppliers, like those providing animals, are regularly audited to ensure that quality management systems exist at the supplier site. It is of course in the interest of both parties that a “partnership” approach develops between the test facility and the supplier. Management should have an SOP which indicates how appropriate and adequate supplies are obtained by the facility.

o) ensure for a multi-site study that clear lines of communication exist between the study director, principal investigator(s), the quality assurance programme(s) and study personnel;

In the multi-site situation, rapid communications between the different actors is of great importance. It is good practice for the persons involved to verify that communications between them are functioning properly before embarking on research work together. Management should make sure that these lines of communication are open.

p) ensure that test and reference items are appropriately characterized;

Characterization of the test item and the test system is one of the five fundamental points dealt with in the main chapters of this manual. Characterization may be very simple and the characterization needed is study and test item dependent. An SOP

describing what should happen in each case is the best way of ensuring that some characterization does occur. There are no hard and fast rules about what appropriate characterization is, or who should perform this work, or when exactly it should be done.

q) establish procedures to ensure that computerized systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with these Principles of Good Laboratory Practice.

Computerized systems are used frequently in studies for various purposes; data capture, statistical analysis, planning steps etc. Some of these activities are crucial to GLP compliance, others less so. Management should decide which systems impact on GLP; these systems must be validated. Management usually appoints a person, or a team, to be responsible for validation work. There is a separate section on computer systems in an appendix to this manual.

When a phase(s) of a study is conducted at a test site, test site management (if appointed) will have the responsibilities as defined above with the following exceptions: g), i), j) and o).

There is an appendix in the manual that specifically deals with the multi-site situation.



Management

Management

Roles & Responsibilities

Appendix 2:1

Instructor's notes

This section presents the roles and responsibilities of management.



Management

Management



“Test facility management means the person(s) who has the authority and formal responsibility for the organisation and functioning of the test facility according to the Principles of Good Laboratory Practice.”

Appendix 2:2

Instructor's notes

Management is the person ultimately responsible for the organization of a facility or test site.

Obviously certain responsibilities of top management can be delegated to other “managers”, as no one person can possibly do everything on his/her own, but the overall responsibility of the way in which an institution is organized and functions stays with top management.

 Management
<ul style="list-style-type: none">● Management has the overall responsibility for ensuring that all documentation, procedures, supplies etc are in compliance with the Principles of GLP.● Management should ensure that a statement exists which identifies the individual(s) who fulfil the responsibilities of management
Appendix 2:3

Instructor's notes

As mentioned earlier, management responsibilities can be delegated. When this happens you should make sure that documents exist which clearly define what responsibilities are being delegated, to whom and for what period of time.

 Management
Responsibilities : General Management should ensure that: <ul style="list-style-type: none">● Test & reference items are appropriately characterised● Adequate facilities & qualified / trained personnel are available● Test facility supplies meet requirements appropriate to their use in a study● The master schedule is maintained
Appendix 2:4

Instructor's notes

The general responsibilities that management has for the correct functioning of a GLP test site or facility are summarized here. As you can see they are organizational responsibilities designed to ensure that all the fundamental points of GLP are implemented correctly.



Management

Responsibilities : Personnel

Management should ensure that:

- There are sufficient number of qualified personnel for the timely and proper conduct of the study
- Records of qualifications, professional experience and job descriptions are maintained for each professional & technical individual
- Personnel clearly understand the functions they are to perform and where necessary provide training
- The organisation chart is kept up to date

Appendix 2:5

Instructor's notes

Management has particular responsibilities regarding the personnel working for the laboratory and for all persons involved in performing a GLP study.

In many large organizations the responsibilities for assuring that proper records regarding personnel are kept up to date is delegated to a Human Resources department.

It is essential that people in this kind of support department are aware that the way they implement internal processes and conduct their work may have far reaching impact on the GLP status of the organization as a whole.



Management

Responsibilities : Personnel

Management should ensure that :

- A Study Director is appointed for each study
- There is a Quality Assurance Programme (QAP) with designated personnel
- The QAP operates in compliance with the Principles of GLP.
- An individual is identified as responsible for the management of the archive(s)

Appendix 2:6

Instructor's notes

Management appoints a person responsible for each study. This person is the study director.

GLP states that management must appoint an appropriately trained person to perform the QA tasks. This person acts as a link between the actors performing studies and the management of the test site / facility.

As we have already mentioned in the section on quality assurance, QA must be independent from the studies performed and must have direct access to management because it is the work of QA to keep management informed about how the test site/facility processes are performing.

GLP also mentions that management must appoint an archivist.



Management



Responsibilities : Personnel
Management should ensure that:

All personnel are aware of their responsibilities:

- Be knowledgeable in those parts of the Principles of GLP applicable to their involvement in the study
- Comply with the instructions given in SOPs and study plans which should be accessible to them.
- Document and communicate any deviations from these instructions to the Study Director and/or Principal Investigator

Appendix 2:7

Instructor's notes

Management is also responsible for putting into place systems which ensure that all personnel are aware of their roles, trained to perform their functions and cognisant of the way in which their work contributes to GLP compliance.



Management



Responsibilities : Personnel
Management should ensure that:

All personnel are aware of their responsibilities:

- Be responsible for the quality of their data.
- Be responsible for recording raw data promptly and accurately
- Exercise health precautions to minimise risk to themselves & to ensure integrity of the study.
- Communicate to the appropriate person any relevant known health condition that might affect the study.

Appendix 2:8

Instructor's notes

This slide continues the responsibilities of personnel that management must develop.



Management

Responsibilities : SOPs

Management should ensure that SOPs :

- Are appropriate
- Are technically valid
- Are followed by all relevant personnel
- Cover all standard procedures in the test facility
- Are available in an historical file (all SOPs traceable)



Appendix 2:9

Instructor's notes

Part of the management systems concerns the work instructions or Standard Operating Procedures (SOP). Management has the final responsibility of ensuring that such a system is implemented and functions correctly.



Management

Responsibilities : Study-based

Management should ensure that :

- One Study Director is appointed for each study before it starts.
- The Study Director has the appropriate qualifications, training and experience
- The Study Director is replaced if necessary (this can be done via a procedure – replacement must be documented).

Appendix 2:10

Instructor's notes

This slide and the next shows the responsibility of management concerning actual studies.

The primary responsibility is to appoint suitably qualified people to perform the studies, specifically the study director, who will take overall responsibility for the study.

 Management
Responsibilities : Study-based Management should ensure : <ul style="list-style-type: none">● Documented approval of the study plan by the Study Director● That the study director has made the approved study plan available to the Quality Assurance personnel.
Appendix 2:11

Instructor's notes

As you can see here, management must set up processes which guarantee that the study director provides information on time to other important actors in the study and particularly to quality assurance.

 Management
Responsibilities : Facilities Management should ensure that <ul style="list-style-type: none">● Facilities are adequate to accommodate the staff and functions required without risk of mix ups and contamination.● Facilities are designed to<ul style="list-style-type: none">➢ Allow for cleaning➢ Preclude cross contamination & mix ups➢ Permit for separation of operations
Appendix 2:12

Instructor's notes

Management must also provide sufficient physical resources for the study to be conducted correctly. GLP stipulates the special requirements regarding facilities as shown in this slide.



Management

Responsibilities : Equipment

Management should ensure that

- **Equipment is adequate for the proper conduct of the study.**
- **Equipment is:**
 - **Suitable**
 - **Calibrated**
 - **Maintained**
- **Equipment Use, Calibration and Maintenance is documented**

Appendix 2:13

Instructor's notes

Management must provide other physical resources so that the study may be conducted correctly. GLP stipulates the special requirements regarding equipment as shown in this slide.



Management

Responsibilities : Computerized systems

Management should :

- **Establish procedures to ensure that :**
 - **Computerised systems are suitable for the intended purposes**
 - **Are validated**
 - **Are operated and maintained in accordance with the Principles of GLP**



Appendix 2:14

Instructor's notes

Computers are considered as equipment like any other piece of apparatus. Management is therefore responsible for making sure that they are fit for use and that they operate in accordance with acceptable standards.

Validation assures that they are operating acceptably. Hence management has the responsibility of implementing processes to ensure that the systems are appropriately validated before use and operated correctly afterwards.

	<h2>Management</h2>
<p>Responsibilities : Multi-site studies</p> <p>Management should ensure that</p> <ul style="list-style-type: none"> ● A Principle Investigator (PI) is designated ● The PI is appropriately trained, qualified and experienced to supervise the delegated phase(s) of the study ● The replacement of the PI (if necessary) is done according to established procedures and is documented ● Clear lines of communication exist between the Study Director, PI, QA and study personnel 	
<p>Appendix 2:15</p>	

Instructor's notes

As studies are often conducted on several different sites, Management needs to organize the way in which different parts of the study will be performed.

Of primary concern is the appointment of necessary staff, including the people who will take responsibility for those parts of the study which are done on separate test sites. Management must also ensure that all the people involved at the different sites communicate between each other; so good communication processes are essential in this type of complex study organization.

There is a section in the manual which specifically deals with Multi-Site Studies.

	<h2>Management</h2>
<p>Responsibilities : Others</p> <p>Management should fix policies / procedures for:</p> <ul style="list-style-type: none"> ✓ Training of staff ✓ Health Surveillance ✓ Safety in the Test facility ✓ Receiving visitors to the Test facility ✓ Ensuring supplies of chemicals, equipments etc ✓ Equipment Maintenance ✓ Supplies of power, water etc ✓ Waste disposal ✓ Housekeeping 	
<p>Appendix 2:16</p>	

Instructor's notes

GLP itemises other areas where management must take responsibility. These are provided in this slide.

APPENDIX 3: GLP AND THE STUDY DIRECTOR

In the following text the citations *in italics* are from the OECD documents on “The role and responsibilities of the study director in GLP studies”.

THE ESSENTIAL ROLE OF THE STUDY DIRECTOR

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The OECD has a definition for study director: “..the individual responsible for the overall conduct of the nonclinical health and environment safety study”

The study director is the single point of control for all the studies he/she supervizes. This means that the study director has the final responsibility for the scientific conduct of the study; all the GLP responsibilities incumbent on the study director stem from this concept.

“Experience has shown that unless responsibility for the proper conduct of a study is assigned to one person, there is a potential for personnel to receive conflicting instructions, which can result in poor implementation of the study plan. There can be only one study director for a study at any given time. Although some of the duties of the study director can be delegated, as in the case of a subcontracted study, the ultimate responsibility of the study director as the single central point of control cannot.”

So, the study director has an **individual** responsibility; it is not a group or collegiate responsibility. This has important moral and even legal implications. The study director is responsible for all aspects of the study under his/her control including the organizational and GLP parts.

“...the study director serves to assure that the scientific, administrative and regulatory aspects of the study are controlled. The study director accomplishes this by coordinating the inputs of management, scientific/technical staff and the quality assurance programme.”

“In addition to a strong technical background, the coordinating role of the study director requires an individual with strengths in communication and problem solving and managerial skills.”

APPOINTMENT OF THE STUDY DIRECTOR

This is the responsibility of management. All appointments to this position should be documented; including replacements when this is necessary. There is no defined method for this documentation; it may be via an SOP, a management memo or other document. The record of appointments should, of, course be kept and management should have a policy document (or SOP) on how appointments will be handled.

Appointments should be made taking into consideration the workload of the appointee.

“When appointing a study director to a study, management should be aware of that person’s current or anticipated workloads. The master schedule, which includes information on the type and timing of studies allocated to each study director, can be used to assess the volume of work being performed by individuals within the testing facility and is a useful management tool when allocating studies”.

TRAINING OF THE STUDY DIRECTOR

Since the study director is responsible for both the scientific and the organizational aspects of the study, he/she should have education/training in both these aspects. For example, it is essential that study directors have training in GLP so that they can ensure compliance. All training must be documented. It is expected that training will be on-going with new training for new responsibilities such as taking directing new kinds of safety studies.

“Training may include work experience under the supervision of competent staff. Observation periods or work experience within each discipline involved in a study can provide a useful basic understanding of relevant practical aspects and scientific principles, and assist in the formation of communication links. Attendance at in-house and external seminars and courses, membership in professional societies and access to appropriate literature may allow study directors to maintain current awareness of developments within their scientific field. Professional development should be continuous and subject to periodic review.”

STUDY DIRECTOR RESPONSIBILITIES

As the study director has overall responsibility for the study, his/her tasks fall into three steps: what is done before the study starts, what is done during the study, how the study is reported upon completion.

Study initiation

The study director is normally involved with the planning of the study and with its design. However, even when these tasks are the responsibility of some other group, the study director assumes total responsibility for the study when he/she signs the study plan. This is the moment of study initiation.

“The study director should take responsibility for the study by dated signature of the study plan, at which stage the study plan becomes the official working document for that study (study initiation date). If appropriate, the study director should also ensure that the study plan has been signed by the sponsor and the management, if required by national programmes.”

