

TRAINING MANUAL

GOOD LABORATORY  
PRACTICE (GLP)

TRAINEE



UNDP/World Bank/WHO  
Special Programme for Research and Training in Tropical Diseases (TDR)

TDR/PRD/GLP/01.1B

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## PARTICIPANTS IN THE GLP TRAINING WORKSHOPS

1. **Bangkok, Thailand 1999 : People's Republic of China** – Dr Lin Shu Xian, Dr Runhua Yao ; **India** – Dr S. K. Singh, Dr Sharad Sharma ; **Philippines** – Prof. C. H. Santos, Dr G. V. Dalmacion : **Thailand** – Dr Sumalee Kamchonwongpaisan, Dr Bongkoch Tarnchompoo, Dr Chanya Puttikhunt, Ms Panjaporn Phutthatesk, Dr Chongdee Wongpinairat, Dr Sathit Pichyangkul, Dr Urusa Intrasukri ; **Viet Nam** – Dr Trinh Ngoc Hai, Dr Truong Van Nhu
2. **Nairobi, Kenya 1999 : Ghana** – Dr A. K. Nyarko, Dr Nii-Ayi Ankrah ; **Kenya** – Dr B. Ogutu, Mr S. Ndirangu, Ms M. Kibata, Mr F. M. Tolo, Dr G. Murilla & Dr C. Gichuki ; **Nigeria** – Prof. K. S. Gamaniel, Mr A. Samson ; **S. Africa** – Prof. A. Walubo ; **Tanzania** – Dr M. J. Moshi, Dr G. Rimoy ; **Uganda** – Dr T. G. Egwang
3. **Cali, Colombia 2000 : Colombia** – Dr M. H. Hazbon, Dr Ludwig Luis Antonio Albonoz Tovar, Dr Myriam Arevalo Herrera, Dr Jorge Boshell Samper, Dr John Mario Gonzales Escobar, Dr Socrates Herrera ; **Venezuela** – Dr Hilda Antonieta Perez, Dr Carlos G. Torres-Viera ; **Brazil** – Dr Hernando Antonio del Portillo Obando, Dr Mariano Gustavo Zalis, Dr Leonardo Josede Moura Carvalho ; **Honduras** – Dr Maria de los Angeles Mendoza Bogran ; **Peru** – Dr Julia J. Chu Cayatopa, Dr Patricia Herrera-Velit
4. **Cotonou, Benin 2000 : Mali** – Dr Fanta Traore, Dr Rokia Sanogo ; **Togo** – Prof. Comlan de Souza, Prof. Messavi Gbeassor ; **Burkina Faso** – Prof. Issiaka Kabore, Prof. Pierre Guissou ; **Bangui** – Dr Jean Koudou ; **Republic du Congo** – Dr Ange Abena ; **Cameroon** – Dr Mari-Solange B. Evehe, Dr Gabriel Lando, Dr Vincent Pryde K. Titanji ; **Madagascar** – Dr Milijaona Randrianarivelosia, Mr David Ramanitrahasimbola ; **Benin** – Dr Martin Akogbeto, Prof. Mansour Moudachirou, Prof. Ambaliou Sanni ; **Senegal** – Prof. Alioune Dieye & Dr Aissatou Toure-Balde

## TRAINERS IN THE WORKSHOPS

- Bangkok, Thailand (1999)**, David Long (GLP consultant) & Andreas Edelmann (F Hoffmann-la Roche Ltd), Deborah Kioy (WHO/TDR)
- Nairobi, Kenya (1999)**, David Long (GLP consultant) & Andreas Edelmann (F Hoffmann-la Roche Ltd), Deborah Kioy (WHO/TDR)
- Cali, Colombia (2000)**, David Long (GLP Consultant), Deborah Kioy (WHO/TDR)
- Cotonou, Benin (2000)**, Corinne Jumel-Jobit (Pfizer laboratories), Deborah Kioy (WHO/TDR)



UNDP/World Bank/WHO Special Programme for Research  
and Training in Tropical Diseases (TDR)

GOOD LABORATORY PRACTICE  
TRAINING MANUAL  
**FOR THE TRAINEE**

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



The Good Laboratory Practice (GLP) training manual is a set of two documents (one each for the trainer and for the trainee) that have been designed for use as an introductory course in GLP. TDR has conducted four GLP training workshops (Africa 2x, Asia and Latin America) as part of its technology transfer and capacity building programme in the area of pre-clinical product development in disease endemic countries. The participants of these workshops expressed the need for additional training in their countries. The training manuals have been compiled for TDR by **David Long** (GLP consultant, 30 Chemin de Cappy, 60410 St. Vaast de Longmont, France), based on the materials that were used in the workshops. The training manuals will provide a tool for training and promoting GLP concepts in disease endemic countries.

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

**Dr Deborah Kioy  
Pre-clinical Coordinator  
Product Research and Development  
TDR/WHO, GENEVA**

**Tel: +41 22 791 3524**

**Fax: +41 22 791 4854**

**E-mail: [kioyd@who.int](mailto:kioyd@who.int)**



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# ABOUT THIS TRAINING MANUAL

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This manual is a support document for the WHO good laboratory practice (GLP) training programme. The training is designed to provide information about the Organisation for Economic Cooperation and Development (OECD) GLP Principles which are recognized as the international standard for GLP. The training is spread over a three-day period. In general the first 1½ days will be spent on presentations relating to GLP Principles. The next 1½ days will be devoted to workshops and discussion groups.

The training programme first explains GLP requirements and then examines in more detail, through intensive workshop activities, the problems relating to writing study plans (protocols) and standard operating procedures (SOPs). Thanks should be expressed to the following people who contributed to the completion of this manual: David Long, Nick Kail, David Ford, Nadya Gawadi and Phil Withers. Without the help of these people the manual could not have been compiled.

The manual is divided into two main parts. **The first part** (Chapters 1-6) deals with the GLP requirements through presentations based on the five fundamental points (Resources, Rules, Characterisation, Documentation and Quality Assurance). These are first explained very briefly in Chapter 1, where you will also find an introduction to the subject of GLP and a few remarks on the history of GLP including why it was necessary to implement this regulation.

Each of the first 6 chapters has the same format: a text to explain the subject, followed by a copy of each of the slides used during the presentation. Participants can thus follow the presentation on the screen at the same time as in the manual (where they can make notes if they wish). The explanatory notes can then be used at some convenient time after the course has finished to read up about the subject.

**The second part** of the manual (Chapters 7-9) contains limited information on the workshops relating to protocols and to SOPs. The instructors have all the workshop material and this will only be distributed when necessary, on days 2 and 3 of the course.

The first two workshops are designed to encourage participants to think about the salient points when writing protocols (Chapter 7) and SOPs (Chapter 8). The participants will be able to use the information acquired during the more formal first day of presentations to help them during their workshops.

In both workshops there are, of course, many ways of dealing with the problems presented, so that each workshop group may well have a different approach. This is perfectly normal. It is both interesting and instructive to have diverse opinions on how to respond positively to the GLP requirements. One of the reasons for doing workshops on these topics is to stimulate discussion between participants, because it is through debate that a real understanding of the issues develops.

The third workshop (Chapter 9) is really a private exercise. You are provided with a multiple-choice questionnaire *and with the answers*. Answer the questionnaire at your leisure and check whether you have the correct answers. If you get the right answer, all well and good. If your answer is inaccurate, you should re-read the chapter in the manual that deals with the problem and also refer to the OECD GLP Principles or the consensus documents until you find the answer you are looking for.

# 1. INTRODUCTION TO THE OECD PRINCIPLES OF GLP

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## INTRODUCTION

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

The malpractice included some cases of fraud, but by far the most important aspect of poor practice was the lack of proper management and organization of studies used to complete regulatory dossiers. The investigations of the US Food and Drug Administration (FDA) in the toxicology laboratories in the USA demonstrated a lack of organization and poor management which, it was decided, could only be dealt with by imposing regulations. These regulations are the GLP regulations. First the US FDA, then the US Environmental Protection Agency (EPA), instituted GLP regulations, and eventually many nations of the world followed suit.

In 1981, the OECD also published GLP Principles and these have now dominated the international scene – so far 30 countries (the member states of the OECD) have signed agreements that make the OECD GLP Principles binding on them. This effectively makes the OECD Principles an international text.

The intent of GLP was to regulate the practices of scientists working on the safety testing of prospective drugs. With the obvious potential impact on consumers and patients recruited for clinical trials, the safety of drugs became a key issue and GLP was seen as a means of ensuring that scientists did not invent or manipulate safety data and a means of ensuring that GLP compliant studies are properly managed and conducted. Hence GLP became the champion of the consumer, the regulatory safeguard, the guarantee that the safety data were being honestly reported to the registration or receiving authorities as the basis of a decision whether or not to allow a new drug onto the market. GLP was imposed on the industry by regulatory authorities, in the same way as good manufacturing practice (GMP) had been before, and good clinical practice (GCP) was to be afterwards.

## THE FUNDAMENTAL POINTS OF GLP

While the regulations set out the rules for good practice they also help the researcher to perform his work in compliance with his own pre-established plan and they standardize procedures worldwide. The regulations do not concern the scientific or technical content of the research programmes. They do not aim to evaluate the scientific value of the studies.

All GLP texts, whatever their origin or the industry targeted, stress the importance of the following points:

1. Resources: organization, personnel, facilities and equipment.
2. Rules: protocols and written procedures.
3. Characterization: test items and test systems.
4. Documentation: raw data, final report and archives.
5. Quality assurance unit.

The training programme of the WHO takes each of these five fundamental points in turn and explains the rules of GLP in each case. The major points are summarized here.

### *1. Resources*

#### **Organization and Personnel**

GLP regulations require that the structure of the research organization and the responsibilities of the research personnel be clearly defined.

GLP also stresses that staffing levels must be sufficient 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 in order to perform the studies.

All equipment must be in working order. A strict programme of qualification, calibration and maintenance attains this.

### *2. Rules*

#### **Protocols and Written Procedures**

The main steps of research studies are described in the study plan or protocol. However, the protocol does not contain all the technical details necessary to exactly repeat

the study. Since being able to repeat studies and obtain similar results is a *sine qua non* of mutual acceptance of data (and, indeed, a central tenet in the scientific method), the routine procedures are described in written standard operating procedures (SOPs). Laboratories may also need to standardize certain techniques to facilitate comparison of results; here again written SOPs are an invaluable tool.

### 3. *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 to evaluate the properties of pharmaceutical compounds during the pre-clinical phase, it is a pre-requisite to have details about the test item and about the test system (often an animal or plant) to which it is administered.

### 4. *Documentation*

#### **Raw Data**

All studies generate raw data. These are the fruits of research and represent the basis for establishing results and arriving at conclusions. The raw data must also reflect the procedures and conditions of the study.

#### **Final Report**

The study report, just like all other aspects of the study, is the responsibility of the study director. He/she must ensure that the contents of the report describe the study accurately. The study director is also responsible for the scientific interpretation of the results

#### **Archives**

Storage of records must ensure safekeeping for many years, coupled with logical and prompt retrieval.

