World Health Organization

SECOND EDITION

TRAINING MANUAL

GOOD LABORATORY PRACTICE (GLP)

TRAINEE

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

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GOOD LABORATORY PRACTICE TRAINING MANUAL

FOR THE TRAINEE

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

World Health Organization

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FOREWORD

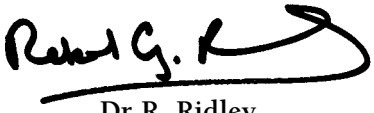
In order to assist countries in conducting non-clinical research and drug development, TDR developed a ***Good Laboratory Practices (GLP)*** series in 2001, comprising a *GLP Handbook* as well as *GLP Training manuals* for trainers and trainees.

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 Trainees* 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, and 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 disease endemic countries to develop and lead research activities at internationally-recognized standards of quality. This revised GLP series will support that goal, assisting DEC institutions in performing research and drug development studies to international standards. 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 version of the WHO/TDR GLP training manual for trainees. 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 trainees is part of a suite of three documents. These are:

1. The WHO/TDR GLP Handbook (blue),
2. GLP Training Manual for Trainers (red),
3. 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 and
- Quality Assurance.

However, the major difference seen in this version is the additional material to be found in the 7 appendices. As there is far too much material for it all to be used in a single three-day training course, the trainers will select what to use from the appendices depending upon the level of GLP knowledge of the trainees.

Presentation of material

There are 6 chapters and 7 appendices each one dealing with a separate topic. The six chapters cover the essential core topics which will be used for all the basic training courses. The appendices provide optional presentation material.

Each of the chapters and appendices has the same format:

- ***Summary section***

This is for your reference, it is worth reading through this section before attending the course, or afterwards to refresh your memory.

- ***Slide Presentation***

The presentations are in the form of slides. You are encouraged to make additional personal notes on these.

During this course, you will be asked to participate in workshops. The workshops are group activities and are very important parts of this course. The trainer will provide you with the workshop materials, put each of you into a group, and tell you how to proceed and how long you have to complete the workshop. The point of workshops is to discuss the topic with the group participants, to share your ideas and to learn from the group's collective experience. Workshops are always followed by a plenary session where feedback from all groups and from the trainers will help you enormously to understand all the principles of GLP.

ACKNOWLEDGEMENTS

The Good Laboratory Practice (GLP) Training Manual comprise two documents; one for the trainer (red), one for the trainee (green). They 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 version and on the input from the many international GLP training sessions and workshops organised by the WHO/TDR Pre-clinical 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 Disease Endemic countries.

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 countries 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 assess the scientific value of the studies.

All GLP texts, irrespective of their origin, stress the importance of the following 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.

Fundamentals of OECD GLP Principles

Introduction

and

Fundamentals of GLP

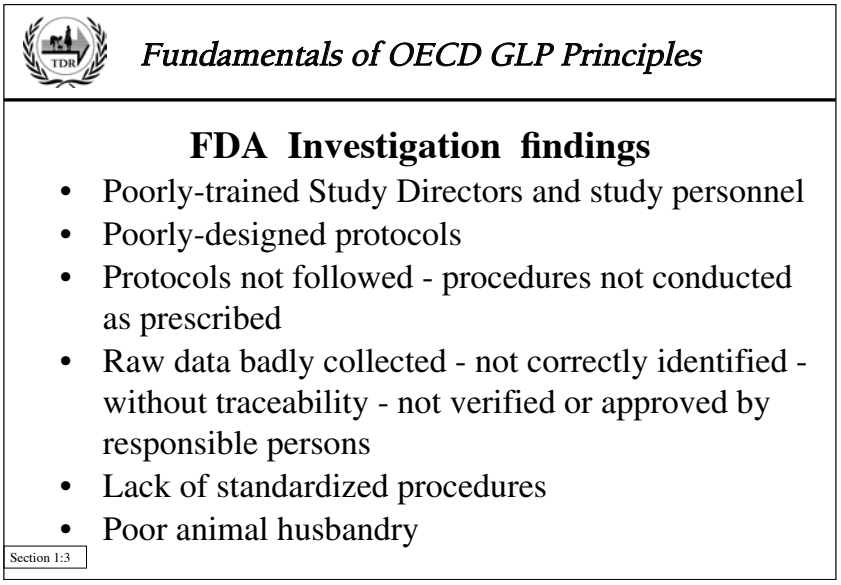
Section 1:1

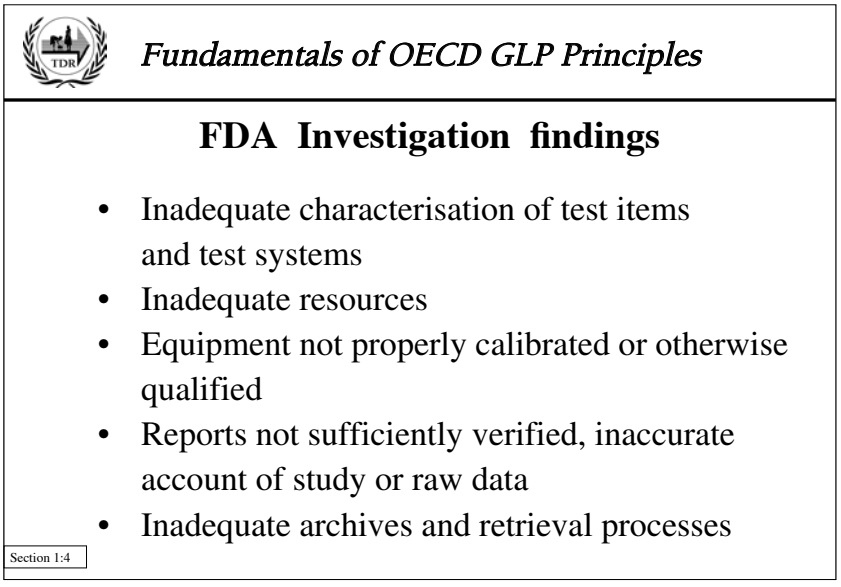
Fundamentals of OECD GLP Principles

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


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


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

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

Fundamentals of OECD GLP Principles

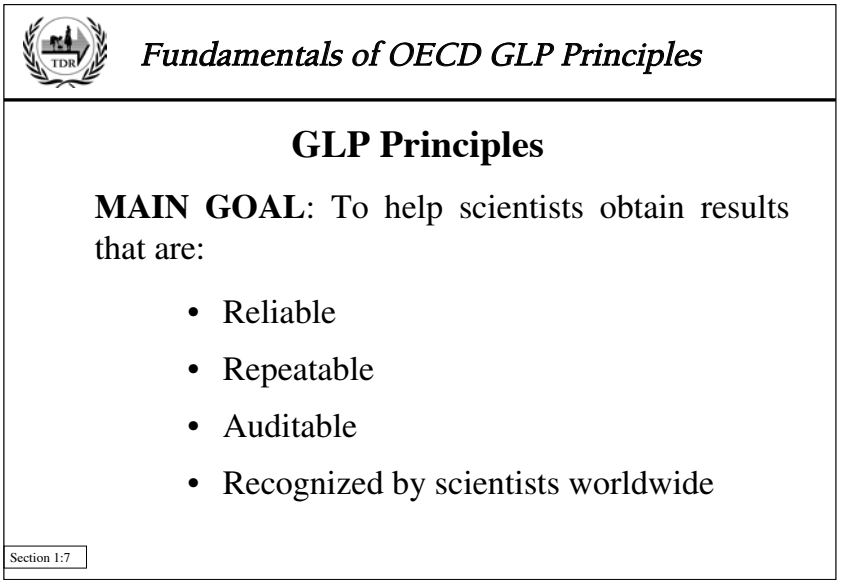
GLP

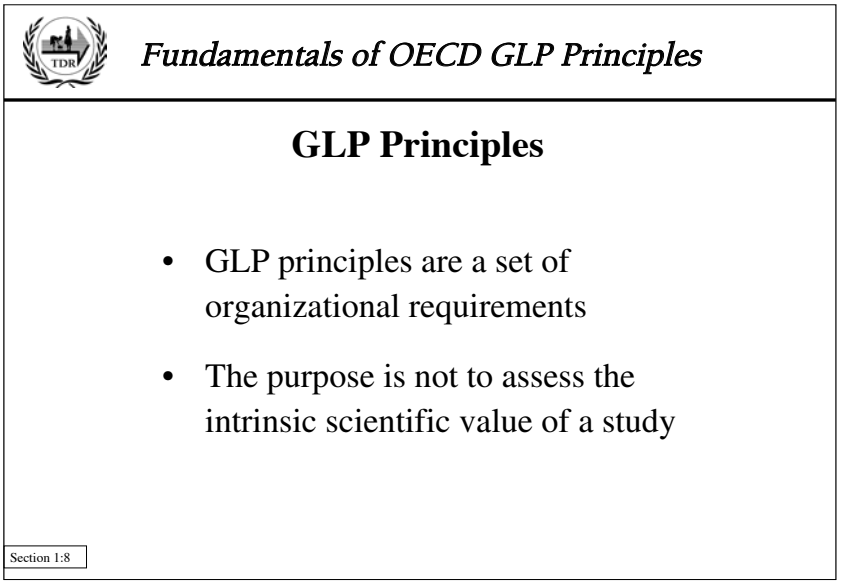
promotes

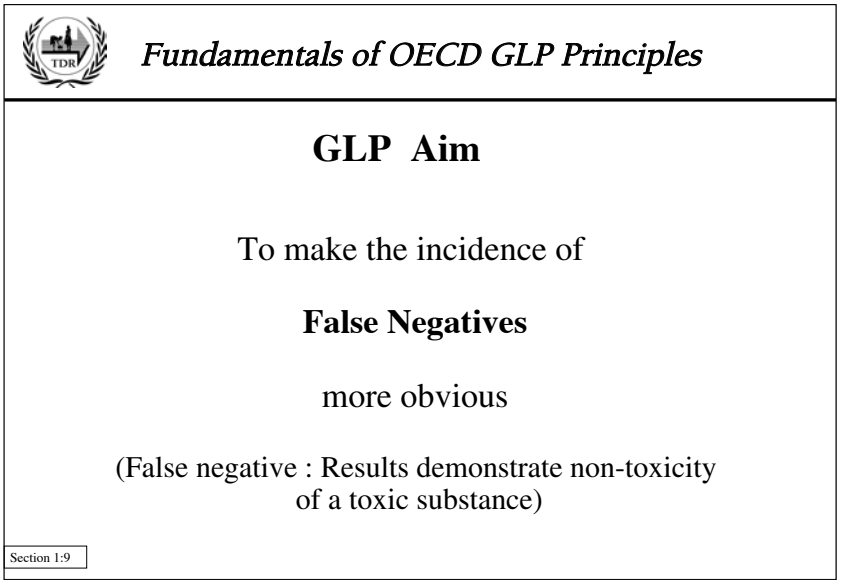
Quality and Validity

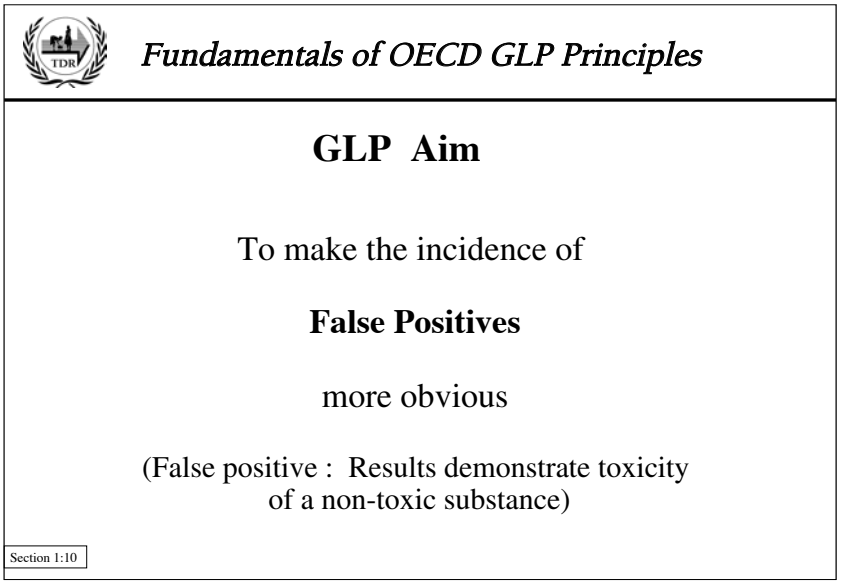
of test data

Section 1:6


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


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


Fundamentals of OECD GLP Principles
GLP Aim
To make the incidence of
False Negatives
more obvious
(False negative : Results demonstrate non-toxicity of a toxic substance)
Section 1:9


Fundamentals of OECD GLP Principles
GLP Aim
To make the incidence of
False Positives
more obvious
(False positive : Results demonstrate toxicity of a non-toxic substance)
Section 1:10

Fundamentals of OECD GLP Principles

GLP Aim

To promote mutual recognition of study data across international frontiers

Section 1:11

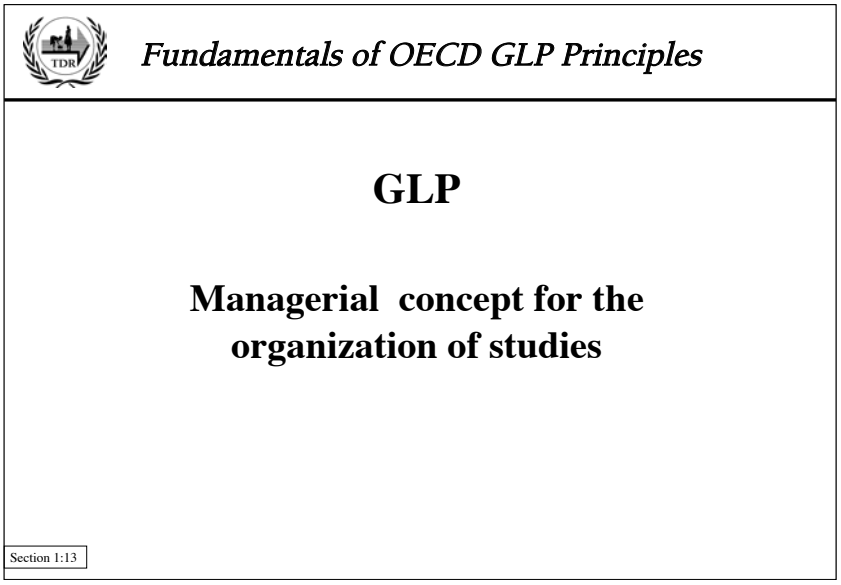
Fundamentals of OECD GLP Principles

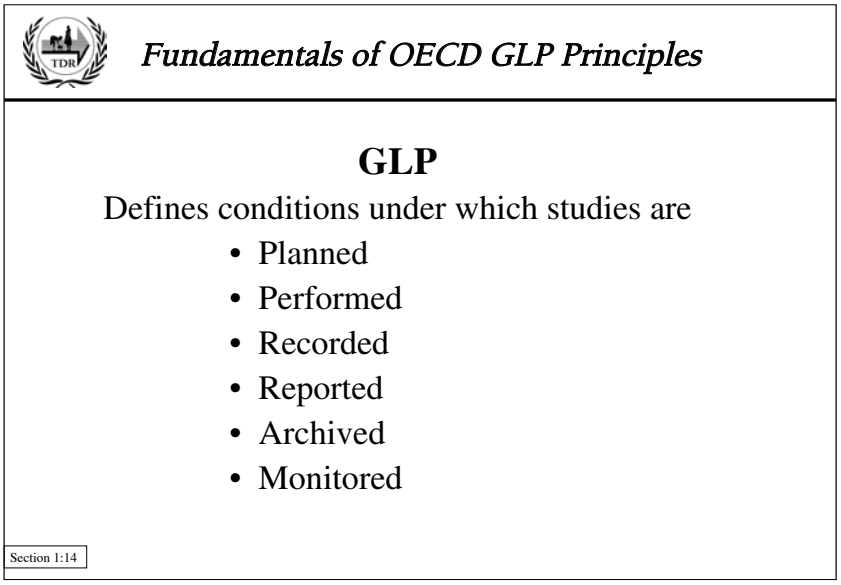
GLP

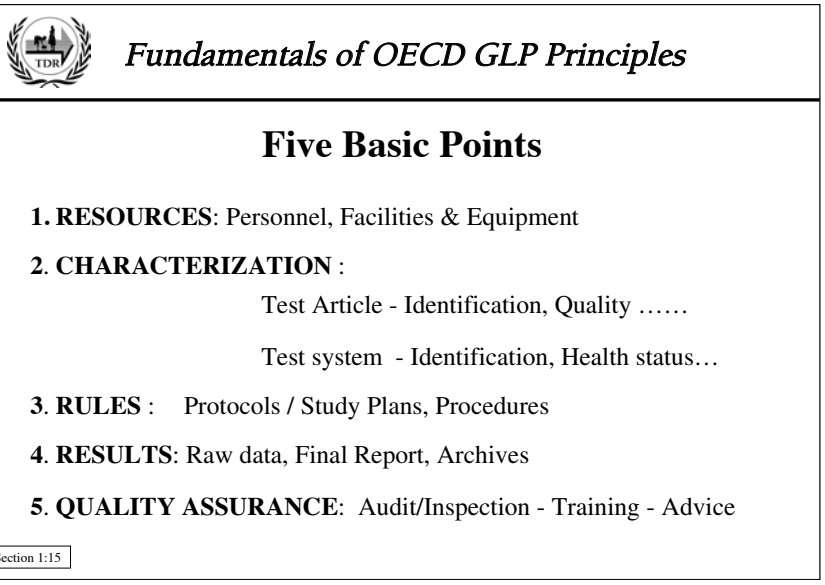
- ***Limit waste*** of resources
- Ensure ***high quality*** of results
- Ensure ***comparability*** of results
- Promote ***mutual recognition*** of results

(Preamble to European Directive 87/18 EEC)

Section 1:12


Fundamentals of OECD GLP Principles
GLP
Managerial concept for the organization of studies
Section 1:13


Fundamentals of OECD GLP Principles
GLP
Defines conditions under which studies are
• Planned
• Performed
• Recorded
• Reported
• Archived
• Monitored
Section 1:14


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

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 organizational 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 organizing 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 maintained 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 practice 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 Descriptions

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 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.

Minimizing 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, without crevices.

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

Such procedures may include:

- minimizing the number of staff allowed to enter the building;
- restricting entry into animal rooms;
- organizing 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, or immediate access to an engineer or 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 responsibile 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 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 that staff are well instructed in the use of equipment and aee able to take appropriate action when problems arise.

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

SOP: SOPs for instructions in the routine use, cleaning, calibration etc. of the facility or equipment.

SOP for the regular verifications or services performed on buildings or equipment.

Qualification documents: 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, and a report including the test results and a conclusion.

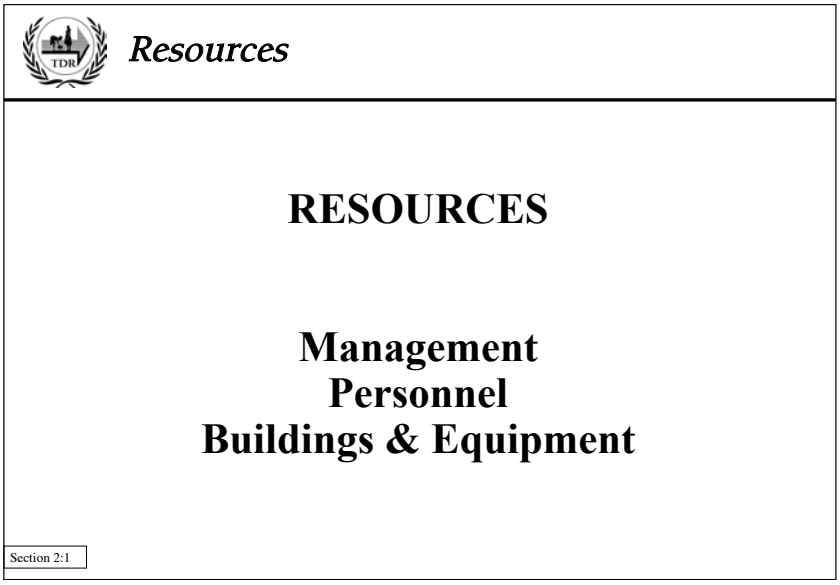
When no formal qualification is required, the study director or the management of the institution should define, usually in an SOP, the purpose of the equipment. For example, a balance with a precision to the nearest gram will be suitable for weighing in an animal house but not in the analytical laboratory.

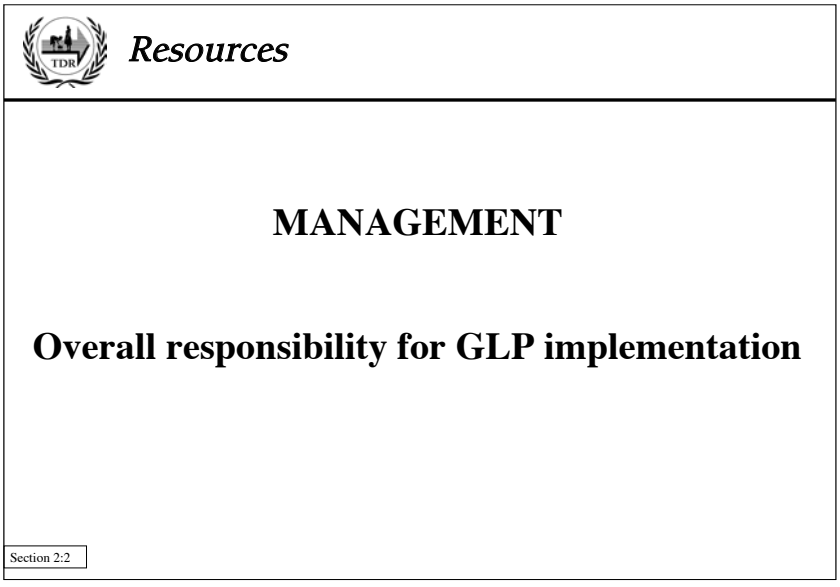
Logbook: Logbooks are kept to record the use of equipment (e.g. HPLC column used for product "x" – with dates, then for product "y" – with dates).

They are also used for recording regular checks (e.g. regular use of check-weight for balances, temperature record for refrigerator, etc.).

Service report: Service reports and equipment labels indicates 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.

Fault action report: 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 equipment is fit or unfit for use.


Resources
RESOURCES
Management
Personnel
Buildings & Equipment
Section 2:1


Resources
MANAGEMENT
Overall responsibility for GLP implementation
Section 2:2

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**

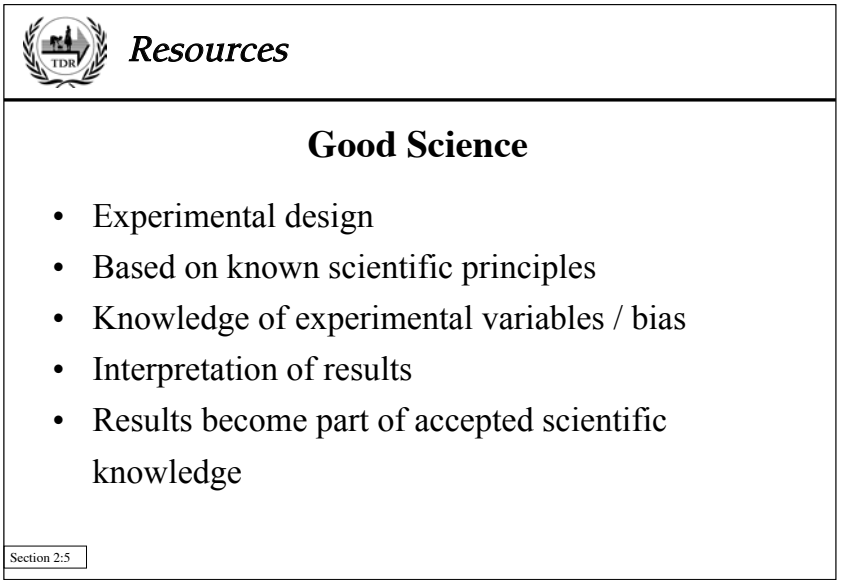
Section 2:3

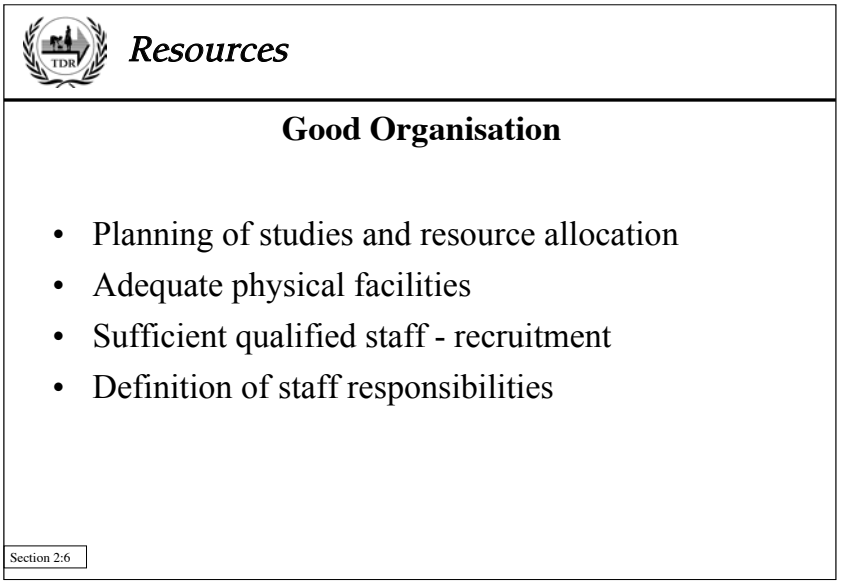
Resources

MANAGEMENT

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

Section 2:4


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


Resources
Good Organisation
• Planning of studies and resource allocation
• Adequate physical facilities
• Sufficient qualified staff - recruitment
• Definition of staff responsibilities
Section 2:6

Resources

Good Organisation

- Staff training
- Ensuring proper conduct of studies
- Good record keeping & organized archives
- Implementation of verification procedures for study conduct and results

Section 2:7

Resources

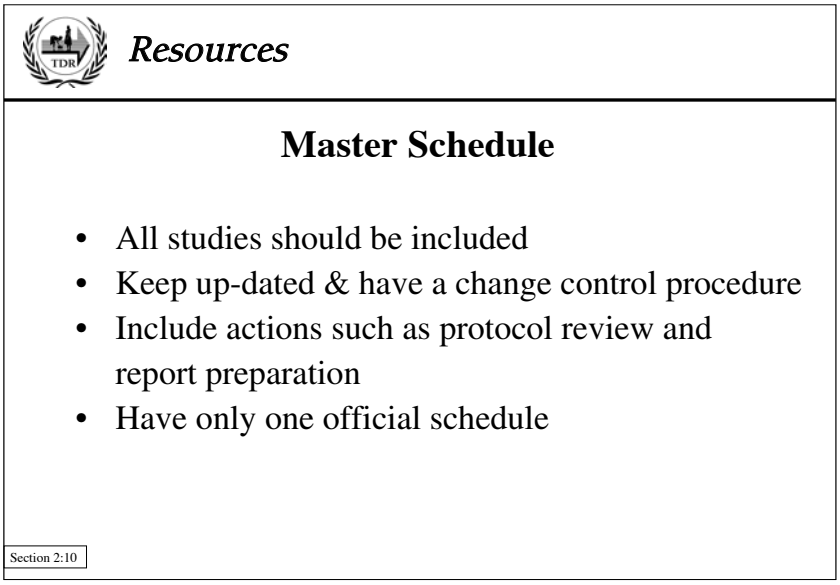
Good Organisation

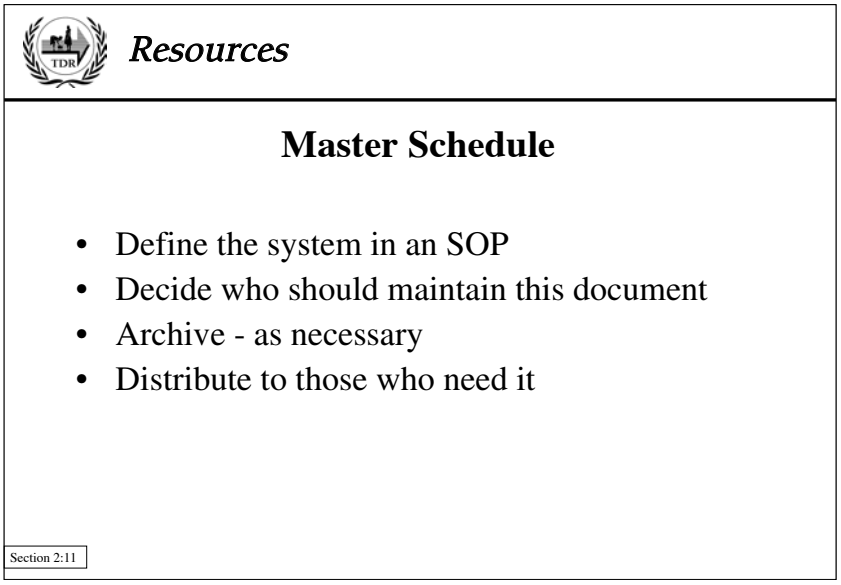
- All these organisational aspects are covered by **GLP**