Before beginning the experimental phases of study, the study director should make sure that:

- The study plan has been signed by other designated persons (this depends on local organization and sometimes national requirements; it often includes management and the sponsor)
- The study plan is sent to all the personnel that will use it, including the QA group
- The study director should not start the study if there are any doubts about the qualification or competence regarding the staff who will be conducting experiment.
- All necessary resources including supplies, test items and test systems have been made available by management.

During the Study

The study plan outlines the objectives and the design of the study. Normally it will include detailed study procedures; these are provided by the Test Facility SOPs. It is the study director who ensures that all aspects of the study plan and the relevant procedures are followed by staff.

The study director should remain in close contact with the study and carefully supervise its progress. All decisions relating to the conduct of the study, particularly any amendments to the study must be approved and documented by the study director.

“This is of particular importance following temporary absence from the study and can only be achieved by maintaining effective communication with all the scientific, technical and administrative personnel involved, and for a multi-site study with principal investigator(s). Of necessity, lines of communication should ensure that deviations from the study plan can be rapidly transmitted and that issues arising are documented.”

Part of the supervision of the study involves regular review of the data generated during the study. This is best achieved by the study director formally signing off data to demonstrate this review. For data recorded on paper this is easy to perform and record. For electronically recorded data a record should be kept either electronically or in another kind of document.

It is also part of the study director’s responsibilities to make certain that any computerized system with GLP impact has been properly validated before being used on a study.

At Study Completion

The study director is responsible for the study report. This covers the scientific content of the report and the interpretation of the study data and the GLP compliance of the report and associated study activities.

The study director must add a GLP Compliance Statement to the report indicating the extent of GLP compliance reached by the study he/she has been responsible for.

“If the study director is satisfied that the report is a complete, true and accurate representation of the study and its results, then and only then, should the study director sign and date the final report to indicate acceptance of responsibility for the validity of the data. The extent of compliance with the GLP Principles should be indicated. He should also assure himself that there is a QA statement and that any deviations from the study plan have been noted.”

Amendments and Deviations

The study director is responsible for amending the plan as necessary during the course of the study. **An amendment is a planned** change to the study design. It must be formalized, signed and dated by the study director, and provided to all the personnel who received the original study plan.

Deviations are not planned; they are unexpected events which occur during the study. As they are not planned, they cannot be incorporated into amendments and provided to staff before the event. But they must be documented and acknowledged by the study director, as soon as possible after the event. This acknowledgement becomes part of the

study data. The impact of the deviation should be evaluated and this should be reported in the final study report by the study director.

Archives

When a study has been completed, or terminated before the planned end point, the study plan and the report and all the study data, specimens, samples and files relating to the study should be transferred to the facility archives. The transfer should be formalized and the archivist, once in possession of the study material becomes responsible for it from that point on.

Interface with the Study

For all studies, but particularly for those which take place at more than one site (multi-site studies), good communication between the study director and the various actors in the study is of great importance. Although the study director has overall responsibility for the conduct of the study, he/she cannot be ubiquitous and must rely on his/her personnel and delegates.

“The study director has the overall responsibility for the conduct of a study. The term responsibility for the overall conduct of the study and for its final report may be interpreted in a broad sense for those studies where the study director may be geographically remote from parts of the actual experimental work. With multiple levels of management, study personnel and QA staff, it is critical that there are clear lines of authority and communication, and assigned responsibilities, so that the study director can effectively carry out his GLP responsibilities.”

The main actors in a study will include:

- The technical study staff.
- His /her management.
- The sponsor and the sponsor’s monitor (especially for studies conducted at a CRO).
- The quality assurance team(s) (both Lead QA and Site QA in a multi-site study).
- The principal investigator (PI) in a multi-site study.

The OECD document, “The role and responsibilities of the study director in GLP studies” draws particular attention to the need for good communication between the study director and quality assurance.

“Communication between the study director and QA is required at all stages of the study.

This communication may involve:

- an active involvement with QA, for example, review of study plans in a timely manner, involvement in the review of new and revised Standard Operating Procedures, attendance of QA personnel at study initiation meetings and in resolving potential problems related to GLP.*
- responding to inspection and audit reports promptly, indicating corrective action and, if necessary, liaising with QA staff and scientific and technical personnel to facilitate responses to inspection/audit findings.”*

Naturally, all communications should be documented.



The Study Director

***Study Director
Role and Responsibilities***

Appendix 3:1

Instructor's notes

This presentation details the roles & responsibilities of the study director.



The Study Director

GLP Definition

- The individual responsible for the overall conduct of the non-clinical study
- The Study Director is the single point of study control, even when there are other contributing scientists to the study
- The Study Director has responsibility both for the science of the study and for the GLP aspects (organisational parts) of the study

Appendix 3:2

Instructor's notes

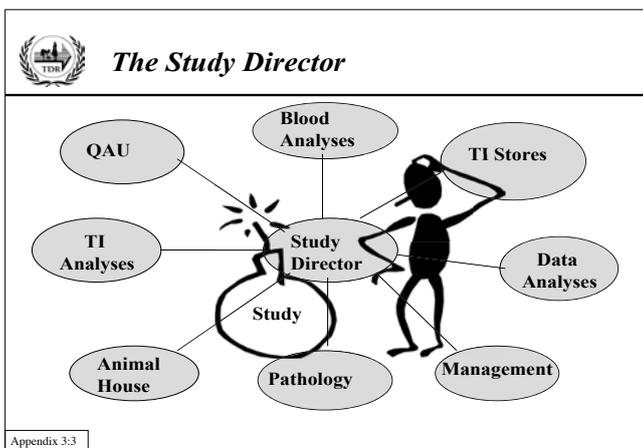
The study director has overall responsibility for the study: the planning, conduct and interpretation of the results.

This is the case even if there are other contributing scientists to the study.

The study director is the single point of control for the study.

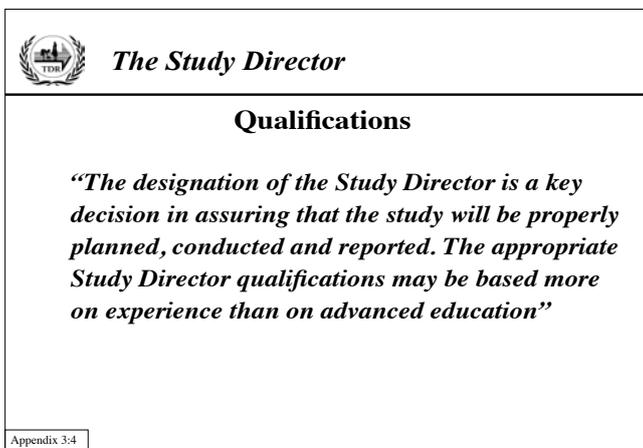
He / she is responsible as a scientist for the hypothesis and for testing the hypothesis through the experimental work; the study director is, therefore, responsible for the study design.

He/she is also responsible as an organizer for the conduct of the study; respecting the GLP Principles is a recognized way of reaching excellent study organization.

**Instructor's notes**

The study director is pictured here in the midst of the various activities of the study, or the various persons with which he/she will interact throughout the study.

This is what is meant by the single point of control for the study.

**Instructor's notes**

This slide is a quote from the OECD document on Short-Term Studies. It brings to our attention the fact that the qualifications of the study director should be matched to the kind of study being performed.

Obviously for a short term study (for example a melting point test or a test on explosive properties of test items) the study director profile would be quite different from that of a long term animal study (oncogenicity or reproductive toxicology).

Discuss with the participants what educational profile might be required to perform the kind of studies they are interested in.



The Study Director

GLP defines conditions under which studies are

Planned

Performed

Recorded

Reported

Archived

Monitored

The Study Director is responsible for organising these conditions for his/her studies

Appendix 3:5

Instructor's notes

This sentence is one of the key phrases which can be located in the introductory text to the OECD GLP Principles (upon which this course is based).

GLP defines the working environment under which studies are:

PLANNED.....which is why great emphasis is given to the study plan (protocol) and to possible planned changes throughout the study.

PERFORMED.....this refers to the Standard Operating Procedures (SOPs) which are a GLP requirement.

RECORDED.....the collection of raw data and the recording of deviations during the study are concerned here.

REPORTED.....one of the problems pre-GLP was that study reports did not always accurately reflect the study data, so assuring accuracy in the report has become an essential part of GLP.

ARCHIVED.....as studies may be audited many years after their completion, it is important that the study data, specimens, samples and reports are correctly stored after the study.

MONITORED.....monitoring by study staff, quality assurance personnel and national inspectors helps assure GLP compliance.

The study director, being responsible for the scientific and the GLP nature of the study is, therefore, responsible for assuring that the points mentioned above are fully functional during the study.



The Study Director

Qualifications

- Selected by management
- Study dependent :
 - One study = One Study Director (SD)
 - One study = One Study Plan approved by SD
 - One study = One Report written by SD
- Qualifications of SD should be documented
- Strong technical background
- Leadership & communication skills
- Editorial capabilities

Appendix 3:6

Instructor's notes

The qualifications required by a study director depend to a great extent upon the nature of the study for which he/she is asked to take responsibility.

A well experienced technician is often appointed as a study director for short term studies, both biological and physico-chemical, whereas a post graduate scientist may well be appointed for studies of greater complexity.



The Study Director

Appointment

- Management appoints the Study Director for each study
- Appointments should be documented
- Appointment based upon experience and qualifications
- Appointment also takes into consideration workload from other responsibilities

Appendix 3:7

Instructor's notes

One of the points that will always be considered by monitoring authorities during an inspection is the workload of study directors. In some organizations study directors have so many studies under their responsibility that it is hard to see how they can have a “hands on” approach with all of them.

It is essential for study directors to have an intimate knowledge of how each of their studies is progressing.



The Study Director

Replacement of Study Director

- Not defined in GLP – Management responsibility
- Replacement should be documented
- Replacement may be defined by a standard document (SOP) in the test facility
- Replacement may be temporary, e.g. holiday, sickness, congress
- The returning SD should find out what deviations or amendments occurred during absence.

Appendix 3:8

Instructor's notes

Some organizations with many capable staff arrange for a list of replacement (or deputy) study directors to be drawn up and the replacement automatically takes over a study in the absence of the original study director.

Smaller organizations with few study directors need to document the choice of each replacement on an *ad hoc* basis whenever the study director is absent.

	<i>The Study Director</i>
Interface with study personnel	
<ul style="list-style-type: none"> • There must be clear lines of authority from top management through SD to all study staff • Assigned responsibilities known by everyone • Good communication between all parties. <i>This is particularly essential in the multi-site situation</i> 	
<small>Appendix 3:9</small>	

Instructor's notes

Management appoints the study director on the basis of the qualifications and experience of the person, and the type of study that is to be conducted. The study director also needs good communication and organizational skills.

The appointment must be before the study director approves the study plan and this appointment should be documented.

	<i>The Study Director</i>
Interface with Quality Assurance	
<p>The Study Director should:</p> <ul style="list-style-type: none"> • Ensure that the study plan has been reviewed by QA • Involve QA in the study initiation meeting • Request QA review of new SOPs • Involve QA in continuous improvement 	
<small>Appendix 3:10</small>	

Instructor's notes

The relationship between the study director and the QA personnel should be one of partnership, not of conflict.

Both have important roles to play during the study. QA personnel are independent of study staff which allows them to be free from conflicts of interest when inspecting or auditing. However, all staff in a facility, whatever their role, want each study to be successfully performed and each contribute in their different ways; this is why good relationships between all actors is imperative.

The best organizations are those that encourage open and guilt-free exchange of opinion between responsible persons.



The Study Director

Interface with Quality Assurance

The Study Director should:

- Respond quickly and positively to QA audit/inspection reports
 - Indicate corrective actions
 - Liaise with QA and technical staff to implement preventive and corrective actions

Appendix 3:11

Instructor's notes

In order to reach GLP compliance, and to progress generally, those parts of the organization that are observed to be functioning sub-optimally should be improved.

Quality assurance helps to identify the failures and non-conformities. But it is the responsibility of management and the study director to put things right. So, QA findings should be addressed completely and quickly. Often QA can contribute by suggesting ways in which the failures can be addressed, hence the need for open and constructive relationships between management and QA.



The Study Director

Responsibilities

Before the study starts, the Study Director should:

- Define the study objectives
- Ensure that the study plan has been reviewed by QA
- Approve the study plan : sign and date
- Approve any amendments to study plan : sign and date
- Obtain sponsor signature of study plan if necessary
- Make sure that all persons requiring the study plan do in fact receive it

Appendix 3:12

Instructor's notes

Upon appointment by management to be the director of a study, the study director must approve the study design as stipulated in the study plan. Usually he/she is involved in the writing of the study plan.

When the study plan is written it must be independently reviewed. This is usually the responsibility of QA. It is preferable to conduct the review at the draft stage (before study director signature) so that any modifications can be made without needing an amendment. When the study director signs the study plan this indicates that he takes full responsibility for the scientific and the organizational aspects of the study, including compliance to GLP.