### 5. *Quality Assurance*

Quality assurance (QA) as defined by GLP is a team of persons charged with assuring management that GLP compliance has been attained within the laboratory. They are organized independently of the operational and study programme, and function as witnesses to the whole pre-clinical research process.

## THE OECD GLP PRINCIPLES

GLP started when the FDA issued mandatory requirements on June 20 1979. Subsequently the FDA has revised these regulations a number of times but has never changed the basics. At no time has the FDA changed the scope of the regulations; they still apply to non-clinical studies used to evaluate safety. Preliminary pharmacological studies and pharmacokinetic studies not designed to test safety are still exempt from GLP requirements. A little later, the OECD brought out Principles for GLP concerning the testing of any chemical substances. This GLP text is binding on all OECD member states and, as a consequence, has dominated GLP worldwide. This is why these GLP Principles have been used as the basic rules for the training programme devised for the WHO.

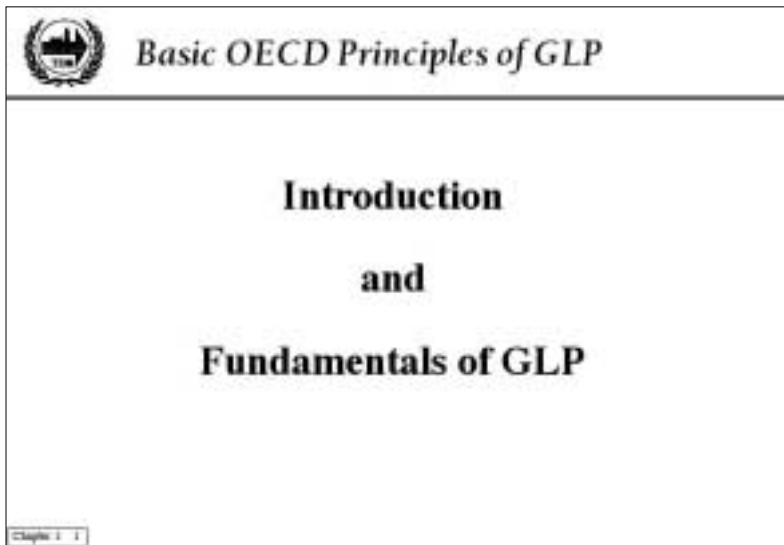
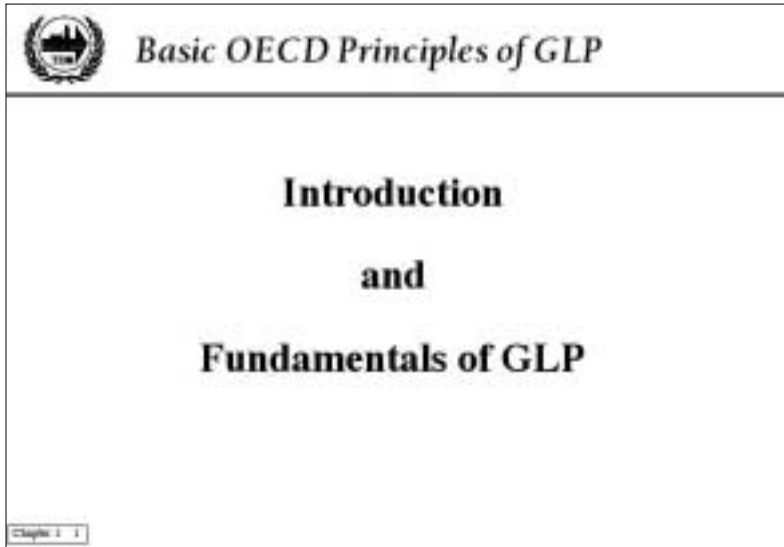
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The OECD recognizes that not all parts of the GLP Principles are easy to interpret. This is why the OECD has instituted a series of advisory documents on various aspects of GLP organization. There are seven consensus type documents. They have mostly been derived through discussion between the regulators and industry during consensus workshops. The contents of the consensus documents represent the current thinking of the OECD on the domain covered by the document. Any member state can request that a particular subject be discussed during a consensus meeting, it is up to the organization of the OECD to decide whether or not the subject is of general interest and merits a full three-day consensus type meeting.

The OECD has 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. These activities include the organization of training courses for GLP inspectors from all over the world and the organization of joint inspections, which are performed with a view to harmonizing the approach of various member states to GLP inspections.

## 1. Introduction to the OECD Principles of GLP

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## 1. Introduction to the OECD Principles of GLP

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### *Basic OECD Principles of GLP*

#### **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

Chapter 1 3



### *Basic OECD Principles of GLP*

#### **FDA Investigation findings**

- Inadequate characterisation of test items and test systems
- Inadequate resources
- Equipment not properly calibrated or otherwise qualified
- Reports not sufficiently verified, not an accurate account of the actual study, not a proper reflection of raw data
- Archives inadequate

Chapter 1 4

## 1. Introduction to the OECD Principles of GLP

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### *Basic OECD Principles of GLP*

#### **FDA Decision**

- Introduce a new regulation to cover  
NON-CLINICAL SAFETY STUDIES
- Good Laboratory Practice regulations
- Draft GLPs in 1976
- An enforceable US regulation in 1979

Chapter 1 3

9



### *Basic OECD Principles of GLP*

#### **GLP**

**promotes**

**Quality and Validity**

**of test data**

Chapter 1 8

## 1. Introduction to the OECD Principles of GLP

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### *Basic OECD Principles of GLP*

#### **GLP Principles**

**MAIN GOAL:** To help scientists obtain results which are:

- Reliable
- Repeatable
- Auditable
- Recognized by scientists worldwide

Chapter 1 1



### *Basic OECD Principles of GLP*

#### **GLP Principles**

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

Chapter 1 2

## 1. Introduction to the OECD Principles of GLP

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*Basic OECD Principles of GLP*

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**GLP Aim**

To make the incidence of


**False Negatives**

more obvious

(e.g. Results demonstrate non-toxicity  
of a toxic substance)

Chapter 1 8

11



*Basic OECD Principles of GLP*

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**GLP Aim**

To make the incidence of

**False Positives**

more obvious

(e.g. Results demonstrate non-toxicity  
of a toxic substance)

Chapter 1 10

## 1. Introduction to the OECD Principles of GLP

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### *Basic OECD Principles of GLP*

#### GLP Aim

**Promote mutual recognition of study  
data across international frontiers**

Chapter 1 [1]



### *Basic OECD Principles of GLP*

#### GLP


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

(Preamble to Directive 87/18 EEC)

Chapter 1 [2]

## 1. Introduction to the OECD Principles of GLP

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*Basic OECD Principles of GLP*

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**GLP**

**Managerial concept for the  
organization of studies**

Chapter 1 13



*Basic OECD Principles of GLP*

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**GLP**

Defines conditions under which studies are

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

Chapter 1 14

## 1. Introduction to the OECD Principles of GLP

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### *Basic OECD Principles of GLP*

#### **Five Basic Points**

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

Chapter 1 10



### *Basic OECD Principles of GLP*

#### **“International” GLP Principles of the OECD**

Chapter 1 10

## 1. Introduction to the OECD Principles of GLP

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### *Basic OECD Principles of GLP*

#### **Key Dates**

- 1978 USA - FDA GLP Regulations
- 1980 USA - EPA GLP Regulations
- 1981 OECD GLP Principles
- 1986 European Union GLP Directives

Also, 6 different Japanese GLP texts

Chapter 1 17

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### *Basic OECD Principles of GLP*

#### **How the OECD functions**

- Members are 30 major industrial countries including all EU countries, USA, Japan.
- Functions as an international agency; state representatives have ambassador status

Chapter 1 18

## 1. Introduction to the OECD Principles of GLP

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### *Basic OECD Principles of GLP*

#### **OECD GLP Principles**

- Agreed to by all 30 member states
- All states accept validity of studies performed in compliance with OECD GLP Principles
- Known as the “MAD” agreement

Chapter 1 19



### *Basic OECD Principles of GLP*

#### **The GLP Group**

- Made up of the heads of all GLP monitoring bodies (at least 30)
- Meets regularly
- Plans OECD GLP activities
- Verifies harmonization of approach between states

Chapter 1 20

## 1. Introduction to the OECD Principles of GLP

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### *Basic OECD Principles of GLP*

#### **GLP Principles recently revised**

- Latest version revised 1997, published 1998
- The Principles
- Acts relating to GLP and compliance monitoring

Chapter 1 11

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### *Basic OECD Principles of GLP*

#### **The OECD Consensus Documents**

- Quality Assurance
- Laboratory Suppliers
- Field Studies
- Study Director responsibilities

Chapter 1 22

## 1. Introduction to the OECD Principles of GLP

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### *Basic OECD Principles of GLP*

#### **OECD Consensus Documents (continued)**

- Computerized systems
- Responsibilities of the sponsor
- Short-term studies

Chapter 1 13



### *Basic OECD Principles of GLP*

#### **Consensus workshops**

- Preparation of a position paper
- Delegates chosen by member countries
- 3-day workshop session
- Chair & rapporteur produce 1st draft

Chapter 1 14

## 1. Introduction to the OECD Principles of GLP

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### *Basic OECD Principles of GLP*

#### **After the workshop (6-9 months)**

- 2nd draft prepared by GLP Group
- Various OECD administrative committees
- Final signature at OECD “ministerial level”

## CHAPTER 1 • PERSONAL NOTES

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## 2. RESOURCES

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### PERSONNEL

Laboratory management and organizational requirements take up about 15% of GLP texts, but unfortunately are still seen by regulators and QA as one of the principal sources of non-compliance with the spirit if not the text of GLP. Indeed, without full management commitment and the formal involvement of all personnel, GLP systems lack credibility and will not function as they should. These systems therefore are a critical element of setting up GLP in a laboratory.

It is obvious that the managers of a test facility have the overall responsibility for the implementation of both **good science** and **good organization**, including GLP.

#### *Good Science*

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

#### *Good Organization*

- Provision of adequate physical facilities and qualified staff.
- Planning of studies and allocation of resources.
- Definition of staff responsibilities and training of staff.
- Good record keeping and organized archives.
- Implementation of a process for the verification of results.
- Compliance with GLP.

#### *Personnel and Management*

The key relevant managerial systems which will be briefly described are:

- Planning / resource allocation.
- Personnel management traced through documents.
- Training.

### *Planning (Master Schedule)*

The requirement for a master planning system seems obvious but how many laboratories suffer from “Monday morning syndrome” where project activities are modified with inadequate provision for the resources necessary or the impact on existing work?

It is a management responsibility to ensure that sufficient personnel resources are allocated to specific studies and support areas.

The planning/resource allocation system required by GLP is called the master schedule or plan. These may take many forms but each system must ensure that:

- All studies (contracted and in-house) are included.
- Change control reflects shifts in dates and workload.
- Time-consuming activity such as protocol review and report preparation is provided for.
- The system is the “official” one (i.e. don’t have two or more competing systems for the same purpose).
- The system is described in an approved SOP.
- Responsibility for its maintenance and updating are defined.
- The various versions of the master schedule are approved and maintained in the archive as raw data.
- Distribution is adequate and key responsibilities are identified.