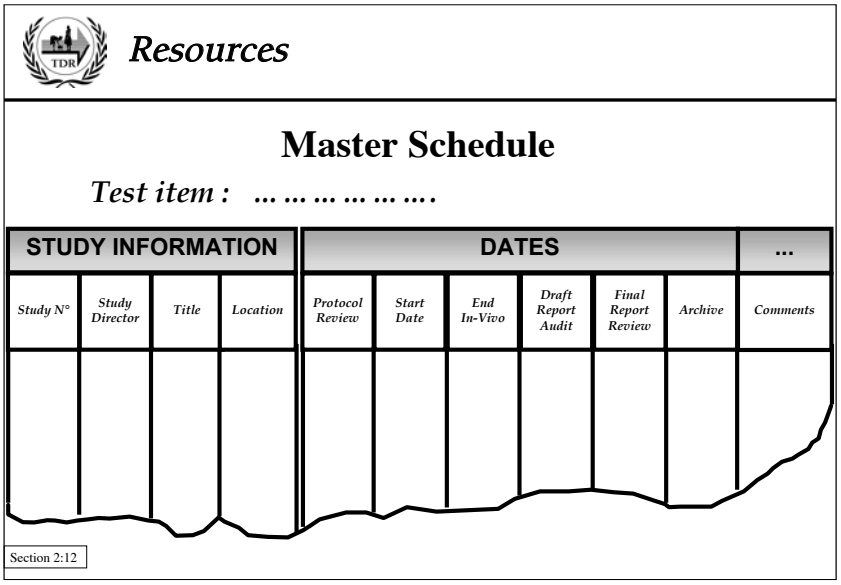
- **GLP is about ensuring good organisation of studies**

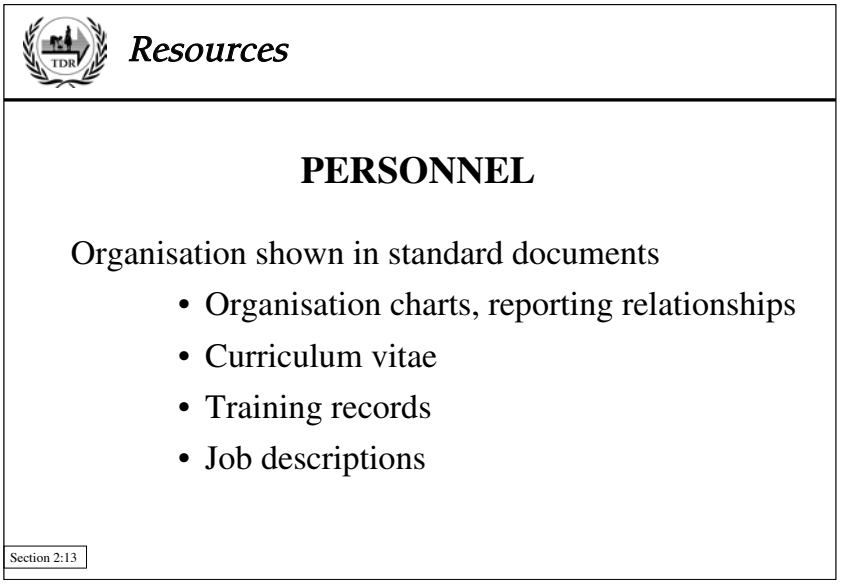
Section 2:8

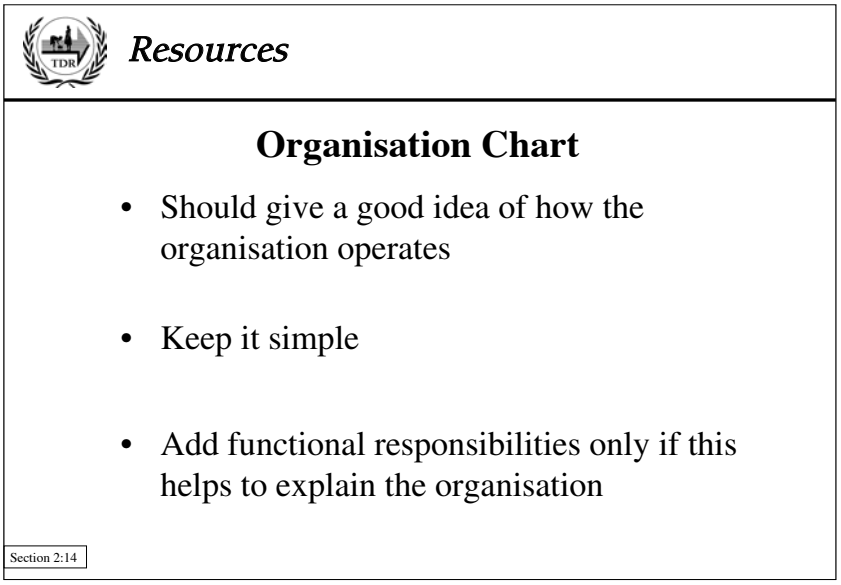

Resources
Planning / Resource Allocation
• Management responsibility
• Sufficient physical resources and personnel
MASTER SCHEDULE
Section 2:9

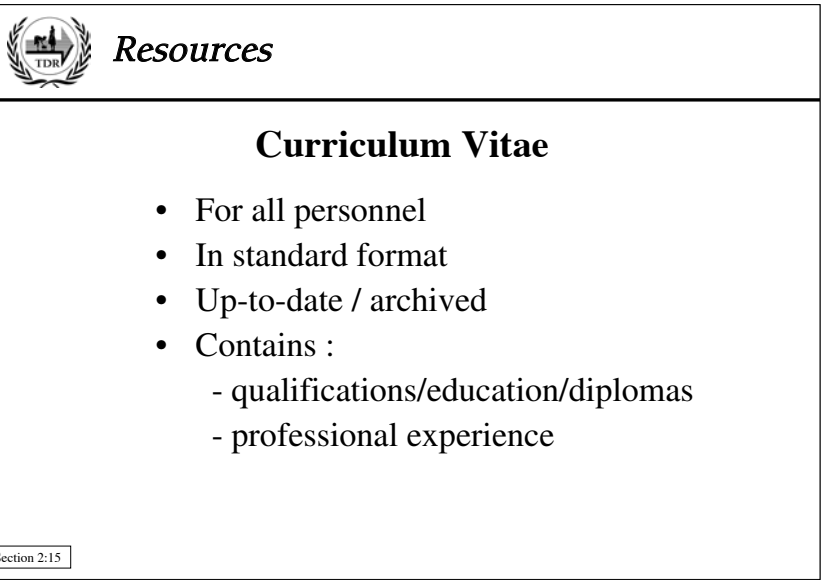

Resources
Master Schedule
• All studies should be included
• Keep up-dated & have a change control procedure
• Include actions such as protocol review and report preparation
• Have only one official schedule
Section 2:10

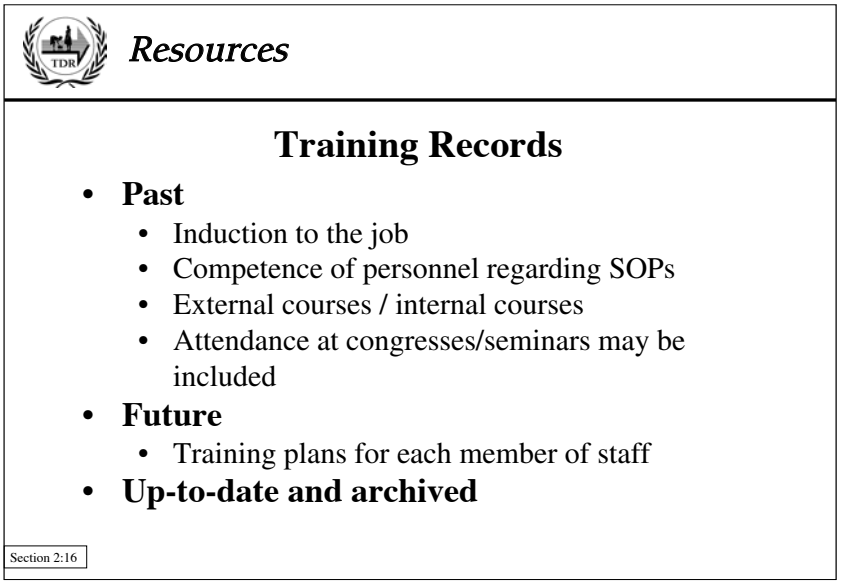

Resources
Master Schedule
• Define the system in an SOP
• Decide who should maintain this document
• Archive - as necessary
• Distribute to those who need it
Section 2:11

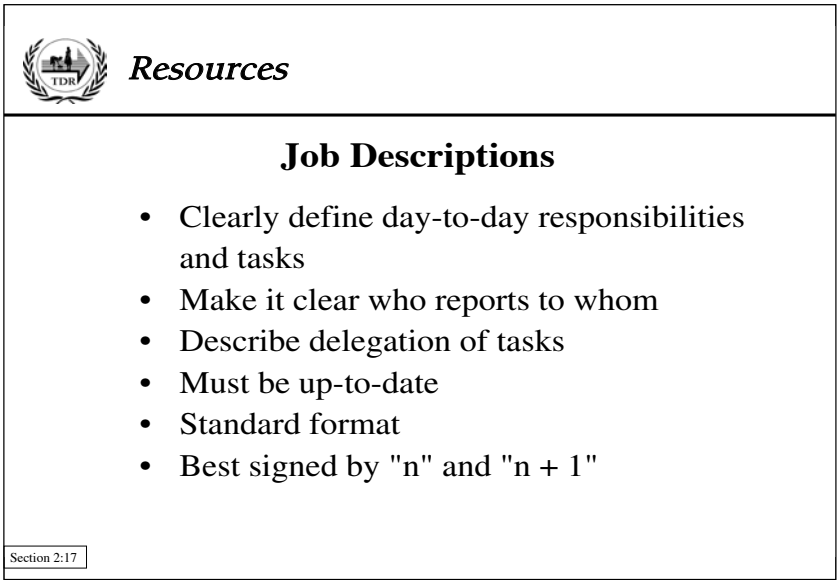

Resources
Master Schedule
Test item : ……
STUDY INFORMATION
DATES
...
Study N°
Study Director
Title
Location
Protocol Review
Start Date
End In-Vivo
Draft Report Audit
Final Report Review
Archive
Comments
Section 2:12

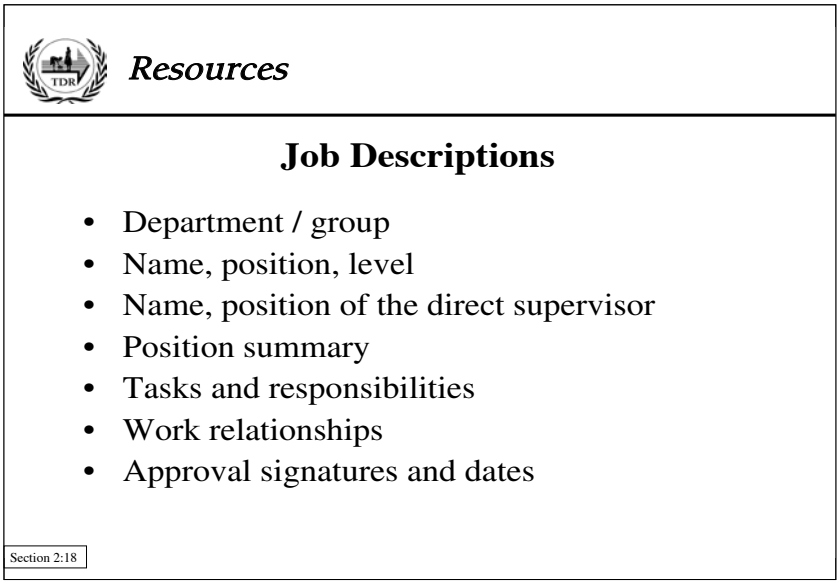

Resources
PERSONNEL
Organisation shown in standard documents
• Organisation charts, reporting relationships
• Curriculum vitae
• Training records
• Job descriptions
Section 2:13

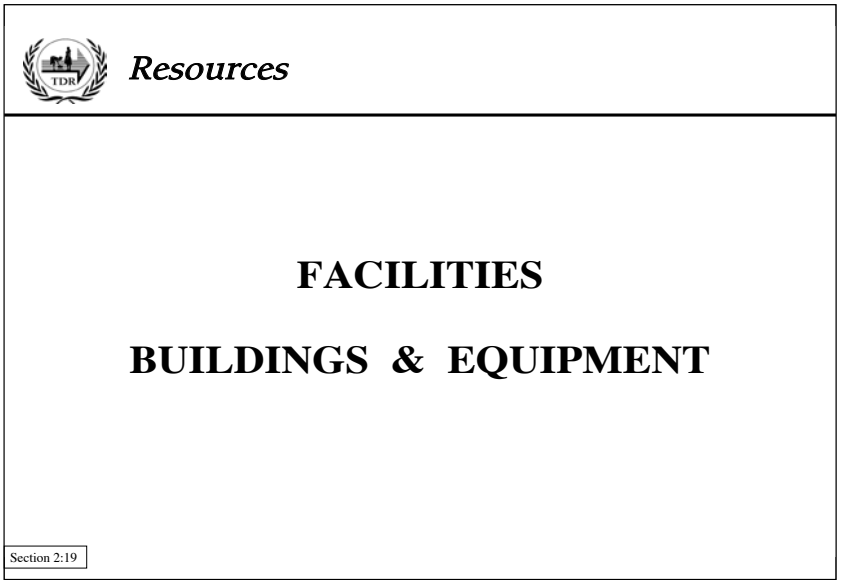

Resources
Organisation Chart
• Should give a good idea of how the organisation operates
• Keep it simple
• Add functional responsibilities only if this helps to explain the organisation
Section 2:14

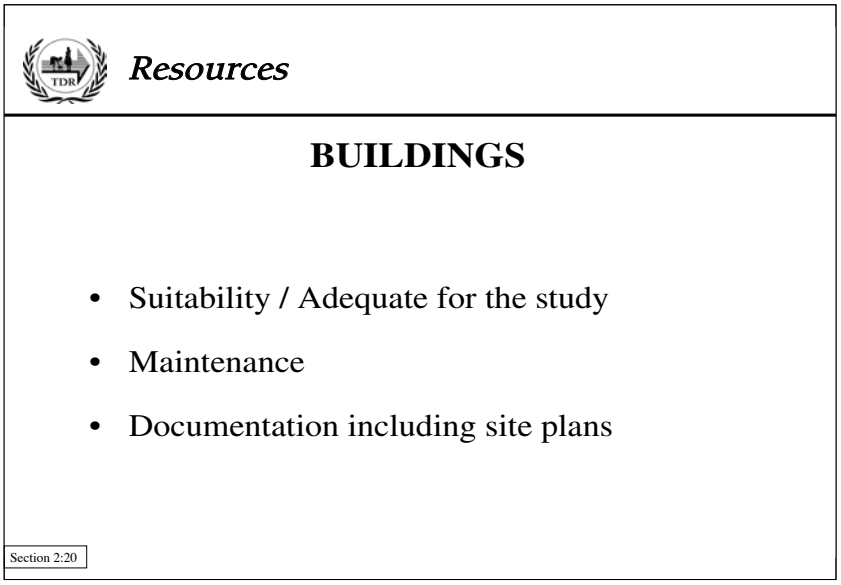

Resources
Curriculum Vitae
• For all personnel
• In standard format
• Up-to-date / archived
• Contains :
- qualifications/education/diplomas
- professional experience
Section 2:15

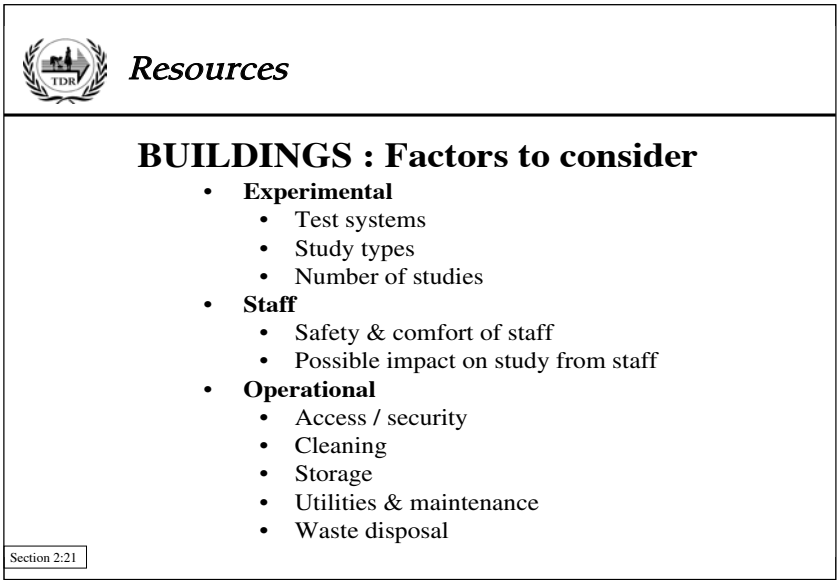

Resources
Training Records
• Past
• Induction to the job
• Competence of personnel regarding SOPs
• External courses / internal courses
• Attendance at congresses/seminars may be included
• Future
• Training plans for each member of staff
• Up-to-date and archived
Section 2:16

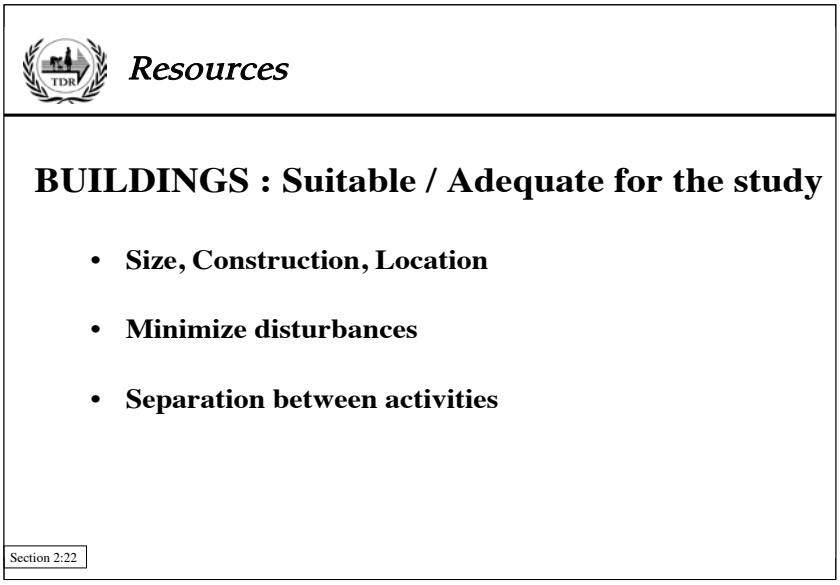

Resources
Job Descriptions
• Clearly define day-to-day responsibilities and tasks
• Make it clear who reports to whom
• Describe delegation of tasks
• Must be up-to-date
• Standard format
• Best signed by "n" and "n + 1"
Section 2:17

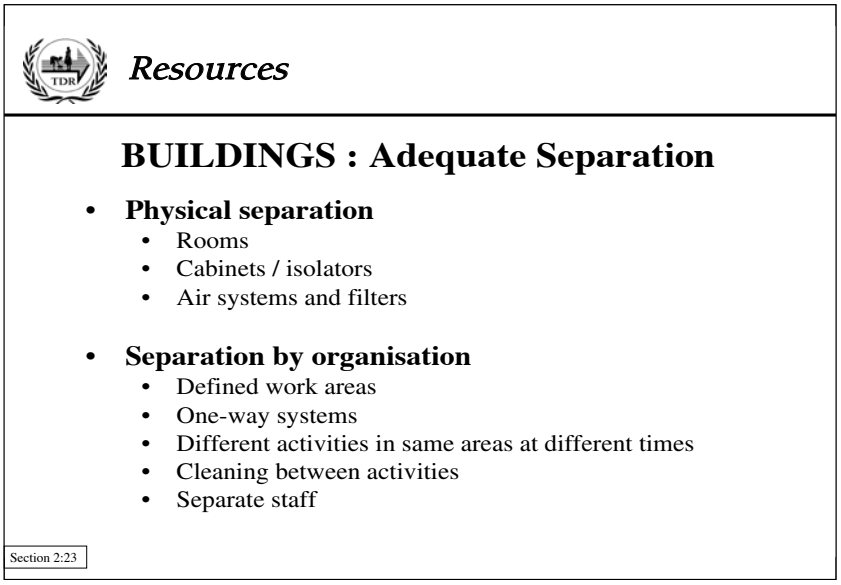

Resources
Job Descriptions
• Department / group
• Name, position, level
• Name, position of the direct supervisor
• Position summary
• Tasks and responsibilities
• Work relationships
• Approval signatures and dates
Section 2:18

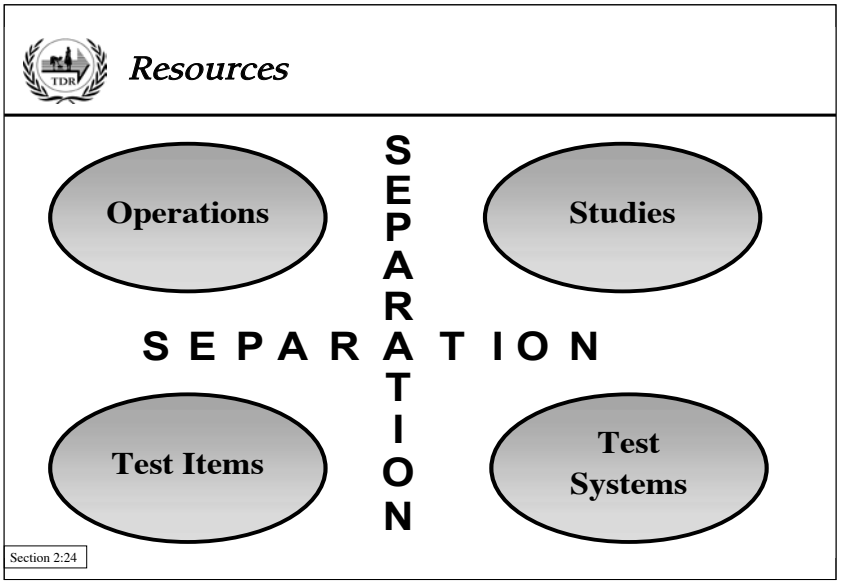

Resources
FACILITIES
BUILDINGS & EQUIPMENT
Section 2:19


Resources
BUILDINGS
• Suitability / Adequate for the study
• Maintenance
• Documentation including site plans
Section 2:20


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


Resources
BUILDINGS : Suitable / Adequate for the study
Size, Construction, Location
Minimize disturbances
Separation between activities
Section 2:22


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


Resources
Operations
Studies
SEPARATION
SEPARATION
Test Items
Test Systems
Section 2:24

Resources

BUILDINGS : Examples

Two examples :

- Dose mixing unit
- Animal facilities

Section 2:25

Resources

Dose Mixing Unit

Deals with test and control items and their :

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

Section 2:26

Resources

Dose Mixing Unit

- **Size**
  - Accommodates all activities (including paperwork) without risk of mix-ups or cross contamination
  - Sufficient working area, separate storage and waste disposal
- **Construction**
  - Materials allow for easy cleaning
  - Air flow / filters protect test items & personnel

Section 2:27

Resources

Dose Mixing Unit

LOCATION - Separate areas for :

- 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

Resources

Animal House Facilities

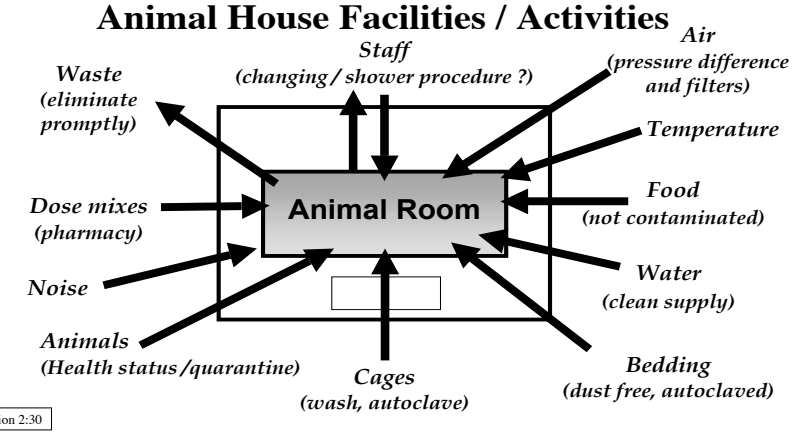
- Design should :
  Reduce risk of test system :
  - being affected by environmental variables
  - encountering disease
  - encountering other test articles

- Separate activities where possible, use barriers

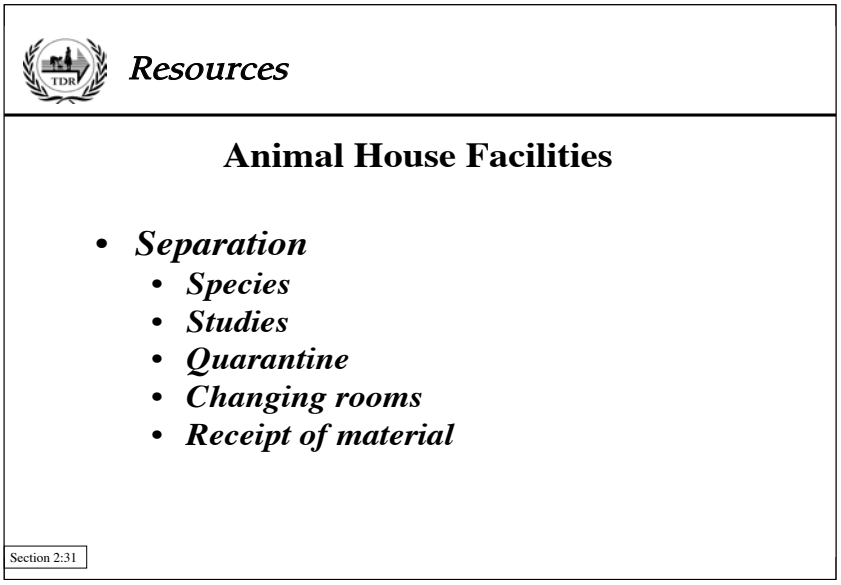
Section 2:29

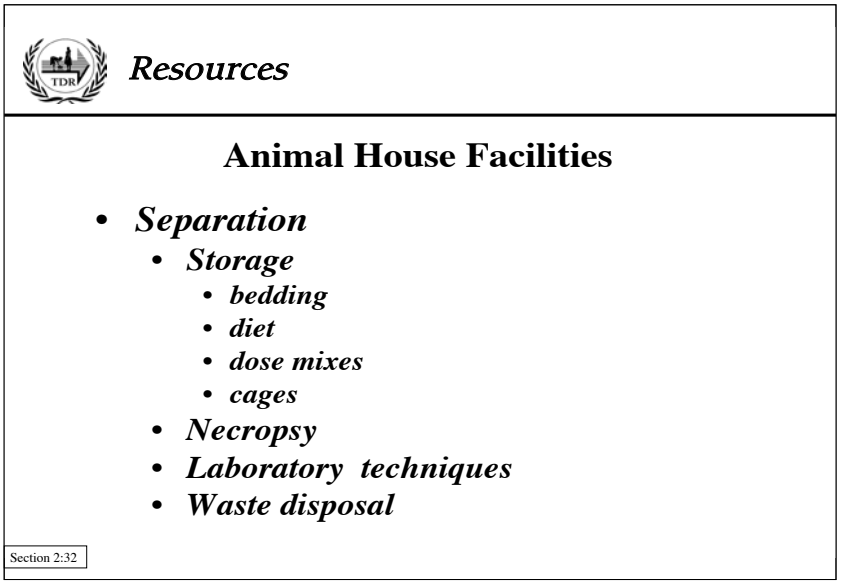
Resources

Animal House Facilities / Activities



Section 2:30


Resources
Animal House Facilities
• Separation
• Species
• Studies
• Quarantine
• Changing rooms
• Receipt of material
Section 2:31


Resources
Animal House Facilities
• Separation
• Storage
• bedding
• diet
• dose mixes
• cages
• Necropsy
• Laboratory techniques
• Waste disposal
Section 2:32

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

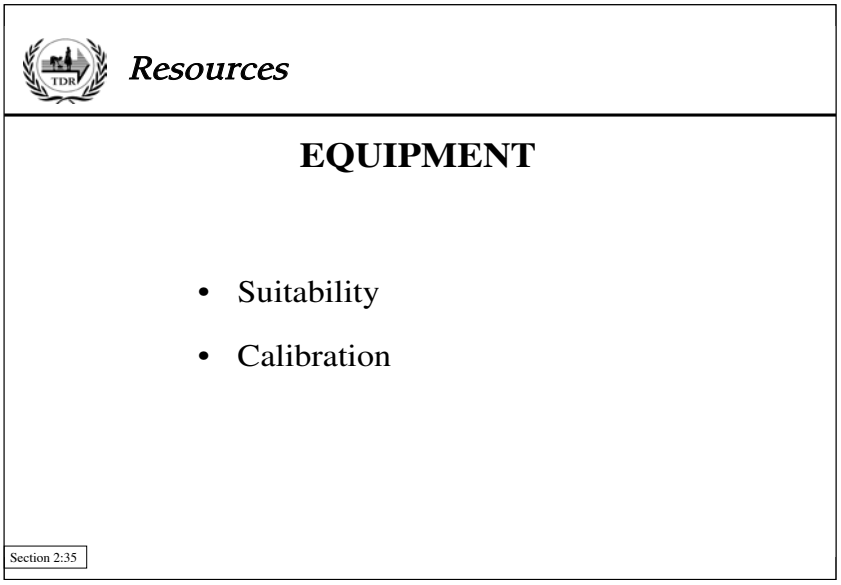
Section 2:33

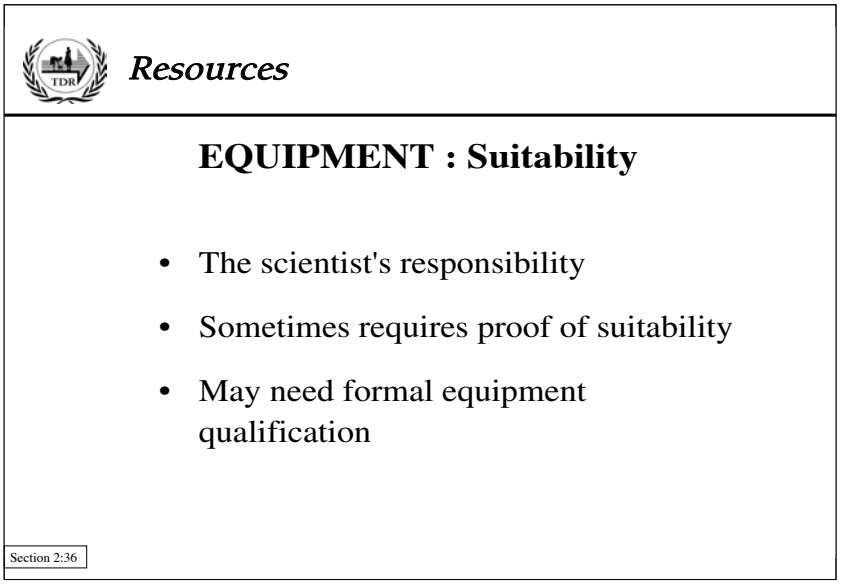
Resources

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


Resources
EQUIPMENT
• Suitability
• Calibration
Section 2:35


Resources
EQUIPMENT : Suitability
• The scientist's responsibility
• Sometimes requires proof of suitability
• May need formal equipment qualification
Section 2:36