	<i>The Study Director</i>
Responsibilities	
<p>Before the study starts, the Study Director should :</p> <ul style="list-style-type: none"> • Make sure that QAU gets a copy of the study plan • Ensure that resources are available for the study <ul style="list-style-type: none"> • facilities, equipment, trained personnel • Ensure that all relevant SOPs for the study are available to personnel 	
<small>Appendix 3:13</small>	

Instructor's notes

QA must receive a copy of the study plan before the study starts.

The study director must also make sure that all necessary SOPs are in place and that his/her staff know how to use them.

	<i>The Study Director</i>
Responsibilities	
<p>During the study, the Study Director should :</p> <ul style="list-style-type: none"> • Make sure that the study plan and the procedures are followed • Ensure that data are collected properly • Ensure that any deviations are fully documented • Assess the significance of any deviations • Ensure that the study is appropriately monitored 	
<small>Appendix 3:14</small>	

Instructor's notes

The study has been carefully planned by the study director. It is pointless doing careful planning if the plan is not followed scrupulously. The role of the study director and his/her staff is to ensure that the study is conducted in compliance with the plan.

Collecting study data is always a crucial part of the study. The data collected represent the fruits of the study: the study is performed to generate data. So, special attention must always be given to the collection of data and to make sure that data is collected accurately and is not lost. This is a principal role of the study director who should organize his/her team with this goal in mind.



The Study Director

Responsibilities

At the end of the study, the Study Director should :

- Prepare a report on the study, its results, and conclusions
- Make sure that the report is a complete and accurate representation of the study data and sign the study report
- Write a GLP compliance statement
- Make sure that the study data, other supporting material and the report are properly archived

Appendix 3:15

Instructor's notes

The study report must accurately reflect the study data. This does not mean that all the data from a study need to be included in the report. It does mean that any summaries made should be accurate interpretations of the body of data summarized.

The study director will include a GLP compliance statement in the report. This statement is a declaration with moral and legal connotations and should not be taken lightly. The study director must know if there were any parts of the study which were not GLP compliant so that this can be mentioned in the report.



The Study Director

Amendments & Deviations

Amendment:

An intended, planned change in the study design after the study has started

- Documented and maintained with the study plan
- The reason and the effective date of the planned change must be recorded in the amendment
- Amendments should be uniquely identified

Appendix 3:16

Instructor's notes

There is often confusion between what is an amendment, and what is a deviation. These two slides define the two concepts.

Remember that amendments, because they are planned events, are consigned to a study plan amendment, signed by the study director before coming into force. Amendments are "before the event".



The Study Director

Amendments & Deviations

Deviation:

An unintended, unplanned event during the course of the study

- Documented in the raw data
- Often written by study personnel, but acknowledged, signed and explained by Study Director rapidly after the deviation
- Impact of deviation assessed by Study Director
- Mentioned and discussed in final report

Appendix 3:17

Instructor's notes

Deviations are written down as study data as they occur (or very rapidly afterwards). So they cannot be consigned to an amendment. Deviations are “after the event”.



The Study Director

Multi-Site Studies

The Study Director retains responsibility of the whole of the study, including the part performed at a test site

- Ensure that selected test sites are acceptable
- Advise management concerning status of PI
- Approve study plan including parts to be conducted at test site and contributions from PI
- Approve all amendments
- Acknowledge all deviations
- Facilitate movement of materials (test item, samples, specimens) between test sites

Appendix 3:18

Instructor's notes

Remember that the following applies to multi-site studies:

1. The test facility is the main site, where the study director is
2. The test site is the subsidiary site where the principal investigator (PI) is
3. The study director remains responsible for the whole study, including those parts performed under the responsibility of the PI on the test site
4. Both the test facility and the test site (if GLP compliant) will have a QA function
5. One QA has to be appointed the lead QA. This is usually the QA at the test facility.
6. The test site QA reports to his/her test site management, PI, study director and to the lead QA
7. The study director should maintain regular communication with the PI and the lead QA
8. The study director should approve the details of the organization of his/her study at both the test facility and the test site
9. There may be one or more test sites



The Study Director

Multi-Site Studies

The Study Director retains responsibility of the whole of the study, including the part performed at a test site

- Ensure that the PI understands his/her role in the study
- Make sure that communications between all the actors are open and working (SD, PI, Site QA, Lead QA, Sponsor...)
- Make sure that the final report contains all contributions from study staff at all sites
- Make sure that the final report is provided to Lead QA for review
- Sign and date final report, incorporating GLP compliance statement

Appendix 3:19



The Study Director

Multi-Site Studies

The Study Director retains responsibility of the whole of the study, including the part performed at a test site

“When parts of a study are contracted out, the study director should have knowledge of the GLP compliance status of that facility. If a contract facility is not GLP compliant, the Study Director should indicate this in the final report.”

Appendix 3:20

Instructor's notes

Remember that some countries hold the study director legally responsible for the GLP statement in the report. Cases of heavy fines and even prison sentences for study directors that have written untrue GLP compliance statements are not uncommon in such countries.

Even if there is no national law, the moral responsibility for the conduct of a study and its GLP compliance are very heavy.



The Study Director

Legal status of the Study Director

By signing the study report, the Study Director assumes responsibility for:

- The conduct of the study according to the facilities rules as detailed in SOPs
- The GLP compliance of the study
- The accurate representation of the study data in the report
- Legal situation may be defined at a national level, depending on the country

Appendix 3:21

Instructor's notes

Remember that some countries hold the study director legally responsible for the GLP statement in the report. Cases of heavy fines and even prison sentences for study directors that have written untrue GLP compliance statements are not uncommon in such countries.

Even if there is no national law, the moral responsibility for the conduct of a study and its GLP compliance are very heavy.

APPENDIX 4: GLP AND THE MULTI-SITE STUDIES

Direct quotations from the OECD guidance document are in “quotation marks and italics”.

More and more individual non-clinical health and environmental safety studies are being conducted at more than one site. Companies frequently use facilities which specialize in different activities that may well be located far apart, even in different countries. It is because of this tendency that the OECD decided that a guidance document on the organizational aspects of multi-site studies was necessary.

As the guidance document states: “A study can be a “multi-site” study for a variety of reasons. A single site that undertakes a study may not have the technical expertise or capability to perform a particular task that is needed, so this work is performed at another site. A sponsor who has placed a study at a contract research organization may request that certain study activities, such as bioanalysis, be contracted out to a specified laboratory or the sponsor may request that specimens be returned to them for analysis.”

The aim of the OECD guidance document on multi-site situations is to provide recommendations for the organization of such studies. The topics covered include the planning, performance, monitoring, recording, reporting and archiving of multi-site studies. The OECD puts it in these words: *“The planning, performance, monitoring, recording, reporting and archiving of a multi-site study present a number of potential problems that should be addressed to ensure that the GLP compliance of the study is not compromised. The fact that different study activities are being conducted at different sites means that the planning, communication and control of the study are of vital importance.”*

In this appendix we will look at the roles of management, the study director, the principal investigator and quality assurance in the multi-site situation.

THE ROLE OF MANAGEMENT IN THE PERFORMANCE OF MULTI-SITE STUDIES

Management at the main site is known as the **test facility management** and at the other sites is known as the **test site management**.

Test Facility Management:

- In order to successfully run multi-site studies, it is primordial to establish good lines of communication between the sites. It is the role of test facility management to establish the ways in which communication between the sites operate. *“In order... to deal with any events that may need to be addressed during the conduct of the study, the flow of information and effective communication among the sponsor, management at sites, the study director, principal investigator(s), quality assurance and study personnel is of paramount importance”.*
- The way in which study-related information is communicated to interested parties should be agreed in advance and written down.
- The sponsor assigns a study to a test facility. Test facility management appoints the study director. The study director need not be located at the site where the majority of the experimental work is done, but usually this is the case.
- Test facility management decides where the study activities are performed and which phases are conducted at sites other than the test facility.
- Test facility management appoints a lead quality assurance, who has overall responsibility for quality assurance of the entire study
- Test facility management informs all test site quality assurance units of the location of the lead quality assurance.
- *“Test facility management should make test site management aware that it may be subject to inspection by the national GLP compliance monitoring authority of the country in which the test site is located”.*
- If the study director cannot perform his/her duties at a test site because it is impracticable (perhaps because it is distant) there is a need to appoint a principal investigator(s) at that test site(s).

Test Site Management

- Test site management must provide adequate resources at the site
- Test site management appoints an appropriately skilled principal investigator.

Study Director

- The study director assures that the tests sites are acceptable. This may require a visit to each site
- As for any GLP study, the study director is responsible for the approval of the study plan. This responsibility also covers those parts of the protocol contributed by the principal investigators.
- Equally, the study director will approve and issue amendments to the study plan, including those relating to work undertaken at test sites.
- The study director must make sure that all staff, including those at distant sites, are aware of the requirements of the study. He/she should also make sure that the study plan and amendments are available to all relevant personnel.
- The study director should establish, monitor and maintain communication systems between the test facility and the test sites. The OECD guide adds...*“For example, it is prudent to verify telephone numbers and electronic mail addresses by test transmissions, to consider signal strength at rural field stations, etc. Differences in time zones may need to be taken into account. The study director should liaise directly with each principal investigator and not via an intermediary except where this is unavoidable (e.g., the need for language interpreters)”*.
- The study director should co-ordinate and schedule events such as the dispatch of samples, specimens or data between sites, and make sure that the principal investigators understand the procedures concerning the chain of custody.
- The study director should be in direct contact with the principal investigators to discuss the findings of the test site quality assurance. All the communications between responsible persons should be documented and follow rules of traceability.
- The study director is responsible for the writing of the final report, incorporating contributions from other scientists including the principal investigators.
- The study director should submit the final report to the lead quality assurance for inspection.
- The study director signs and dates the final report. His/her signature indicates the acceptance of responsibility for all data including those derived at the test site and under the direct responsibility of the principal investigator.
- If there is no principal investigator at a particular site, *“the study director should liaise directly with the personnel conducting the work at those sites. These personnel should be identified in the study plan”*.

PRINCIPAL INVESTIGATOR (PI)

- The principal investigator acts on behalf of the study director for those parts of the study that are performed at the test site.
- The principal investigator is responsible for making sure that the GLP Principles are respected at the test site for the study phases concerned.
- There must be a written agreement from the PI that the study phases performed on the test site will be conducted in compliance with GLP. “Signature of the study plan by the principal investigator would constitute acceptable documentation”.
- If there are any deviations from the protocol for those parts of the study conducted at the test site, they must be reported to the study director, after being acknowledged by the PI.
- The status of GLP compliance for the part of the study performed at the site should be communicated to the study director by the PI.
- The PI will provide his/her scientific contributions to the study director so that they can be included in the final report.
- *“The principal investigator should ensure that all data and specimens for which he/she is responsible are transferred to the study director or archived as described in the study plan. If these are not transferred to the study director, the principal investigator should notify the study director when and where they have been archived. During the study, the principal investigator should not dispose of any specimens without the prior written permission of the study director.”*

QUALITY ASSURANCE (QA)

Because of the difficulties in ensuring overall GLP compliance in the case of multi-site studies, it is important to carefully plan and organize the activities of QA. The major issues revolve around the fact that the study is managed by multiple personnel and that there may be several quality assurance programmes involved. As explained above, management appoints a lead QA person; there will also be test site QA.

Lead Quality Assurance

- Lead quality assurance must regularly communicate with test site QA so that there is proper inspection coverage of the whole study.

- The respective responsibilities for the lead QA and site QA must be established before experimental work starts.
- The lead quality assurance must make sure that the study plan is checked and that the final report is inspected.
- *“Quality assurance inspections of the final report should include verification that the principal investigator contributions (including evidence of quality assurance at the test site) have been properly incorporated.”*
- The lead quality assurance must make sure that the quality assurance statement in the final report covers both the work undertaken at the test facility and the work performed at the various test sites.

Test Site Quality Assurance

- Test site management is responsible for the appointment of QA and the conduct of QA functions at the test site.
- Test site QA must review those parts of the study plan that relate to activities at their site.
- *“[Test site QA] should maintain a copy of the approved study plan and study plan amendments.”*
- Test site QA is responsible for the inspection of the study phases performed the test site and report in writing to the PI, test site management, study director, test facility management and lead quality assurance.
- *“Quality assurance at the test site should inspect the principal investigator’s contribution to the study according to their own test site SOPs and provide a statement relating to the quality assurance activities at the test site.”*



Multi-Site Studies

Multi-Site Studies

Appendix 4:1



Multi-Site Studies

What is a Multi-Site Study?