In most laboratories, the system includes these elements; a brief description follows below:

Once the protocol is signed and distributed, the study is entered onto the master schedule. This may or may not be a QA function in a lab. Often it is a project management function and 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 regularly as raw data. In contract facilities, sponsor and product names are usually coded to provide confidentiality. The QA inspection plan will be described later.

### *Personnel Organization*

Management has the responsibility of the overall organization of the test facility. With respect to personnel, this organization is usually reflected in the ORGANIZATION CHART. This is often the first document requested by national monitoring authorities to obtain an idea of how the facility functions.

GLP requires that personnel have the competence (education, experience, training) necessary to perform their functions.

Personnel organization is reflected in *job descriptions, CVs and training records*.

These documents should be defined in SOPs and verified regularly in QA audits.

### **Definition of Tasks and Responsibilities / Job Descriptions**

Any quality system is based on making people responsible for their actions.

“Don’t do something where you don’t understand the reason, the context and the consequences.”

“Each person signs his work and feels completely responsible for its correct completion.”

There must be a clear definition of tasks and responsibilities.

The contents of job descriptions should correspond to the qualifications as 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.

An annual review of all job descriptions, or in the event of any reorganization, helps top management ensure that their organization is coherent.

### ***Curriculum Vitae***

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.

All staff should have a CV. Even if some staff do not have extensive qualifications, they will have professional experience which should be listed in their CV. It is usual to include in a CV:

- Name, age and sex of the person.
- Education, including diplomas and qualifications awarded by recognized institutions.
- Professional experience both within the institution and before joining it.
- Any publications.
- Membership of associations.
- Languages spoken.

### Training

Finally, training complements CVs and job descriptions: job competence depends largely on internal and external specialized training. GLP explicitly requires that all personnel understand GLP, its importance, and the position of their own job within GLP activities. Training must be formally planned and documented. New objectives and new activities always involve some training. Training systems are usually SOP based. A new SOP therefore requires new certification of the involved personnel. Some companies have advanced training schemes linking training to motivation, professional advancement and reward.

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 standard operating procedure and historical reconstruction is possible through the archive.

For example, the participant's attendance at this course should be documented in their training records.

## FACILITIES: BUILDINGS AND EQUIPMENT

### *Buildings*

#### General Principles

Testing facilities should be of suitable size, **construction and location to meet the requirements** of the study and to **minimize disturbances** that would interfere with the validity of the study. They should be designed so as to provide an **adequate degree of separation** of the various aspects 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” construction, but carefully considering the objectives of the study and how to achieve these.

Separation ensures that different functions or activities do not interfere with one another or affect the study, and minimizes disturbances. This can be done by:

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

As an illustration of the principles involved we shall consider:

- Areas concerned with test material control and mixing with vehicles (although the same considerations would apply to other areas such as analytical or histopathology laboratories).
- Animal facilities.

### **Pharmacy and Dose Mixing Areas**

The pharmacy and dose mixing area is a laboratory dealing with test item workflow: receipt, storage, dispensing, weighing, mixing, dispatch to the animal house and waste disposal.

#### ***Size***

The laboratory is big enough to accommodate the number of staff working in it and allow them to carry on their work without risk of getting in each other's way or mixing up different materials.

Each operator has a workstation sufficiently large to be able to carry out the operation efficiently. There is also a degree of physical separation between the workstations to reduce the chance of mix-up of materials or cross contamination.

The pharmacy is a sensitive area and, to such facilities, access should be restricted so as to limit the possible contamination of one study or compound by another.

#### ***Construction***

The laboratory is built of materials that allow easy cleaning and are not likely to allow test materials to accumulate and cross contaminate others. There is a ventilation system that provides a flow of air away from the operator through filters, which both protects personnel and prevents cross contamination. Most modern dose mix areas are now designed in a "box" fashion, each box having an independent air system.

### **Arrangement**

There are separate areas for:

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

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### **Animal Facility**

To minimize the effects of environmental variables on the animal, the facility should be designed and operated to prevent the animal 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 facilities.

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 would have separation maintained by provision of areas for:

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

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

The environment system maintains the temperature, humidity and airflow constantly at the defined levels for the species concerned.

The surfaces of walls, doors, floors and ceilings are capable of being easily and completely cleaned and there are no gaps or ledges where dirt and dust can build up, nor uneven floors where water can build up.

Whatever the capabilities or needs of your laboratory, sensible working procedures reduce potential danger to the study from outside influences and maintain a degree of separation. You can achieve this by:

- 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 day, and 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*

Adequate equipment should be available for the proper conduct of the study. All equipment should be suitable for its intended use, and be properly calibrated and maintained to ensure accurate performance. 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.

### **Suitability**

This can only be assessed by consideration of the job which the equipment is expected to do. Just as there is no need to have a balance capable of weighing to decimals of a milligram to obtain the weekly weight of a rat, there may well be a need for a balance of this precision in the analytical laboratory.

### **Calibration**

Equipment that is performing to specification, whether it is generating data (e.g. analytical equipment or balances) or maintaining standard conditions (e.g. refrigera-

tors or air conditioning equipment), should have some proof that the specification is being achieved. This will generally be furnished by periodic checking.

In the case of measuring equipment, this is likely to involve the use of standards. For example, a balance will be checked by the use of known standard weights. In the case of a piece of analytical equipment, a sample of known concentration will be used to ensure that the equipment is functioning as expected as well as providing a basis to calculate the final result. Other equipment such as air conditioning plants or constant temperature storage will be checked periodically, at a frequency that allows action to be taken in time to prevent any adverse effect on the study should the equipment be demonstrated to be running out of specification.

### Maintenance

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 quite distinct ways:

- planned, when a regular check is made irrespective of the performance of the equipment, and reparative work when the calibration or regular checking suggests that the machine is not functioning according to specification. Planned maintenance may be a useful precaution for large items of equipment or items that do not possess suitable back-up or alternatives. Regular maintenance, therefore, reduces the risk of breakdown.
- on the other hand, some equipment such as modern computer driven analysers or electronic balances, do not easily lend themselves to routine maintenance of this sort and a better approach may be to check it regularly and to ensure that suitable contingencies are available should a problem occur. These contingencies may include having equipment duplicated or immediate access to an engineer.

Back-up for vital equipment should be available whenever possible as well as back-up in the event of service failures such as power cuts. A laboratory should have the ability to continue with essential services to prevent animals or data being lost and studies irretrievably affected. A laboratory, for example, carrying out animal studies may, as a minimum, need a stand-by generator capable of maintaining the animal room environment, even if it does not allow all the laboratory functions to continue, because the loss of the animals would irretrievably affect the study whereas samples may be stored for a period until power is returned.

Early warning that equipment is malfunctioning is important. The checking interval should be assigned to assure this, but the use of alarms will often assist in this, particularly if the problem occurs at a time when the staff is not present in the laboratory.

### **Documentation**

The planning of routine maintenance mentioned above should be documented in such a way that users of the equipment can ensure that it has been adequately maintained and is not outside its service interval. A “sticker” attached to equipment, or provision of a clear service plan, may do this.


Records of equipment calibration, checking and maintenance demonstrate that the laboratories SOPs have been followed and that equipment used in any study was adequate for the job and was delivering to its specification.

The records should also demonstrate that the required action was taken as a result of the checks that had been made.

Records should show that that all relevant staff knew about, and took, appropriate action when parameters went out of acceptable limits.

## 2. Resources

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*Resources*

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**RESOURCES**

Chapter 1



*Resources*


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**RESOURCES**

Chapter 1

## 2. Resources

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*Resources*

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**MANAGEMENT**

Chapter: 3

31



*Resources*

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**MANAGEMENT**

- Good science
- Good organization

Chapter: 4

## 2. Resources

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### *Resources*

#### **Good Science**

- Experimental design
- Based on known scientific procedures
- Control of variables
- Interpretation of results
- Results become part of accepted body of knowledge

Chapter 1. 3



### *Resources*


#### **Good Organization**

- Adequate physical facilities and qualified staff
- Planning of studies and resource allocation
- Definition of staff responsibilities & training of staff
- Good record keeping and organized archives
- Implementation of verification processes
- Compliance with GLP

Chapter 1. 4

## 2. Resources

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 *Resources*

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**Planning / Resource Allocation**


- Management responsibility
- Sufficient physical resources and personnel

↓

**MASTER SCHEDULE**

Chapter 2: 1

33

 *Resources*

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

Chapter 2: 1

## 2. Resources

STUDY INFORMATION				DATES						...
Study#*	Study Director	Title	Location	Practical Review	Start Date	End In-Site	Final Report Audit	Final Report Review	Archive	Comments

Chapter: 8

Resources
<h1>PERSONNEL</h1>

Chapter: 8

## 2. Resources

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### *Resources*

#### **PERSONNEL**

Organisation shown in standard documents

- Organisation charts
- Job descriptions
- Curriculum vitae
- Training records

Chapter 11

35



### *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

Chapter 11

## 2. Resources

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### *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
- Best signed by "n" and "n + 1"

Chapter 13



### *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

Chapter 14

## 2. Resources

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### *Resources*

#### **Curriculum Vitae**

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

Chapter 1.11

37



### *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

Chapter 1.12

## 2. Resources

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*Resources*

### **FACILITIES BUILDINGS & EQUIPMENT**

Chapter 1. IV




*Resources*

### **BUILDINGS**

Chapter 1. II

## 2. Resources

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 *Resources*

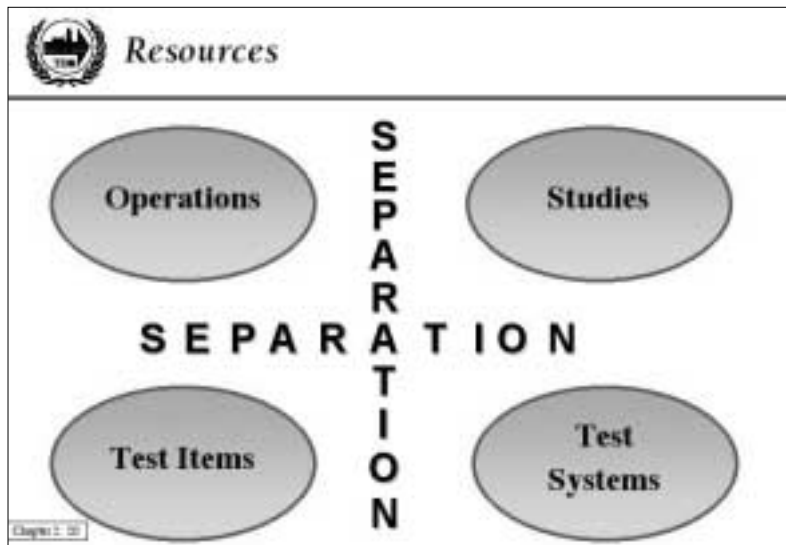
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**BUILDINGS**

- **BUILDINGS : Adequate for study**
  - Size, Construction, Location
  - Minimize disturbances
  - Separation between activities