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

Resources

BUILDINGS and EQUIPMENT

- Maintenance
- Documentation

Section 2:38

Resources

BUILDINGS / EQUIPMENT : Maintenance

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

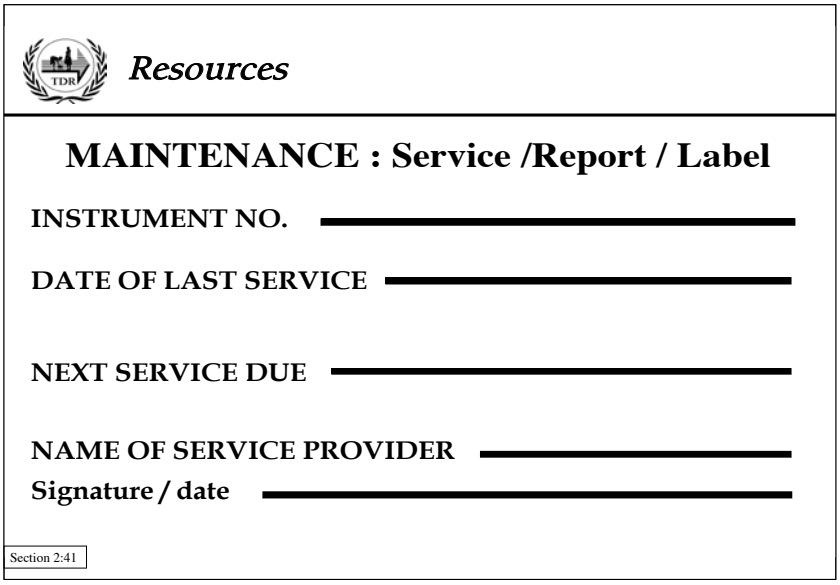
Section 2:39

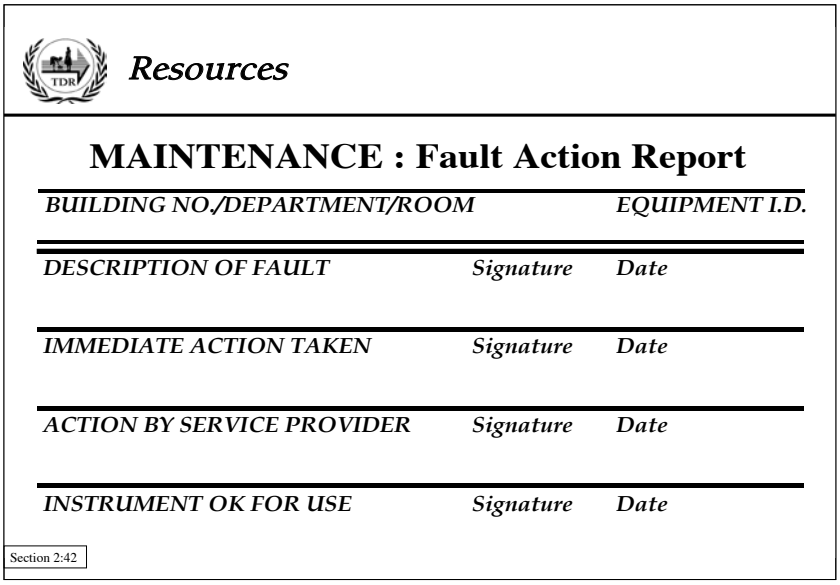
Resources

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


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


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

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

Resources

COMPUTERISED SYSTEMS

Should be:

- Developed
- Validated
- Operated
- Maintained

In compliance with the Principles of GLP

Section 2:44

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

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

Resources

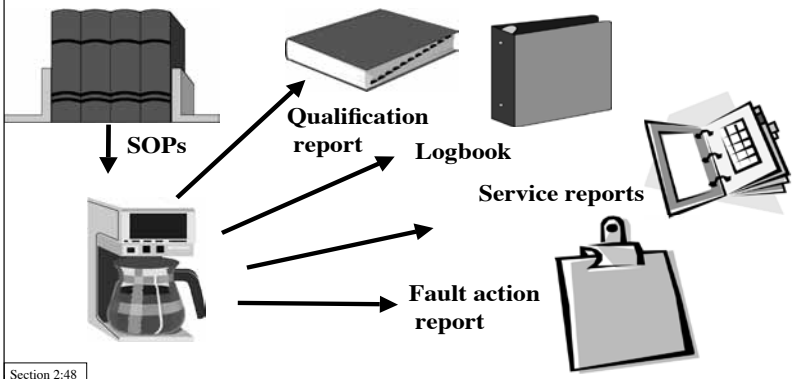
COMPUTERISED SYSTEMS

- 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

Resources

Documentation for Buildings / Equipment



Section 2:48

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 those duties may fall on 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 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 stocks 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 the test material or the 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 identification. 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 the 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 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 is 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 its 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 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 healthy animals, 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, meas-

urements, environmental conditions and ny 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)is 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 coded 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 includes 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 condition 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 to 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

Example: 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 norms should trigger review of animal care and environmental control procedures.

Characterization

CHARACTERIZATION

Part I

TEST ITEM

Section 3:1

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

Characterization

TEST ITEM

- **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

Characterization

TEST ITEM

- **Characterization is essential to ensure no major quality problems**
- **Chemical production changes can lead to physico-chemical variability**
- **Physico-chemical variables affect bioavailability**
  - **Impurity profile**
  - **Particle size**

Section 3:4

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

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

Characterization

CHARACTERIZATION

Part II

TEST SYSTEMS

Section 3:7

Characterization

What are Test Systems ?

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

can also be

- **Analytical equipment**

Section 3:8

Characterization

TEST SYSTEMS : Animals

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

Section 3:9

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

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

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

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

Characterization

ANIMALS - Acclimatization

- **Length depends on species / protocol**
- **Health check at specified times**
- **Document preparation / approval of study room**

Section 3:15

Characterization

ANIMALS - Receipt

- **Inspect upon arrival - SOP**
  - **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

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

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

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. 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-

tocol 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.

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. To 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 are 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.

oIf 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, 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 deviation's impact on the study are maintained as raw data in the study file for audit and consideration when writing the final report.

Rules

RULES

1. **Protocol or Study Plan**

2. **Standard Operating Procedures (SOPs)**

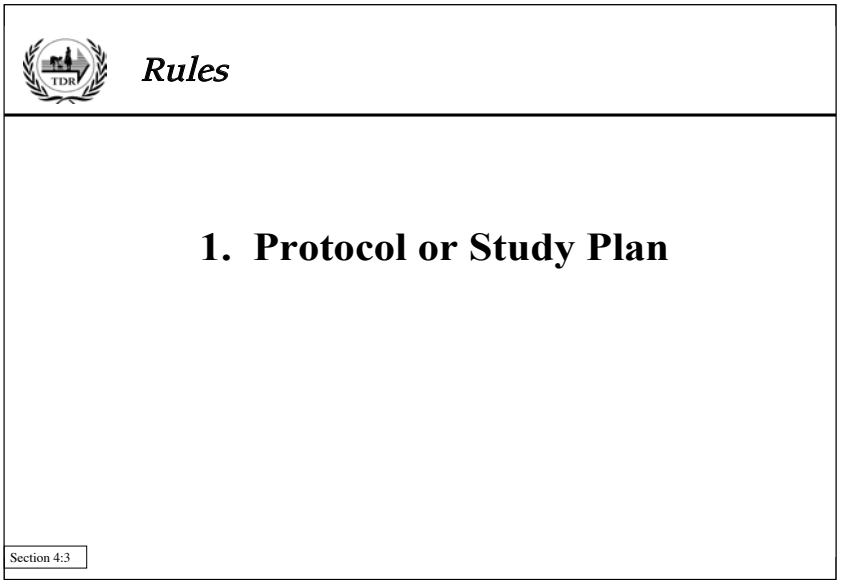
Section 4:1

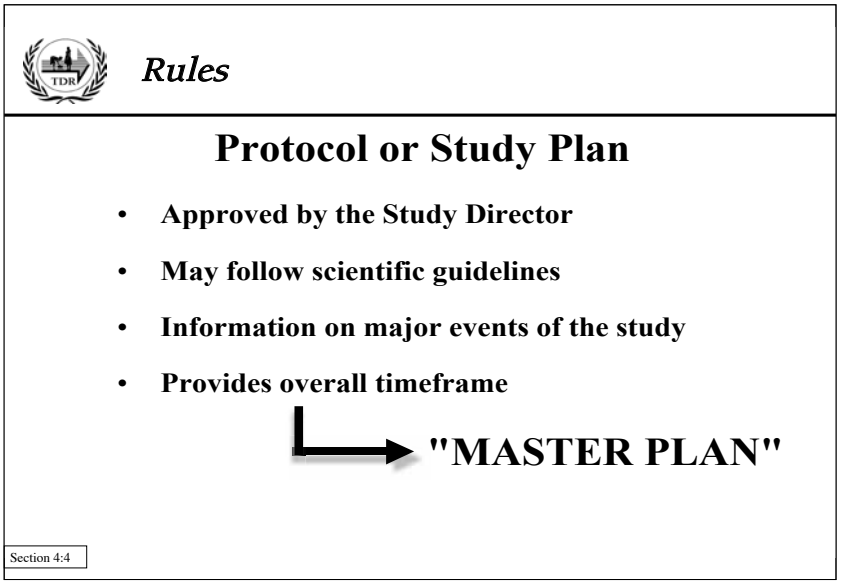
Rules

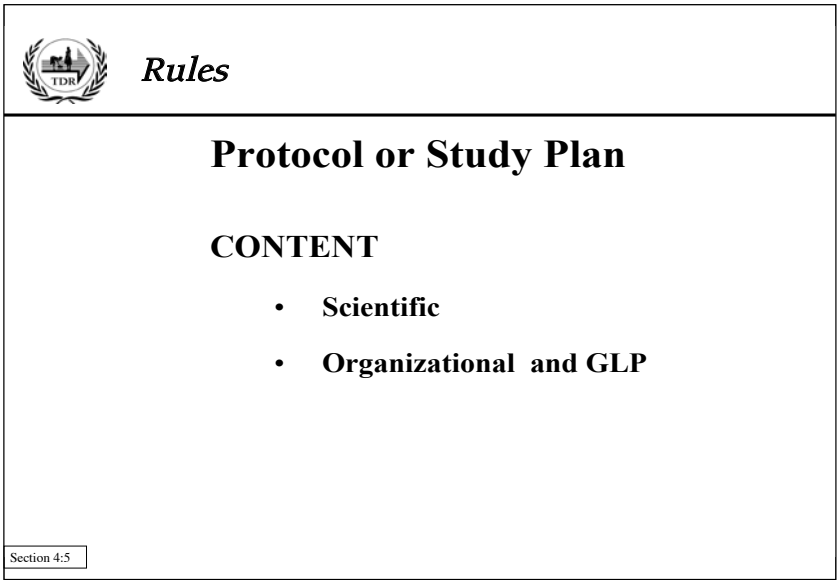
RULES

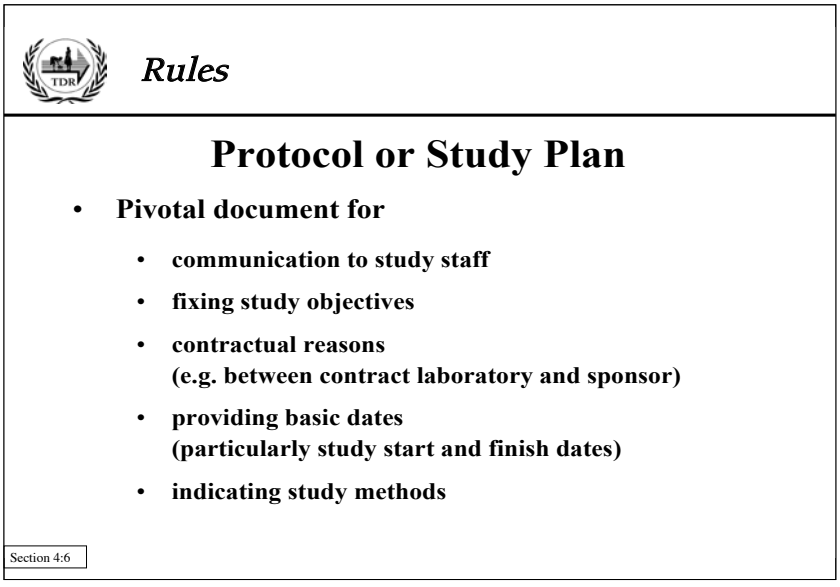
- **Protocol / Study Plan – overall plan of experiment**
- **Standard Operating Procedures (SOPs) – detailed instructions for all routine processes**
- **These are *PRESCRIPTIVE* documents.**
- **These tell us *who* is going to do *what*, *when*, *where* and *how* (and sometimes *why*)**

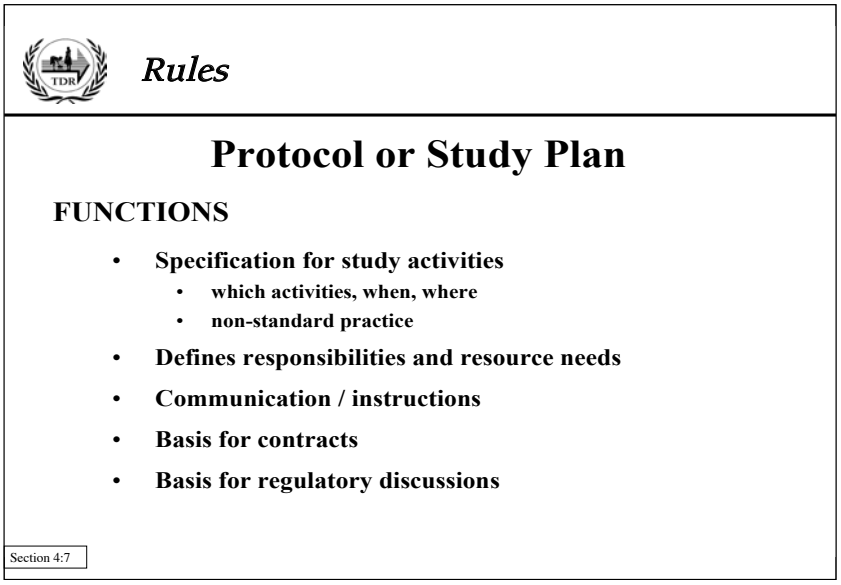
Section 4:2

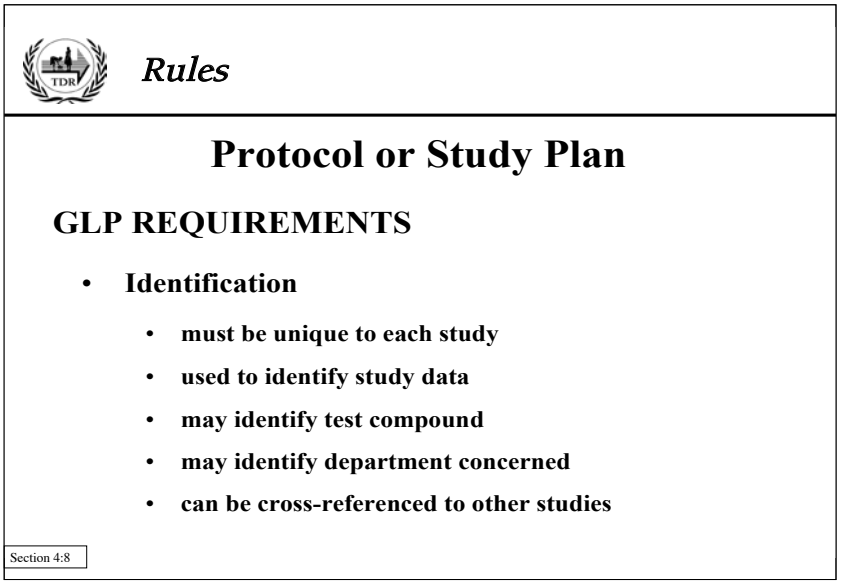

Rules
1. Protocol or Study Plan
Section 4:3


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


Rules
Protocol or Study Plan
CONTENT
• Scientific
• Organizational and GLP
Section 4:5


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


Rules
Protocol or Study Plan
FUNCTIONS
• Specification for study activities
• which activities, when, where
• non-standard practice
• Defines responsibilities and resource needs
• Communication / instructions
• Basis for contracts
• Basis for regulatory discussions
Section 4:7


Rules
Protocol or Study Plan
GLP REQUIREMENTS
• Identification
• 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

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

Rules

Protocol or Study Plan

GLP REQUIREMENTS

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

Section 4:10

Rules

Protocol or Study Plan

GLP REQUIREMENTS

- **Test facility / sponsor information**
  - **Addresses / Location (s) of study (could be a multi-site study)**
  - **Identity of consultants**
  - **Identity of sub-contractors**

Section 4:11

Rules

Protocol or Study Plan

GLP REQUIREMENTS

- **Study Director and responsible personnel**
  - **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

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

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

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

Rules

Protocol or Study Plan

APPROVAL / REVIEW

- **Approved and dated by the Study Director <u>before</u> 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

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

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

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

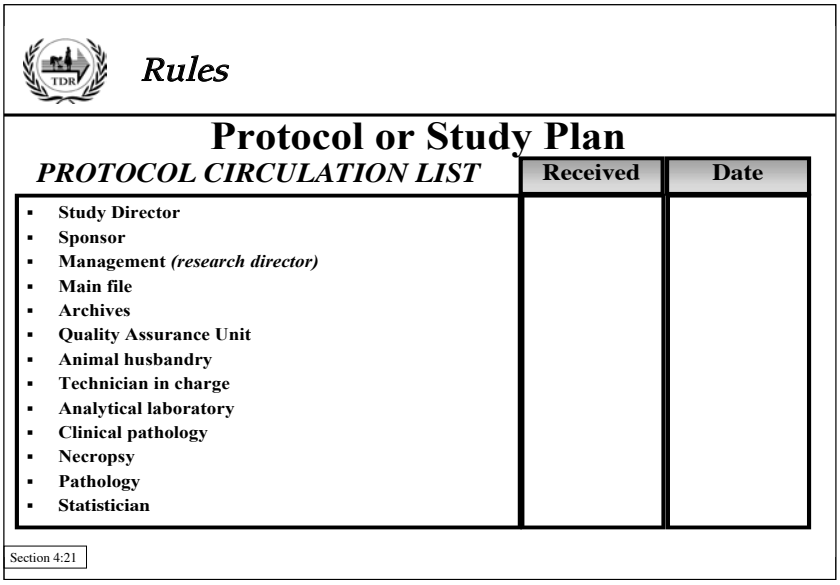
Rules

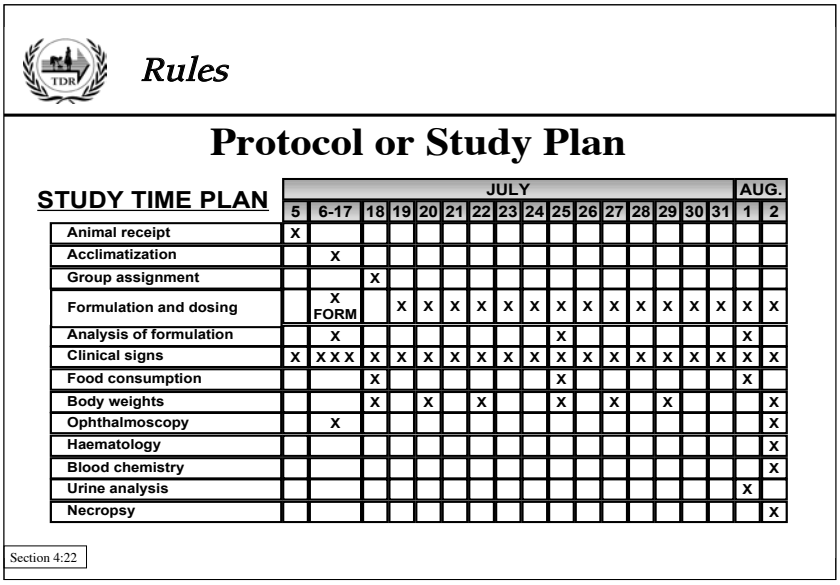
Protocol or Study Plan

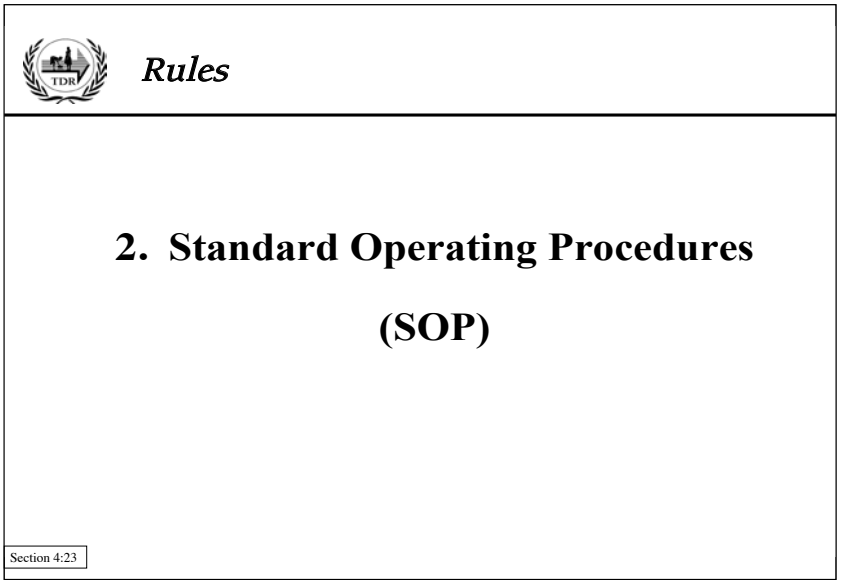
AMENDMENTS versus DEVIATIONS

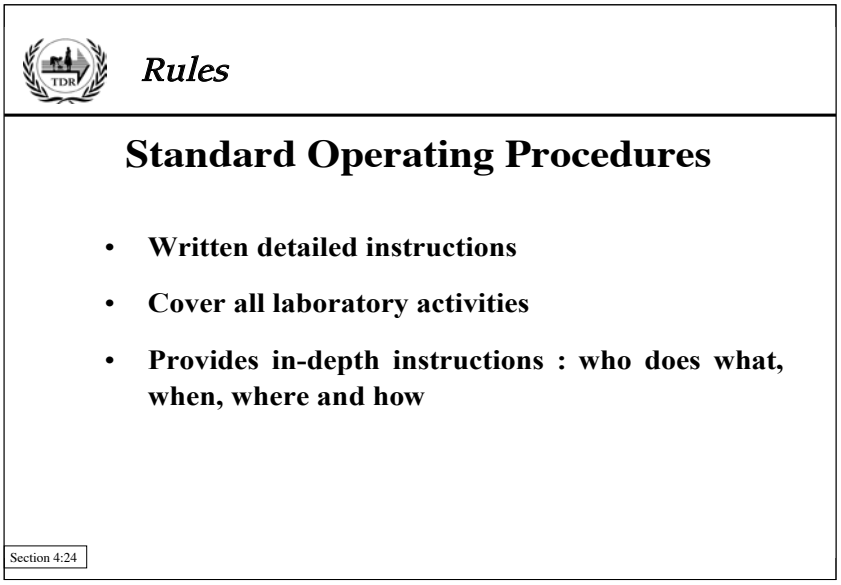
- **Amendments are planned changes to the protocol**
  - **Formalised in document called "Protocol Amendment" signed by the Study Director before the change is made**
- **Deviations are unplanned events**
  - **Recorded in study file & brought to the attention of the Study Director**
  - **Impact evaluated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

Section 4:20


Rules
Protocol or Study Plan
PROTOCOL CIRCULATION LIST
Received
Date
Study Director
Sponsor
Management (research director)
Main file
Archives
Quality Assurance Unit
Animal husbandry
Technician in charge
Analytical laboratory
Clinical pathology
Necropsy
Pathology
Statistician
Section 4:21


Rules
Protocol or Study Plan
STUDY TIME PLAN
JULY
AUG.
5 6-17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 1 2
Animal receipt X
Acclimatization X
Group assignment X
Formulation and dosing X FORM X X X X X X X X X X X X X X
Analysis of formulation X X
Clinical signs X X X X X X X X X X X X X X X X X X
Food consumption X X X
Body weights X X X X X X X
Ophthalmoscopy X X
Haematology X
Blood chemistry X
Urine analysis X
Necropsy X
Section 4:22


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

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

Rules

Standard Operating Procedures

For successful SOP implementation:

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

Section 4:26

Rules

Standard Operating Procedures

SYSTEM CHARACTERISTICS

- **Part of laboratory master documentation system**
- **Cover all activities**
  - **Administration / personnel management**
  - **Safety / hygiene**
  - **Technical**
- **Readable, clear, precise, practical**
- **Fully understood and followed**

Section 4:27

Rules

Standard Operating Procedures

SYSTEM CHARACTERISTICS

- **Responsible person for each SOP**
- **Immediately available**
- **Formal change control**
- **Central organization**

Section 4:28

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

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

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)**

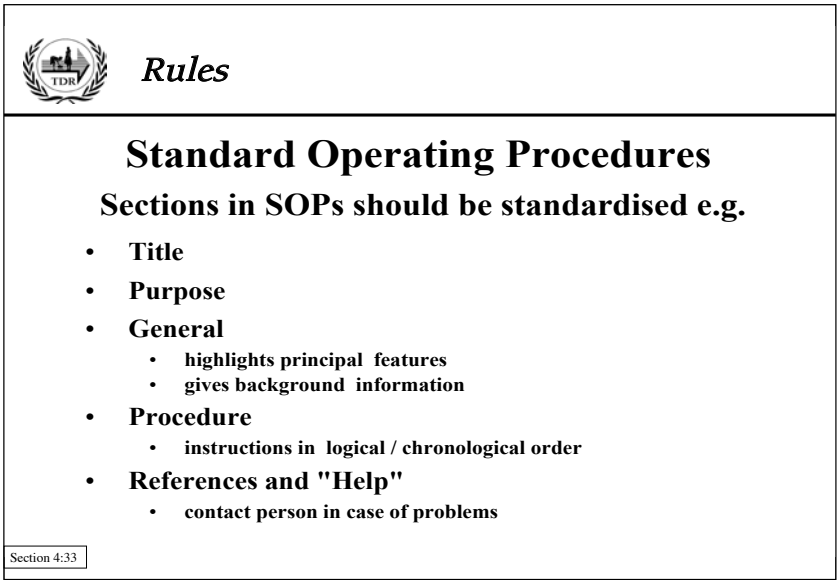
Section 4:31

Rules

Standard Operating Procedures

DEPARTMENT:		**GROUP: .....**
TITLE: STANDARD OPERATING PROCEDURES (Writing, Reviewing, Approval, Distribution, Use and Modifications)		
N°: ABC/123/001		**PAGE 1 OF 5**
Approval / Date:		
Author/Responsible	**Management**	**Quality**
Name	**Name .....**	**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


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

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 labs unless the machine is moved.) The operator should ensure 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 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 and 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 me 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 for 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 somee 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 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 a place simply 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 indefintely. 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 originals 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.