- Any study which is performed on more than one site is a Multi-Site Study
- A study can be multi-site for a variety of reasons
 - Single site may not have all the required techniques to deal with all study phases
 - Sponsors may wish to perform certain phases (bioanalysis, pathology) at their own site, while the rest of the study is contracted out

Appendix 4:2

Instructor's notes

Very many studies performed to GLP require input from more than one place. Any study in this situation is a multi-site study; the applicable guidelines in this situation are outlined in this section.



Multi-Site Studies

What is a Multi-Site Study?

- **When there is a multi-site study, the sites are named as follows:**
 - **Test facility = main site, usually where the Study Director is found**
 - **Test Site (s) = the other site (s) where certain phases of the study are performed. The work here is under the responsibility of a Principal Investigator (PI)**

Appendix 4:3

Instructor's notes

The study is performed in more than one location and it is important to differentiate between the location where the main part of the study is performed and the location where only certain phases of the study are conducted.

The main location is called the Test Facility. Usually the study director is at this location.

All the other locations where phases of the study are performed are called Test Sites. In these places the conduct of the study phases are under the responsibility of the Principle Investigator. He/she has a role and responsibilities similar to the study director, but only for the phases under his/her responsibility.



Multi-Site Studies

What are the Responsibilities ?

- **Test Facility Management**
 - **Establish the ways in which the sites will communicate between each other, with the sponsor, the study director, the principal investigator (s) and the QAU (s)**
 - **Lines of communication should be agreed in advance and documented**
 - **The sponsor contracts (assigns) responsibility for a study to a test facility and its management**

Appendix 4:4

Instructor's notes

For the proper organization of studies the test facility management must put into place good communication systems between all the actors.

In this slide and the next two the responsibilities of test facility management are underlined.



Multi-Site Studies

What are the Responsibilities ?

- **Test Facility Management**
 - **Appoints the Study Director he/she is usually , but not necessarily, located at the test facility where the bulk of the work is performed**
 - **The Study Director has overall responsibility for the entire study, including phases at the test sites**
 - **Decides where the study activities will be performed – assigns test sites**

Appendix 4:5



Multi-Site Studies

What are the Responsibilities ?

- **Test Facility Management**
 - **Appoints a Lead Quality Assurance – who has overall responsibility for the QA activities during the study**
 - **Informs all test site QA groups of the name and location of the Lead QA group**
 - **Arranges with test site management for the appointment of a Principal Investigator**

Appendix 4:6



Multi-Site Studies

What are the Responsibilities ?

- **Test Site Management**
 - **Agrees with test facility management on the appointment of the Principal Investigator**
 - **Provides all resources at the test site**
 - **Informs the test facility management about GLP compliance status of the test site**

Appendix 4:7

Instructor's notes

In parallel to the test facility management, the manager at the test site has responsibilities, these are outlined in this slide.



Multi-Site Studies

What are the Responsibilities ?

- **Study Director**
 - **Assures that the level of expertise at the test sites is acceptable**
 - **Approves Study Plan and takes responsibility for all GLP aspects of the study**
 - **Issues and approves amendments to study plan, including those which affect the test site**
 - **Maintains communication with all study personnel at all sites**

Appendix 4:8

Instructor's notes

The study director must retain overall responsibility for the entire study. This is a basic tenet of GLP.

In the case of multi-site studies, the study director can only achieve this by knowing the GLP status of each of the Test Sites and how they function, and by maintaining close contacts with the principle Investigators at each of the Test Sites.

The study director's responsibilities are given in this slide and the next two.



Multi-Site Studies

What are the Responsibilities ?

- **Study Director**
 - Ensures that the events scheduled in the study plan occur as planned
 - Has direct contact with Principal Investigator to discuss test site QA findings
 - Responsible for the final report incorporating elements from the Principal Investigator (s)

Appendix 4:9

Instructor's notes

Discuss with the participants how the PI could contribute to the final report.

Possibilities could include:

- Send a final signed “phase report” for inclusion in the final study report as an appendix.
- Send a draft document for the study director to include the data and findings in the body of the text of his/her final report.
- Send to the study director the “phase file” including raw data etc. so that the study director can write his/her own account of the phase and incorporate it into the body of the text of the final report.



Multi-Site Studies

What are the Responsibilities ?

- **Study Director**
 - Submits final report to Lead QA for audit
 - Signs and dates final report and includes GLP compliance statement covering all sites. This signature is an acceptance of responsibility for all data including those from the test site
 - If a test site has no Principal Investigator, the Study Director may assume this responsibility at the test site, if practically possible

Appendix 4:10

Instructor's notes

Discuss with the participants under what conditions the study director could take on responsibility for a study phase performed at a different geographical location.

***Multi-Site Studies***

What are the Responsibilities ?

- **Principal Investigator**
 - **Acts on behalf of the Study director for those parts of the study done at the test site**
 - **Is responsible for the application of GLP Principles in the study phases concerned**
 - **Reports to the Study Director any deviations occurring in the phases of the study conducted at the test site**

Appendix 4:11

Instructor's notes

In parallel to the responsibilities of the study director, the principal investigator takes on the scientific and GLP responsibilities for the phases of the study under his/her control.

He/she must keep the study director informed of the progress of the phases concerned and, of course, of any anomalies or deviations during the course of the phases.

The responsibilities of the principal investigator are underlined in this slide and the next one.

***Multi-Site Studies***

What are the Responsibilities ?

- **Principal Investigator**
 - **Communicates the GLP status of the phases of the study to the Study Director**
 - **Provides his/her scientific contribution to the Study Director regarding the phases conducted at the test site**
 - **Transfers all data and specimens to the test facility at the end of the study or archives them at the test site (following pre-established procedures)**

Appendix 4:12



Multi-Site Studies

What are the Responsibilities ?

- **Lead Quality Assurance**
 - **Role of Lead QA and Test site QA must be established before the study starts**
 - **Lead QA must ensure that there is proper inspectional coverage of the whole study**
 - **Lead QA ensures that the study plan and the final report are audited**

Appendix 4:13

Instructor's notes

To comply with GLP, the study must be monitored by QA. Since there are two test locations there could well be two QA units.

One of these must be appointed as the Lead QA. Usually this is the unit working at the Test Facility. The other is the Test Site QA. What each group does must be clearly defined before the start of the study.

The responsibilities of the Lead QA are given in this slide and the next one.



Multi-Site Studies

What are the Responsibilities ?

- **Lead Quality Assurance**
 - **QA inspections of the final report must cover the contributions of the Principal Investigator**
 - **Lead QA makes sure that the QA statement in the final report covers both work done at the Test Facility and that conducted at the Test Site**
 - **Communicates regularly with Test Site QA to discuss QA findings on the phases performed at the Test Site**

Appendix 4:14

Instructor's notes

Discuss with the participants how the Lead QA can cover the responsibility of ensuring that the contribution from the PI is GLP compliant.

Possibilities could include:

- Relies entirely on the Site QA audit of the PI contribution at the test site.
- Ensures that the Site QA has proper procedures for the auditing of the PI report.
- Requires Site QA to provide details of the audit performed on the PI contribution.
- Reviews the PI contribution for internal consistency.
- Re-audits the PI contribution by comparison with the raw data provided by the test site.



Multi-Site Studies

What are the Responsibilities ?

- **Test Site Quality Assurance**
 - **Maintains copy of approved study plan and study plan amendments**
 - **Reviews Test Site study activities, inspects the Principal Investigators contribution to the study and provides a statement relating to the QA activities at the test site**
 - **Reports QA findings to the PI, Test Site management, Study Director, Test Facility Management & Lead QA**

Appendix 4:1

Instructor's notes

In parallel with the Lead QA, the Test Site QA is responsible for monitoring the phases of the study being performed at the Test Site.

The responsibilities of the Test Site QA are provided in this slide.

APPENDIX 5: GLP AND SHORT-TERM STUDIES

Direct citations from the OECD guidance document “The Application of the GLP Principles to Short-Term Studies” are in “quotation marks and italics”.

The OECD recognizes that short term studies pose particular organizational difficulties for facilities when implementing GLP. In particular, these difficulties are related to the writing of protocols and final study reports, the conduct of inspections by QA and the audit of the final report. These topics are dealt with below, but there are other interesting points which are evoked by this document and you are encouraged to read it carefully to see how it may apply to your particular situation.

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WHAT IS A SHORT TERM STUDY?

- The OECD GLP Principles define a short-term study as “*a study of short duration with widely used, routine techniques*”. It is important to remember that a short term study is not only defined by its length, but also by the fact that it uses a number of routine procedures. This aspect has an impact on the monitoring of the study by QA.
- The OECD guideline goes on to say “*Short term biological studies include acute toxicity studies, some mutagenicity studies, and acute ecotoxicological studies*”.
- “*Physical-chemical studies are those studies, tests or measurements which are of a short duration (typically not more than one working week), employ widely-used techniques (e.g. OECD Test Guidelines) and yield easily repeatable results, often expressed by simple numerical values or verbal expressions.*”
- Short term physical chemical studies include, for example, chemical characterization studies, melting point, vapour pressure, partition coefficient, explosive properties and other similar studies for which test guidelines exist.

HOW SHOULD THESE STUDIES BE INSPECTED?

- With reference to the activities of quality assurance, the same approach is applied as described in the guidance document on quality assurance & GLP. This means that the inspections performed should be articulated around the three different types of inspection; Study-based, facility-based and process-based.
- However, since short term studies, by definition, contain a number of routine processes or procedures, it is quite acceptable to perform all of the QA inspections of these studies using the process-based approach.
- The OECD guidance document says “[Process] inspections take place when a process is undertaken very frequently within a laboratory and it is therefore considered inefficient or impractical to undertake study based inspections. **It is recognized that performance of process-based inspections covering phases which occur with a very high frequency may result in some studies not being inspected on an individual basis during their experimental phases.**” (my emphasis).
- And also....”*In these circumstances, a process based inspection programme may cover each study type. The frequency of such inspections should be specified in approved quality assurance standard operating procedures, taking into account the numbers, frequency and/ or complexity of the studies being conducted in the facility. The frequency of inspections should be specified in the relevant QA standard operating procedures, and there should be SOPs to ensure that all such processes are inspected on regular basis*”.

Specific requirements with regard to biological test systems

- As biological test systems are often cellular or sub-cellular, emphasis is put on the way the maintenance of the system is documented. For example “*Record keeping is required to document the growth, vitality and absence of contamination of batches of in vitro test systems. It is important that the origin, sub-strain and maintenance of the test system be identified and recorded for in vitro studies.*”
- The guidance document underlines the need to ensure that the test systems are adequately defined by its source and health status free of contamination (e.g. historical colony and supplier information, observations, serological evaluation).
- The importance of non-contamination / pollution of the test system is also underlined. “*There should be assurance that water, glassware and other laboratory equipment are free of substances which could interfere with the conduct of the test. Control groups should be included in the study plan to meet this objective. Periodic systems tests may also be performed to complement this goal.*”

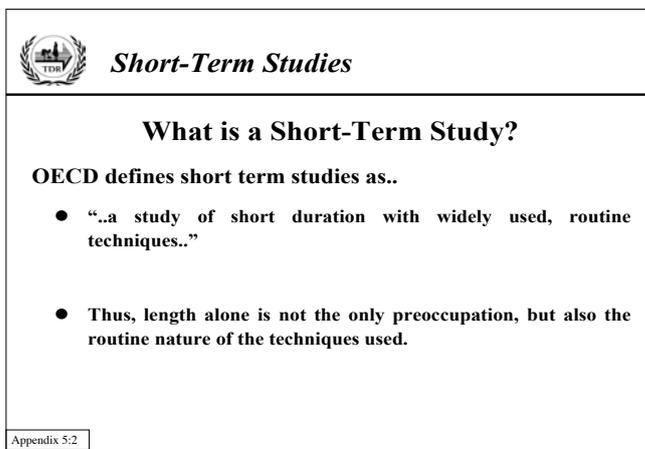
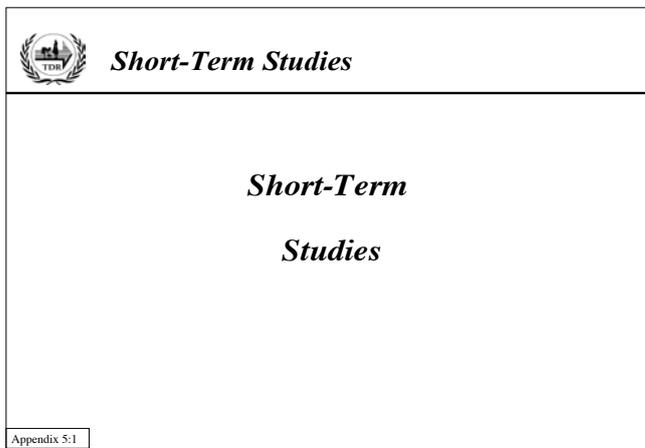
STUDY PLANS (PROTOCOLS) FOR SHORT-TERM STUDIES

- The guidance document recommends that in the case where a short term study is repeatedly performed within the laboratory the protocol may be a generic document.
- This generic protocol would contain “...*the majority of general information required in such a plan and approved in advance by the testing facility management and by the study director(s) responsible for the conduct of such studies and by QA.*”
- Of course such generic protocols contain a description of the study design but they will need to be completed each time with the additional information regarding the particular points relative to each study.
- In the OECD jargon, these additions are called Study specific supplements. The details that you might find in these supplements include: details on test item, experimental starting date, the unique study number, the actual name of the study director, etc.
- The supplement maybe issued as a supplementary document requiring only the dated signature of the designated study director.
- The actual study plan comprises the “*generic*” protocol and the “*supplement*” combined together.
“The combined document — the general study plan and the study-specific supplement — is the study plan. It is important that such supplements are provided promptly to test facility management and to QA assurance personnel.”