Chapter 1: 19

39



## 2. Resources

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### *Resources*

#### **BUILDINGS : Adequate Separation**

- **Physical separation**
  - Rooms
  - Cabinets / isolators
  - Air systems and filters
  
- **Separation by organization**
  - Defined work areas
  - One-way systems
  - Different activities in same areas at different times
  - Cleaning between activities
  - Separate staff

Chapter 2.11



### *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

Chapter 2.12

## 2. Resources

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### *Resources*

#### **BUILDINGS : Adequate for Study**

Examples :

- Pharmacy & dose mixing unit
- Animal facilities

Chapter : 23

41



### *Resources*

#### **Pharmacy and Dose Mixing unit**

Deals with test and control items  
and their :

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

Chapter : 24

## 2. Resources

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### Resources

#### Pharmacy & Dose Mixing area

- **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

Chapter 7: 23



### Resources


#### Pharmacy & Dose Mixing area

**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

Chapter 7: 24

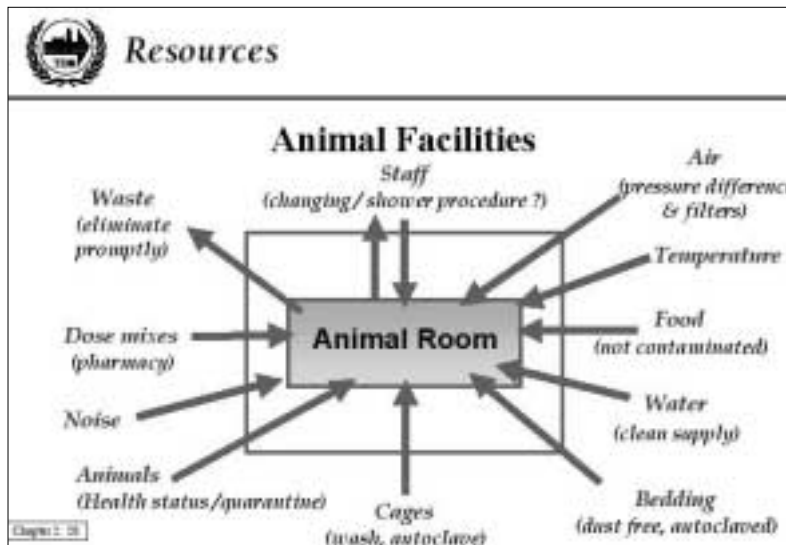
## 2. Resources

 **Resources**

### Animal Facilities

- Design should :
  - Reduce risk of test system :
    - being affected by environmental variables
    - encountering disease
    - encountering other test articles
- One answer :
  - **BARRIER SYSTEM**

Chapter 1: 21



## 2. Resources

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### Resources

#### Animal Facilities

- *Separation*
  - *Species*
  - *Studies*
  - *Quarantine*
  - *Changing rooms*
  - *Receipt of material*
  - *Storage*
    - *bedding*
    - *diet*
    - *doses*
    - *cages*
  - *Necropsy*
  - *Laboratory techniques*
  - *Waste disposal*

Chapter 7: 29




### Resources

#### Animal Facilities

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

Chapter 7: 30

## 2. Resources


 *Resources*

### Animal Facilities


- Even if facilities not "State of the Art" :
  - minimize staff entry into building
  - restrict entry into animal rooms
  - organize work flow (e.g. use of corridors clean / dirty at different times)
  - require staff to adopt dress procedures
  - clean between studies

Chapter 11

45

 *Resources*

### Documentation for Buildings



SOPs & floor plans

Qualification report

Logbook

Service reports

Fault action report

Chapter 11

## 2. Resources

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### *Resources*

## **EQUIPMENT**

Chapter 13



### *Resources*

## **EQUIPMENT**

- Suitability
- Calibration
- Maintenance
- Documentation

Chapter 14

## 2. Resources

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### *Resources*

#### **EQUIPMENT : Suitability**

- The scientist's responsibility
- Sometimes requires proof of suitability
- May need formal equipment qualification

Chapter 10

47



### *Resources*

#### **EQUIPMENT : Calibration**

- Need proof of standard working conditions
- Calibration usually requires use of standards
- Link :
  - "secondary - working" standards to...
  - ... "primary" standards to...
  - ... "national / international" standards
- Fix frequency of calibration

Chapter 10

## 2. Resources

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### *Resources*

#### **EQUIPMENT : Maintenance**

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

Chapter 7.11




### *Resources*

#### **EQUIPMENT : Documentation**

- Have SOPs for :
  - Equipment use
  - All maintenance actions including outside contractors
- Keep records of :
  - Qualification/ use / calibration / checks
  - Equipment service plan
  - Fault action reports

Chapter 7.12

## 2. Resources


 <b>Resources</b>												
<b>EQUIPMENT : Service Plan</b>												
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										

Caption: 39

 <b>Resources</b>
<b>EQUIPMENT : Service Label</b>
INSTRUMENT N° _____
DATE OF LAST SERVICE _____
NEXT SERVICE DUE _____
NAME RESPONSIBLE METROLOGIST _____
Signature / date _____

Caption: 40

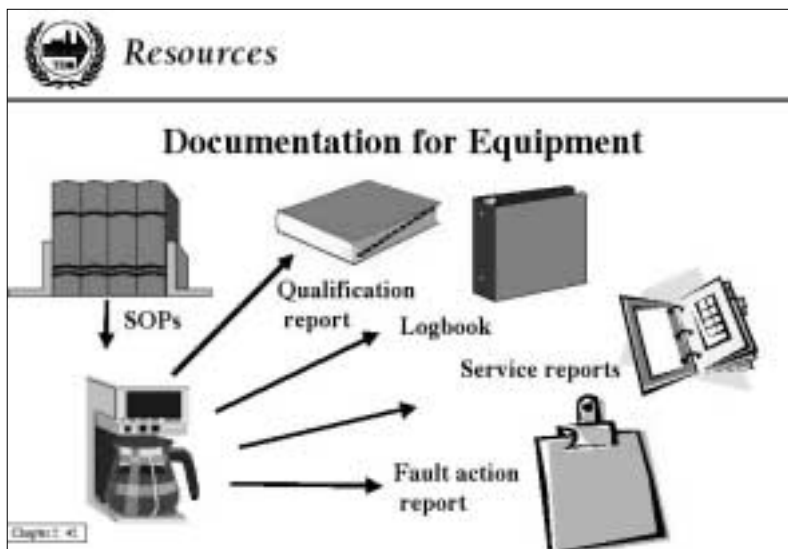
## 2. Resources

 Resources

**EQUIPMENT : Fault Action Report**

<i>BUILDING N°/DEPARTMENT/ROOM</i>	<i>EQUIPMENT I.D.</i>	
<i>DESCRIPTION OF FAULT</i>	<i>Signature</i>	<i>Date</i>
<i>IMMEDIATE ACTION TAKEN</i>	<i>Signature</i>	<i>Date</i>
<i>ACTION BY METROLOGY</i>	<i>Signature</i>	<i>Date</i>
<i>INSTRUMENT OK FOR USE</i>	<i>Signature</i>	<i>Date</i>

Chapter 41



## 3. RULES

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### THE PROTOCOL OR STUDY PLAN

The laboratory should have a number of document types to direct the conduct of the scientific studies. The purpose of these is to:

- State general policies, decisions and principles.
- Inform staff carrying out operations.
- Provide retrospective documentation of what was planned.

The document types range from the general *policy statements*, through *standard operating procedures* describing routine activities, to the *protocol or study plan*, which for each study details how the work will be organized. All these documents are of course supported by the governing guideline, the OECD principles of GLP.

The protocol is the central document whereby the study director communicates both to staff involved in the study and to third parties, such as the quality assurance unit (QAU) or the sponsor if the study is contracted to a contract research organization (CRO). The protocol would function as the basis for a contract in such a situation. The protocol, containing the overall plan of the study and describing the methods and materials that will be used during the study, demonstrates adequate advance planning.

It is most important to remember that, since the protocol is the principal means of instruction of study staff during the conduct of the study, the contents, style and layout should suit that purpose.

#### *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 number must provide a means of uniquely identifying the study in the records of the laboratory and of confirming the identity of all data generated. There are no set rules for the numbering system.

– **Title and statement of purpose**

The title should be both informative and short. It should state the name of the compound, the type of study and the test system as a minimum. It is particularly important to define why a study is being done. A study must be planned and designed in advance. This cannot be done adequately unless the designer has a clear understanding of the purpose of the work. Stating this purpose in the protocol ensures that the results of the study cannot unknowingly be utilized for a purpose for which they are unsuited. The purpose of the study may include both scientific and regulatory reasons.

– **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 characterization, or details about how these will be determined. The protocol must also detail any active control materials, which are 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 organization. The protocol should indicate the location where the test is to be carried out and also the address of any consultants you plan to use. The name of the sponsor should also be included.

– **Name of study director and other responsible personnel**

The name of the study director must appear in the protocol. It is also a requirement to identify any other responsible scientists who are going to contribute significantly to the study. As a rule of thumb, 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 contract studies, it is usual to include the name of the monitor or sponsor contact person.

– **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 performing the work, the protocol may include a more detailed time plan or this may be produced separately.

Dates are notorious for slipping. Rules for changing dates, either by making protocol amendments, or by updating an independent project planning system, should be defined in the SOP for protocol administration.

– **Justification for selection of the test system**

In the case of experiments using animals, the species and possibly the strain may have been defined in test guidelines. However, it is still important that the protocol contains a reason for why the test system has been chosen. Often this is based on the test facility's background (historical) data with the strain concerned, but there may be special scientific or regulatory reasons.

– **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, including:**

- Dosing details:
  - Dose levels.
  - Frequency of dosing.
  - Vehicles used.
  - Method of preparation.
  - Storage conditions of formulation.
  - Quality control.
- Assignment to groups or randomization of animals.
- Parameters to be measured and examined:

These identify the measurements to be made and the frequency of measurement. They will also detail any additions to, or planned deviations from, the SOPs, and give complete details of non-standard procedures or references to them.

*NB. Analytical methods are not included in detail in most protocols but will be available as SOPs or "Methods" documents which are held in the analytical laboratory with the study data.*
- Statistical methods and strength.

- **Data retained after the study** and the period for which they will be retained.
- **Quality assurance**  
Frequently, the protocol outlines the proposed QA programme but this is not mandatory.

### *Approval of the Protocol*

The approval of the protocol before the study begins is vital. Both the sponsor and the study director must have agreed the design of the study before it begins and must do this in good time to ensure that all staff know their scheduled duties.

Allowance of insufficient time between producing the protocol and starting the study may lead to serious problems later in the study.

Sufficient time must therefore be allowed to:

- Produce the protocol.
- Discuss its implications with staff concerned.
- Circulate the protocol for QA review.
- Circulate the protocol for approval.
- Circulate the approved version to all staff involved in the study.

Only then should any preliminary study work start.

Many laboratories place a block on a critical step in the study, such as ordering the animals, until a signed, approved protocol is available.