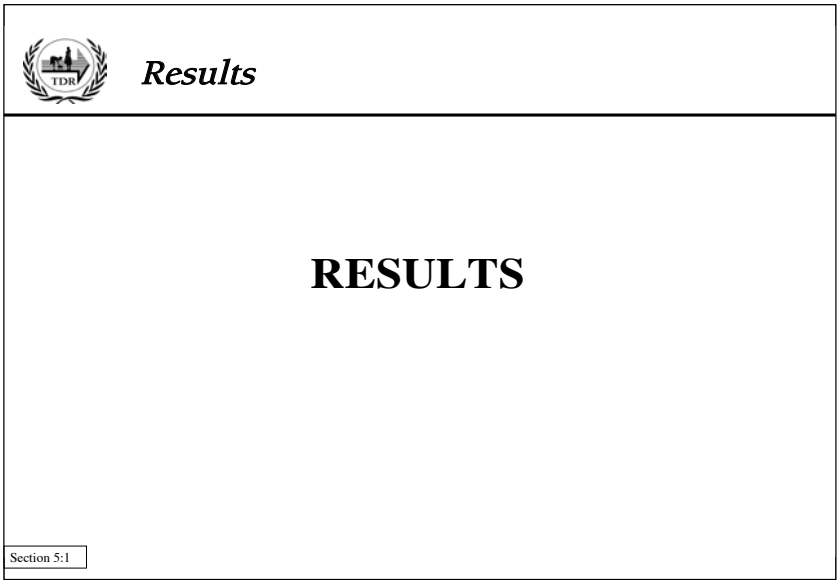
Indexing parameters that are often used include :

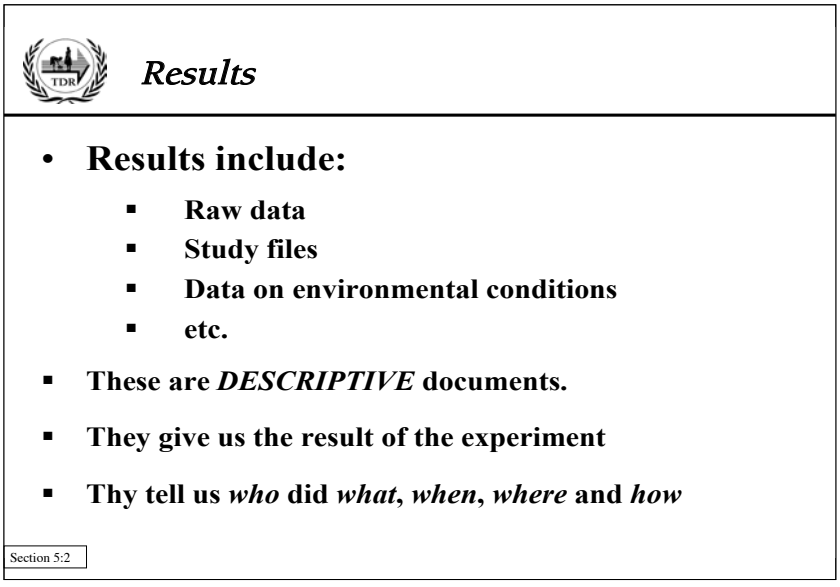
- Project or study number
- Protocol number (often the same as study number)
- Test item or reference item identification number
- Test facility identifier
- Test site identifier
- Key word retrieval from study title (route, species…)
- Key word retrieval from comments section of master schedule (regulatory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

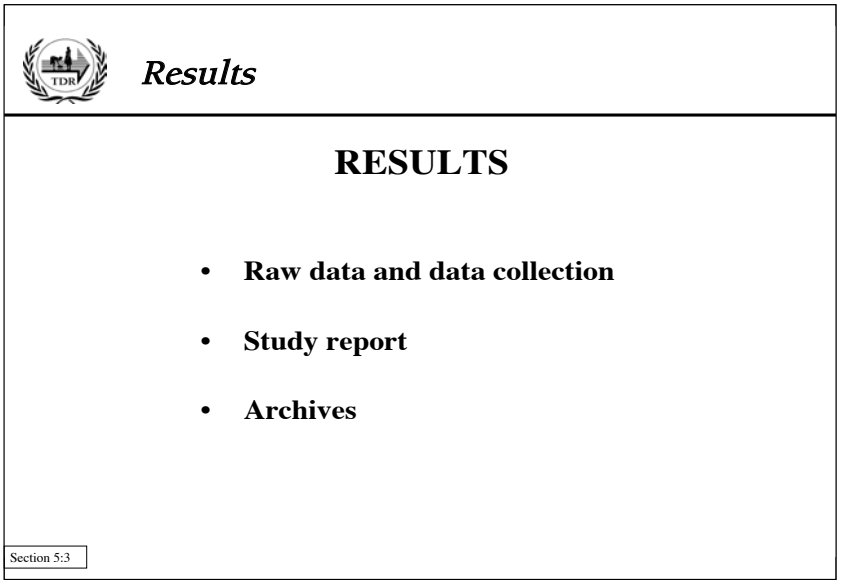
Retrieval from Archives

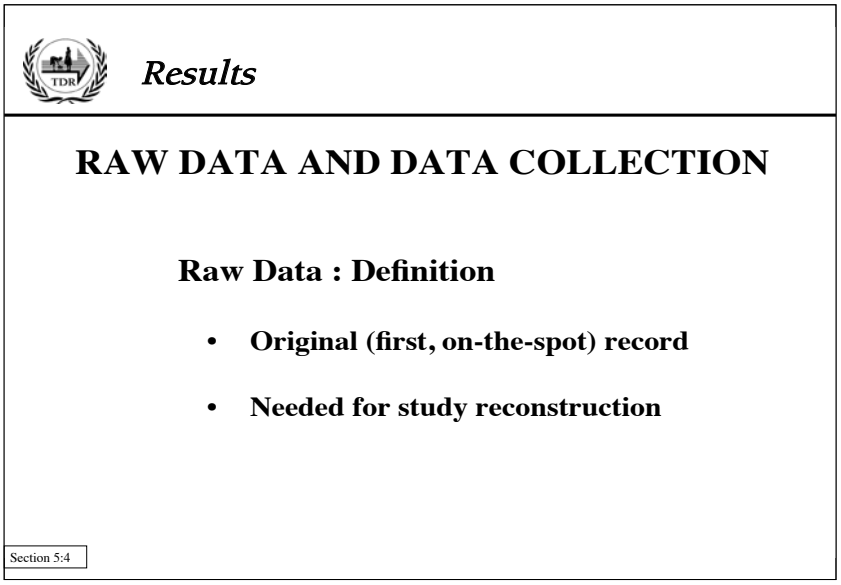
Once an item has been officially deposited in the archives, access to the the original should be restricted. It should be examined in situ within the archive area and in the presence of the archivist. Photocopies may be made on request.

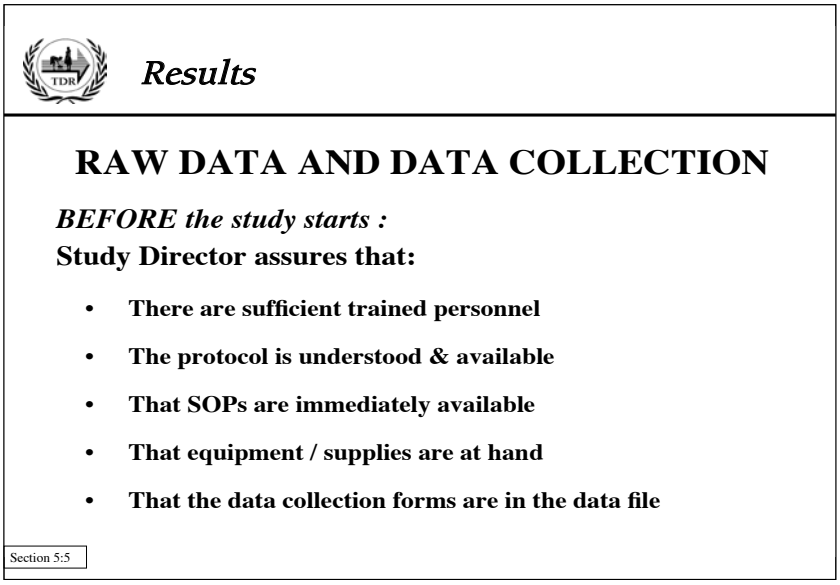
Any removal of items from the archives should only be allowed in exceptional circumstances. This removal should be authorized in writing by senior management. The history of each holding is recorded and signed by the archivist and the person taking responsibility for the material removed.

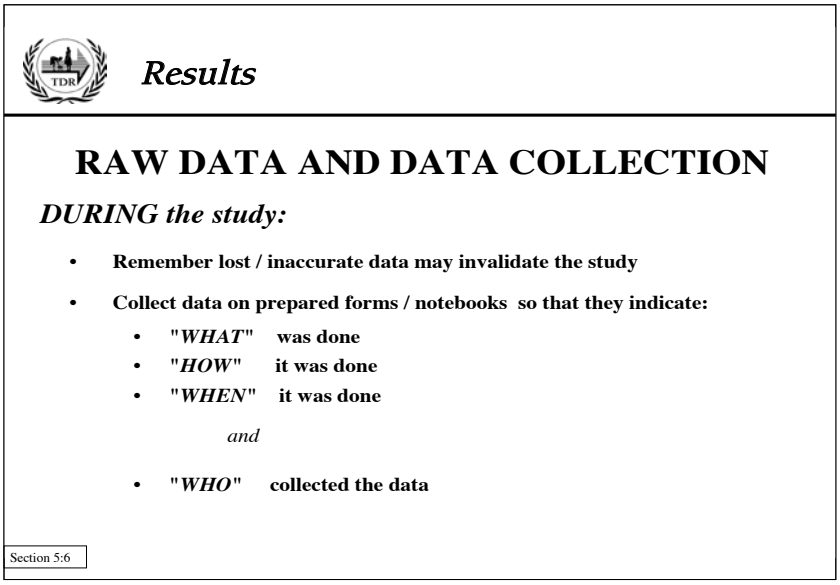

Results
RESULTS
Section 5:1


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


Results
RESULTS
• Raw data and data collection
• Study report
• Archives
Section 5:3


Results
RAW DATA AND DATA COLLECTION
Raw Data : Definition
• Original (first, on-the-spot) record
• Needed for study reconstruction
Section 5:4


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


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

Results

RAW DATA AND DATA COLLECTION

DURING the study:

"WHAT"

Data should show :

- **that the protocol was followed**
- **that the process complied with SOP instructions**
- **the results of observations**

Section 5:7

Results

RAW DATA AND DATA COLLECTION

DURING the study:

"HOW"

Data should show that methods were carried out:

- **as indicated in the protocol and SOP**
- **or that any <u>deviations</u> from protocol/ SOPs were recorded**

Section 5:8

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

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

Results

RAW DATA AND DATA COLLECTION

DURING the study:

Data should be recorded:

- **Directly / not transcribed from a rough copy**
- **Promptly**
- **Accurately**
- **Legibly**

Then:

- **Sign & date**
- **Explain corrections**

Section 5:11

Results

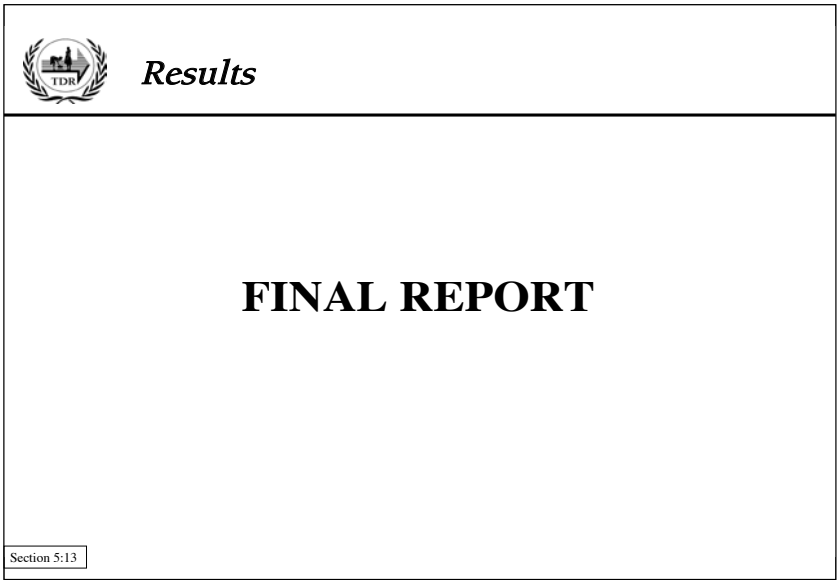
RAW DATA AND DATA COLLECTION

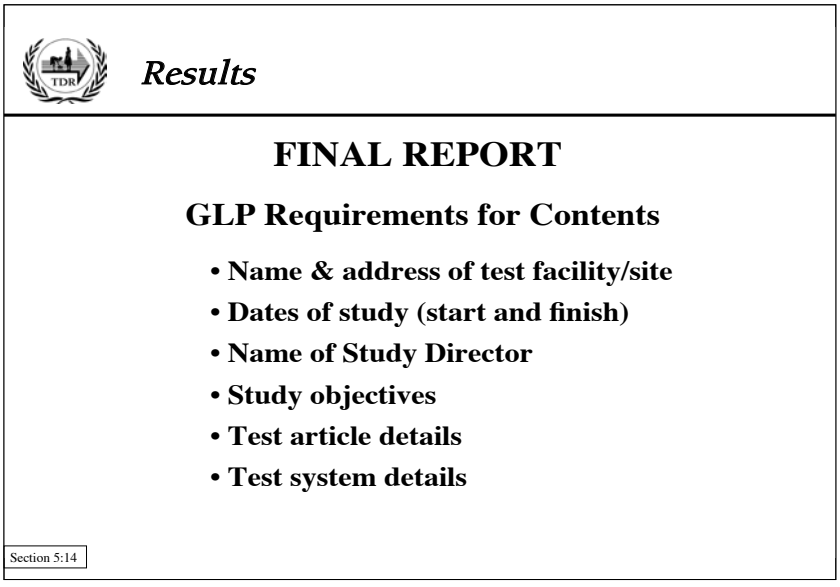
AFTER the study:

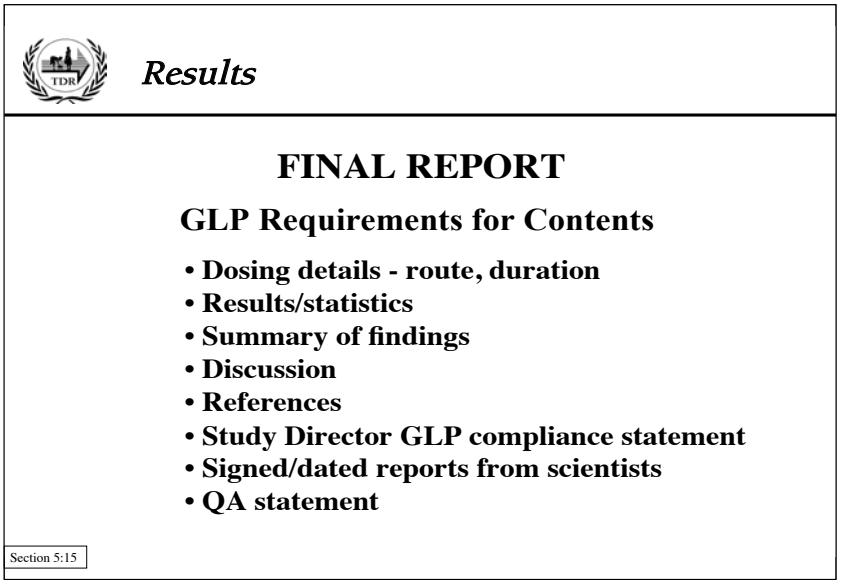
Data should be :

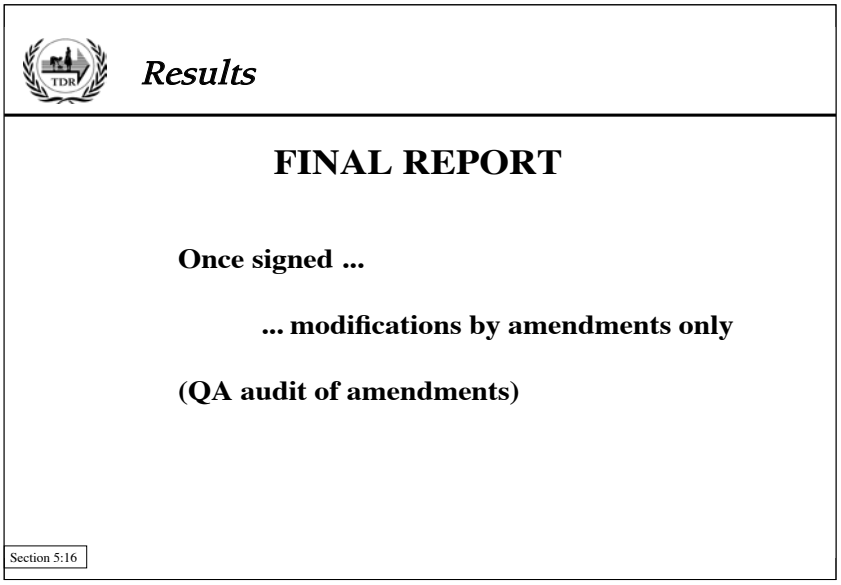
- **Collected together in one place – organized in logical order**
- **Verified for completeness**
- **Handed over to the Study Director**
- **Kept in a safe place**

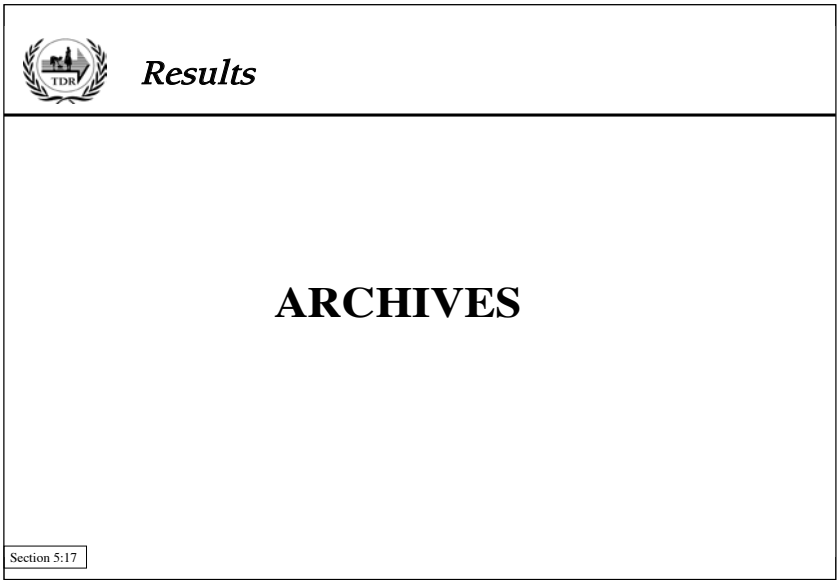
Section 5:12

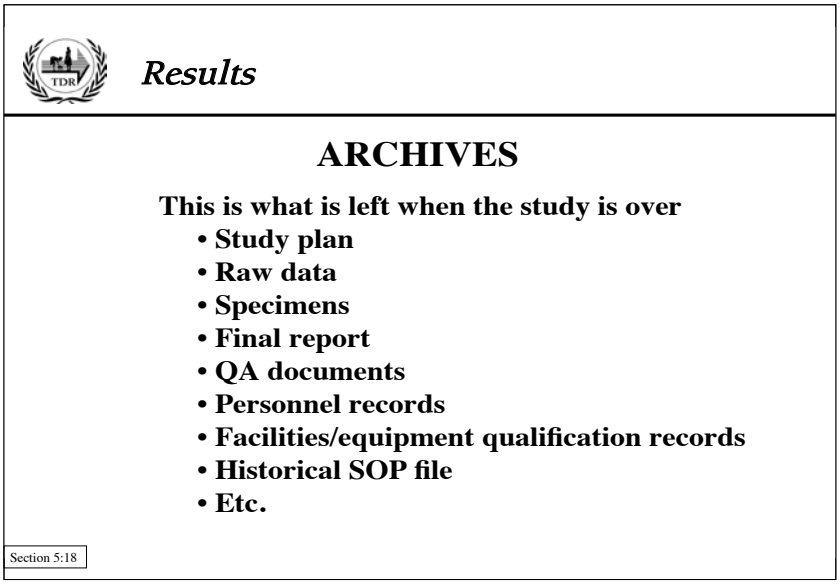

Results
FINAL REPORT
Section 5:13


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


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


Results
FINAL REPORT
Once signed ...
... modifications by amendments only
(QA audit of amendments)
Section 5:16


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

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

Results

ARCHIVES : Submission form

DEPT./GROUP :	**Holding number :**
PROJECT :	
STUDY N° :	

QUANTITY	DESCRIPTION	COMMENTS
Date	**Signature of submitter**	**Signature of archivist**

Section 5:20

Results

ARCHIVES : History / Events Form

DATE	EVENT	AUTHORIZATIONS

Section 5:21

Results

ARCHIVES: Security

- **Only authorized entry permitted - per SOP**
- **Examination *in-situ* of documents is preferred**
- **Photocopies made in place, if possible**
- **Protection against fire, flood and vandalism if possible**

Section 5:22

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

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

6. QUALITY ASSURANCE

GLP defines the minimum quality assurance requirements necessary to ensure the validity of experimental results. The quality assurance unit (QAU), a the group of persons with a set of defined duties, ensures management that all the quality processes implemented in an institution are functioning correctly. Most organizations use the abbreviations QA (quality assurance) so 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/her 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 a solution 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.

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 by one person and usually requires input from scientific specialists such as the study director. 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, is 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. A 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.

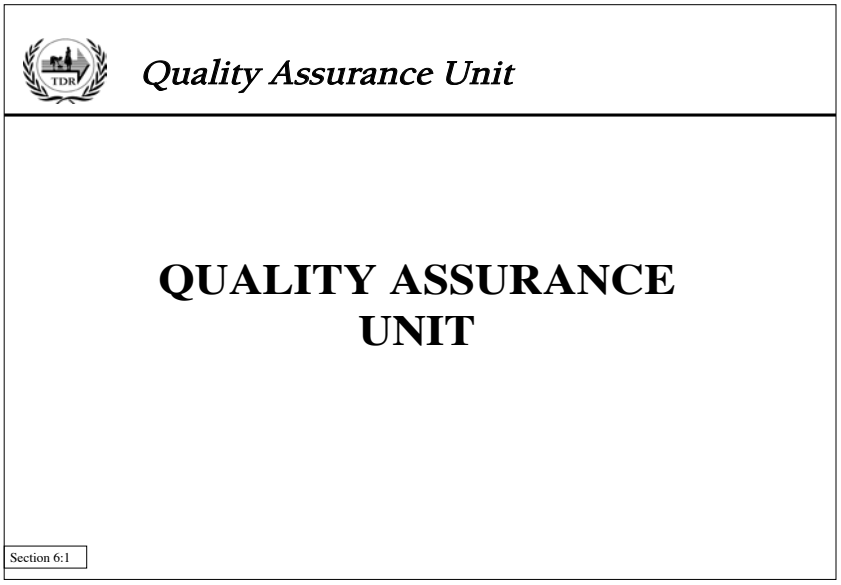
ISSUING AND ARCHIVING OF QA FILES AND REPORTS

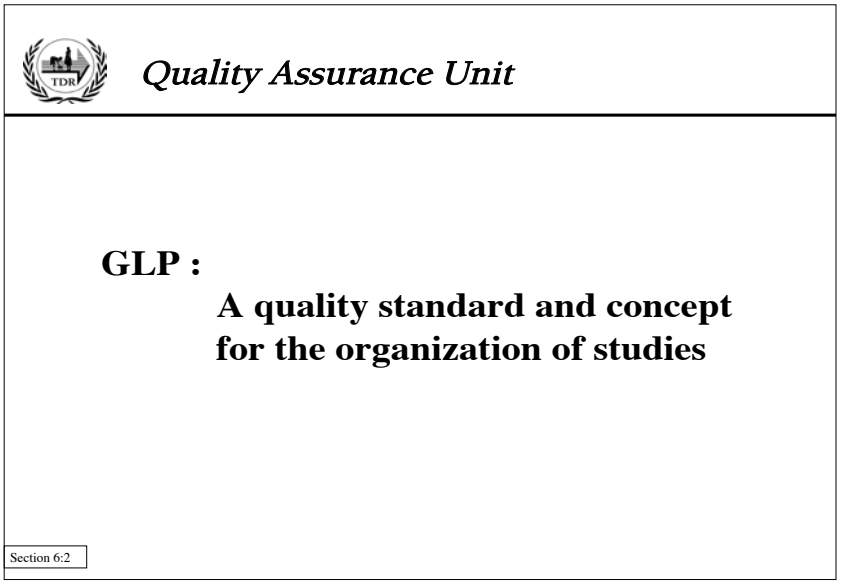
QA serves as both:

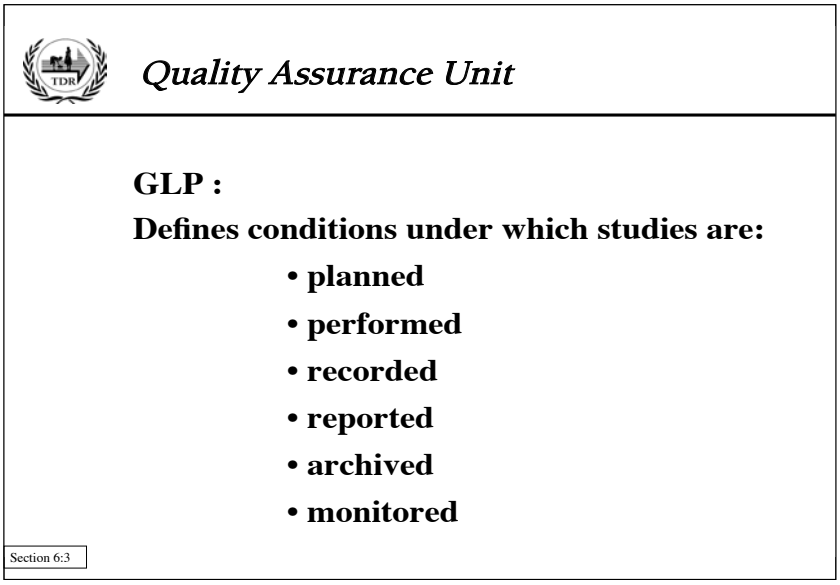
- an internal control function;
- a guarantee to the public at large, that preclinical studies are performed in a way that will result in valid data.

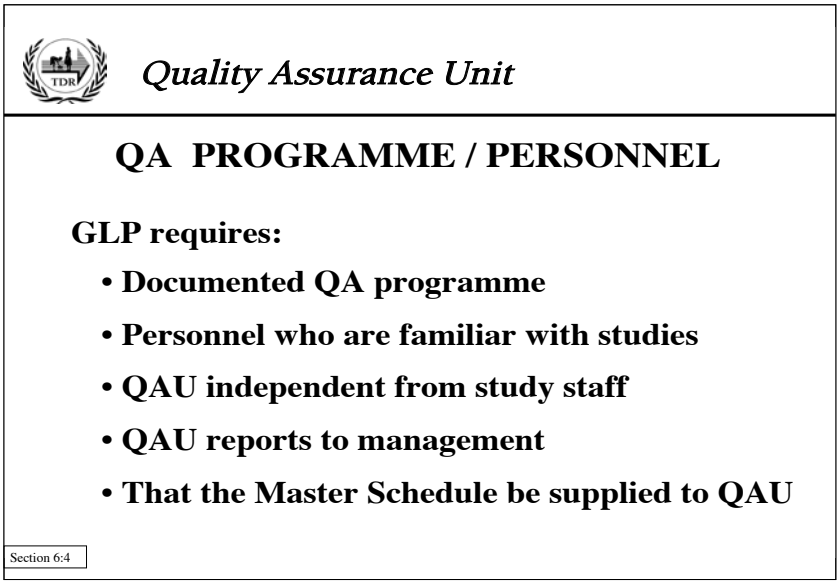
QA reports issued to the study director and to management should be strictly regarded as internal working documents. They are particularly valuable if important findings are picked up during the QA activities, reported accurately, discussed and acted upon. Therefore, the QA audit reports are not normally 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.

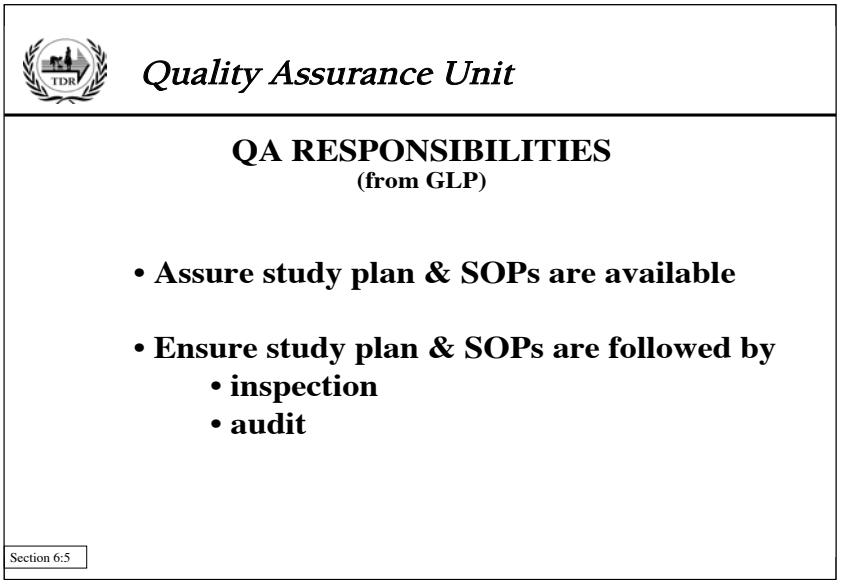
It follows that the QA reports are not for general distribution, and should be handled with discretion. It is best to archive reports separately from the study files so that regulatory authorities or external auditors do not access them inadvertently during inspections.