REPORTING SHORT-TERM STUDIES

- It is important that the report of a short-term study should be as reliable and credible as the report from any other study. Hence the principles of GLP, responsibilities of the study director, inspection by QA etc. must be respected.
- However, in the case where a short-term study is conducted with the use of a generic protocol plus a supplement, it is also possible to use “*standardized final reports*”.
- These are reports that have been prepared in advance and contain “*the majority of general information required in such reports and authorized in advance by the testing facility management, and by the study director(s) responsible for the conduct of such studies.*” These documents would describe the rationale and the conduct of the standard part of the study (i.e. most of what you would expect to find in a full final report).

- In the same way as for the generic and study specific supplements to protocols, you may issue as a supplement to the standardized report. It would contain all relevant information specific to the study in question and, of course, the actual study results, discussion and conclusion. The OECD guidance documents says “*Study specific extensions to such [standardized] reports (e.g. with details of the test item and the numerical results obtained) may then be issued as a supplementary document requiring only the dated signature of the study director.*”
- But, it is “*not acceptable to utilize a ‘standardized final report’ when the study plan is revised or amended prior to or during the conduct of the study unless the “standardized final report” is amended correspondingly.*”
- There must be a quality assurance audit of the report and the study data.
- There must also be a quality assurance statement as part of the final report. This should reflect the use of process-based inspections if this was the case and should also indicate that the QA has audited the final report.

**Instructor's notes**

The definition of a short-term study is double barreled:

- the study must not be of long duration
- The study must be composed of routine techniques that are frequently used within the laboratory



Short-Term Studies

What is a Short-Term Study?

OECD adds some guidance...

- “Physical-chemical studies are those studies, tests or measurements which are of short duration (typically not more than one working week), employ widely used techniques (e.g. OECD Test Guidelines) and yield easily repeatable results, often expressed by simple numerical values or verbal expressions.”
- “Short term biological studies include acute toxicity, some mutagenicity studies and acute ecotoxicological studies”

Appendix 5:3



Short-Term Studies

What is a Short-Term Study?

In practice...

- **Most physical-chemical studies**
 - **Characterisation studies**
 - **Melting point**
 - **Vapour pressure**
 - **Partition coefficient**
 - **Explosive properties...**

Appendix 5:4

Instructor's notes

These are typical studies which can be defined as short-term. But this list is not exhaustive.

Discuss with the participants what might be defined as short term in their organizations



Short-Term Studies

What is a Short-Term Study?

In practice...

- **Biological studies of less than one month**
 - Ames tests
 - Acute toxicity tests
 - Micronucleus

Appendix 5:5



Short-Term Studies

Requirements for biological studies

As biological test systems are often cellular or sub-cellular, there is emphasis on the maintenance of systems:

- **Records and document growth, vitality, absence of contamination etc.**
- **Record of origin, strain, maintenance of test systems, cell banks etc.**
- **Control groups should be used to demonstrate that the test or maintenance conditions keep the test system free of contamination or pollution**

Appendix 5:6

Instructor's notes

The GLP Principles were designed with classical toxicology studies in mind.

For other types of short term biological studies, there are a number of points which do not apply to classical toxicology safety studies; some of these are listed in this slide.



Short-Term Studies

What is different about Short-Term Studies?

The OECD recognises that GLP may be applied differently to these studies in the following areas:

- Writing and approval of study plans
- Writing and approval of final reports
- QA inspection /auditing procedures

All the differences are due to the routine nature of the processes of the studies

Appendix 5:7

Instructor's notes

As the performance of short-term studies is often routine in nature, certain aspects of the GLP Principles may be modified to reflect this.

The major points of difference between short-term studies and others is in the way in which the studies are planned and the way in which the studies are reported.

Since the approach to writing protocols and reports is different when performing short-term tests, it is not surprising that the way in which QA monitors such studies may also differ from the way in which long term-studies are monitored.



Short-Term Studies

Writing and Approval of Study Plans

When the study is repeatedly performed:

- A generic study plan can be written in advance and used for several studies
- This generic protocol contains most of the general information about the intended study, its design and conduct
- It is approved, in advance, by the test facility management, the Study Director (s) and by QA

Appendix 5:8

Instructor's notes

Using a flip chart or a white board, create a diagram to show the way in which protocols are written and approved under this simplified system.

The next slides provide the further information regarding the General and Specific study plan approach allowable when performing short-term studies.



Short-Term Studies

Writing and Approval of Study Plans

When the study is repeatedly performed:

- The generic study plan is completed for each study with study-specific supplements
- These study specific supplements include details concerning each study:
 - Study identification & dates
 - Name of test item
 - Name of Study Director

Appendix 5:9

Instructor's notes

Continue compiling your diagram with the information in this slide.



Short-Term Studies

Writing and Approval of Study Plans

When the study is repeatedly performed:

- The study-specific supplement is issued as a separate document and is signed only by the study director, QA audit of the supplement is not required
- For GLP compliance the study plan comprises both the generic study plan + the study specific supplement
- The combined document must be supplied promptly to test facility management and to QA

Appendix 5:10

Instructor's notes

Continue compiling your diagram with the information in this slide.



Short-Term Studies

Writing and Approval of Study Reports

When the study is repeatedly performed:

- The report may be in the form of a standardised final report
- The standardised final report contains the general study information, methods and materials and study conduct.....
- The standardised study report is authorised in advance by the test facility management and by the Study Directors

Appendix 5:11

Instructor's notes

Using a flip chart or a white board, create a diagram to show the way in which study reports are written and approved under this simplified system.

The next slides provide the further information regarding the General and Specific study report approach allowable when performing short-term studies.



Short-Term Studies

Writing and Approval of Study Reports

When the study is repeatedly performed:

- The standardised final report is completed by a study specific extension which supplements the generic document
- The study specific extension would include details such as
 - Test item details
 - Results of the study
 - Discussion & conclusion if appropriate

Appendix 5:12

Instructor's notes

Continue compiling your diagram with the information in this slide.



Short-Term Studies

Writing and Approval of Study Reports

When the study is repeatedly performed:

- The study specific extension is issued as a separate document and signed by the study director
- The standardised report plus the study specific extension comprises the final report
- It is not acceptable to use this standardised report when the study protocol has been amended prior to the study, unless the standardised report has also been amended accordingly

Appendix 5:13

Instructor's notes

Continue compiling your diagram with the information in this slide.



Short-Term Studies

Writing and Approval of Study Reports

When the study is repeatedly performed:

- The final report = standardised report + study specific extension must be audited by QA
- The final report must have a GLP compliance statement from the Study Director
- It must have a QA statement & dated signature
 - What processes inspected for this type of study
 - Date of final report audit

Appendix 5:14

Instructor's notes

Continue compiling your diagram with the information in this slide.

When the diagram is finished it should be clear that it mirrors the diagram you built up to explain the way in which protocols may be written



Short-Term Studies

QA Inspection / Audit of Short Term Studies

The three types of QA inspection still apply:

- Study-based inspections
- Facility-based inspections
- Process-based inspections

But, by definition, these studies contain multiple routine procedures so that Process-based inspections are frequently applied to them

Appendix 5:15

Instructor's notes

As the performance of short-term studies is often routine in nature, the way in which QA monitors these studies can also be different from the way in which QA approaches longer term studies.

OECD GLP recognizes that as very many routine short-term studies may be performed in a relatively short time, it would be inefficient for QA to individually inspect each one.

Applying the Process-based inspection approach is therefore very common practice for these studies.



Short-Term Studies

QA Inspection / Audit of Short Term Studies

Read this citation from the OECD document on Short-Term Studies:

1. “[Process] inspections take place when a process is undertaken very frequently within a laboratory and it is therefore considered inefficient or impractical to undertake study-based inspections”

Appendix 5:16

Instructor's notes

Take time to find these two quotations (see also next slide) from the consensus document on short-term studies and read it with the participants. You will find the text in the WHO/TDR Handbook on GLP.

Discuss with them the full implication of these passages. In particular underline the fact that it is reasonable for a particular short term study not to be inspected individually by QA.

	<i>Short-Term Studies</i>
QA Inspection / Audit of Short Term Studies	
Read this citation from the OECD document on Short-Term Studies:	
<ol style="list-style-type: none"> 2. “It is recognised that performance of process-based inspections covering phases which occur with a very high frequency may result in some studies not being inspected on an individual basis during their experimental phases” 	
<small>Appendix 5:17</small>	

	<i>Short-Term Studies</i>
QA Inspection / Audit of Short Term Studies	
When QA uses process-based inspection for short-term studies	
<ul style="list-style-type: none"> ● The frequency of the inspections should be indicated in QA SOPs ● All procedures / processes should be covered over a specified period of time ● The QA statement in the final report should reflect the use of process-based inspections 	
<small>Appendix 5:18</small>	

Instructor's notes

Whatever the approach adopted by QA, it is essential that the QA SOPs explain how the QA inspection programme has been defined and what QA actually does with regard to short-term studies. As for the other aspects of QA work, the policy adopted must be justified in a document (usually an SOP) and management's approval must be obtained.

In the short-term study report QA will include a QA statement and describe what kind of inspection programme applied to the study concerned.

APPENDIX 6: GLP AND COMPUTERIZED SYSTEMS

In the following text the citations in italics are from the OECD documents on “The Application of the Principles of GLP to Computerized Systems”

DEFINITION AND SCOPE

The definition of computerized systems is important in that it includes the hardware and the software components. They are considered together as constituting the entity that performs a particular function.

“A computerized system is defined as a group of hardware components and associated software designed and assembled to perform a specific function or group of functions.”

Which computerized systems are subject to GLP compliance? Essentially, the answer to that question is that any system having a potential impact on the quality or integrity of the data provided in a submission dossier is a candidate for GLP compliance.

The activities that are targeted in this OECD Consensus document are:

- System development,
- System validation,
- Use/operation of systems,
- Maintenance of systems.
- Modification /retirement of systems

“All computerized systems used for the generation, measurement or assessment of data intended for regulatory submission should be developed, validated, operated and maintained in ways which are compliant with the GLP Principles.”

From development, through validation, use and maintenance, the OECD document advises a life-cycle approach which is now the industrial and regulatory standard.

RESPONSIBILITIES

Management

As elsewhere in GLP, management has overall responsibility for compliance. In the field of computerized systems, management should assure that GLP compliance applies to the life cycle of the system and that the appropriate documentation at each stage is in place and, in the case of prescriptive documents followed. Clearly some of these responsibilities are delegated to senior staff and specialists. This delegation may be documented in SOPs, policy documents, job description etc.

“Management is responsible for ensuring that computerized systems are suitable for their intended purposes. It should establish computing policies and procedures to ensure that systems are developed, validated, operated and maintained in accordance with the GLP Principles. Management should also ensure that these policies and procedures are understood and followed, and ensure that effective monitoring of such requirements occurs.”

Study Director

“Since many such studies will utilize computerized systems, it is essential that study directors are fully aware of the involvement of any computerized systems used in studies under their direction. The study director’s responsibility for data recorded electronically is the same as that for data recorded on paper and thus only systems that have been validated should be used in GLP studies.”

Personnel

As with any other equipment, it is a GLP responsibility of all personnel to use computerized systems in compliance with GLP. Compliance concerns systems in all of the steps of their life cycle: development, validation, use and maintenance. Thus all operations must be properly planned, conducted and documented. Only properly trained persons should operate systems. Such training must, of course, be fully documented.

Quality Assurance

Management should define the responsibilities that QA have with respect to computerized systems. These responsibilities must be set out in documents such as policy documents and SOPs. Again, responsibilities should be tailored to the life cycle approach, with QA involvement right through the various steps. If the steps include development stages, there should be QA activities related to this, if the steps start with the purchase of systems QA should be involved in this. Once in place QA should monitor both use and maintenance.

nance of computerized systems.

In order to avoid any conflicts, QA is usually given read only access to files and access to the audit trail functions.