### *Circulation of the Protocol*

All involved staff should receive a copy of the protocol. In order to ensure that everybody does get a copy, it is often worth obtaining a signature from each person and holding meetings before the study begins to ensure that everybody is aware of their role in the study.

### *Protocol Amendments*

Although the protocol is the document which directs the conduct of the study, it should never be thought of as being immutable, or 'cast in tablets of stone'. It is a document that can be amended to allow the study director to react to results or to other

factors during the course of the work. However, any change to the study design must be justified.

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, the study director must produce and sign a file and obtain the sponsor's authority by phone, fax, or e-mail. This is then followed by a protocol amendment as soon as possible.

It is not acceptable practice to use the amendment to legalize omissions or errors during the study. In most laboratories such unplanned "one off" occurrences are documented in a file note attached to the relevant raw data.

The important elements of a protocol amendment are:

- That the study being amended is clearly identified.
- That the amendment is uniquely numbered.
- That the reason for the amendment is clear and complete.
- That the section of the original protocol being amended is clearly identified.
- That the new instruction is clear.
- That the circulation is the same as that of the original protocol.

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 the staff who will carry out the amended procedure are instructed in the clearest way. Once again they must have adequate notice and it is vital that they all receive the amendment and are made aware of its contents, because otherwise the instructions in the original protocol will still be followed.

As with the original protocol, the study director is the person who approves and is responsible for issuing the document. He/she is also responsible for ensuring that the new instruction is performed correctly. It is as essential to review amendments as the main protocol for GLP compliance. This is a QA function. Because amendments are, by their very nature, extremely urgently required by study staff, this review is often performed retrospectively.

The original signed protocol and all amendments must be lodged at the archives as part of the study file. It is a good idea to archive the protocol at the beginning of the study, and work from authorized photocopies.

## STANDARD OPERATING PROCEDURES (SOPs)

A collection of good standard operating procedures (SOPs) is a prerequisite for successful GLP compliance. Setting up the SOP system is often seen as the most important and most time-consuming compliance task.

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

*Based on W. Edwards DEMING idea, standards (i.e. SOPs) should be used 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*

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 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.** The SOPs should follow a standard layout (standards and guidelines exist for this). The procedures should be written (or translated) into the local language of the operational personnel and expressed in an appropriate vocabulary. All personnel should be encouraged to improve the SOPs. Ideally, the people who do the work should also write the SOPs, thus promoting their sense of responsibility for the work they do.

- **Usability and traceability.** For reasons of traceability and easy use, a two-tier system of SOP is often the preferred approach. For example, one tier reflects general policies and procedures (e.g. protocol writing, review, approval, distribution and modification, SOPs, general rules for equipment use and maintenance, archives, etc.), the second represents technical methods (e.g. methods of staining in histology, analytical methods, specific procedures for use and maintenance of equipment, etc.). It is advisable to present the SOPs (SOP manuals) as a binder with an up-to-date table of contents, logical chapter divisions and selective distribution, to avoid a mushrooming packet of dust-gathering paper that often gets misplaced. In some laboratories, SOPs are available directly from a screen, but in this case you will need to implement special rules about printing out the SOPs (expiry dates etc.) and rules about signatures.
- Staff must fully understand the SOP and follow it rigorously. If deviations are expected or occur, easy communication with the study director and management must be allowed to ensure respect of GLP requirements and to preserve the credibility of the system.
- **Somebody should be responsible for each SOP** (author or person responsible) to handle queries and keep each procedure updated. It is a good idea to impose a minimal requirement for **periodic review**.
- **A formal change control system which ensures historical reconstruction.** An SOP system, if working properly, tends to seem perpetually incomplete because of additions, deletions and modifications reflecting the normal rate of improvements or changes. Indeed, changes and amendments are good evidence that the laboratory uses the SOPs. Therefore update should be easy and rapid – authorization should not involve too many signatures.
- **Centralized organization** of formatting, numbering, issuance, modification and withdrawal, in order to avoid duplication of effort, incoherence, delays, lack of traceability and incomplete distribution.
- SOPs should be **immediately available** to the person doing the work.
- All withdrawn SOPs must be archived carefully in order to make a complete historical record of the test facility's procedures.

Properly designed SOPs will bring the following benefits to the laboratory:

- Standardized, consistent procedures (person-to-person, test-to-test variability minimized).
- An opportunity to optimize processes.
- 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.
- A means of study reconstruction after the event, also after a lapse of years.
- Means of communication in case of audit, visits, technology transfer, etc.

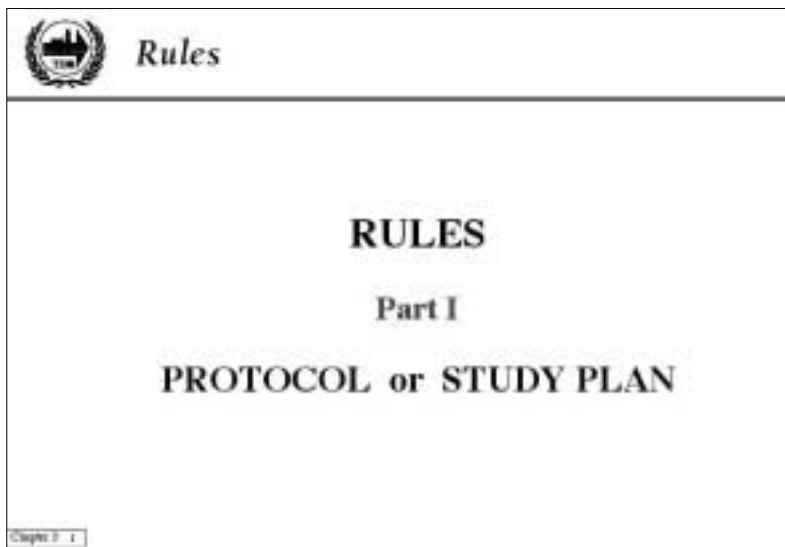
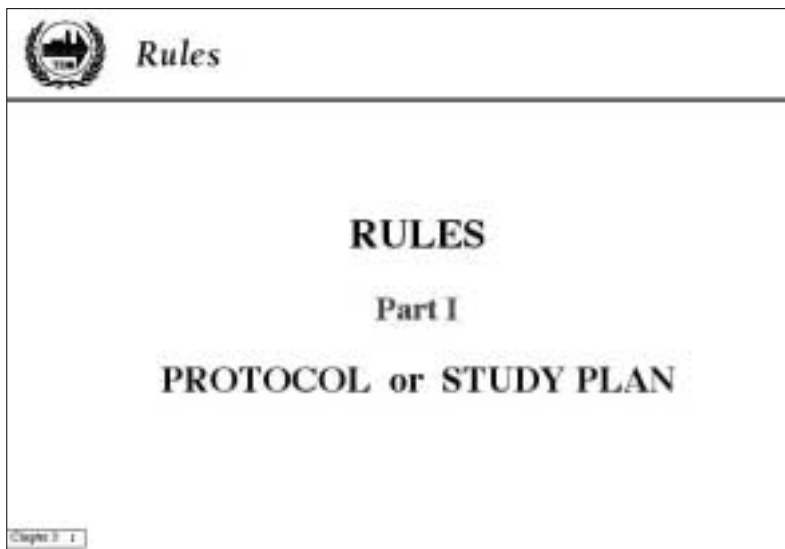
In summary, most laboratories incorporate the necessary characteristics into the following approach:

- A two-tier system.
- A defined format.
- Thorough review, including QAU review.
- Formal approval by at least two people:
  - a designated author.
  - an appropriate member of management.
- A formal change control system, co-ordinated by a designated person/group.

During the course of the study, a general SOP (tier 1) requires that all deliberate deviations to operational SOPs should be approved in advance by the study director. If this is impossible he/she should be informed in writing. This record, along with the technical person's and/or the study director's assessment of the deviation (no impact on the study, extent of impact on the study, include deviation in report, etc.), are maintained as raw data in the study file for audit and consideration when writing the final report.

### 3. Rules

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### 3. Rules

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#### *Rules*

#### GUIDELINES

- Established by internationally recognized scientific experts
- Define what should be included in studies

Chapter 3 - 3



#### *Rules*

#### PROTOCOL / STUDY PLAN

- Approved by the Study Director
- May follow guidelines
- Description of major events in study
- Provides overall timelines

↳ "MASTER PLAN"

Chapter 3 - 4

### 3. Rules

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#### *Rules*

### PROTOCOL / STUDY PLAN

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

Chapter 3 1

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#### *Rules*

### PROTOCOL / STUDY PLAN

#### CONTENT

- **Scientific**
- **Organizational & GLP**

Chapter 3 4

### 3. Rules

---



#### *Rules*

### PROTOCOL / STUDY PLAN

#### FUNCTIONS

- Specification for study activities
  - which activities, when
  - non-standard practice
- Defines responsibilities
- Defines resource needs
- Communication & instructions
- Basis for contracts
- Basis for regulatory discussions

Chapter 3 1



#### *Rules*

### PROTOCOL / STUDY PLAN

#### GLP REQUIREMENTS

- Identification
  - must be unique to each study
  - used to identify study data
  - must identify test compound
  - may identify department concerned
  - can be cross-referenced to other studies

Chapter 3 2

### 3. Rules

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#### *Rules*

### PROTOCOL / STUDY PLAN

#### GLP REQUIREMENTS

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

Chapter 3 11

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#### *Rules*

### PROTOCOL / STUDY PLAN

#### GLP REQUIREMENTS

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

Chapter 3 12

### 3. Rules

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#### *Rules*

### **PROTOCOL / STUDY PLAN GLP REQUIREMENTS**

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

Chapter 3 11



#### *Rules*

### **PROTOCOL / STUDY PLAN GLP REQUIREMENTS**

- **Study Director & 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 if one is appointed

Chapter 3 12

### 3. Rules

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#### *Rules*

### PROTOCOL / STUDY PLAN

#### GLP REQUIREMENTS

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

Chapter 3 13

65



#### *Rules*

### PROTOCOL / STUDY PLAN

#### GLP REQUIREMENTS

- **Test System**
  - **Description**
    - species, strain, health status
    - age, weight, source
    - environmental conditions, husbandry
    - diet, source and possible contaminants
  - **Justification of choice**
    - guidelines, regulations
    - background data

Chapter 3 14

### 3. Rules

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#### *Rules*

### PROTOCOL / STUDY PLAN GLP REQUIREMENTS

- **Experimental design** (depending on study)
  - Dosing details
    - dose levels & frequency
    - vehicles
    - preparation
    - QC
  - Randomization of animals
    - pre-test
    - during study / cages / racks

Chapter 3 21



#### *Rules*

### PROTOCOL / STUDY PLAN GLP REQUIREMENTS

- **Experimental design**
  - Parameters during study
    - body weights
    - clinical pathology
    - necropsies / pathology
    - etc.
  - Statistical methods
  - Archives post-study
  - Quality Assurance