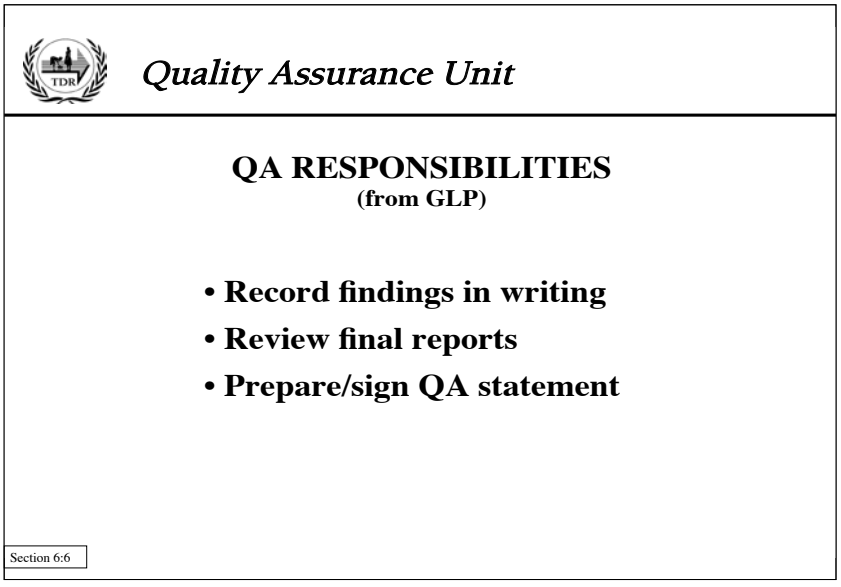

Quality Assurance Unit
QUALITY ASSURANCE UNIT
Section 6:1

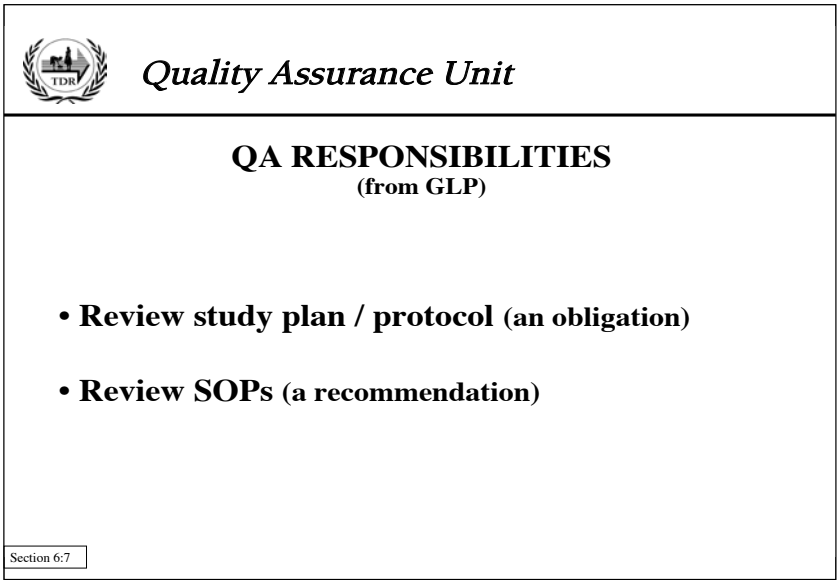

Quality Assurance Unit
GLP :
A quality standard and concept for the organization of studies
Section 6:2

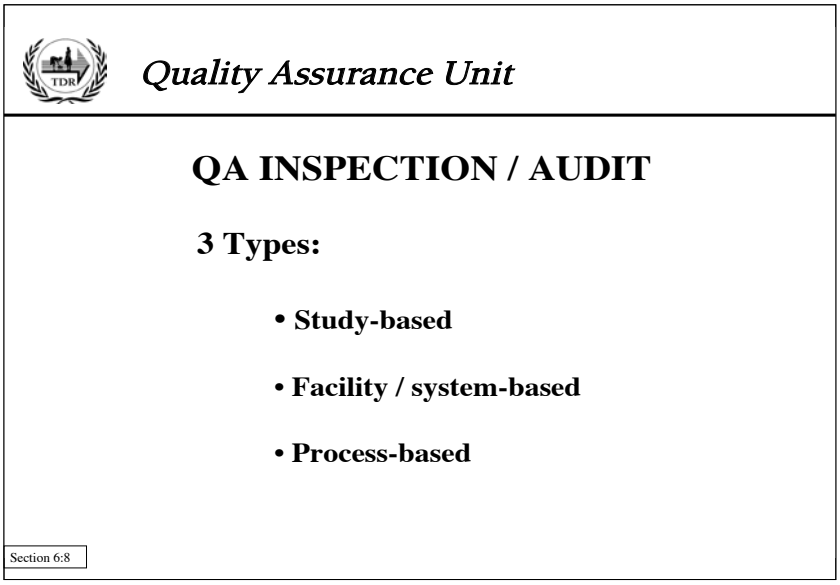

Quality Assurance Unit
GLP :
Defines conditions under which studies are:
• planned
• performed
• recorded
• reported
• archived
• monitored
Section 6:3

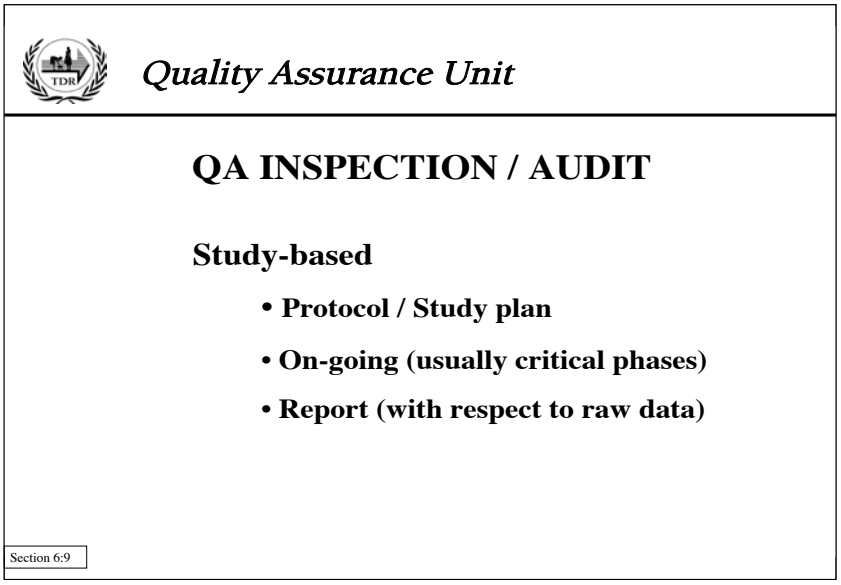

Quality Assurance Unit
QA PROGRAMME / PERSONNEL
GLP requires:
• Documented QA programme
• Personnel who are familiar with studies
• QAU independent from study staff
• QAU reports to management
• That the Master Schedule be supplied to QAU
Section 6:4

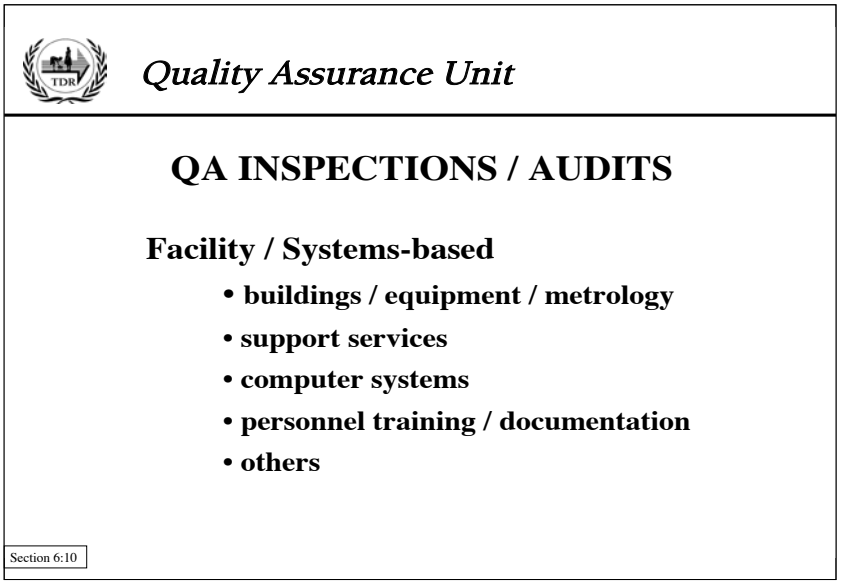

Quality Assurance Unit
QA RESPONSIBILITIES
(from GLP)
• Assure study plan & SOPs are available
• Ensure study plan & SOPs are followed by
• inspection
• audit
Section 6:5

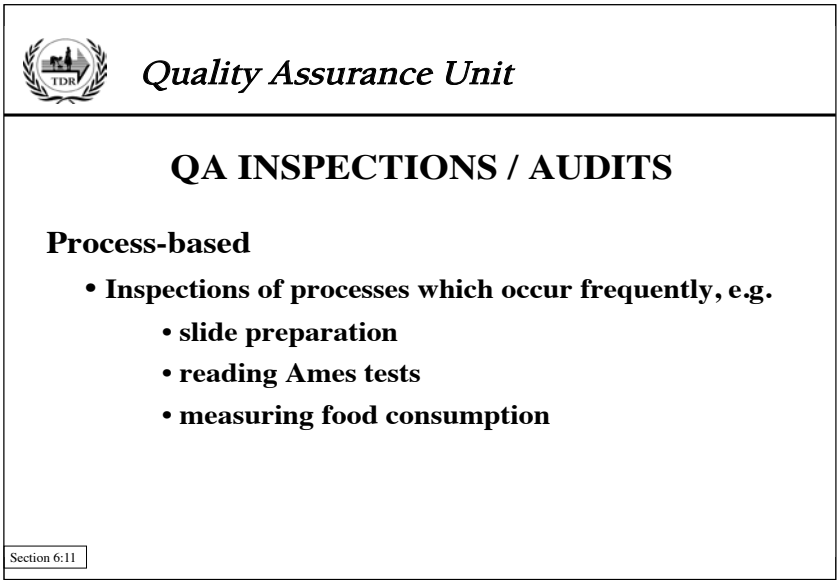

Quality Assurance Unit
QA RESPONSIBILITIES
(from GLP)
• Record findings in writing
• Review final reports
• Prepare/sign QA statement
Section 6:6


Quality Assurance Unit
QA RESPONSIBILITIES
(from GLP)
• Review study plan / protocol (an obligation)
• Review SOPs (a recommendation)
Section 6:7


Quality Assurance Unit
QA INSPECTION / AUDIT
3 Types:
• Study-based
• Facility / system-based
• Process-based
Section 6:8


Quality Assurance Unit
QA INSPECTION / AUDIT
Study-based
• Protocol / Study plan
• On-going (usually critical phases)
• Report (with respect to raw data)
Section 6:9


Quality Assurance Unit
QA INSPECTIONS / AUDITS
Facility / Systems-based
• buildings / equipment / metrology
• support services
• computer systems
• personnel training / documentation
• others
Section 6:10


Quality Assurance Unit
QA INSPECTIONS / AUDITS
Process-based
• Inspections of processes which occur frequently, e.g.
• slide preparation
• reading Ames tests
• measuring food consumption
Section 6:11


Quality Assurance Unit
QA INSPECTIONS / AUDIT
• Suppliers
• Sub-contractors
Section 6:12

Quality Assurance Unit

QA INSPECTION REPORT

Header		
Phase audited	**QA comments**	**Responses/corrective action planned**
	Signature Date	**Signature Date**

Section 6:13

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 6:14

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	KOREA
AUSTRIA	LUXEMBOURG
BELGIUM	MEXICO
CANADA	NETHERLANDS
CZECH REPUBLIC	NEW ZEALAND
DENMARK	NORWAY
FINLAND	POLAND
FRANCE	PORTUGAL
GERMANY	SLOVAK REPUBLIC
GREECE	SPAIN
HUNGARY	SWEDEN
ICELAND	SWITZERLAND
IRELAND	TURKEY
ITALY	UNITED KINGDOM
JAPAN	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 responds 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 finalised 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 organise 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 harmonisation 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 MUTAL 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 harmonisation 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

What the aims of the OECD GLP Principles?

- The MAIN GOALis 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**	The basic regulatory text. The Principles of GLP as agreed by the member states through the MAD. Defines the conditions under which studies are – Planned – Performed – Recorded – Reported – Archived – Monitored Provides the responsibilities of all the actors in a GLP study.
2.	**Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice**	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. It is recognised 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.

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 characterisation 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 Computerised Systems (1995)

Throughout recent years there has been an increase in the use of computerised systems by test facilities undertaking health and environmental safety testing. These computerised 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 computerised 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 recognised 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**

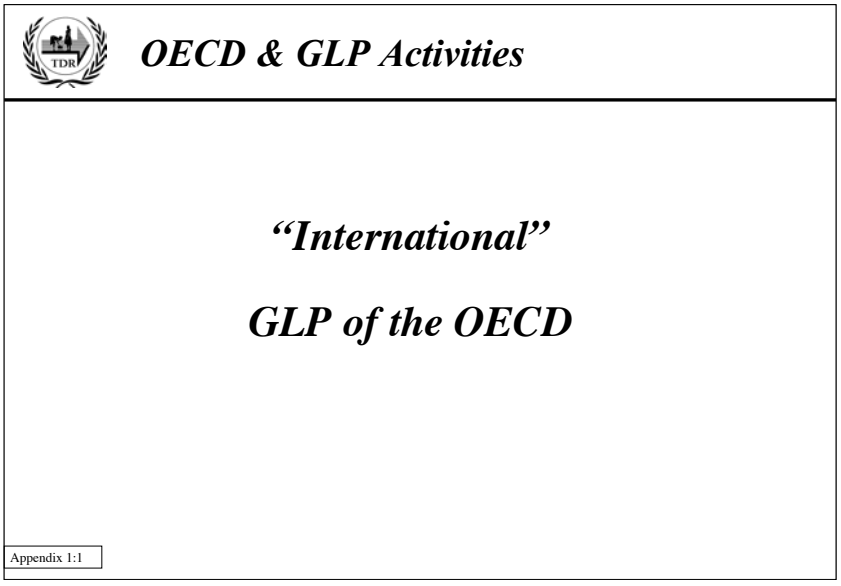
Provides guidance relative to the responsibilities of personnel running GLP studies when activities are conducted at two or more sites. In particular it describes the responsibilities and the relationships between the Study Director at the test facility and the Principal Investigators at the different 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

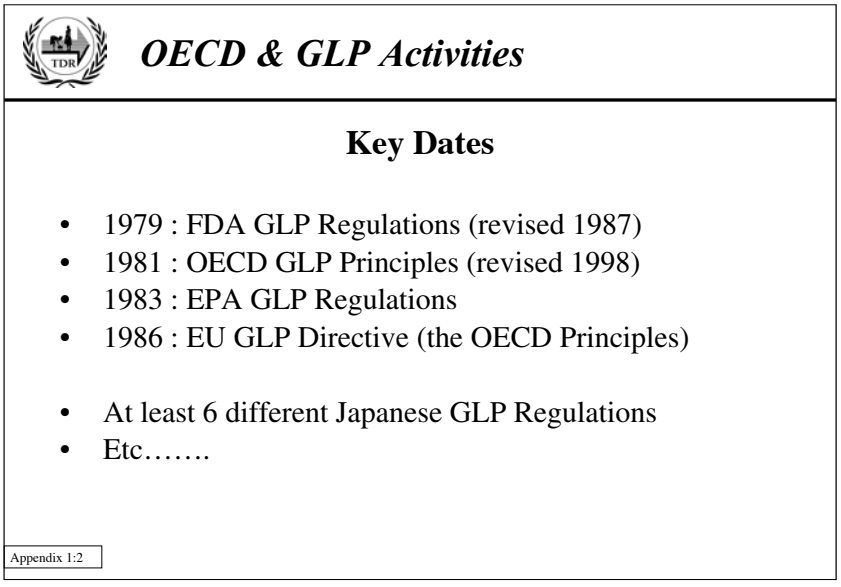
14. **The Application of the Principles of GLP to *in vitro* Studies**

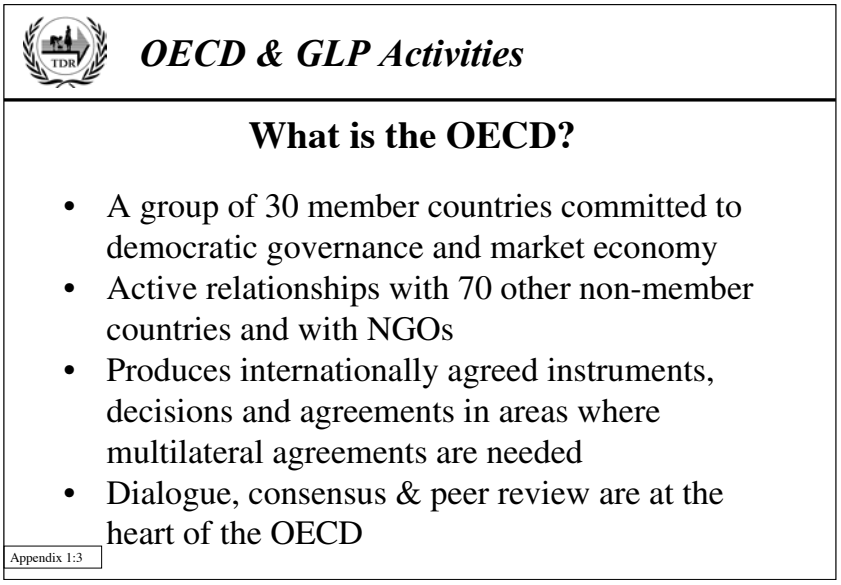
This Advisory Document of the Working Group on Good Laboratory Practice was developed in 2003 and 2004 with the assistance of experts in *in vitro* testing. This area of non-clinical safety testing is especially important in light of animal welfare concerns. The document should be considered together 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.)

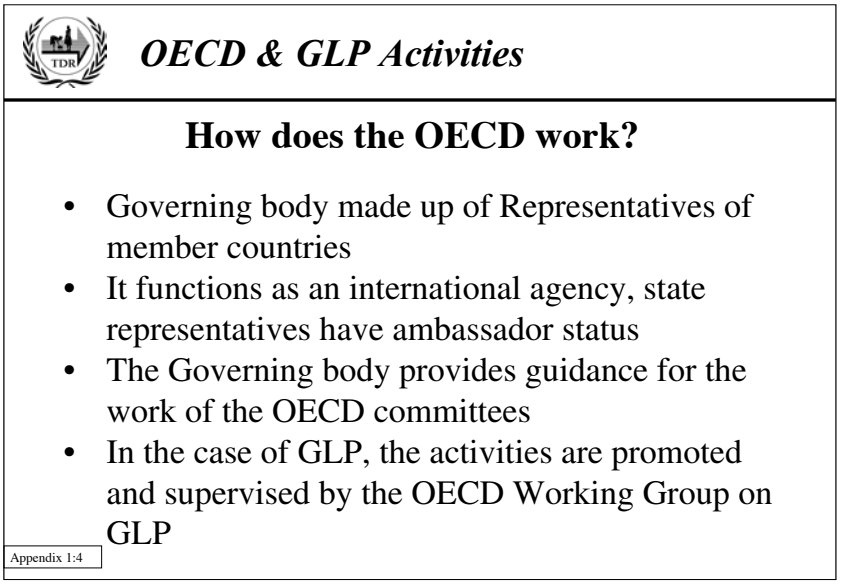
15. **Establishment and Control of Archives that Operate in Compliance with the Principles of GLP**

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.

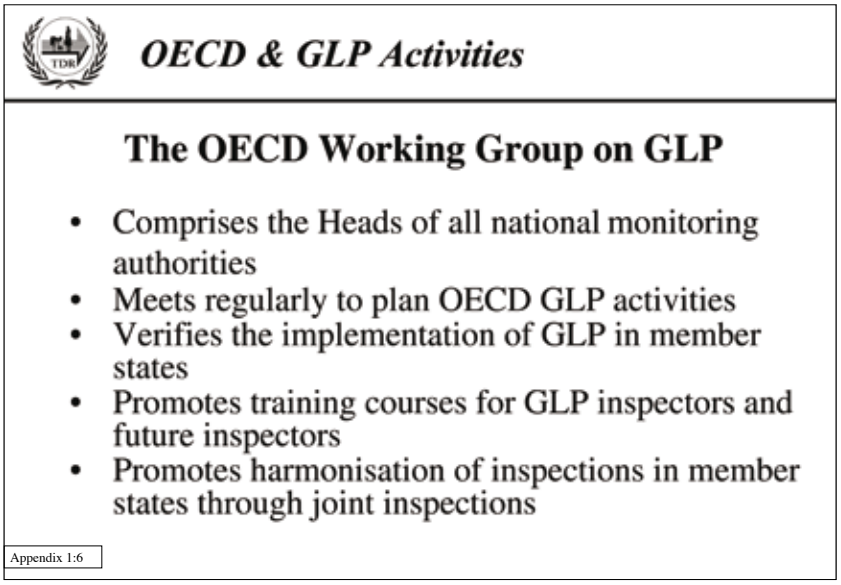

OECD & GLP Activities
"International"
GLP of the OECD
Appendix 1:1

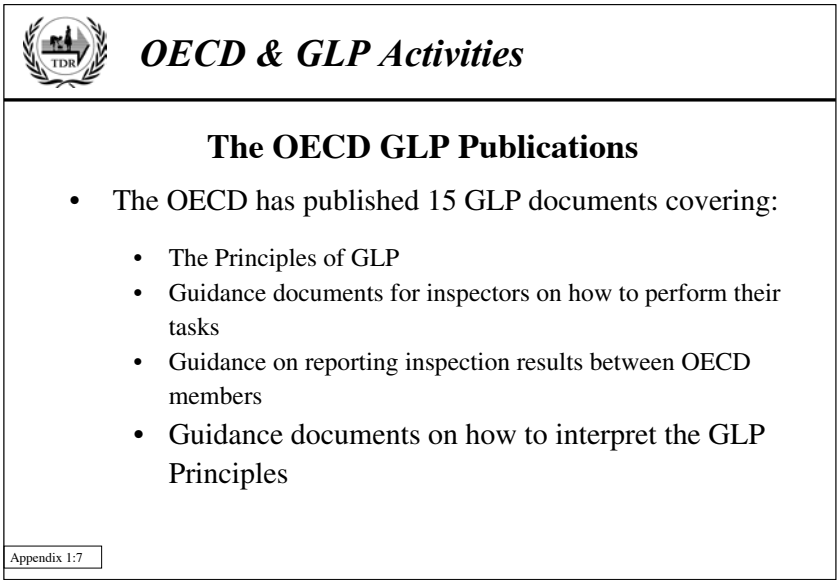

OECD & GLP Activities
Key Dates
• 1979 : FDA GLP Regulations (revised 1987)
• 1981 : OECD GLP Principles (revised 1998)
• 1983 : EPA GLP Regulations
• 1986 : EU GLP Directive (the OECD Principles)
• At least 6 different Japanese GLP Regulations
• Etc…….
Appendix 1:2

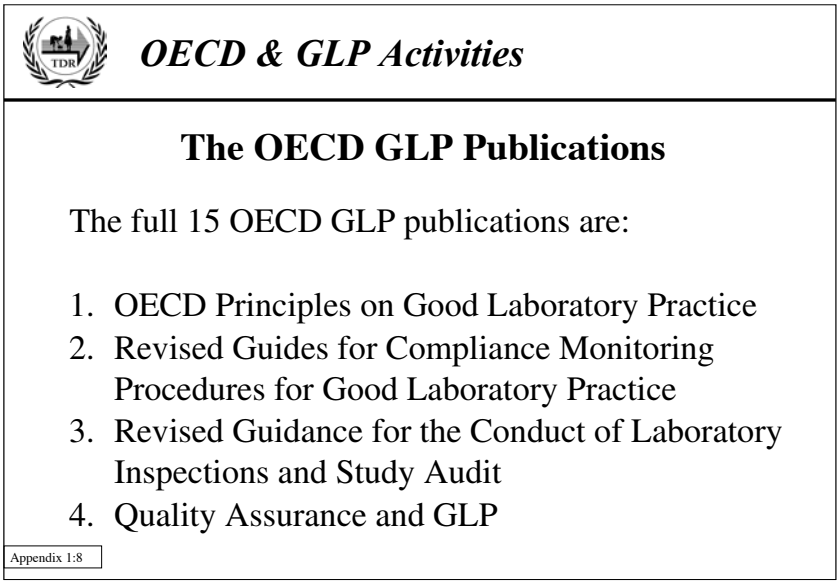

OECD & GLP Activities
What is the OECD?
• A group of 30 member countries committed to democratic governance and market economy
• Active relationships with 70 other non-member countries and with NGOs
• Produces internationally agreed instruments, decisions and agreements in areas where multilateral agreements 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


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


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


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

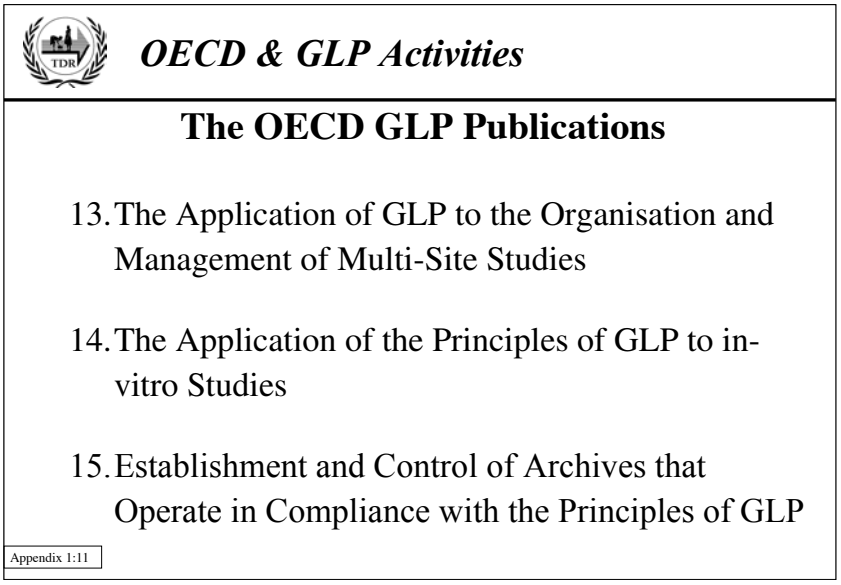
Appendix 1:9

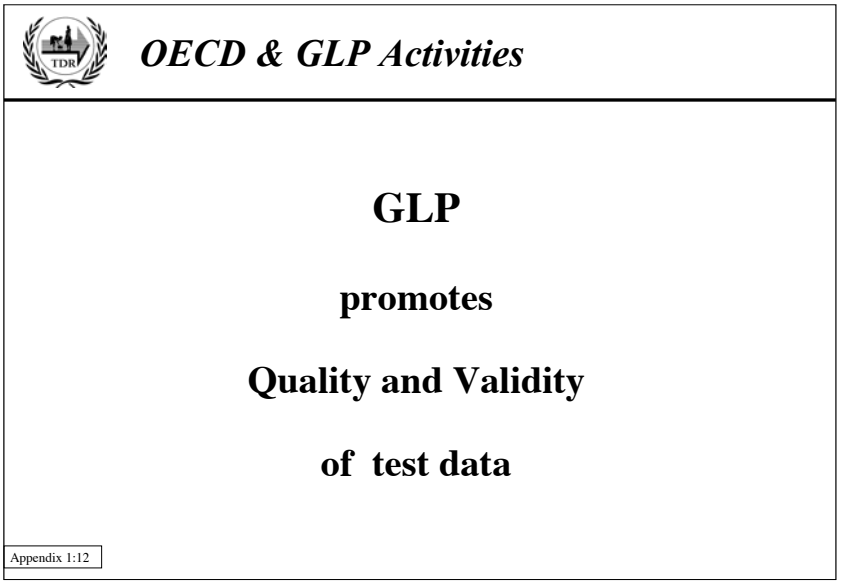
OECD & GLP Activities

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

OECD & GLP Activities

GLP Principles

MAIN GOAL: To help scientists obtain results which are:

- Reliable
- Repeatable
- Auditable
- Recognized by scientists worldwide

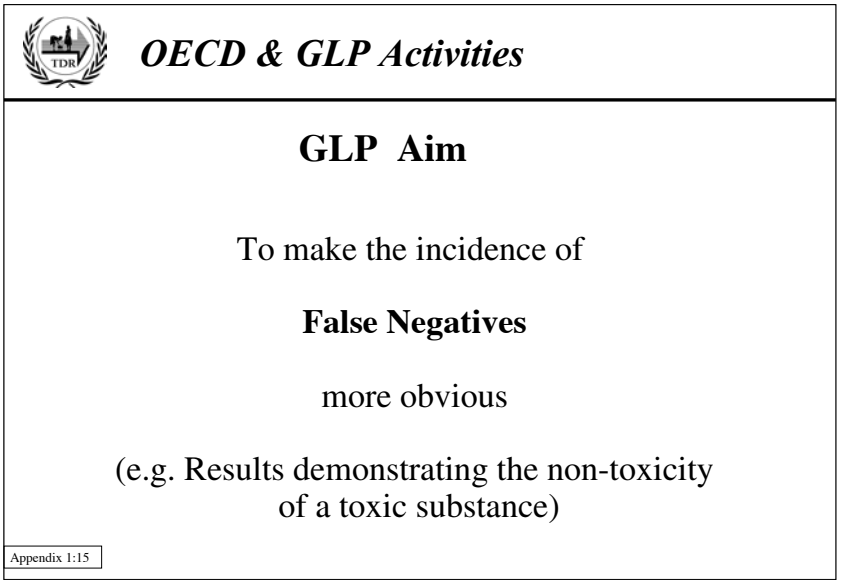
Appendix 1:13

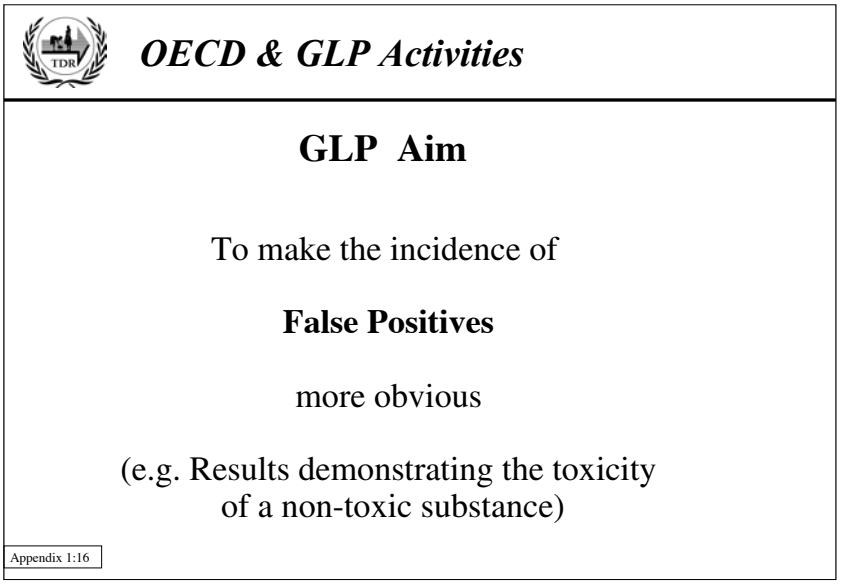
OECD & GLP Activities

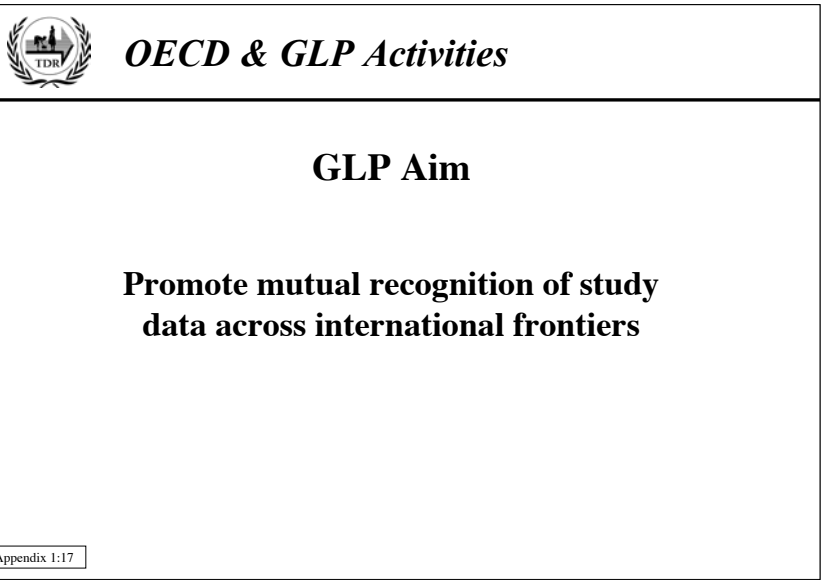
GLP Principles

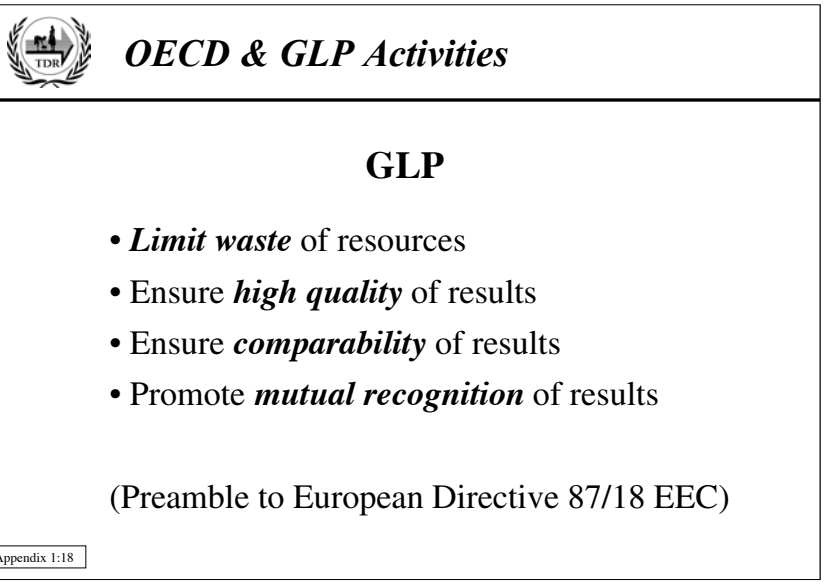
- The purpose is not to assess the intrinsic scientific value of a study
- GLP principles are a set of organizational requirements

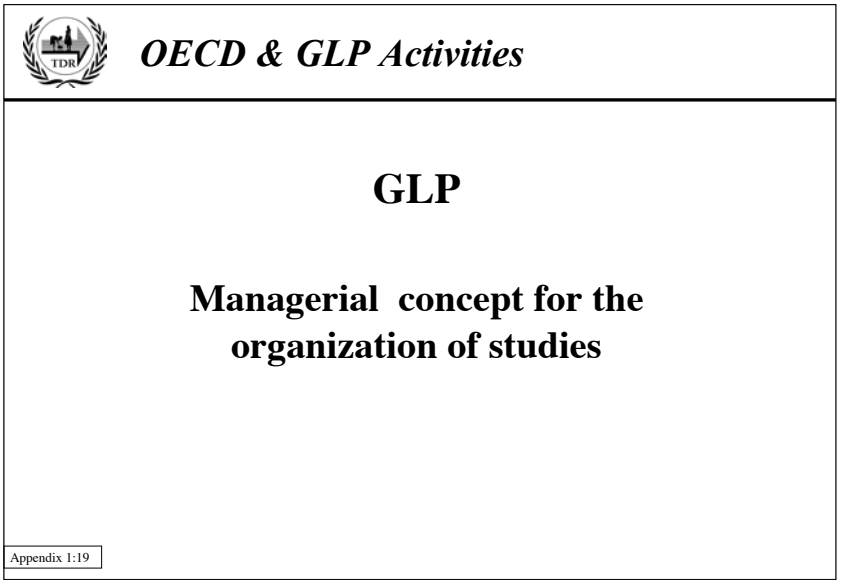
Appendix 1:14

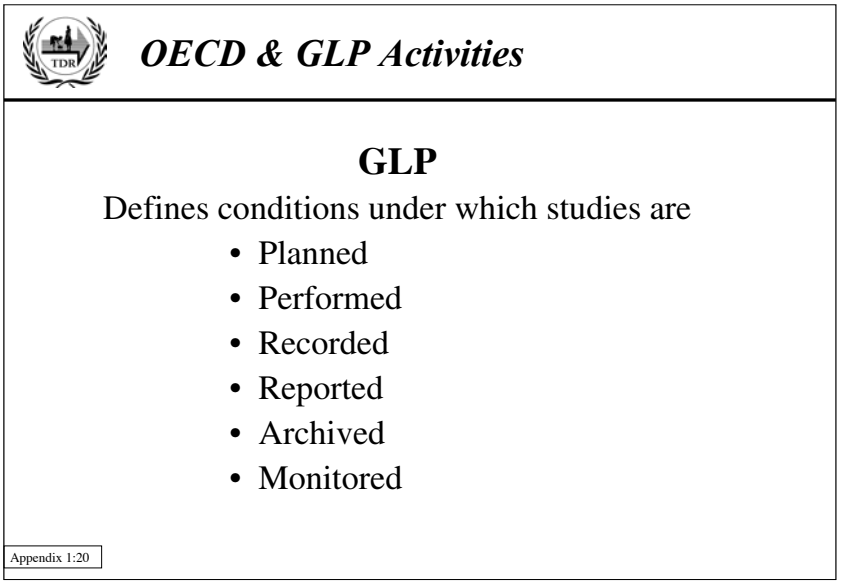

OECD & GLP Activities
GLP Aim
To make the incidence of
False Negatives
more obvious
(e.g. Results demonstrating the non-toxicity
of a toxic substance)
Appendix 1:15

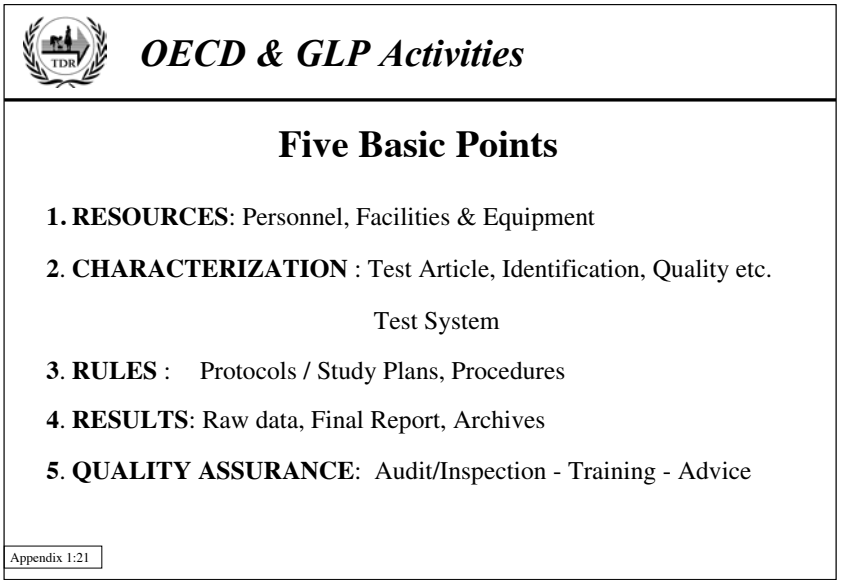

OECD & GLP Activities
GLP Aim
To make the incidence of
False Positives
more obvious
(e.g. Results demonstrating the toxicity
of a non-toxic substance)
Appendix 1:16


OECD & GLP Activities
GLP Aim
Promote mutual recognition of study data across international frontiers
Appendix 1:17


OECD & GLP Activities
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)
Appendix 1:18


OECD & GLP Activities
GLP
Managerial concept for the organization of studies
Appendix 1:19


OECD & GLP Activities
GLP
Defines conditions under which studies are
• Planned
• Performed
• Recorded
• Reported
• Archived
• Monitored
Appendix 1:20


OECD & GLP Activities
Five Basic Points
1. RESOURCES: Personnel, Facilities & Equipment
2. CHARACTERIZATION : Test Article, Identification, Quality etc.
Test System
3. RULES : Protocols / Study Plans, Procedures
4. RESULTS: Raw data, Final Report, Archives
5. QUALITY ASSURANCE: Audit/Inspection - Training - Advice
Appendix 1:21

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 organisation 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 organisational 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 buy 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 summarises 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 organisation 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 organisations. 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 specialised 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 organisational 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 organisations 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 finalise 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 organisation

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 characterised;

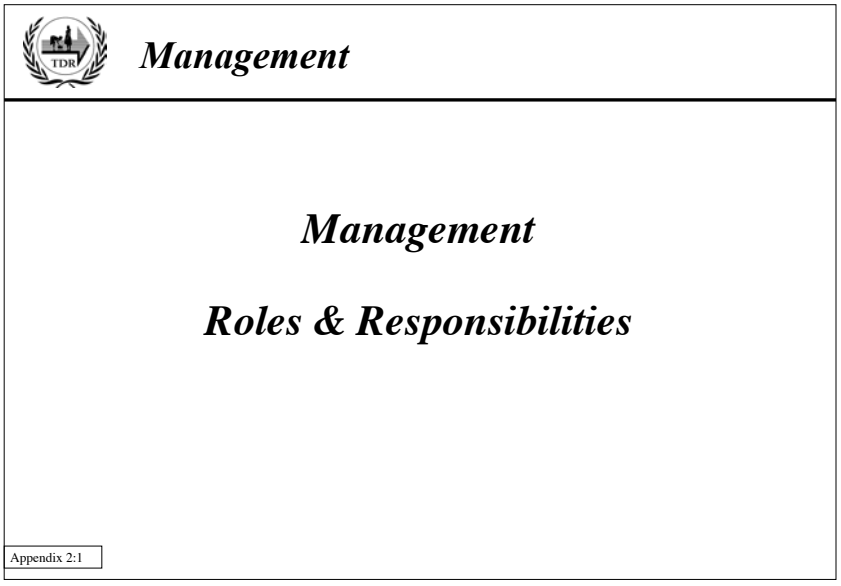
Characterisation of the test item and the test system is one of the five fundamental points dealt with in the main chapters of this manual. Characterisation may be very simple and the characterisation needed is study and test item dependent. An SOP describing what should happen in each case is the best way of ensuring that some characterisation does occur. There are no hard and fast rules about what appropriate characterisation is, or who should perform this work, or when exactly it should be done.

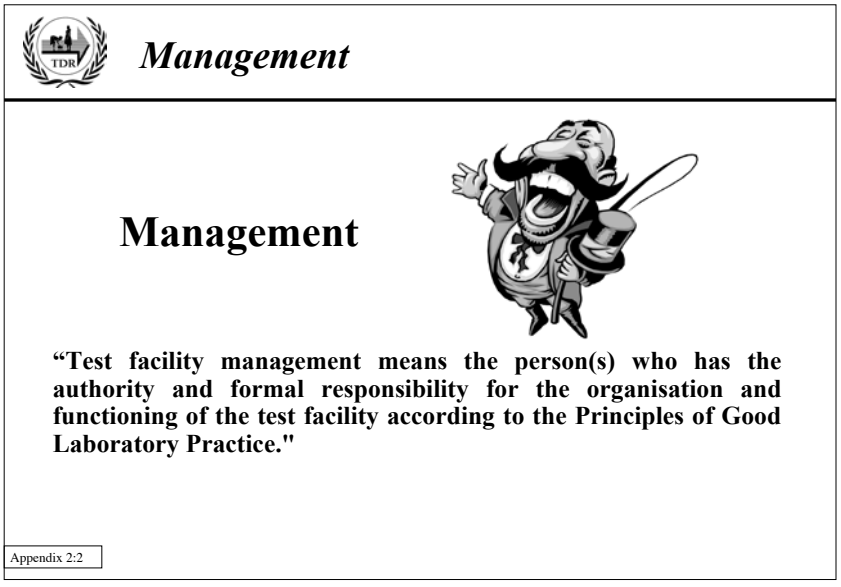
q) establish procedures to ensure that computerised systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with these Principles of Good Laboratory Practice.

Computerised 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


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

Management

- **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

Management

Responsibilities : General

Management should ensure that:

- **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

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

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

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

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

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

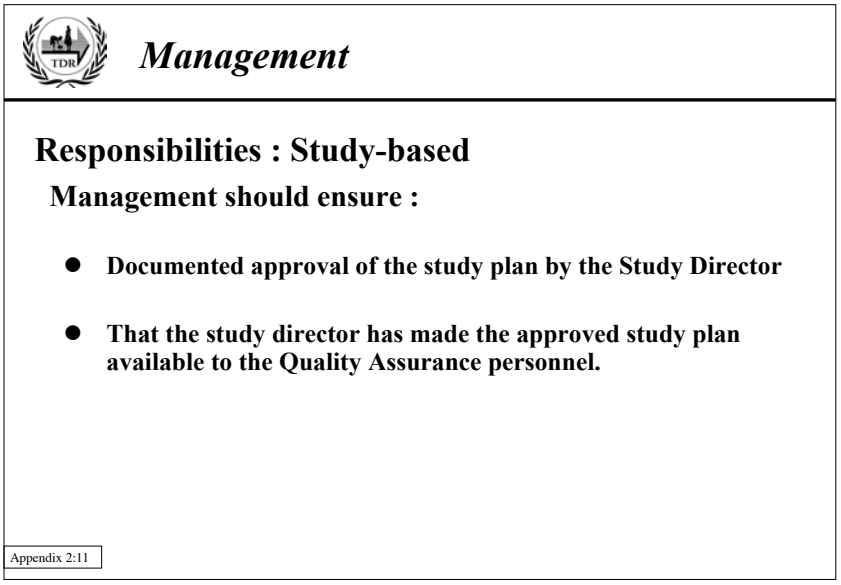
Management

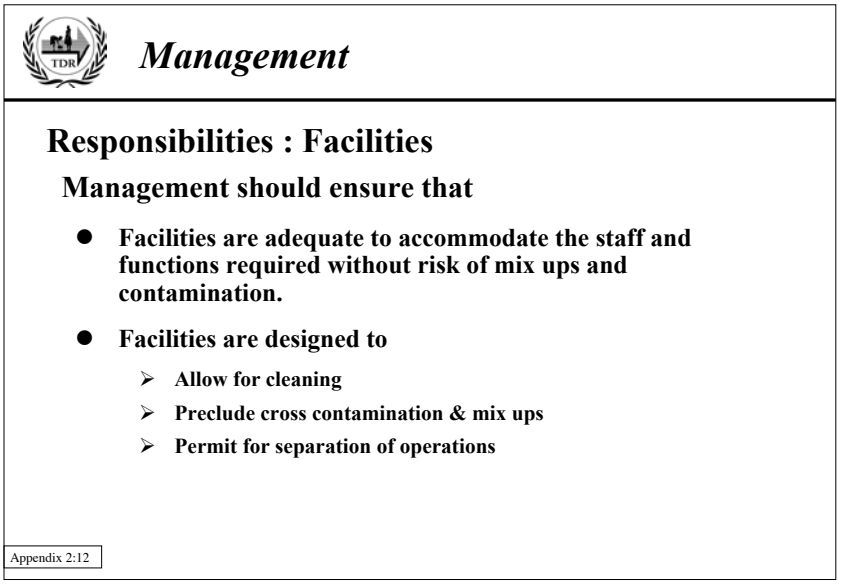
Responsibilities : Study-based

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


Management
Responsibilities : Study-based
Management should ensure :
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


Management
Responsibilities : Facilities
Management should ensure that
Facilities are adequate to accommodate the staff and functions required without risk of mix ups and contamination.
Facilities are designed to
Allow for cleaning
Preclude cross contamination & mix ups
Permit for separation of operations
Appendix 2:12

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

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

Management

Responsibilities : Multi-site studies

Management should ensure that

- **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**

Appendix 2:15

Management

Responsibilities : Others

Management should fix policies / procedures for:

- ✓ **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**

Appendix 2:16

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

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 supervises. 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 organisational 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 organisational 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 organisation 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 computerised 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 formalised, 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 formalised 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.

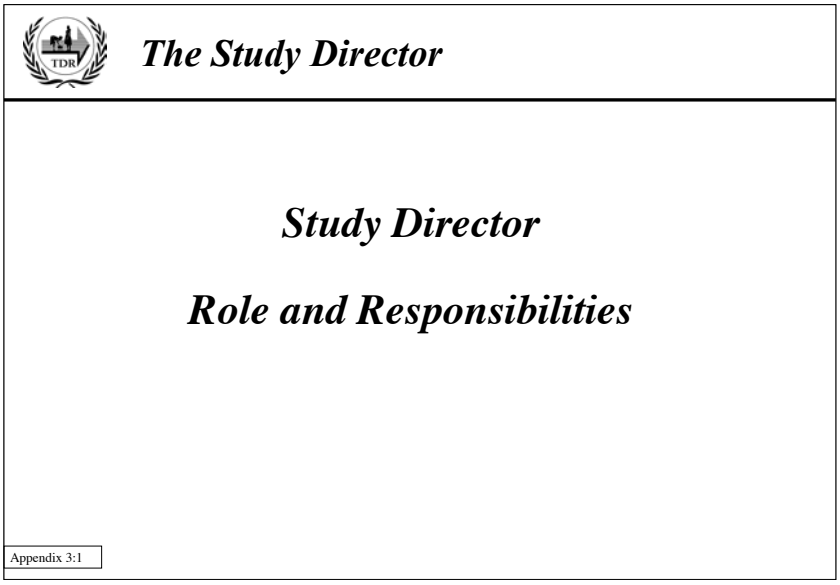
The OECD document, "The role and responsibilities of the Study Director in GLP studies" draws particular attention to the need for good communication between the Study Director and Quality Assurance.

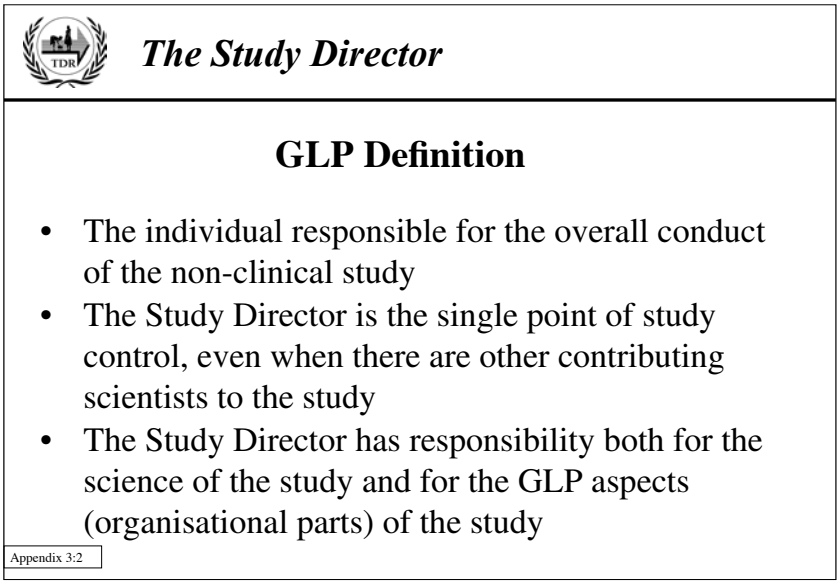
"Communication between the Study Director and QA is required at all stages of the study. This communication may involve:

– *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


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

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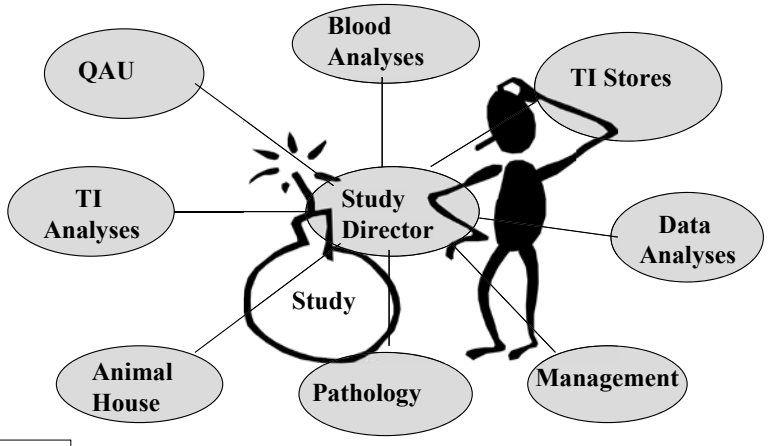
The Study Director



Appendix 3:3

The Study Director

Qualifications

"The designation of the Study Director is a key decision in assuring that the study will be properly planned, conducted and reported. The appropriate Study Director qualifications may be based more on experience than on advanced education"

Appendix 3:4

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

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

181

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

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

The Study Director

Interface with study personnel

- 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. *This is particularly essential in the multi-site situation*

Appendix 3:9

The Study Director

Interface with Quality Assurance

The Study Director should:

- 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

Appendix 3:10

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

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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

The Study Director

Responsibilities

Before the study starts, the Study Director should :

- Make sure that QAU gets a copy of the study plan
- Ensure that resources are available for the study
  - facilities, equipment, trained personnel
- Ensure that all relevant SOPs for the study are available to personnel

Appendix 3:13

The Study Director

Responsibilities

During the study, the Study Director should :

- 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

Appendix 3:14

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

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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

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

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

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

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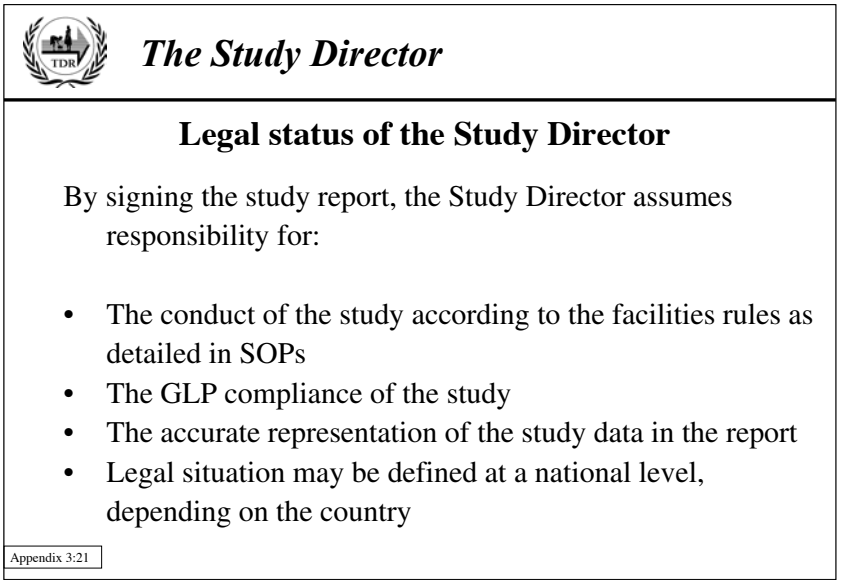
The Study Director

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


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

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 specialise 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 organisational 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 organisation 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 organisation 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.
- The 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 organise 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.

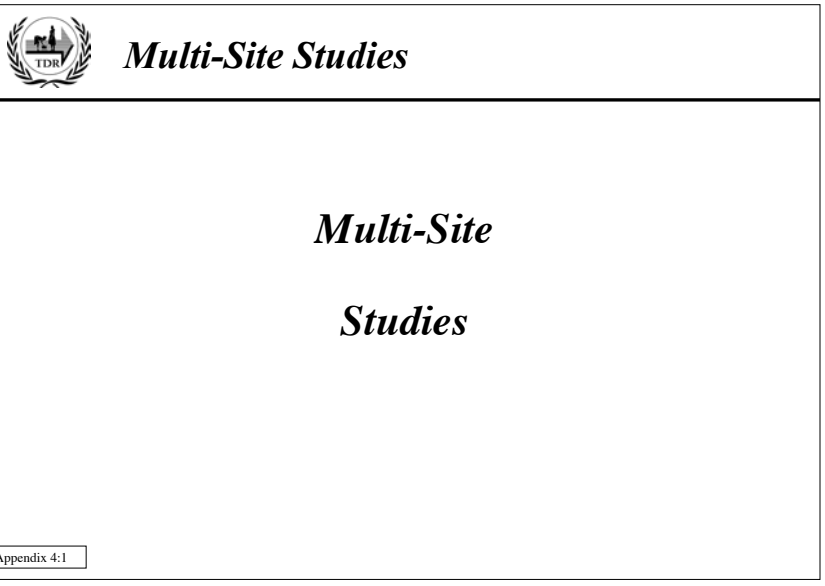
Lead Quality Assurance

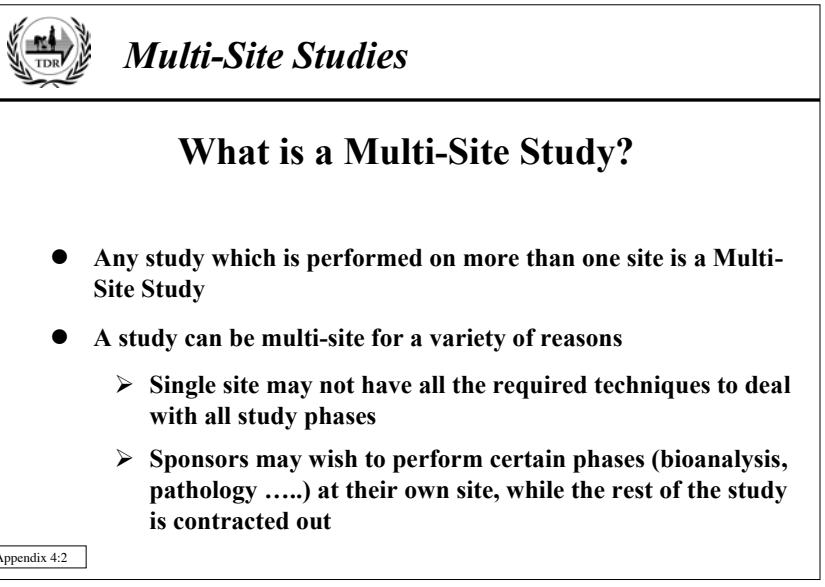
- Lead Quality Assurance must regularly communicate with test site QA so that there is proper inspection coverage of the whole study.

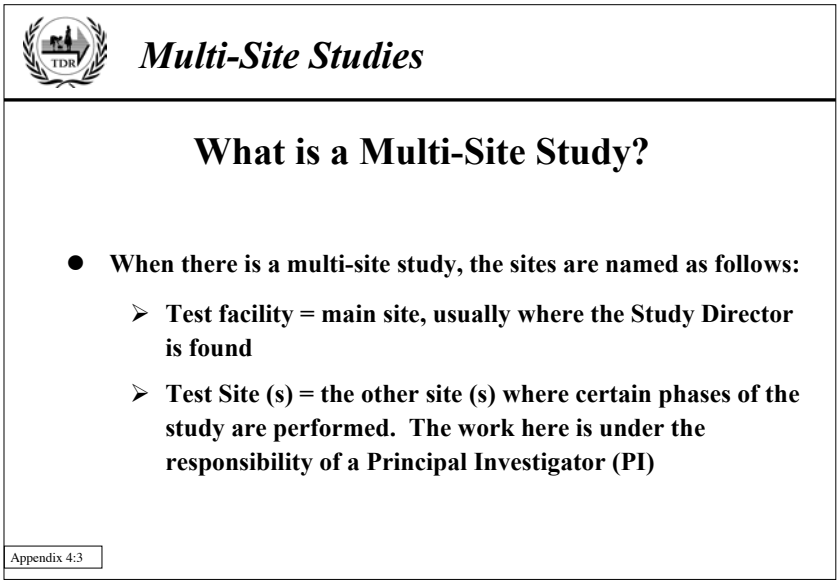
- The respective responsibilities for the lead QA and site QA must be established before experimental work starts.
- The lead Quality Assurance must make sure that the study plan is checked and that the final report is inspected.
- *"Quality assurance inspections of the final report should include verification 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.