Facilities and Equipment

“Due consideration should be given to the physical location of computer hardware, peripheral components, communications equipment and electronic storage media. Extremes of temperature and humidity, dust, electromagnetic interference and proximity to high voltage cables should be avoided unless the equipment is specifically designed to operate under such conditions. Consideration must also be given to the electrical supply for computer equipment and, where appropriate, back-up or uninterruptible supplies for computerized systems, whose sudden failure would affect the results of a study. Adequate facilities should be provided for the secure retention of electronic storage media.”

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MAINTENANCE AND DISASTER RECOVERY

Computerized systems should be considered in the same manner as any equipment in that preventive and curative maintenance is essential. Maintenance should be planned and documented when it is performed. Procedures for maintenance should exist.

Sometimes it may be necessary to revalidate systems after maintenance, adding patches or version changes. Decisions of this sort should be based on a rationale, often after risk analysis.

Disaster Recovery

Because of the problems that could arise due to partial or complete breakdown, institutions should implement contingency procedures to deal with such problems. The most commonly encountered is to return to a paper-based system in the event of computer shut down. It is also possible in some circumstances to reinstall systems from back up copies.

DATA

Raw data are defined as : “... all original laboratory records and documentation, including data directly entered into a computer through an instrument interface, which are the results of original observations and activities in a study and which are necessary for the reconstruction and evaluation of the report of that study.”

Whether electronic or not, it is essential to define all raw data. As for paper data, elec-

tronic raw data should provide the possibility of performing a full audit trail showing. *“All changes to the data without obscuring the original data. It should be possible to associate all changes to data with the persons making those changes by use of timed and dated (electronic) signatures. Reasons for change should be given.”*

The difficulty associated with the rapid development of new systems is discussed in the OECD document. Long term retention of data may be difficult if the associated hardware and software is rapidly changing.

“Where system obsolescence forces a need to transfer electronic raw data from one system to another then the process must be well documented and its integrity verified. Where such migration is not practicable then the raw data must be transferred to another medium and this verified as an exact copy prior to any destruction of the original electronic records.”

SECURITY AND DATA INTEGRITY

“Documented security procedures should be in place for the protection of hardware, software and data from corruption or unauthorized modification, or loss. In this context security includes the prevention of unauthorized access or changes to the computerized system as well as to the data held within the system.”

Physical security measures cover, for example:

- Restricting access to facilities where hardware, storage disks, terminals are held.
- Assuring an adequate environment where computers, servers etc are located.
- Providing special safes for the retention of disks and tapes.

Software security measures cover, for example:

- Prevention of unauthorized access by pass word implementation.
- Coding confidential data.
- Anti virus systems, firewalls etc.
- Procedures for adding new software to existing systems.

All persons working with computer systems must be aware of the security needed to protect data. It is good practice to perform regular back-ups of data to avoid loss. Retention of duplicate data sets, usually at two different sites is also standard practice.

VALIDATION OF COMPUTERIZED SYSTEMS

It is the responsibility of management to demonstrate that computerized systems are suitable for the processes they perform. In addition, it must be demonstrated that the systems are operating in compliance with their specifications (functional, operational...). This can be demonstrated by formal validation.

Validation tests:

“There should be adequate documentation that each system was developed in a controlled manner and preferably according to recognized quality and technical standards (e.g. ISO/9001)”.

When a system has been developed by the vendor, the documentation regarding development will usually be retained by the vendor. However, there should be evidence that this development has been correctly conducted and tested at the site where the system is used. There is usually evidence of audits performed at the vendor site to support the vendor’s documentation.

Acceptance testing should be conducted against acceptance criteria. There should be a plan (protocol) prescribing the tests to be conducted, results of tests should be retained, and a formal report should be written containing the results and conclusion of the tests.

Retrospective Evaluation:

Inevitably, some systems exist that were not at first intended for use in a GLP environment but that are later deployed under GLP. In this case, retrospective evaluation would be acceptable.

“Retrospective evaluation begins by gathering all historical records related to the computerized system. These records are then reviewed and a written summary is produced.”

If supplementary validation work is required this should be conducted and reported.

Change Control

Any modifications to the computerized system should be achieved by following a change control procedure. This procedure prescribes the method for evaluating the impact of the proposed change. A decision concerning the need for full or partial revalidation will be taken, and documented, after the impact analysis.

DOCUMENTATION

The OECD guide to GLP and computerized systems lists the documents typically required for the development, operation and maintenance of computerized systems. These are:

Policies

“There should be written management policies covering, inter alia, the acquisition, requirements, design, validation, testing, installation, operation, maintenance, staffing, control, auditing, monitoring and retirement of computerized systems.

Application Description

For each application there should be documentation fully describing:

- *The name of the application software or identification code and a detailed and clear description of the purpose of the application.*
- *The hardware (with model numbers) on which the application software operates.*
- *The operating system and other system software (e.g., tools) used in conjunction with the application.*
- *The application programming language(s) and/or data base tools used.*
- *The major functions performed by the application*
- *An overview of the type and flow of data/data base design associated with the application.*
- *File structures, error and alarm messages, and algorithms associated with the application*
- *The application software components with version numbers.*
- *Configuration and communication links among application modules and to equipment and other systems.*

Standard Operating Procedures (SOPs)

Much of the documentation covering the use of computerized systems will be in the form of SOPs. These should cover but not be limited to the following:

- *Procedures for the operation of computerized systems (hardware/software), and the responsibilities of personnel involved.*
- *Procedures for security measures used to detect and prevent unauthorized access and programme changes.*
- *Procedures and authorization for programme changes and the recording of changes.*
- *Procedures and authorization for changes to equipment (hardware/software) including testing before use if appropriate.*

- *Procedures for the periodic testing for correct functioning of the complete system or its component parts and the recording of these tests.*
- *Procedures for the maintenance of computerized systems and any associated equipment.*
- *Procedures for software development and acceptance testing, and the recording of all acceptance testing.*
- *Back-up procedures for all stored data and contingency plans in the event of a breakdown.*
- *Procedures for the archiving and retrieval of all documents, software and computer data.*
- *Procedures for the monitoring and auditing of computerized systems.”*

Source Code

Some OECD countries require the source code (human readable version of the program) to be made available to monitoring authorities. In this case, the test facility will usually have an agreement with the system vendor to allow inspectors to see the code if they so wish.

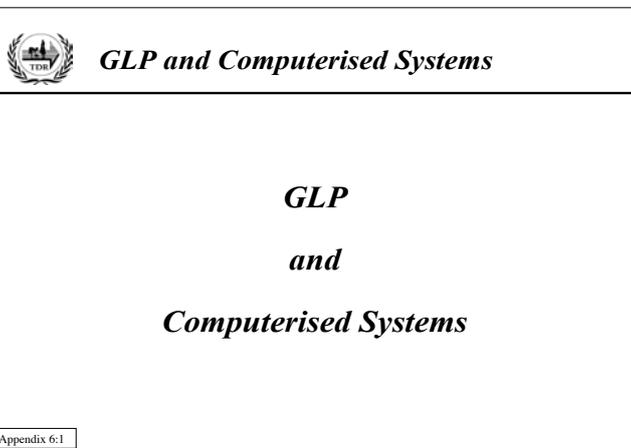
225

ARCHIVES

The OECD Principles relating to archives must be applied in the same way for electronic data as for data held on other material. To ensure data integrity, access to the archived material should be limited. Disks and tapes holding data should be stored in a way that will preclude corruption. Retrieval should be facilitated by appropriate indexing

Electronic data should not be destroyed without documented high level management authorization.

The storage periods for electronic data are the same as for other data and documents relating to studies.



The slide features a header with the TDR logo and the title "GLP and Computerised Systems". The main content is titled "What are Computerised Systems?" and lists several bullet points. A small box in the bottom left corner contains the text "Appendix 6:2".

What are Computerised Systems?

- Hardware (physical) and associated Software (electronic) components assembled to perform specific function
- Systems include :
 - Computer hardware
 - Peripheral components
 - Communication / interfacing equipment
 - Electronic storage media

Instructor's notes

Computerized systems cover both hardware and software. They are considered together as constituting the entity that performs a particular function.

Discuss with then trainees the different types of computer systems in use at their institutions.



GLP and Computerised Systems

What are Computerised Systems?

- Examples of Computerised Systems:
 - A programmable analytical instrument
 - A personal computer
 - A laboratory information management system (LIMS) with multiple functions
 - A programmable system to record data from instruments in an animal house

Appendix 6:3

Instructor's notes

List on a paperboard the different computerized systems in use at the trainees institutions.



GLP and Computerised Systems

Criteria for GLP Compliance cover

- Use of computerised systems
 - Direct or indirect capture of data
 - Processing, reporting and storage of data
 - Integral part of operation/control of automated equipment
- What types are covered by GLP?
 - Those used for the generation, measurement or assessment of data intended for regulatory submission

Appendix 6:4

Instructor's notes

Using the list established on the paperboard, indicate those which would be considered as having a potential impact on the GLP compliance of studies.

Remind participants that computerized systems used for the acquisition or assessment of data, particularly if the data are destined for a regulatory submission, are covered by GLP compliance issues.

OECD uses a life cycle approach, this means paying attention to GLP compliance from the development stage through validation, operation and maintenance.



GLP and Computerised Systems

Purpose & Responsibilities

- Computerised Systems must be
 - Developed
 - Validated
 - Operated
 - Maintained
 in compliance with GLP
- Written procedures are needed to control and maintain these systems

Appendix 6:5

Instructor's notes

Explain the life cycle approach.

Remember that development of systems is often performed by a vendor company and not by a GLP laboratory. Nevertheless, the laboratory should take precautions to ensure that the development was conducted to international standards and well documented.

Following development, or when a system has been purchased, the validation, operation and maintenance is the responsibility of the test facility. These aspects must also be in compliance with GLP, notably in terms of documentation.



GLP and Computerised Systems

Responsibilities

- Management – Overall responsibility
 - Policies and procedures for suitability, development, validation operation and maintenance
- Study Director - Responsibility for use in study
 - Awareness of extent computerised systems are used in his/her studies
 - Responsibility for electronic data handling; just as for paper data
 - Ensure that only validated systems are used

Appendix 6:6

Instructor's notes

Note that the study director of a GLP study has the responsibility of making sure that the computerized systems used in his/her study are suitable, validated, operated correctly and well maintained. This is the case even if the study director has no line management responsibility for the computerized system in question.

Discuss with trainees the ways in which the study director should exercise this particular responsibility.

	<i>GLP and Computerised Systems</i>
Responsibilities	
<ul style="list-style-type: none"> • Personnel – GLP compliance during operations <ul style="list-style-type: none"> • Use of recognised technical standards for the development of systems • Respect of procedures for the validation, use and maintenance of systems • Quality Assurance - Responsibility for monitoring <ul style="list-style-type: none"> • Read only access to stored data • Sufficient familiarity for objective comment • May need specialist training for some aspects of monitoring use or validation of systems 	
<small>Appendix 6:7</small>	

Instructor's notes

All personnel must be trained in the use of the computerized system they are operating; just as for any other equipment. Such training must, of course, be fully documented.

Quality assurance responsibilities must be defined by management. In particular, the responsibilities of QA with respect to validation, the monitoring of use and maintenance should be established in relation to those of other groups such as IT.

Usually QA is involved in the audits performed to ensure that vendors of systems are using appropriate development standards and that their documentation is adequate for GLP and will be available in the event of a test facility inspection by a GLP monitoring authority.

	<i>GLP and Computerised Systems</i>
Training	
<p>“Appropriate qualified and experienced personnel”</p>	
<ul style="list-style-type: none"> • Documented training programmes (on-the-job or external) • Records of all training • Training for all personnel involved in development, validation, use or maintenance of computerised systems 	
<small>Appendix 6:8</small>	

Instructor's notes

Explain that the training approach described here mirrors exactly the general training requirements found in the OECD GLP Principles.

***GLP and Computerised Systems*****Facilities & Equipment**

“Adequate facilities & equipment”

- Facilities
 - Proper physical location
 - Care about temperature, humidity, dust electromagnetic fields and electrical supply
 - Back up provision
 - Secure retention of electronic storage media

Appendix 6:9

Instructor's notes

By their nature and their sensitivity to environmental conditions, computerized systems require specific facilities, as noted here and in the following slide.

***GLP and Computerised Systems*****Facilities & Equipment**

“Adequate facilities & equipment”

- Equipment
 - Suitable
 - Reliable
 - Secured
- Communication – between computers and components
 - All communication links are potential sources of error, corruption or loss of data

Appendix 6:10



GLP and Computerised Systems

Maintenance & Disaster Recovery

“Ensure the continuity of accurate performance”

- Maintenance
 - Define all responsibilities of persons concerned
 - Written procedures for preventive maintenance and fault repair
 - Record all problems encountered and the remedial actions taken

Appendix 6:11

Instructor's notes

Computerized systems are considered the same as any other equipment in that preventive and curative maintenance is essential. Maintenance should be planned and documented when it is performed. Procedures for maintenance should exist.