Chapter 3 22

### 3. Rules

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#### *Rules*

#### **PROTOCOL / STUDY PLAN**

#### **APPROVAL / REVIEW**

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

Chapter 3 17

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#### *Rules*

#### **PROTOCOL / STUDY PLAN**

#### **AMENDMENTS**

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

Chapter 3 18

### 3. Rules



#### Rules

### PROTOCOL / STUDY PLAN

#### AMENDMENTS

• **Main elements:**

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

Chapter 3.11



#### Rules


### PROTOCOL / STUDY PLAN

#### PROTOCOL CIRCULATION LIST

	Received	Date
- Study Director		
- Sponsor		
- Management ( <i>research director</i> )		
- Main file		
- Archives		
- Quality Assurance Unit		
- Animal husbandry		
- Technician in charge		
- Analytical laboratory		
- Clinical pathology		
- Necropsy		
- Pathology		
- Statistician		

Chapter 3.12

### 3. Rules



*Rules*

**PROTOCOL / 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																																			
Randomization				X																																	
Formulation and dosing		X FORM			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Analysis of formulation		X										X																								X	
Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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		X		X		X		X		X		X		X		X		X		
Ophthalmoscopy			X																																	X	
Haematology																																				X	
Blood chemistry																																				X	
Ultrasound																																				X	
Necropsy																																				X	

Chapter 3 21



*Rules*

**RULES**

**Part II**

**Standard Operating Procedures**

Chapter 3 22

### 3. Rules

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#### *Rules*

#### **STANDARD OPERATING PROCEDURES**

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

Chapter 3 23



#### *Rules*

#### **STANDARD OPERATING PROCEDURES**

**Use standards (i.e. SOP's) 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

Chapter 3 24

### 3. Rules

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#### *Rules*

### STANDARD OPERATING PROCEDURES

#### **For successful SOP implementation:**

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

Chapter 3 23

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#### *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

Chapter 3 24

### 3. Rules

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#### *Rules*

### **STANDARD OPERATING PROCEDURES**

#### **SYSTEM CHARACTERISTICS**

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

Chapter 3 21



#### *Rules*

### **STANDARD OPERATING PROCEDURES**

#### **Centralized organization - Roles**

- **Set standard format imposed**
- **Be single point for i.d. / numbers / issuance**
- **Manage changes (versions) : traceability**
- **Ensure distribution / destruction**
- **Ensure cross-departmental coherence of SOPs**
- **Review by QAU**

Chapter 3 22

### 3. Rules

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#### *Rules*

### **STANDARD OPERATING PROCEDURES**

#### **Benefits from good SOP system**

- **Standardized, consistent procedures, reduce test-to-test variability**
- **Means of study reconstruction**
- **Optimizes the way we do things**
- **Record technical & administrative improvements**

Chapter 3 28

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#### *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)**

Chapter 3 29



## 4. CHARACTERIZATION

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### THE TEST ITEM

The identity, activity and bioavailability of the test item are central to the validity of the study. It must be demonstrable that the test system has received the correct amount of material. This is assured by proper control of the test item at all stages of its use and the preparation of records to document every stage of its disposition.

A GLP quality assurance programme should systematically attempt to minimize the possibility that the test item is affected by any quality problems.

#### *Test Item Control Before Formulation*

##### **Receipt**

The test item will be delivered from the manufacturer. This may be a section within the same organization as the test facility or a separate organization altogether. In either case, and irrespective of the size of the test facility and 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 are a central group who log the arrival, identity and issue of test item, but in small facilities the designated person may be the study director or an authorized technician. Designation of responsibility should be documented in an SOP.

The responsible person should be aware in advance of test item arrival so as to ensure correct storage conditions and necessary handling requirements. In the case of a contract study, the sponsor should provide this information to the CRO. A standard form to provide this information is helpful. During the development of the protocol, the sponsor fills it out to give the testing facility essential information necessary for safe and adequate handling of the test item as well as other details which may help in the preparation of the dose formulation.

The sponsor will either supply, or indicate that he has obtained, the chemical characterization of the test material. The manufacturer, meanwhile, will archive and store batch records.

The test item container should be robust enough to withstand transfer between facilities, and should ideally be suitable for further use. Packaging of the test item is

very important. The sponsor should consider the method of transport used and the duration of the journey. This is particularly true when the material is packed in fragile containers, such as glass bottles, or needs to be transported long distances using public transport under special conditions, e.g. kept frozen. Consideration should always be given to the unexpected such as airport delays, strikes or bad weather.

The test item should be accompanied by a delivery form detailing:

- Manufacturer's name or sponsor's name.
- Date of despatch.
- Number of containers or items, type, amount of contents.
- Identity of test item.
- Batch number(s).
- Identity of person responsible for despatch.
- Name of carrier.

Each test material *container* should be clearly labelled with sufficient information to identify it and allow the testing facility to confirm its contents. Ideally, labels should contain the following information:

- Test item name.
- Batch number.
- Expiry date.
- Storage conditions.
- Container number.
- Tare weight.
- Initial gross weight.

On arrival of the test item, the testing facility should have a procedure for handling and documentation of receipt. It is most important that the compound is logged in immediately 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 if designated person is absent or if the container is damaged on receipt. The study director should be informed of the arrival of the test item.

A test facility's documentation, on arrival of the test item, normally includes the following information:

- Compound name.
- Batch number(s).

- Description of the test item that is completed on its arrival at the laboratory and compared with the description supplied by the sponsor. This ensures that any concern about the identity of the material can be sorted out at an early stage.
- Container number, to allow identification of the container in use.
- Container type.
- Net weight of the contents and container tare weight.
- Storage conditions and location of the container.
- Initials of the person receiving the container.
- Date of arrival of the container at laboratory.
- Condition of goods on arrival.

### Storage

Test items must be stored under closely controlled conditions, particularly with respect to access and environment. The store 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 ambient temperature, +4 and -20°C.

The storage of test item is arranged to minimize the risk of any cross contamination between compounds and containers. Where possible, the primary containers are housed within an outer container in case of 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 main 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 some test item is required, for example for confirmatory analysis.

### Use

A record of each use of test item on a record form allows a running check. Not only does this provide a complete trail of all the test item used, but it also provides a means of monitoring actual use against expected use. The type of information 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 split 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 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 amount weighed out.
- Discrepancy. This allows explanation of any discrepancy (e.g. spillage).
- Stock remaining. This provides a running total of quantity of material in the container and gives a warning of the need to order additional material.

### **Disposal**

Following the completion of a study, surplus amounts of test item should be disposed of in an environmentally acceptable way. This final event must appear in the data so as to account for the total amount of test item.

### ***Preparation of the Dose Formulation***

If the test system receives an incorrect dose, or if there is doubt about the dose, the rest of the experiment is almost certainly compromised. The following well-specified procedures and the documentation of every stage of the process are necessary.

### **Initial Preparation and Planning**

Before the study begins, a number of factors must be considered and communicated to staff by the study director. Some of these may be considered before the protocol is finally signed:

- 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 ensure that sufficient is available throughout the course of the study. As part of this consideration he/she also checks on the purity of the test item. In most studies, the

test item is assumed to be 100% active ingredient, but if significantly less than this it will be necessary to adjust the amounts to be weighed out (and to investigate what impact the impurities may have for 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, and the study director will keep this under review. To ensure that this is done regularly, the study director is often required to produce a request form every two weeks.
- SOPs must exist for each procedure in the preparation of the formulation, the analysis, the documentation and data required, and operation of all equipment.
- The method of preparation of the dose form should be tested prior to study start. This entails a trial preparation of at least the highest dose level, to confirm that the various standard procedures detailed in the SOPs produce an acceptable dose of the right concentration and homogeneity.
- This trial preparation may indicate the need for further development of the method, for example experimentation with other vehicles or different mixing techniques.
- The stability of the dose form must also be assessed in the vehicle used.

Following the trial preparation, the SOP for the formulation may need amending.

### **Formulating the Test Item**

In many test facilities an independent group formulates the test item. This situation emphasizes the importance of recording 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 part of the final record.

Before the container of material is opened, the persons carrying out the procedure will have ensured that:

- there is a dedicated workstation of adequate size for the procedure.
- the preparation surface 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 instructions or order. Following these instructions the correct amount is weighed out.

The control mixes are usually done first. Then the test item is mixed with the vehicle exactly following, without deviation, the method determined during the trial preparation before the start of the study. In most cases this involves making up each concentration from a separately weighed out amount of test item, mixing it first with a small volume of vehicle, and gradually increasing the amount of vehicle to achieve the required total volume. In some cases where the test item is dissolved in the vehicle or where the diet is the vehicle, it may be preferable to make up the highest concentration and dilute samples of that for the lower dose 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 quite carefully in order to preserve the integrity of the dose form including:

- Composition. The container must neither react with test item nor vehicle.
- Size. If the formulation needs to be mixed using a magnetic stirrer in the animal house to keep it in homogeneous suspension, the container must be big enough to develop a vortex, but not so big, in relation to the volume made up, to prevent the mixer working.

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, sex).
- Weight of container and contents.
- Date formulated.
- Storage conditions.

In many laboratories, the label is colour coded for each dose to coincide with the colours of the cage labels.

### **Sampling and Quality Control of Dose Formulation**

Analysis of the formulation is required by the protocol to fulfil GLP requirements and assure that concentration, stability and homogeneity of test item/vehicle mixtures is assessed. This information may be generated after the start of the study. It is an advantage to conduct some of these analyses before the study starts, to prevent waste

of time and resources, and unnecessary dosing of test system, using a dose form that is subsequently shown to be unsuitable for the experiment.

As indicated above, the measurement of stability and homogeneity of the test material/vehicle formulation should have been done on a trial preparation. Samples of this preparation are taken under conditions as closely identical to the dosing situation as possible. The dose is left for the same period of time as will be the case between preparation and administration in the real situation. Then samples are taken from different positions in the dosing vessel. For long-term studies where a stock solution is made for generating dose formulation throughout the study, aliquots will also be taken and analysed periodically to assess the “shelf-life” of the formulation.

The samples taken as indicated above give a good estimate of the effectiveness of the dose preparation process. However periodic checks are also required to confirm that the process is being carried out correctly throughout the study even if doses are made up fresh each time. Only the chemist who takes the samples (but not the persons making up the mixture or performing the dosing) knows the day they will be taken. It is preferable to take the sample in the animal room from the residue following dosing, as this gives not only information on the concentration dosed to the animals, but also some further confirmation of homogeneity and stability of the test article in real use.

### Formulation Records

The following records are made of the formulation process:

- Date.
- 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 material to the animal accurately and consistently. Therefore, the procedure used must be very conscientiously carried out and the records capable of confirming that all the animals have been dosed with the correct volume and concentration.

Detailed records with built in cross-references document the fact that the dosing has been correctly carried out.

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

On arrival in the animal area, the dose should be checked for identity and to confirm that the amount is the same as the amount issued from the formulation department. Staff should ensure that the container is still intact. The containers are then placed kept appropriately (e.g. on a magnetic stirrer) until dosing starts.

The dosing procedure is done in a fixed order taking into account the need to minimize the possibility of cross contamination and confusion between animals, dose groups and different formulations.