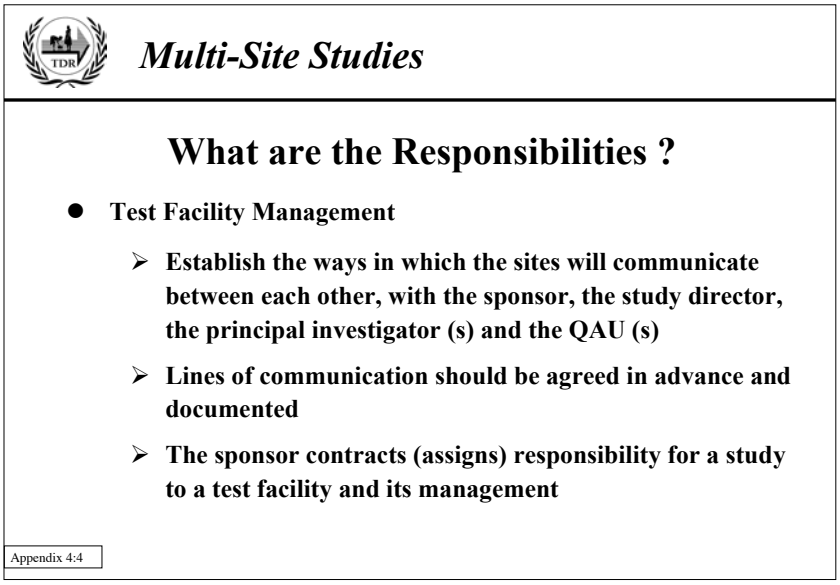
Test site Quality Assurance

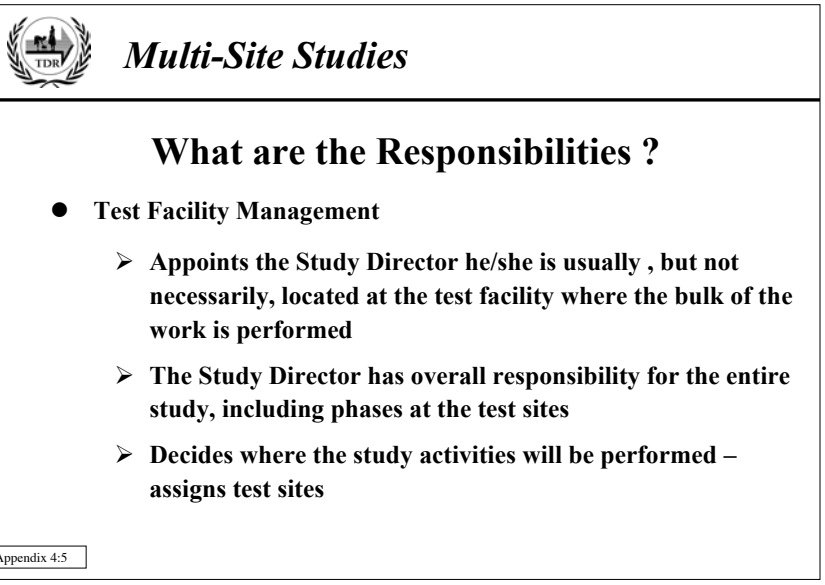
- Test site management is responsible for the appointment of QA and the conduct of QA functions at the test site.
- Test site QA must review those parts of the study plan that relate to activities at their site.
- "*[Test site QA] should maintain a copy of the approved study plan and study plan amendments."*
- 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."*

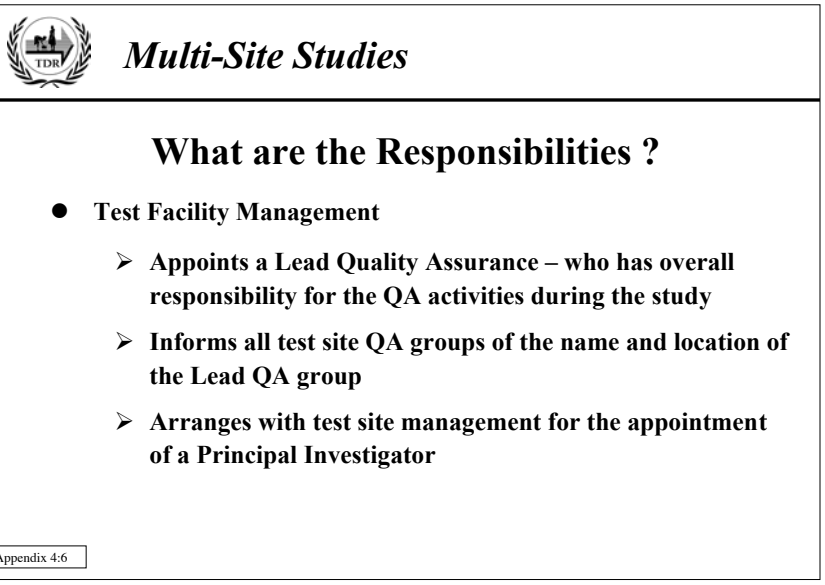

Multi-Site Studies
Multi-Site
Studies
Appendix 4:1


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


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


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


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**

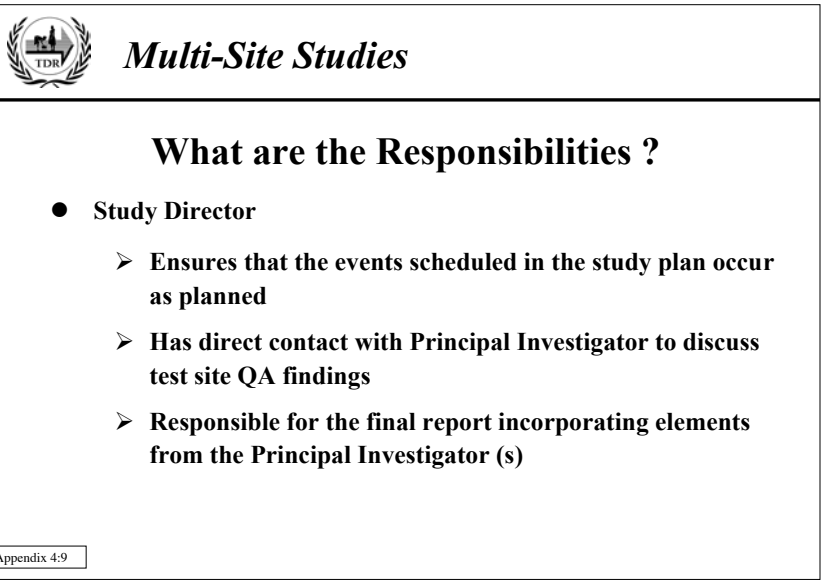
Appendix 4:7

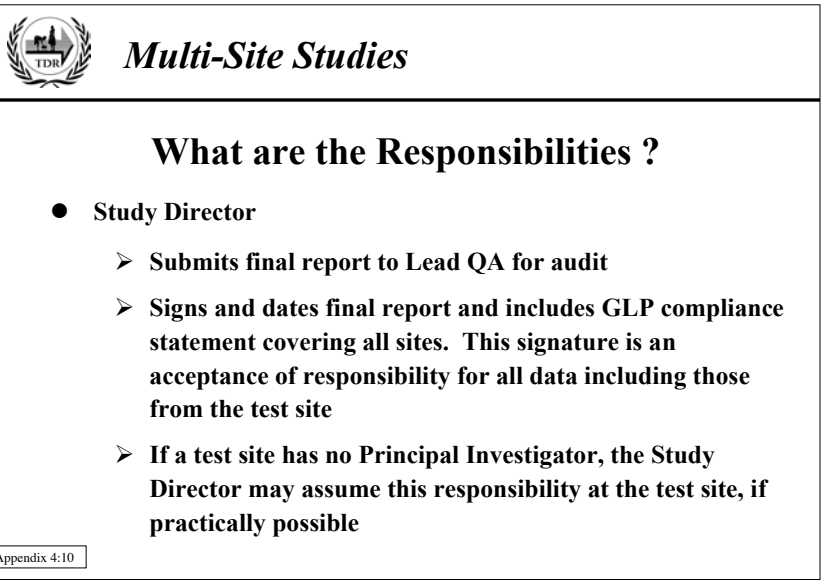
Multi-Site Studies

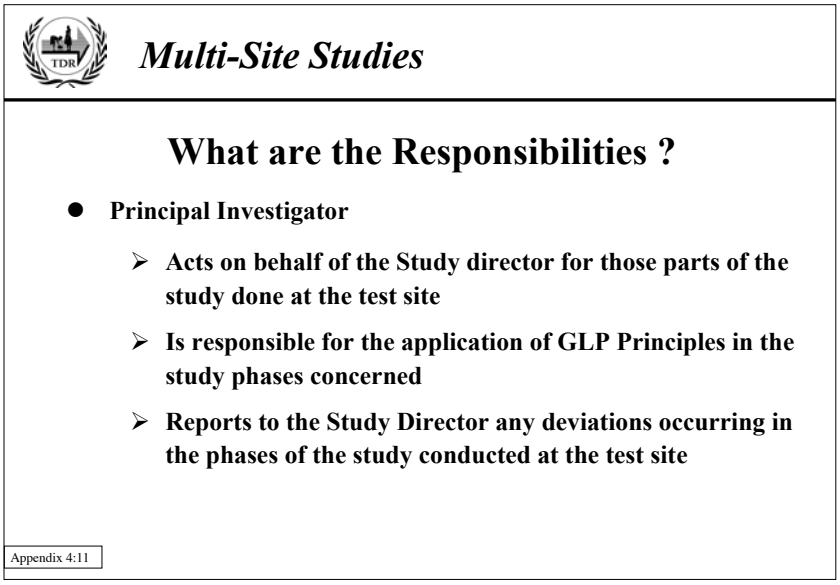
What are the Responsibilities ?

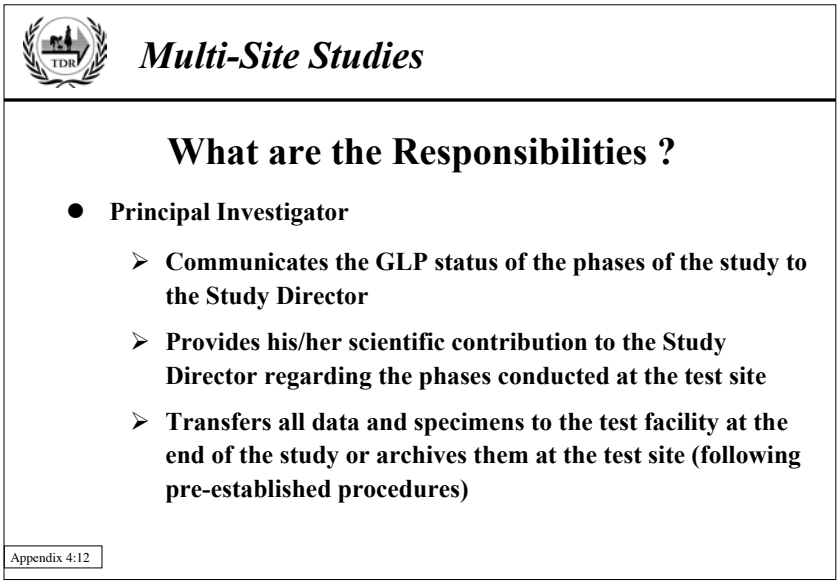
- **Study Director**
  - **Assures that the level of expertise at the test sites is acceptable**
  - **Approves Study Plan and takes responsibility for all GLP aspects of the study**
  - **Issues and approves amendments to study plan, including those which affect the test site**
  - **Maintains communication with all study personnel at all sites**

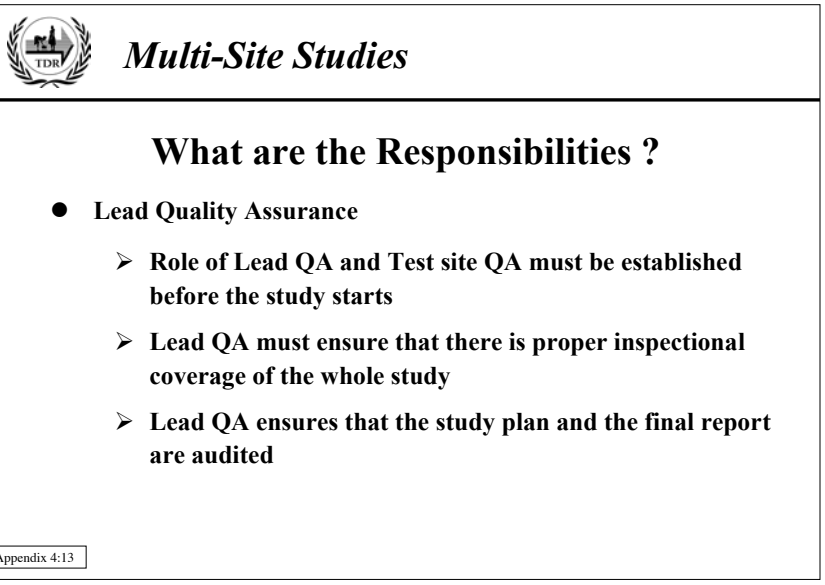
Appendix 4:8

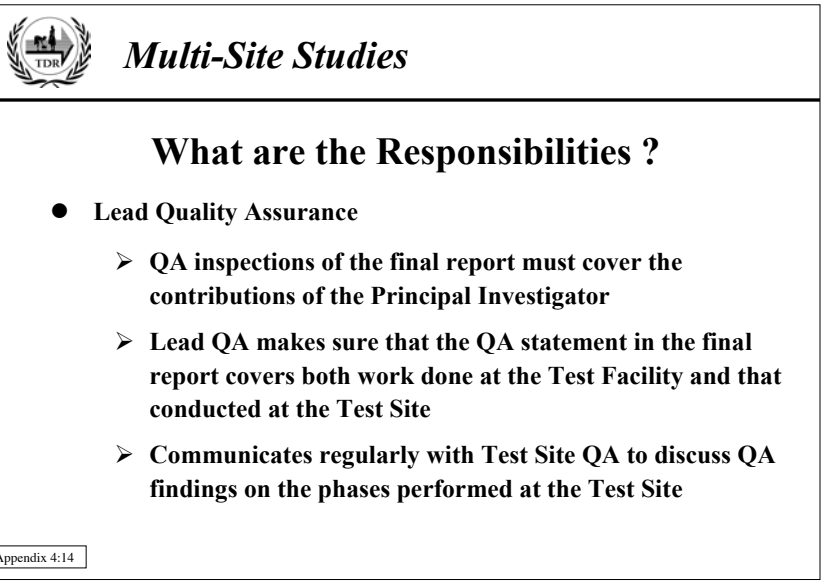

Multi-Site Studies
What are the Responsibilities ?
Study Director
Ensures that the events scheduled in the study plan occur as planned
Has direct contact with Principal Investigator to discuss test site QA findings
Responsible for the final report incorporating elements from the Principal Investigator (s)
Appendix 4:9

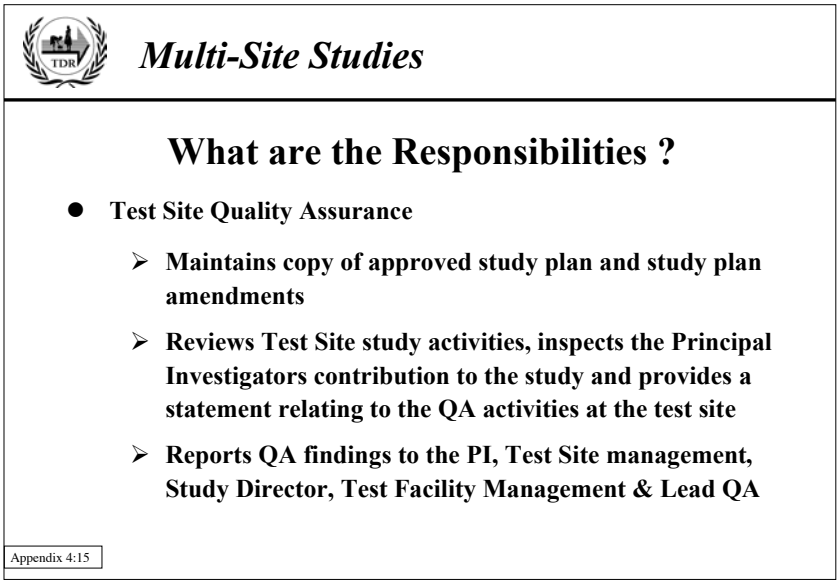

Multi-Site Studies
What are the Responsibilities ?
Study Director
Submits final report to Lead QA for audit
Signs and dates final report and includes GLP compliance statement covering all sites. This signature is an acceptance of responsibility for all data including those from the test site
If a test site has no Principal Investigator, the Study Director may assume this responsibility at the test site, if practically possible
Appendix 4:10


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


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


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


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 4:15

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 recognises that short term studies pose particular organisational 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.

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 characterisation 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 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.****"* (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.

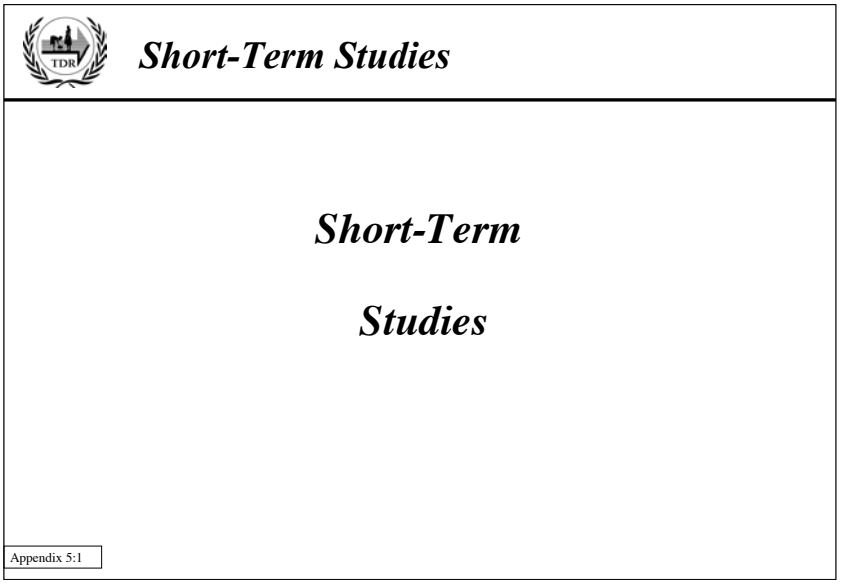
- In the OECD jargon, these additions are called Study specific supplements. The details that you might find in these supplements include: details on test item, experimental starting date, the unique study number, the actual name of the Study Director, etc.
- The supplement maybe issued as a supplementary 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."

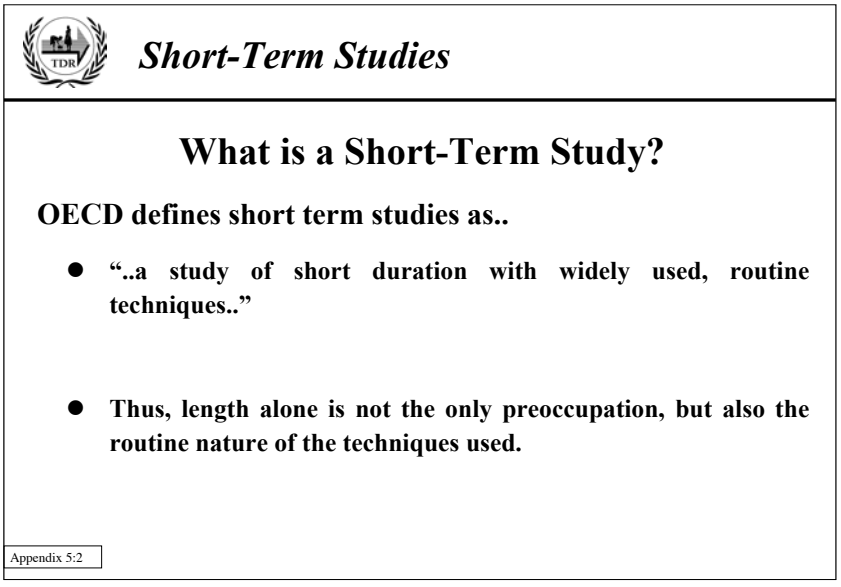
REPORTING SHORT-TERM STUDIES

- 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 *"standardised final reports"*.
- These are reports that have been prepared in advance and contain *"the majority of general information required in such reports and authorised 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 standardised 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 [standardised] 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 utilise a 'standardised final report' when the study plan is revised or amended prior to or during the conduct of the study unless the "standardised 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.


Short-Term Studies
Short-Term
Studies
Appendix 5:1


Short-Term Studies
What is a Short-Term Study?
OECD defines short term studies as..
"..a study of short duration with widely used, routine techniques.."
Thus, length alone is not the only preoccupation, but also the routine nature of the techniques used.
Appendix 5:2

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

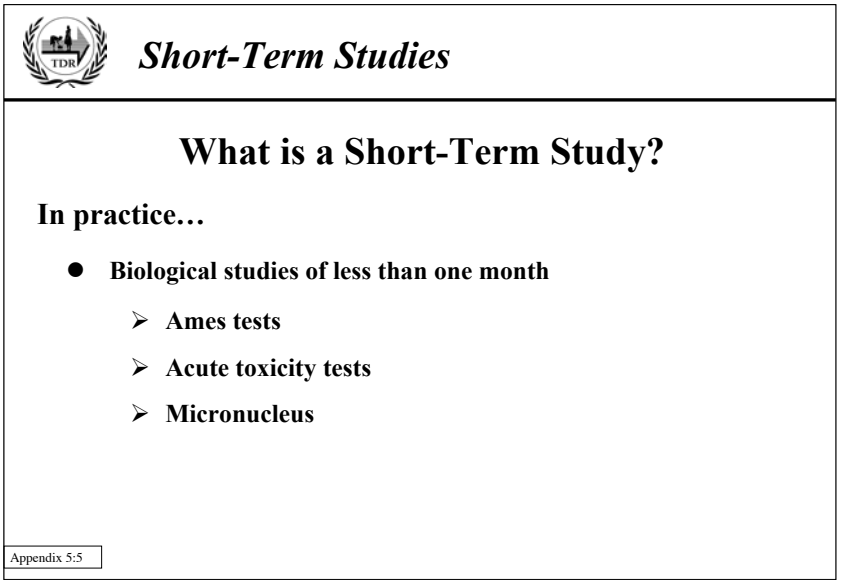
Short-Term Studies

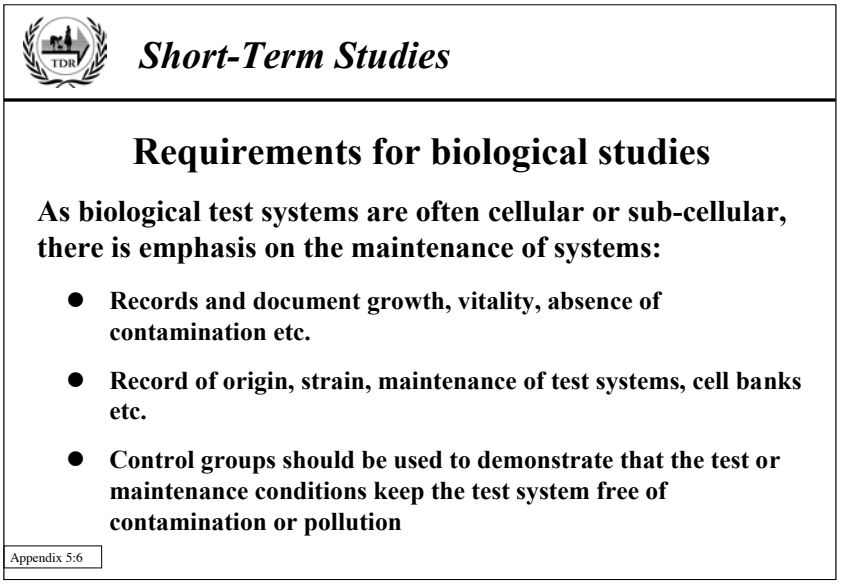
What is a Short-Term Study?

In practice…

- **Most physical-chemical studies**
  - **Characterisation studies**
  - **Melting point**
  - **Vapour pressure**
  - **Partition coefficient**
  - **Explosive properties…**

Appendix 5:4


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

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 o f final reports**
- **QA inspection /auditing procedures**

All the differences are due to the routine nature of the processes of the studies

Appendix 5:7

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

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

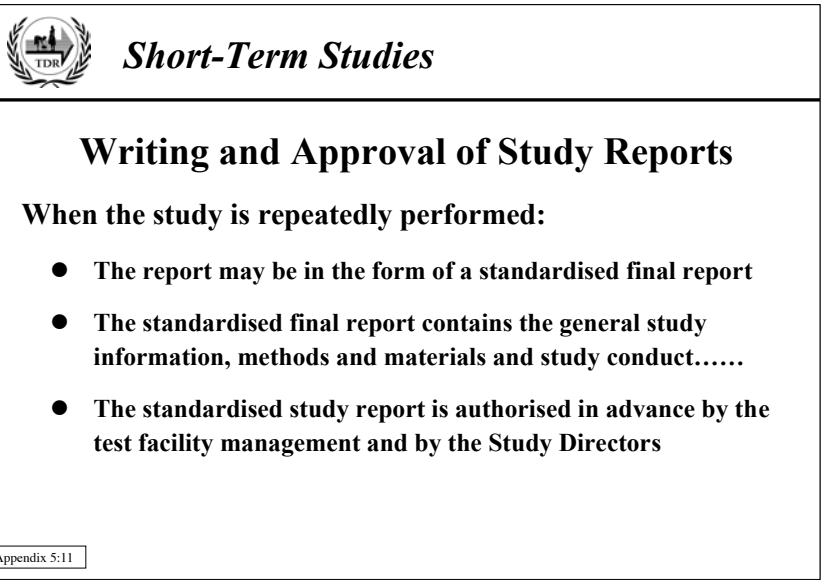
Short-Term Studies

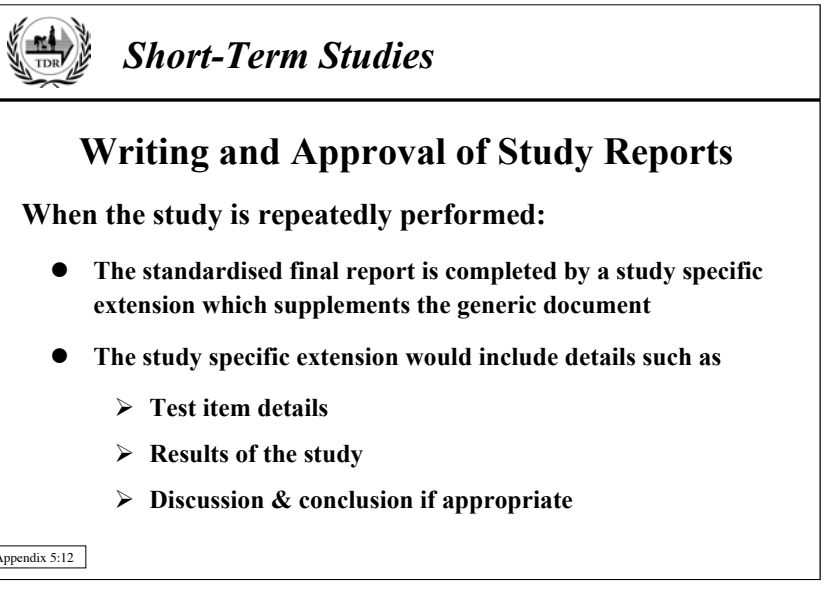
Writing and Approval of Study Plans

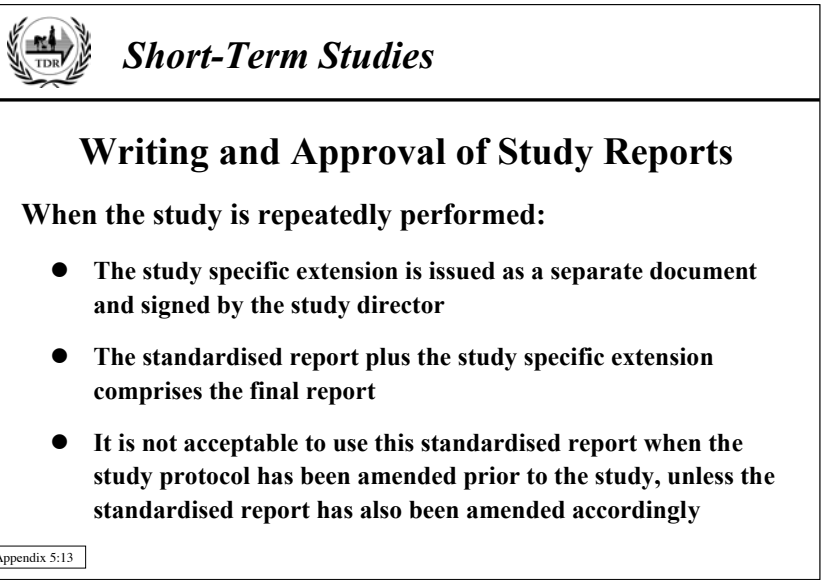
When the study is repeatedly performed:

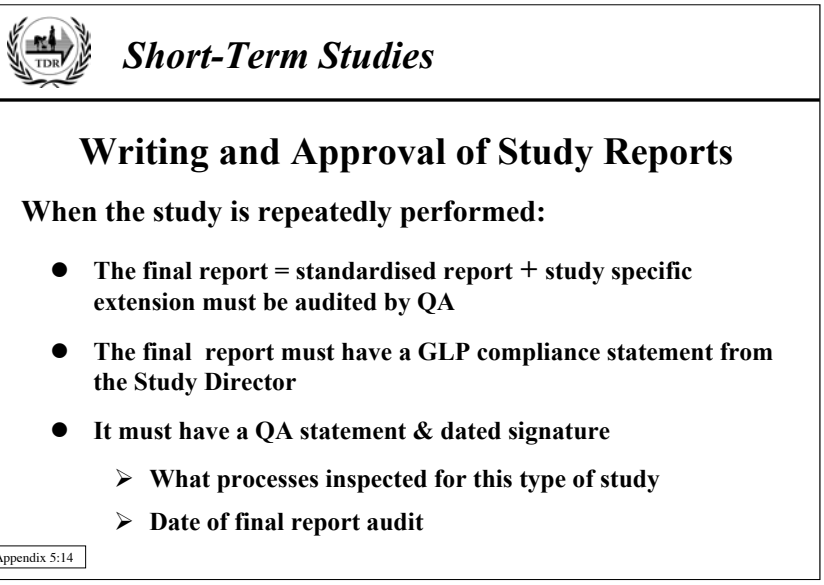
- **The study-specific supplement is issued as a separate document and is signed only by the study director, QA audit of the supplement is not required**
- **For GLP compliance the study plan comprises both the generic study plan + the study specific supplement**
- **The combined document must be supplied promptly to test facility management and to QA**

Appendix 5:10


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


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


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


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

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

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

Short-Term Studies

QA Inspection / Audit of Short Term Studies

Read this citation from the OECD document on Short-Term Studies:

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"**

Appendix 5:17

Short-Term Studies

QA Inspection / Audit of Short Term Studies

When QA uses process-based inspection for short-term studies

- **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**

Appendix 5:18

APPENDIX 6:
GLP AND COMPUTERISED SYSTEMS

In the following text the citations in italics are from the OECD documents on "The Application of the Principles of GLP to Computerised Systems"

DEFINITION AND SCOPE

The definition of Computerised 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 computerised 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 computerised 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 computerised 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 n GLP, Management has overall responsibility for compliance. In the field of computerised 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 computerised 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 utilise computerised systems, it is essential that Study Directors are fully aware of the involvement of any computerised 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 computerised 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 o computerised 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 of computerised 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 computerised systems, whose sudden failure would affect the results of a study. Adequate facilities should be provided for the secure retention of electronic storage media."