Sometimes it is necessary to revalidate systems after maintenance, after adding patches or after version changes. Decisions of this sort are based on a rationale such as risk analysis.



GLP and Computerised Systems

Maintenance & Disaster Recovery

“Ensure the continuity of accurate performance”

- Disaster Recovery
 - Keep back-up copies of all software
 - Make valid contingency plans and train staff
 - Written instruction to deal with cases of partial or total failure
 - Implement alternative methods of data capture in case of failure
 - Planned hardware redundancy
 - Transition to paper-based system
 - Recovery of computerised system

Appendix 6:12

Instructor's notes

A process for recovery due to a “disaster” (such as complete power failure, computer breakdown, physical destruction of all or part of a system.....) should be in place at all institutions. Essentially this means having contingency plans in place to deal with each type of disaster.

Examples of the kind of disaster recovery processes adopted by test facilities are provided here: discuss with trainees what other procedures could be regarded as contingency measures.



GLP and Computerised Systems

Raw Data

“Original laboratory records and documents”

- Define raw data for each computerised system
- Data entered through a computer interface must be included in definition
- Provision for audit trails
 - Show all data changes without obliterating the first data
 - Identify persons making change by electronic signature and by date/time
 - Give reason for change

Appendix 6:13

Instructor's notes

Electronic raw data must be defined.

As for paper data, electronic raw data should provide the possibility of performing a full audit trail showing. “...*all changes to the data without obscuring the original data. It should be possible to associate all changes to data with the persons making those changes by use of timed and dated (electronic) signatures. Reasons for change should be given.*”

(Italics = citation from OECD document: “The Application of the Principles of GLP to Computerized Systems”)



GLP and Computerised Systems

System obsolescence

- Transfer electronic raw data from one system to another
 - Document the process and verify that it has functioned correctly

OR

- Transfer raw data to another medium (such as paper)
 - Document the process and verify as an exact copy before destroying original electronic data

Appendix 6:14

Instructor's notes

Discuss with trainees the problems related to the fast moving world of systems development.

Long term retention of data may be difficult if the associated hardware and software is rapidly changing.

Contingency plans (like those in this slide) should be in force at the test facility to deal with the problem of obsolete systems, or systems that cannot access archived data.



GLP and Computerised Systems

Security

“Controlled access and use”

- Document security procedures for the protection of:
 - Hardware (may need a computer room)
 - Portable components and modem links etc.
- Take measures against viruses, worms, bugs etc.
 - No internet (or secured internet) on GLP computers
- Logical security
 - Control introduction of data and software from external sources
 - Only approved versions and validated software to be used
 - Have a system of unique user i.d. and associated password

Appendix 6:15

Instructor's notes

Protecting systems and data from corruption is all important.

Attacks from viruses, Trojan horses etc. are frequent, particularly when a system is in communication with networks which are accessible through internet facilities.

But there are also potential problems from the non-controlled installation of software on systems which have been validated.

Hardware often needs special environmental conditions in order to maintain optimum performance.

Policies regarding all these points should be in place.



GLP and Computerised Systems

Validation of Computerised Systems

“Demonstrable suitability”

- Purchase and installation acceptance:
 - Purchase policy for high quality of computerised systems
 - Written acceptance criteria (documented testing for conformance)
- Vendor supplied systems
 - Formal assessment and/or vendor audits
- Retrospective evaluation
 - Documented justification for use of the system
 - Document all records of the system and write a summary of the extent of validation

Appendix 6:16

Instructor's notes

Demonstrating that a system is suitable for use and is working in conformity with previously fixed criteria is known as validation.

Validation must be fully documented.

The validation process is like a study in that it is divided into 3 stages:

1. Writing & Approval of a validation protocol
2. Execution of the protocol, including the collection of data
3. Writing and Approval of the validation report, including a conclusion as to the validation status of the system

These are described more fully below



GLP and Computerised Systems

Validation of Computerised Systems

“Demonstrable suitability”

- **Change Control:**
 - Description and approval of any change to the system
 - Identify the persons and their respective responsibilities
 - Describe how you decide if revalidation is needed
- **Support Mechanisms**
 - Ensure that the system is function & being used correctly by periodic checks, audit, servicing & performance assessments
 - Train all users
 - Revalidate when making changes to hardware or software

Appendix 6:17

Instructor’s notes

Once validated, systems should be well maintained. Maintenance must be documented.

Systems should not be altered in any way without considering the potential effect on the validated system. If changes are considered to be necessary these must be made following a pre-defined process called a Change Control Procedure. Part of this procedure will be the evaluation of the effect of the change and whether or not full or partial validation will be necessary after the change has been made.



GLP and Computerised Systems

Validation of Computerised Systems

“Demonstrable suitability”

- **Validation Protocol:**
 - Description of tests to be performed, with acceptance criteria
 - Responsibilities for the tests
 - Timeframe for tests
- **Performance of the test**
 - Record all tests to enable full traceability of operations
 - Treat records as raw data, sign date
 - Record conformities, non-conformities and anomalies
- **Validation Report**
 - Summary of results
 - Take a position regarding the non-conformities and the impact of these
 - General conclusion regarding GLP compliance and whether the system is validated and can be used routinely

Appendix 6:18

Instructor’s notes

Responsibilities for validation should be clearly defined.

Generally a validation team will be constituted. This team often includes a domain expert (IT) and a user.

QA usually audits the documents (protocol, data, report) and inspects the performance of validation in the same way as they might audit/inspect a study.

The report should take a position regarding the validation status of the computerized system after execution of the protocol and the validation team should follow up on any outstanding actions that need to be taken.



GLP and Computerised Systems

Documents for the Application

For each application:

- Name, identification, code and purpose
- Software components and version numbers
- Hardware being used with the software
- Operating system and other software being used with the application
- Programming language
- Major functions performed by the application
- Overview of the data flow
- File structures
- Configuration & communication links
- Source code available or retrievable

Appendix 6:19

Instructor's notes

Documents are essential to describe, demonstrate suitability and support systems.

This slide summarizes the documents you are expected to have in place in order to claim GLP compliance



GLP and Computerised Systems

Standard Operating Procedures

- How to use the system
- Making and recording program or hardware changes
- Authorisation for program changes
- Security measures & detection of unauthorised entry into the system
- Testing and validation
- Maintenance of systems
- Software development or configuration Back-up procedures
- Contingency plans and disaster recovery
- Archival and retrieval of data
- Passwords and when/how to change them – electronic signatures
- Monitoring of use, validation and maintenance of systems

Appendix 6:20

Instructor's notes

This is a list of the type of SOPs needed in conjunction with your computerized system.



GLP and Computerised Systems

Archives

“Access control, proper indexing and expedient retrieval”

- Details of indexing method
- Environmental controls of computer room
- Procedures for recuperating data from retired systems
- Management authorisation prior to any destruction of data
- Data in support of computerised systems (source code, development, validation, monitoring...) to be kept as long as the study records associated with them

Appendix 6:21

Instructor's notes

Archiving electronic data is just as important as archiving any other media.

Some of the points you will need to consider when archiving electronically are mentioned here.



GLP and Computerised Systems

Definitions of terms

- **Electronic signatures** : magnetic impulse or computer compilation of symbols authorised by a person to be equivalent to his/her handwritten signature
- **Software (Application)** : Programme for controlling processes, data handling, reporting or archiving

Appendix 6:22

Instructor's notes

If there are questions on terminology, these four definitions (on 2 slides) may be useful for discussion with trainees.



GLP and Computerised Systems

Definitions of terms

- **Software (Operating System):** Programmes / routines that control the operations of a computer. May provide services like resource allocation, scheduling, input/output control and data management
- **Source Code:** The original human readable language programme which is made machine readable for execution by the computer

Appendix 6:23

Instructor's notes

If there are questions on terminology, these four definitions (on 2 slides) may be useful for discussion with trainees.

APPENDIX 7: GLP AND IN VITRO STUDIES

In the following text the citations in italics are from the OECD documents on “The Application of the Principles of GLP to *in vitro* Studies”

DEFINITION

In-vitro studies do not use whole animals or plants. They entail the use of subcellular fractions, microorganisms, extracts from animals or plants and isolated organs.

In most cases the studies are of short duration and the OECD consensus document “The Application of GLP Principles to Short Term Studies” is applicable. This would have an impact on the way in which the study plan is put together, the way in which QA inspects the studies and the way in which the report is compiled.

REFERENCE ITEMS

The definition of reference items, used for the more classical GLP safety studies, can be extended to cover the use of reference and control items – both positive and negative – which are frequently employed in *in vitro* studies.

Often such items are used to demonstrate that the test is performing adequately, that the test system is viable and/or of the correct quality. In other words they are often used to support the applicability of the study conditions and to support the results which are obtained.

“Since the purpose of these positive, negative and/or vehicle control items may be considered as analogous to the purpose of a reference item, the definition of the latter may be regarded as covering the terms ‘positive, negative, and/or vehicle control items’ as well”.

Analytical characterization of these items may be quite different from the analytical controls normally applied to “reference substances” used in *in vivo* studies.

RESPONSIBILITIES

Overall, the responsibilities of the test facility management, study director, study personnel and QA are no different in these studies than in other GLP safety studies. However the nature of the tests imposes a different emphasis on certain aspects of these responsibilities as discussed in the bullet points below.

Test facility management

- Greater emphasis on technical training because the test system and the environment that it will be manipulated in are usually very specific and sensitive. This may cover training for the handling of microorganisms, biohazardous material, cleaning and aseptic handling, and waste disposal.
- Provision of specific areas for manipulation. The importance of controlling possible contamination becomes very important, with the consequent emphasis on environmental control.
- Particular attention to the provision of supplies that are appropriate for the special tests performed and that regular good quality material is made available to the researchers.

“Certain in vitro studies may necessitate the use of proprietary materials or test kits. Although the OECD Consensus Document on Compliance of Laboratory Suppliers with GLP Principles states that materials to be used in a GLP compliant study should be produced and tested for suitability using an adequate quality system, thus placing the primary responsibility for their suitability on the manufacturer or supplier, it is the responsibility of the test facility management to confirm that these conditions are adequately fulfilled through assessment of the suppliers practices, procedures and policies”.

Study director

- Special attention to the way in which the study director characterizes the test system and the justification of the use of the test system as stated in the study plan.
“Justification of the test system may require that the study director document that the test method has been validated or is structurally, functionally, and/or mechanistically similar to a validated reference test”.

- Characterization of the *in vitro* system may be achievable with the help from suppliers who should be able to provide documentation on concerns such as cell line, age/passage, origin etc.
- The study director should be able to demonstrate that performs at the required level under the experimental condition in his/her study. This may be achieved by the use of appropriate positive, negative or vehicle controls.
- In the case where test kits are used, the supplier is responsible for the quality and performance of kits. However, the study director must ensure that the kits meet the specific requirements of the study and that they have been validated. It is usual for the kits to be received with documentation regarding their quality; these documents should be verified upon receipt. It is equally good practice to ensure that the supplier's processes and practices are sufficient to guarantee the quality of the kits received; this is normally achieved by conducting reviews and/or audits of the supplier's procedures.

“At a minimum, the study director should be able to judge the appropriateness of the quality system used by the manufacturer, and have available all documentation needed to assess the fitness for use of the test system, e.g., results of performance studies.”

Study Personnel

- Aseptic conditions are often required; Study Personnel follow procedures rigorously to ensure asepsis
- Procedures implemented to preclude cross contamination are of great importance and must be meticulously respected
- Where bihazardous material is used, procedures should be adhered to in order to protect the personnel, the environment and the study.

Quality Assurance

- QA activities can usually be conducted with the same approach as for Short-Term Studies. This has implications for the way in which inspections are performed, with a heavier reliance on process-based inspections.
- QA should work with domain experts, study directors or consultants, in order to identify the really critical aspects of the *in vitro* study and concentrate inspections/audits on these.

“Specific areas to be inspected may include, but not be limited to, the procedures and measures for:

- monitoring of batches of components of cell and tissue culture media that are critical to the performance of the test system (e.g. foetal calf serum, etc.) and other materials with respect to their influence on test system performance;
- assessing and ensuring functional and/or morphological status (and integrity) of cells, tissues and other indicator materials;
- monitoring for potential contamination by foreign cells, mycoplasma and other pathogens, or other adventitious agents, as appropriate;
- cleaning and decontamination of facilities and equipment and minimizing sources of contamination of test items and test systems;
- ensuring that specialized equipment is properly used and maintained;
- ensuring proper cryopreservation and reconstitution of cells and tissues;
- ensuring proper conditions for retrieval of materials from frozen storage;
- ensuring sterility of materials and supplies used for cell and tissue cultures;
- maintaining adequate separation between different studies and test systems.”

FACILITIES

Facilities must meet the requirements of studies and should be able to promote separation between activities, particularly in the case where cross contamination is an important issue as for *in vitro* studies. As *in vitro* studies do not usually require a great deal of space, this is not normally achieved by supplying specific facilities for each test, but rather by ensuring that activities are separated in time and by adequate cleaning or decontamination procedures.