Consequently, the following precautions are typical of those that most laboratories take when dosing animals orally by gavage:

- The animals are dosed group by group, working in ascending dose levels.
  - Ensure that only one dose container is open at any one time and that each dose level has its own catheter and syringe.*
  - All cages from one group should be identified before the group is dosed, using the group number and label colour code as a confirmatory check.*
- A new catheter and syringe are used for each dose level.
- The 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 lung.
- Only one cage of animals is opened at a time. If the study is individually housed, the animals are returned to their cage following dosing. If multiply-housed, the animals should be placed in a second container until all animals from the cage have been dosed and then returned to their cage.
- Each animal is positively identified (e.g. from its tattoo), not merely from the cage number.

The dose volume is calculated from the body weight, using a list giving the required volume for each weight to avoid the risk of calculation error during dosing.

Records identify:

- The staff involved in dosing.

- The dose given to each animal. This acts both as a confirmation of dosing of each individual and a record which can be 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 some check to be made of the expected use against actual use of formulation.

## TEST SYSTEM

Under GLP the definition of a test system is very varied. Very often test systems are animals, but they can also be plants, bacteria, organs, cells or indeed analytical equipment. This section describes the situation when the test system is animals.

Conditions and processes must both satisfy the scientific considerations of the study and accommodate *national animal welfare legislation*. Although this course is not intended to cover these aspects, some references are included since these affect your laboratory and your procedures.

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### *Facilities*

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

### *Choice of Test System*

The scientist must match animal quality and quantity (neither too few nor too many) to research requirements.

The study director and management 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 Arrival*

Given the cost of preclinical testing today, the money spent on test system purchase is almost negligible. We should therefore always insist on the best quality available. No amount of effort spent on facilities, environmental control and equipment can compensate for the impact of poor quality animals on a study.

The quality of the supplier of animals, animal feed and bedding should be assessed by audit. Usually the QAU group and the person responsible for animal care do this. If a supplier enjoys a “monopoly” situation, unified attention by a professional QA society might be more effective. Purchasers should make sure that they get what they pay for and that no variables (e.g. pesticide contamination, colony renewal, sickness, veterinary treatments, transport problems, etc.) are compromising quality. The test facility should be able to deal with the suppliers as partners in research. The suppliers should be experts in their field. They usually appreciate constructive comment, will volunteer useful information and can make 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 will be inspected per SOP, i.e. they are 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) is completed and put in the data file. The animals are then transported to the study room and installed in clean cages with food and water *ad libitum* according to your general SOPs.

### *Acclimatization*

For most studies the SOPs and the protocol require the animals to undergo a period of acclimatization. During this time the health status of the animals is confirmed and unsuitable individuals are eliminated. The length of this acclimatization period depends upon the species, the supplier and the type of study.

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

### *Animal Identification*

Identification of animals must be maintained throughout the study. Most laboratories use a system of cage cards: temporary before group assignment and permanent afterwards; this is as described in the protocol. The animal management department uses the consecutive temporary numbers to ensure animal accountability. Permanent cage-cards (as for dosing materials etc.) often follow a standard internal colour code. 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, the individual animals must be identified to prevent mix-ups. Subsequently, each time that animals are removed from their cages, SOPs require an identity check of the animal. In many laboratories, the identification, e.g. by tail tattoo is even included in the wet tissue pot at the end of the study (after histological processing) and 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 is included in raw data as is the table listing the temporary and permanent animal numbers. Rack and cage locations are documented from this point onwards. Special attention is given to document fully any disqualification of animals during the acclimatization period. These data may indicate systematic problems with the supplier or the animal type. Alarming or 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 per SOP and documented in the daybook or appropriate system. Any relevant observations made at this time (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 our concern over 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 can be covered here. There is, however, substantial and helpful literature on this subject.

Once SOPs are defined and approved for each situation (length and type of study, species), data are collected and evaluated regularly by the professional staff. Variations to the defined norm or alarming and unforeseen circumstances are documented and evaluated for corrective action and for any possible effect on the study and consequent consideration in the final report.

In general, each variable is evaluated regarding:

– **Source**

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

– **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 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.

We can see that much of our 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 the physical and chemical characteristics.

– **Monitoring**

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

– **Control**

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

Both systematic and fortuitous detection of abnormal situations are recorded in the data and the effect on the results considered. By following this approach, systematic monitoring and control should preclude too many undetected influences on the test system.

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

## 4. Characterization

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*Test Item*

# CHARACTERIZATION

## Part I

**TEST ITEM**

Chapter 1



*Test Item*

# CHARACTERIZATION

## Part I

**TEST ITEM**

Chapter 1

## 4. Characterization

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### *Test Item*

#### **BULK TEST ITEM**

- **GMP is not required for the manufacture of batches used in preclinical (GLP) studies**
- **Regulatory authorities require testing to ensure test item is fit for preclinical use**
- **Use single lot throughout study if possible**

Slide 3

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### *Test Item*

#### **BULK TEST ITEM**

- **Characterization 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

Slide 4

## 4. Characterization

---



### *Test Item*

#### PREPARATION OF DOSE-FORM

- **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?

Chapter 4 1



### *Test Item*


#### ANALYSIS

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

Chapter 4 4

## 4. Characterization

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*Test Systems*

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**TEST SYSTEMS**

Chapter 1



*Test Systems*

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**TEST SYSTEMS**

Chapter 1

## 4. Characterization

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### *Test Systems*

#### **TEST SYSTEMS : Animals**

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

Chapter 4.9



### *Test Systems*


#### **ANIMALS**

- **Scientist must match quantity and quality to research requirements**
- **Study Director defines**
  - **phenotype / genotype**
  - **sex, age**
  - **supplier**
  - **number**
- **Reasons for choice Protocol / Study plan**

Chapter 4.10

## 4. Characterization

---


 *Test Systems*

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**ANIMALS**

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

Chapter 4.11

 *Test Systems*

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**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**

Chapter 4.12

## 4. Characterization

---



### *Test Systems*

#### **ANIMALS - Group Assignment**

- **How assigned to groups per protocol, before dosing**
- **Maintain data used for grouping**
- **Log rack / cage locations if applicable**
- **Document all cases of "disqualification"**

Chapter 4.10



### *Test Systems*

#### **ANIMALS / Identification**

- **Must be identified :**
  - during acclimation
  - during 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**

Chapter 4.10

## 4. Characterization

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### *Test Systems*

#### **ANIMALS - Acclimatization**

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

Chapter 4 15

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### *Test Systems*

#### **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

Chapter 4 16

## 4. Characterization

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### *Test Systems*

#### **ANIMALS - Supply**

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

Chapter 4 17



### *Test Systems*

#### **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"**

Chapter 4 18

## 5. DOCUMENTATION

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### RAW DATA AND DATA COLLECTION

This section relates to the collection of experimental data.

#### *Carrying out the Procedures and Making the Observations*

Before the 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 is present where the procedure is to be carried out.
- SOPs are 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 be available to staff following it.*
- Necessary equipment and supplies are available.
- Data recording forms are in the work area.

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

In summary, the important factors which are involved in making these observations are:

- Adequate numbers of well-trained staff.
- Appropriate equipment.
- Good preparation with planning records available.
- Complete instructions.

## Records and Recording

Making a record is critical to complete reconstruction of the study. It is the only way of demonstrating what actually went on at the time and so must not only contain the data generated, but also prove that all the required procedures were correctly carried out at the correct time. Consequently, if the data are lost or a complete record is not made, experimental data are lost.

Raw data are defined as original recordings made during the course of the study. These data are necessary for the “reconstruction” of the study, for example by an inspector, after the study completion date.

The data should therefore indicate:

- “WHAT was done”  
*Describing what was done and demonstrating that the items laid down in the protocol were carried out and the SOPs were followed and, of course, including the results of the observation or measurement.*
- “HOW it was done”  
*The data should indicate that they were collected and recorded in accordance with the methods set out in the SOPs and protocol, or indicate where these were deviations from the instructions.*
- “WHEN the work was performed”  
*Demonstration that the timings laid down in the protocol were followed. This should be done by recording the date, and, if necessary, the time. 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 is involved in a procedure this should be recorded in the data and the responsibilities of each detailed.*

The records retained are therefore a great deal more than a list of figures. All data generated during the conduct of a study should be *identified* and recorded *directly, promptly, accurately, legibly and indelibly* by the person entering the data, and be *signed or initialled, and dated*. Any changes should be made so as *not to obscure the previous entry*, and if necessary *should indicate the reason for such change*. Such changes should be *identified by date and signature of the person making the change*.

**“Identified”**

- Study number, animal number, etc. should be recorded with data in order to ensure that data mix-up does not occur.

**“Directly”**

- Records should *not* be made on scraps of paper and then transcribed into a final form. The first written records are considered to 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 data, the raw data may be a direct print-out or trace or in digital form.

**“Promptly”**

- Data must be recorded as the operation is done. 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 in the minds of the reader thus reducing 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 without this being obvious.

**“Signed”**

- Accountability is one of the basic tenets of GLP, hence the need for a record of who did every job on a study.

**“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* is needed which shows why a change was carried out, who by, and when.

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

Data should be recorded in a logical way, and duplication should be avoided wherever possible.

Pro-forma documents assist in this by encouraging staff to record all the data necessary.

**FINAL REPORT**

The elements required by GLP in the study report are clearly identified in the GLP Principles:

- Name and address of test facility.
- Dates of start and finish of experimental work.
- Name of study director.
- Objectives.
- Details of test substance and vehicles.
- Description of test system.
- Details of dosing, route and duration.
- Summary of findings.
- Statistics.
- Discussion.
- References.
- GLP compliance statement from study director.
- QA statement of inspections/audits.
- Signed/dated reports from scientists.

The study report, just like all other aspects of the study, is the responsibility of the study director. He/she must ensure that the contents of the report describe the study accurately. The study director is also responsible for the scientific interpretation of the results.

Finally, the study director must indicate, in the study director's statement, whether

or not the study was conducted in compliance with GLP. If the study was only partially compliant, the parts that were not compliant should be indicated.

### *Accurate Reporting and Deviations*

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

This means that everything which happened during the study should be reported, but does not necessarily mean that every single item of raw data must be included in the report. The report should, however, allow the reader to follow the course of the experiment and the interpretation of the data without the need to refer to other material not included. In practice therefore, most of the individual data are included. More importantly, the report should not be a selection of the “highlights” of the study, leaving out the parts that did not “work” or where restarts were needed for one reason or another.

It should certainly include any aspects where the study conduct deviated from that laid down in the protocol or SOPs, whether this is considered to have impacted on the study integrity or not.

The report may include input from experts other than the study director, such as specialists within the laboratory or from outside, consultants or the sponsor. These may be included and signed by those specialists. Data supplied from outside sources should comply with GLP. If this is not the case then this should be identified in the study director’s statement.

GLP requires the study director to include a statement in the report accepting responsibility for the validity of the data and confirming that the study conformed to GLP principles.

### *Report Review*

After the report has been drafted, it will pass through a review stage and a QA audit. During this, modifications may be made to the report, but it is important to remember that any alterations made must be agreed and accepted by the study director. The process of approval prior to finalization may be a more distinct process in the case of a study conducted by a contract laboratory, but in any case it is designed to ensure that the report, when finalized, is unlikely to require modification. After finalization, modification can only be achieved by production of a formal amendment approved and signed by the study director and identifying the change made with a reason.