MAINTENANCE AND DISASTER RECOVERY

Computerised 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, 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."*

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 unauthorised modification, or loss. In this context security includes the prevention of unauthorised access or changes to the computerised 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 unauthorised 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 COMPUTERISED SYSTEMS

It is the responsibility of Management to demonstrate that computerised 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 recognised 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 computerised 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 computerised 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 Computerised Systems lists the documents typically required for the development, operation and maintenance of computerised 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 computerised 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 computerised systems will be in the form of SOPs. These should cover but not be limited to the following:

- *Procedures for the operation of computerised systems (hardware/software), and the responsibilities of personnel involved.*
- *Procedures for security measures used to detect and prevent unauthorised access and programme changes.*
- *Procedures and authorisation for programme changes and the recording of changes.*
- *Procedures and authorisation 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 computerised 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 computerised systems."*

Source Code

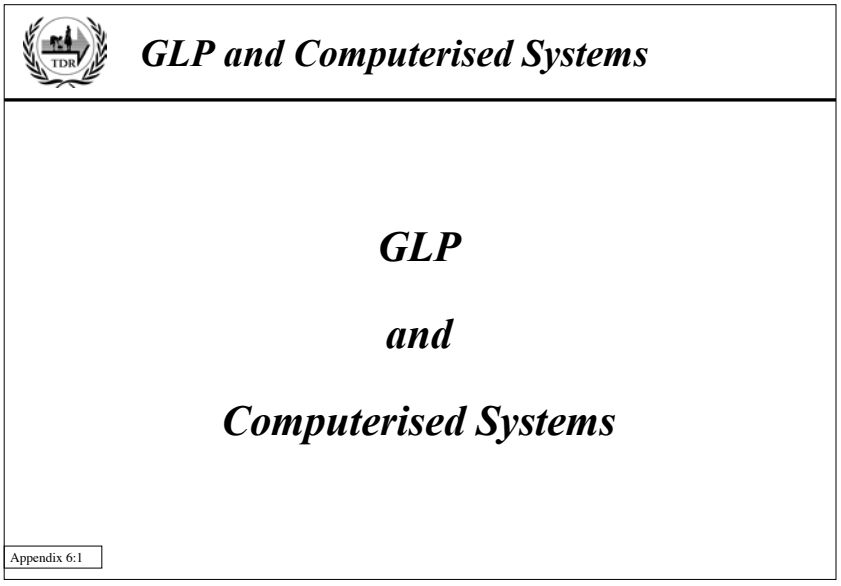
Some OECD countries require the source code (human readable version of the program) to be made available to monitoring authorities. In this case, the test facility will usually have an agreement with the system vendor to allow inspectors to see the code if they so wish.

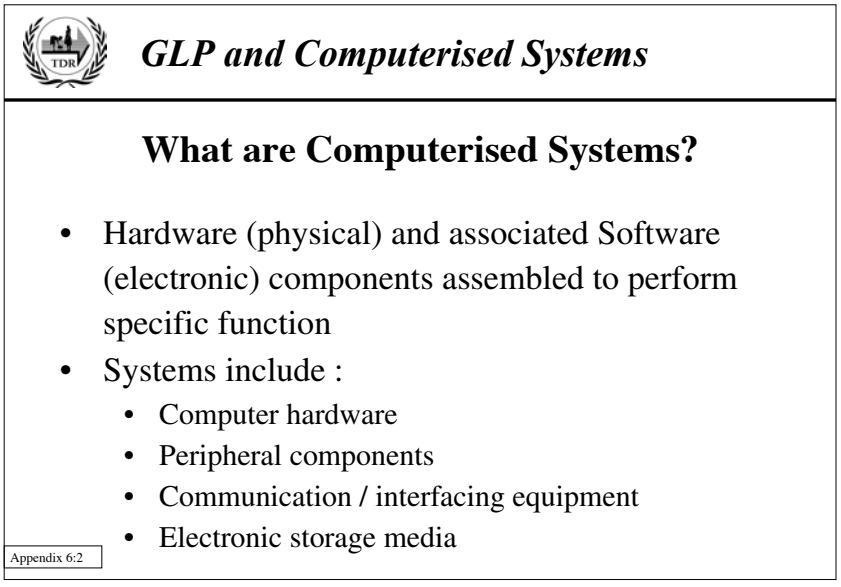
ARCHIVES

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 authorisation.

The storage periods for electronic data are the same as for other data and documents relating to studies.


GLP and Computerised Systems
GLP
and
Computerised Systems
Appendix 6:1


GLP and Computerised Systems
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
Appendix 6:2

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

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

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

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

GLP and Computerised Systems

Responsibilities

- Personnel – GLP compliance during operations
  - 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
  - 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

Appendix 6:7

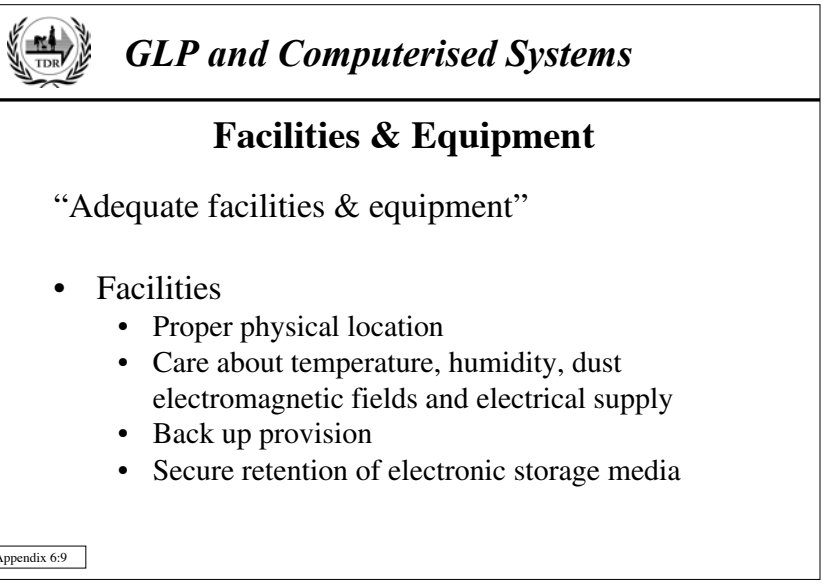
GLP and Computerised Systems

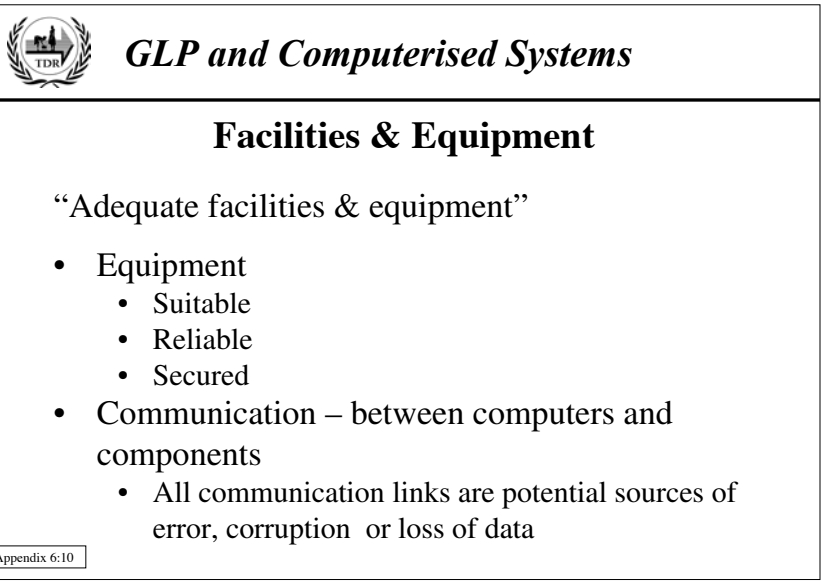
Training

"Appropriate qualified and experienced personnel"

- 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

Appendix 6:8


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


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

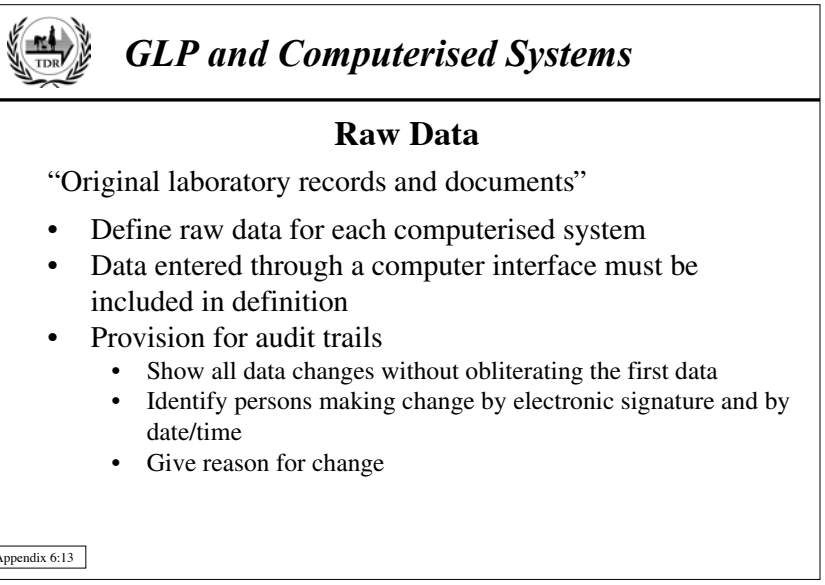
GLP and Computerised Systems

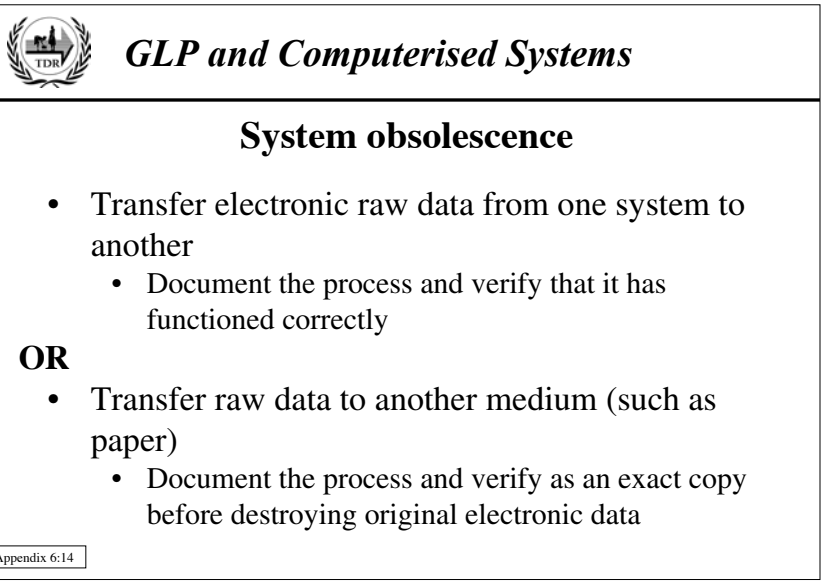
Maintenance & Disaster Recovery

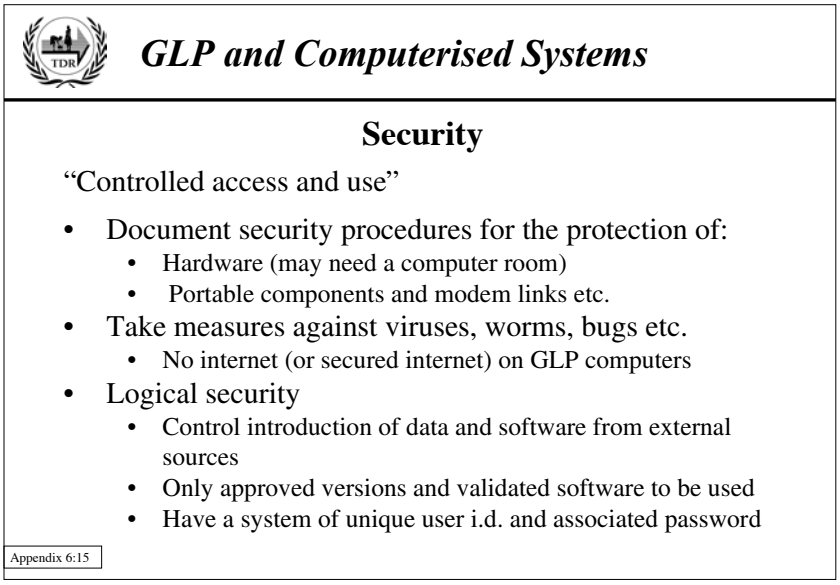
"Ensure the continuity of accurate performance"

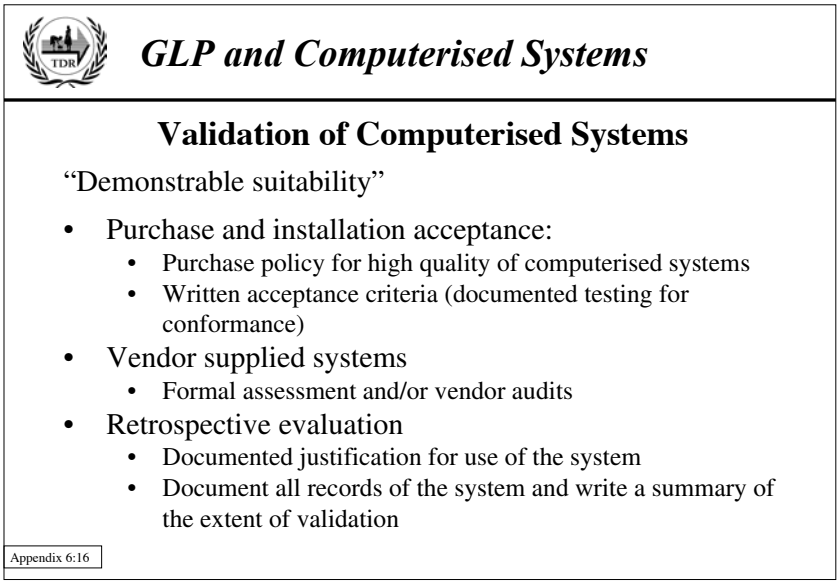
- Disaster Recovery
  - Keep back-up copies of all software
  - Make valid contingency plans and train staff
  - Written instruction to deal with cases of partial or total failure
  - Implement alternative methods of data capture in case of failure
    - Planned hardware redundancy
    - Transition to paper-based system
    - Recovery of computerised system

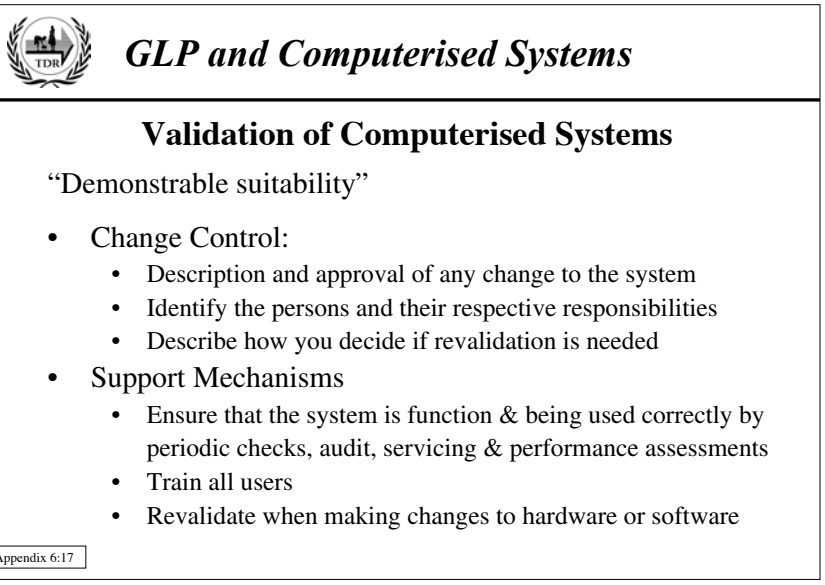
Appendix 6:12

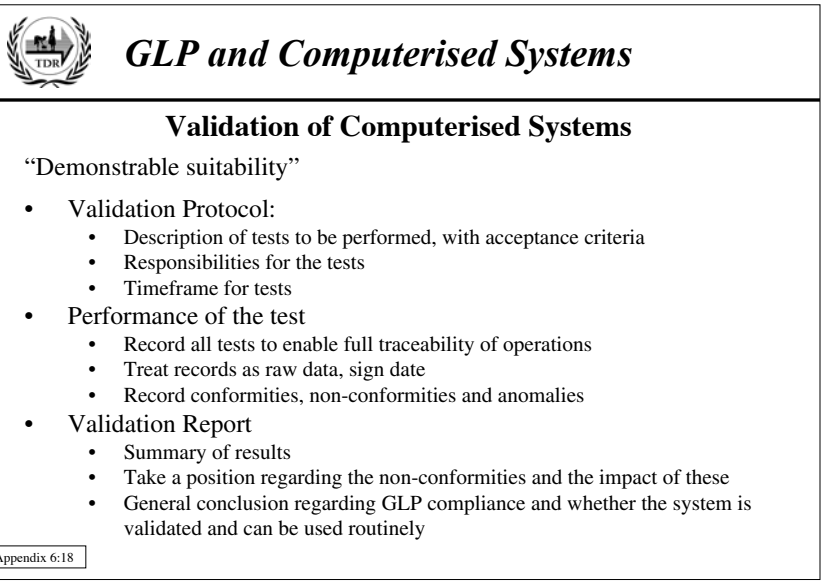

GLP and Computerised Systems
Raw Data
"Original laboratory records and documents"
• Define raw data for each computerised system
• Data entered through a computer interface must be included in definition
• Provision for audit trails
• Show all data changes without obliterating the first data
• Identify persons making change by electronic signature and by date/time
• Give reason for change
Appendix 6:13


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


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


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


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


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

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

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

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

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

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

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 characterisation 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 characterises 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".

- Characterisation 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 specialised 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.

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 specialised 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

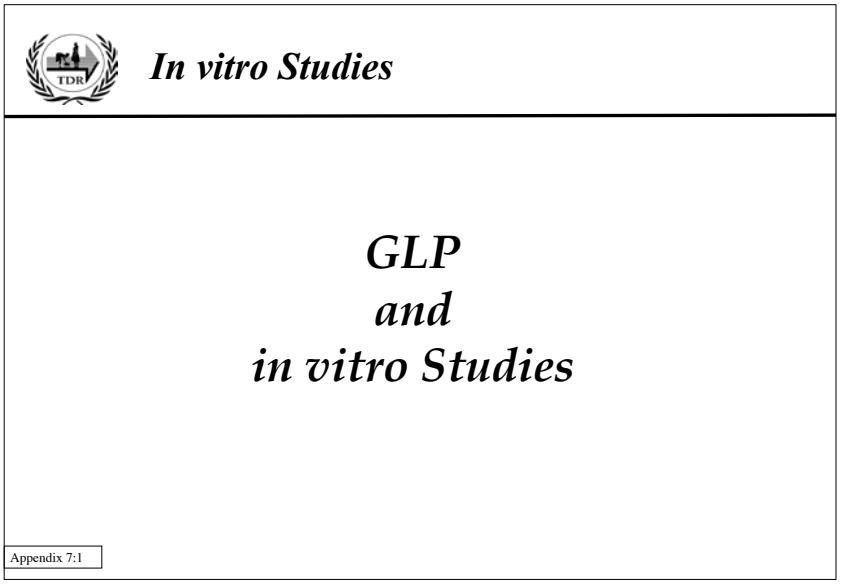
The requirements for *in-vitro* studies are the same as for *in vivo* studies. The OECD consensus document on Short-Term Studies will often apply to in-vitro studies.

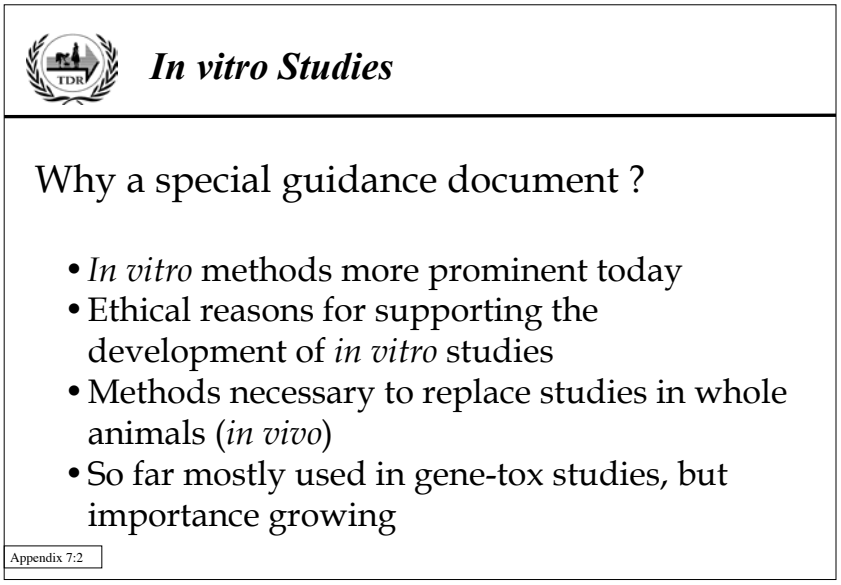
Specific issues that should be addressed in the final report are of a scientific or technical nature, eg.: use of *"appropriate positive, negative, and untreated and/or vehicle controls"*.

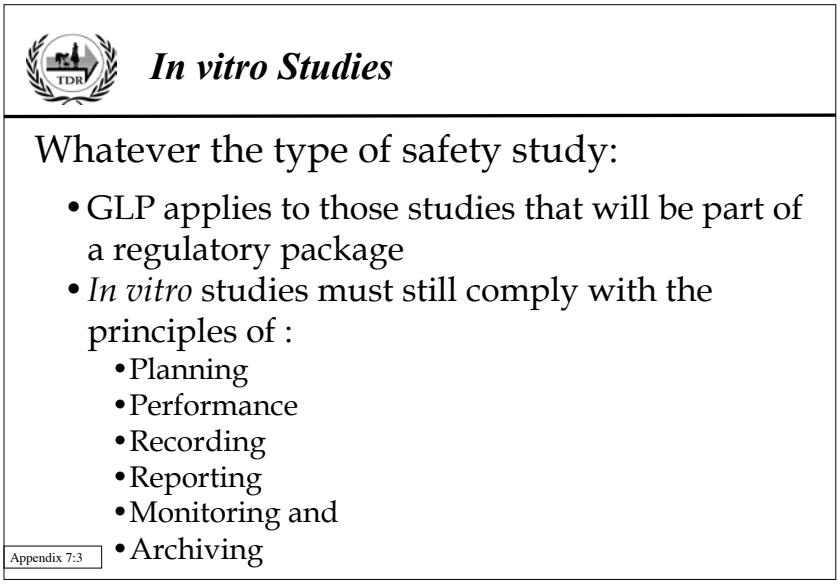
STORAGE AND RETENTION OF RECORDS AND MATERIALS

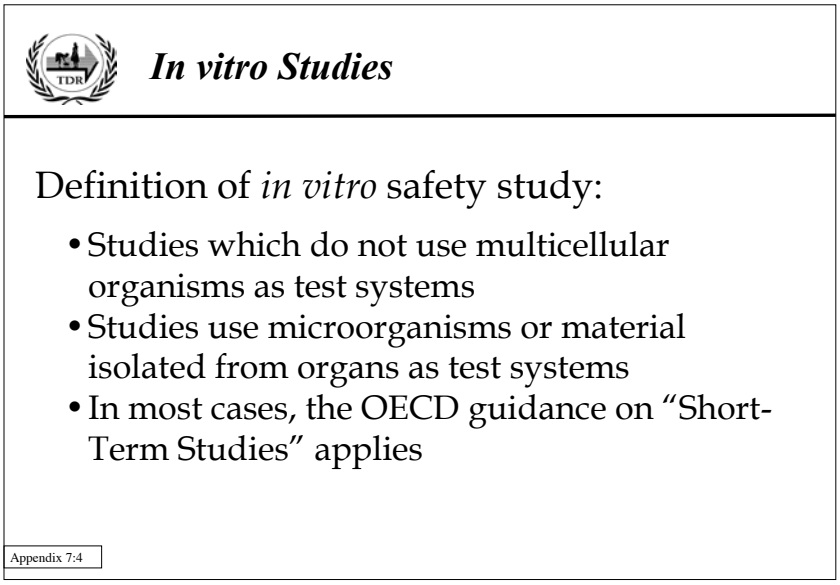
In addition to the requirements for archiving that apply to all GLP studies, the following points should be considered:

- 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


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


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

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

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

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

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

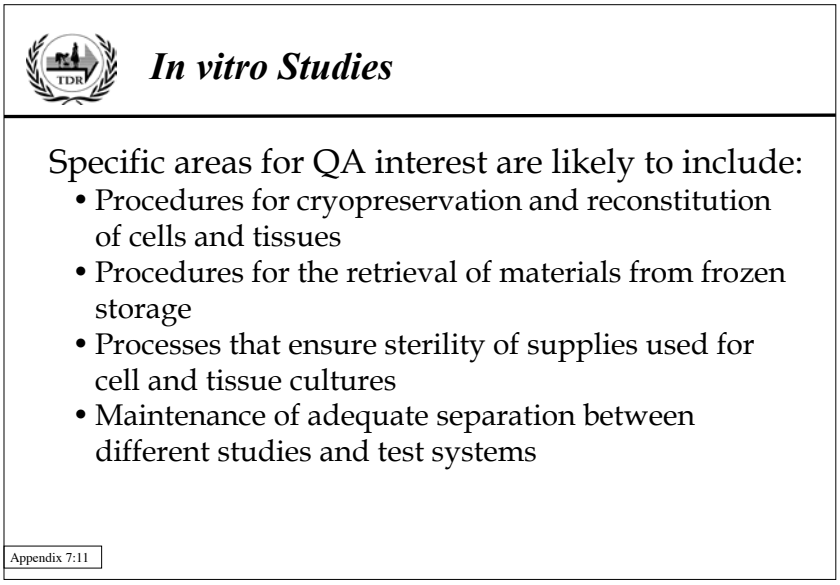
Appendix 7:9

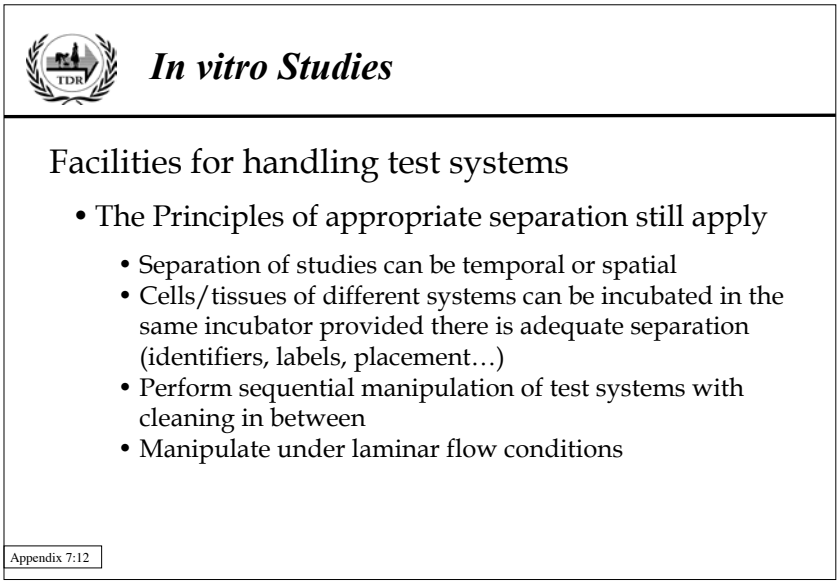
In vitro Studies

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


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


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

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

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

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

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

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