“In this way it may be possible to incubate cells or tissues belonging to different studies within the same incubator, provided that an adequate degree of separation exists (e.g., appropriate identifiers, labelling or separate placement to distinguish between studies, etc.), and that no test item is sufficiently volatile so as to contaminate other studies that are co-incubated”.

The use of laminar flow cabinets to protect the test, the environment and personnel is standard practice for such studies.

Special areas for the storage of materials and test systems is generally imposed for these studies as they often require specific conditions such as freezing.

The preparation of test and control items may pose specific problems as sterility is often a requirement for this type of study.

APPARATUS, MATERIAL, AND REAGENTS

Specific points to consider for these studies are indicated below:

- Equipment may be particularly sensitive; micropipettes, micro balances, laminar flow cabinets. This means that the maintenance and calibration programme must be particularly rigorous.
- It is good practice to identify the critical parameters that need to be monitored in order to avoid jeopardising the studies.
- Use of alarms, having fixed strict limits will be of great value.
- The strict application of expiry dates, related to the rigorous observance of storage conditions, is absolutely necessary for the reagents used in *in vitro* studies because they are often labile.

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TEST SYSTEMS

Most test systems used in *in vitro* tests are of biological origin. They are often highly sensitive and this means that the conditions for their maintenance are particularly important. Attention must be paid to the storage condition, of course, but also to the conditions of use of the test systems.

Particular points for consideration are:

- Monitoring of the viability and performance of the test system.
- Documentation of maintenance.
- Viability and responsiveness before/during tests.
- Records regarding cells passage, population dynamics etc.
- Environmental conditions. “(e.g., liquid nitrogen level in a liquid nitrogen cryostorage system, temperature, humidity and CO₂ concentration in incubators, etc.)”.
- Test system manipulation: “(e.g., treatment with antibiotics or antifungals, subcultivation, selective cultivation for reducing the frequency of spontaneous events)”.

TEST SYSTEM RECORDS

According to GLP, records of test system receipt must be kept. In the context of *in vitro* studies the following should be taken into consideration:

- Receipt of cells, cell lines etc should be recorded using the usual parameters of date time, condition and supplier etc. But the records should show both vendor and the original, derived source: “(e.g., *primary cells or tissues with donor characteristics; established cell lines from recognized sources, etc.*)”
- The way in which the system was originally obtained should also be available: “(e.g., *derived from tissue explants, biopsies of normal or cancer tissues, gene transfer by plasmid transfection or virus transduction, etc.*)”
- The way in which the system has been maintained should also be scrupulously recorded.
- Measures must be taken to ensure that the labels are durable during storage and use. This is particularly the case where the container size is tiny and the conditions extreme: “(e.g., *cryovials in liquid nitrogen, multiple test systems stored in one container*)”.
- The requirements applied to test systems and reagents apply equally to test kits; in particular those concerning expiry dates. Extension of expiry dates must be based on appropriate test results.

STANDARD OPERATING PROCEDURES (SOPS)

SOPs must exist for all aspects of *in vitro* studies. In addition to those noted in the GLP Principles, the following are illustrative examples of what may be further required:

- Monitoring of environmental parameters of specialized test facilities -
- Cleaning, disinfecting, decontaminating facilities/equipment.
- Calibration and monitoring of storage conditions.
- Expiry dates and extension of expiry dates materials and reagents.
- Conditions of storage, freezing and thawing of cells etc.
- Verification and acceptance procedures for test systems.
- Precautions when using biohazardous materials.
- Disposal of materials and test systems.
- Aseptic procedures.

PERFORMANCE OF THE STUDY AND REPORTING OF STUDY RESULTS

The requirements for *in-vitro* studies are the same as for *in vivo* studies. The OECD consensus document on Short-Term Studies will often apply to *in-vitro* studies.

Specific issues that should be addressed in the final report are of a scientific or technical nature, eg.: use of “*appropriate positive, negative, and untreated and/or vehicle controls*”.

STORAGE AND RETENTION OF RECORDS AND MATERIALS

In addition to the requirements for archiving that apply to all GLP studies, the following points should be considered:

- The long term storage and viability of test systems “especially test systems of limited availability (*e.g., special subclones of cell lines, transgenic cells, etc.*), in order to enable confirmation of test system identity, and/or for study reconstructability”.
- Retention of historical records pertaining to “*positive, negative, and untreated and/or vehicle control results used to establish the acceptable response range of the test system...*”.



In vitro Studies

GLP and *in vitro* Studies

Appendix 7:1



In vitro Studies

Why a special guidance document ?

- *In vitro* methods more prominent today
- Ethical reasons for supporting the development of *in vitro* studies
- Methods necessary to replace studies in whole animals (*in vivo*)
- So far mostly used in gene-tox studies, but importance growing

Appendix 7:2

Instructor's notes

In vitro methods are becoming more common in the field of drug safety testing.

Discuss with the trainees why this is so.

***In vitro* Studies**

Whatever the type of safety study:

- GLP applies to those studies that will be part of a regulatory package
- *In vitro* studies must still comply with the principles of :
 - Planning
 - Performance
 - Recording
 - Reporting
 - Monitoring and
 - Archiving

Appendix 7:3

Instructor's notes

To claim GLP compliance *in vitro* methods must adhere to the Principles listed here.

Briefly recall the salient points relating to each of these.

***In vitro* Studies**

Definition of *in vitro* safety study:

- Studies which do not use multicellular organisms as test systems
- Studies use microorganisms or material isolated from organs as test systems
- In most cases, the OECD guidance on "Short-Term Studies" applies

Appendix 7:4

Instructor's notes

Most *in vitro* methods are of short duration, therefore the OECD guidance on Short-Term test would apply.

Discuss with the participants the kinds of *in vitro* studies they perform.



In vitro Studies

Reference items:

- Most *in vitro* studies use trial items in addition to the *test items*: e.g. positive and negative controls etc
- These are generally used to demonstrate that the trial is performing adequately
- These can be assimilated to reference items for GLP purposes, but performing characterisation studies on them may not be appropriate

Appendix 7:5

Instructor's notes

One of the difficulties with *in vitro* methods is that they usually require trial substances in addition to the test item. Substances may be used to demonstrate the appropriateness of the test conditions. This means that the standard GLP definition of the test item and reference substances does not strictly apply in this case.

However, the OECD document on *in vitro* studies says that all these other trial materials should be considered as reference materials for GLP purposes. But, it may not be possible, or appropriate to characterize them in the usual manner.



In vitro Studies

Management responsibilities:

- Responsibilities do not change, but:
 - There may be special needs regarding facilities, e.g. aseptic work areas
 - There will be specific needs for training personnel to perform highly critical procedures, with hazardous materials
 - There will be special needs regarding the disposal of waste materials to avoid risks of contaminating the environment and other test systems

Appendix 7:6

Instructor's notes

The GLP responsibilities of management are no different in *in vitro* studies than any other type of study.

However, due to the nature of the studies, there may be specific requirements to meet, both in terms of facilities and training.

Discuss with participants the three points presented in this slide.



In vitro Studies

Study Director responsibilities:

- Responsibilities do not change, but:
 - Difficult to document the justification of choice and the characterisation of the test system (unlike animals: species, strain, sex, weight, supplier...)
 - May need to justify that the test method (with the test system) has been validated or is functionally very similar to one that has been validated

Appendix 7:7

Instructor's notes

Overall, the GLP responsibilities of the study director are no different in *in vitro* studies than any other type of study.

However, due to the nature of the studies, there may be specific requirements to meet.

Discuss with participants the points presented in this slide and the following one.



In vitro Studies

- Documentation, with the assistance of the supplier, of the cell line and origin may be possible
- Document also that the system provides the desired level of performance
- Include in study the positive, negative, untreated and/or vehicle controls
- When using kits, the responsibility of the supplier is paramount, but the SD must ensure that the kits are performing adequately

Appendix 7:8



In vitro Studies

Quality Assurance responsibilities:

- Responsibilities do not change, but:
 - QA can apply the audit methodology applicable to all short-term studies
 - Use of process-based inspections/audits will be frequent if the test is routine
 - Determine with the SD (or expert consultant) what are the really critical parts of the study type so that QA can concentrate efforts on these

Appendix 7:9

Instructor's notes

Overall, the GLP responsibilities of quality assurance are no different in *in vitro* studies than any other type of study.

However, due to the nature of the studies, QA can usually apply the methodology related to Short-Term studies.

This will entail deciding which processes are "routine" and therefore candidates for "process-based inspections".



In vitro Studies

Specific areas for QA interest are likely to include:

- Monitoring batches of components of cell and tissue culture media that are critical to performance e.g. foetal calf serum)
- Monitoring for potential contamination by foreign cells, mycoplasma, pathogens...
- Cleaning & decontamination procedures
- Use and maintenance of specialised equipment, rooms, autoclaves, filters....

Appendix 7:10

Instructor's notes

Again, due to the nature of the studies, QA may have to implement specific monitoring process.

Some of these are itemised in this slide and the following slide.



In vitro Studies

Specific areas for QA interest are likely to include:

- Procedures for cryopreservation and reconstitution of cells and tissues
- Procedures for the retrieval of materials from frozen storage
- Processes that ensure sterility of supplies used for cell and tissue cultures
- Maintenance of adequate separation between different studies and test systems

Appendix 7:11

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In vitro Studies

Facilities for handling test systems

- The Principles of appropriate separation still apply
 - Separation of studies can be temporal or spatial
 - Cells/tissues of different systems can be incubated in the same incubator provided there is adequate separation (identifiers, labels, placement...)
 - Perform sequential manipulation of test systems with cleaning in between
 - Manipulate under laminar flow conditions

Appendix 7:12

Instructor's notes

In vitro studies often require very specific facilities.

Concerns are centred on the viability and quality of test systems and the levels of potential contamination. The principle of separation between activities and materials is of heightened importance in these circumstances.

This slide and the next one mention some of the issues in the *in vitro* situation.



In vitro Studies

Facilities for handling test & reference items

- The Principles of appropriate separation still apply
 - Rooms for preparation of items may need to provide aseptic conditions as the problem of cross contamination is crucial in these tests
- All the rules regarding receipt, handling of items apply. Traceability of all handling operations are important

Appendix 7:13



In vitro Studies

Apparatus, Materials

- *In vitro* studies are likely to use highly sensitive equipment, regular calibration required
 - Micro balances, micro pipettes...
- Facilities are likely to require qualification before maintenance and regular testing
 - Laminar flow cabinets, autoclaves, incubators
- Critical parameters for continuous monitoring will usually be identified

Appendix 7:14

Instructor's notes

Since the facilities and the equipment used in *in vitro* studies are likely to be sensitive to contamination, or may be critical to the viability of the test system, it is obvious that the related maintenance and calibration processes must be fully controlled and regularly performed.

Frequent monitoring of the environment where tests are performed, or monitoring of the quality or viability of test systems is usual. It is important to determine before the tests are performed which monitoring activities are essential and the frequency at which these will be performed.

Discuss with the participants examples of monitoring in *in vitro* studies.



In vitro Studies

Standard Operating Procedures

- Approach for *in vitro* studies is same as in *in vivo* GLP
- Special consideration in the following domains:
 - Environmental monitoring
 - Cleaning, decontamination
 - Cell / line culture / maintenance
 - Cell bank management
 - Receipt of new test systems.....

Appendix 7:15

Instructor's notes

Again, due to the nature of the studies, specific SOPs will be implemented.

Discuss with participants the types of SOPs which are likely to be necessary in these studies. The SOPs in this slide give ideas for discussion.



In vitro Studies

Performance and Reporting of studies

- *In vitro* studies are likely to be short and thus the OECD guidance on "Short-term studies" usually applies
- Ensure that specific scientific concerns of the *in vitro* study are addressed in study plan
 - Use of laminar flow cabinets, autoclaves, incubators
 - Verification of strains of micro-organisms.....

Appendix 7:16

Instructor's notes

Reporting of *in vitro* studies must be as complete as for other studies. The information required in the report will depend upon the study plan initiated.

In all cases the study director must provide a report which is a true representation of the conduct of the study and an accurate representation of the results. Typically the report will contain information that provides confidence that the test was under control, often with results that demonstrate that the test system was viable and responding appropriately under the study conditions.

If appropriate, the study may be reported using the processes described in the OECD document on Short-Term studies.

***In vitro* Studies****Storage/Retention of Records & Materials**

- Storage/Retention of records same for all archiving to GLP
- Consider retaining samples or lines or sub-clones of test systems in order to be able to verify identification or to repeat work
- Retention of test items same as for *in vivo* GLP

Appendix 7:17

Instructor's notes

When archiving, consideration should be given as to the samples and specimens that need to be retained in order to ensure complete reconstruction of the study. These may be different to those of more classical studies.



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