## ARCHIVES

The archives should not be considered as simply a place for the collection and storage of “dead” materials but also as a source of information, an organizational tool, a functional entity for document distribution and compilation of summary documents, and a resource for reconstructing work if necessary.

### *Function*

The archives (and archivist) provide:

- A centralized, secure repository for the storage and retrieval of original scientific data, master documents and reports.
- A means of controlling and documenting the distribution and modifications of archived material.
- A point of control of format and completeness.
- An efficient organizational tool for preparing project summary documentation (drug master file – DMF, investigational new drug – IND, new drug application – NDA, investigator 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.
- A defined responsibility for updating official documents in circulation (specifications, master records, protocols, SOP’s, etc.).

### *“What” is Archived?*

- Study data.
- Systems data.
- QA files.

For most studies, the core “study file” is described in the protocol. It is important that study files be pre-collated before submission in envelopes, boxes or in loose leaf or bound form. Specimens and samples are inventoried, labelled and packaged according to standard operating procedures.

System generated raw data (e.g. personnel files, animal transport and arrival, HVAC maintenance) and associated quality assurance materials are submitted periodically and filed *separately* from the study file. Notebooks usually have mandatory tables of contents that are used for cross-indexation.

### *“When” it is Submitted and by “Whom”?*

It is the responsibility of the study director or his designee to verify the completeness of the collation/inventory and to physically present all study relevant materials to the central archive. This is required soon after final report approval. If archival requirements are not followed, the central archive may refuse to accept the submission. Archive requirements form part of the general training scheme for the laboratory.

### *Term of Storage*

The OECD GLP Principles require organizations to follow national rules on periods for archiving. As many organizations register compounds internationally, in practice the retention period is often indefinite.

This policy reflects the varying retention schedules required by different GLP/GCP (good clinical practice)/GMP (good manufacturing practice) texts, coupled with the possible internal need to consult old data for product improvement/liability or scientific reasons.

Therefore, laboratories impose strict destruction policies. When a space problem arises, very old holdings and abandoned projects belonging to chemical families holding no current interest may be destroyed upon justification and written authorization of 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 material transferred to the archives should be personally transported by designated persons. The original of all required documents should be submitted. All material submitted should be accompanied by a document submission form.

### *“How” are Archives Stored?*

#### **Securely**

- Only authorized entry permitted.
- Fire, flooding and vandalism protection.

#### **Under conditions which minimize deterioration**

- Usually ventilated general environment.
- Copies of heat sensitive papers made.
- Refrigeration used where necessary.
- General warehousing procedures defined.

- Blocks sealed, tissues wrapped in preservative soaked gauze in heat sealed bags, slides cover slipped, etc.
- Computer back-ups maintained in security cabinet.

## INDEXING

Indexation is often computerized and provides complete and quick retrieval starting from any one of the indexed parameters.

All study or lot specific materials are given a unique holding number that corresponds to location. Facility specific material is filed using common sense (i.e. chronologically, alphabetically).

Indexing parameters which may be used:

- Project or study number.
- Test article/reference article and lot numbers for bulk and formulated material, if appropriate (tie-in with product accountability records).
- Protocol number (may be same as study number).
- Testing facility.
- Key word retrieval from study title (route, species, etc.).
- Key word retrieval from comments section of master schedule (e.g. regulatory information, dates).
- Department.


### *Retrieval from Archives*

Once an item has become an official central archives holding, the original should be subject to restricted access. It should be examined in situ with verbal authorization but only within the central archives area, and in the presence of the archivist. Photocopies should be provided upon request.

Removal of original holdings from the central archive will be allowed only under exceptional circumstances when justified and authorized in writing. The history of each holding must be documented.

## 5. Documentation

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*Documentation*

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**DOCUMENTATION**

Chapter 1



*Documentation*

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**DOCUMENTATION**

Chapter 1

## 5. Documentation

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### *Documentation*

#### **RAW DATA AND DATA COLLECTION**

##### **Raw Data : Definition**

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

Chapter 3



### *Documentation*

#### **RAW DATA AND DATA COLLECTION**

##### ***BEFORE:* Study Director assures that:**

- **There is sufficient trained staff**
- **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**

Chapter 4

## 5. Documentation

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### *Documentation*

#### **RAW DATA AND DATA COLLECTION**

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

Chapter 3 3

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### *Documentation*

#### **RAW DATA AND DATA COLLECTION**

##### ***WHAT***

**Data should show :**

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

Chapter 3 4

## 5. Documentation

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### *Documentation*

#### **RAW DATA AND DATA COLLECTION**

##### ***HOW***

Data should show that methods were :

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

Chapter 7.1



### *Documentation*

#### **RAW DATA AND DATA COLLECTION**

##### ***WHEN***


Data should show:

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

Chapter 7.2

## 5. Documentation

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 *Documentation*

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**RAW DATA AND DATA COLLECTION**


***WHO***

**Data should show:**

- Identity of operator(s)
- Identity of data recorder(s)
- Identity of verifiers / correctors

Chapter 1 8

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 *Documentation*

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**RAW DATA AND DATA COLLECTION**

**RECORD DATA**

**Data should be recorded:**

- directly / not transcribed from a rough copy
- promptly
- accurately
- legibly

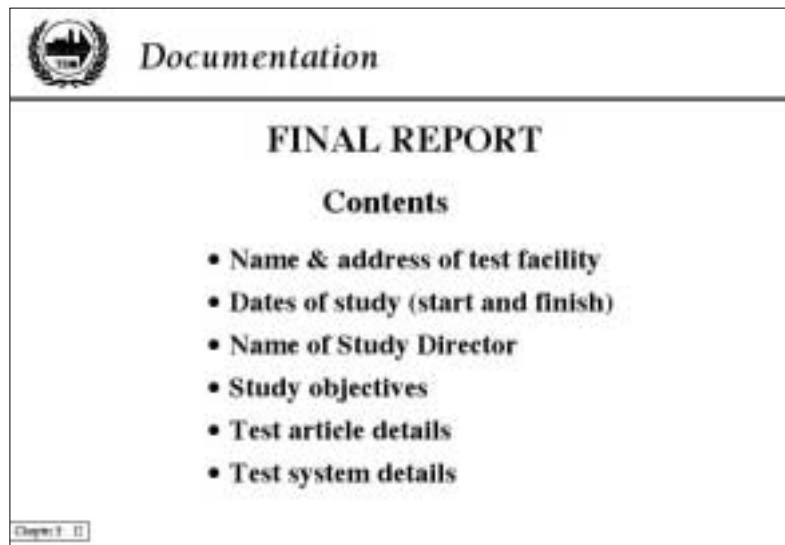
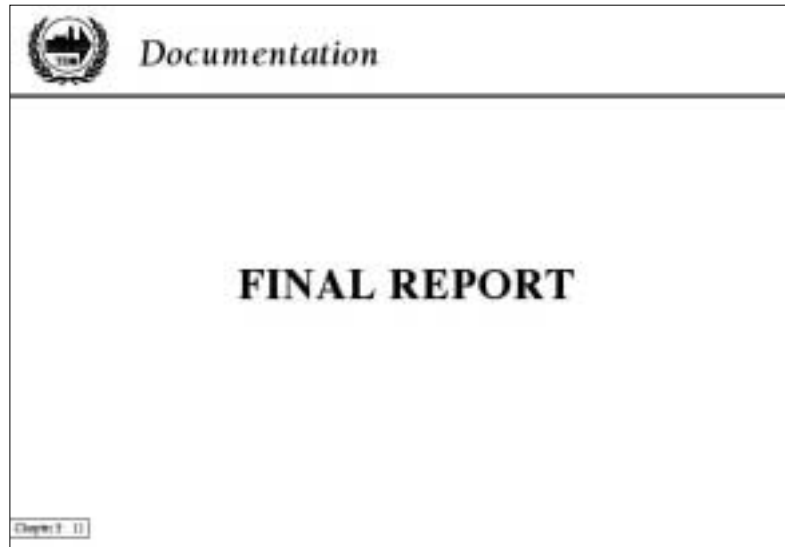
**Then:**

- Sign & date
- Explain corrections

Chapter 1 10


## 5. Documentation

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## 5. Documentation

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 *Documentation*


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**FINAL REPORT**

**Contents**

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

Chapter 11

 *Documentation*

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**FINAL REPORT**

Once signed ...

... modifications by amendments only

(QA audit of amendments)

Chapter 11

## 5. Documentation

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### *Documentation*

## ARCHIVES

Chapter 7 10



### *Documentation*

## 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

Chapter 7 10



## 5. Documentation

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### *Documentation*

#### **ARCHIVES : History**

DATE	EVENT	AUTHORIZATIONS

Chapter 1 19



### *Documentation*

#### **ARCHIVES: Security**

- Only authorized entry permitted per SOP
- Examination in situ of documents
- Photocopies made in place (if possible)
- Fire, flood and vandalism protection

Chapter 1 20

## 5. Documentation

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### *Documentation*

#### **ARCHIVES**

**Under conditions which minimize deterioration**

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

Chapter 2 21

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### *Documentation*

#### **ARCHIVES**

##### **Indexing parameters**

- Project
- Test article/reference article and lot numbers for bulk and formulated material if appropriate (tie-in with product accountability records)
- Protocol/study number
- Testing facility
- Key word retrieval from comments section of master schedule (e.g. regulatory information, dates)
- Department

Chapter 2 21

## CHAPTER 5 • PERSONAL NOTES

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## 6. QUALITY ASSURANCE UNIT

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### QUALITY ASSURANCE UNIT

GLP defines the minimum quality assurance requirements necessary to ensure the validity of experimental results. The QAU (quality assurance unit = the group of persons with a set of defined duties, mostly of an audit and control nature) is part of this total quality assurance process. The QAU's mandated role is that of an independent witness of the whole preclinical research process and its organizational framework.

The role of the QAU as facilitator and “consultant” during the establishment of quality systems is understood, at least implicitly, in most laboratories. However, although the vast majority of laboratories have understood the important overall role of QA, with respect to the GLP regulations, the GLP QAU's mandated role is that of an “independent” control service.

In this capacity, QA must review all phases of preclinical research, from planning, through ongoing studies, to reporting and archiving the documentation.

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

QAU audit files are accessible to facility management, but not normally to regulatory authorities or other external legal persons.

#### *Protocol (or Study Plan) Review*

QAU reviews the protocol for completeness and clarity.

At some laboratories the QAU also signs the protocol – but 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. The QAU receives and maintains a copy of all protocols with any subsequent amendments.

#### *SOP Review*

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

QAU often has the responsibility of reviewing SOPs. In those laboratories where the QAU signs the SOPs, it is 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.

### *Planning (Master Schedule, Inspection Plan)*

Once the protocol is signed and distributed, the study is entered onto the master schedule sheet (MSS), a list of all studies at the facility. The maintenance of the MSS may or may not be a QAU function. However QAU must be aware of all planned studies and must have a copy of, or direct access to, the MSS.

The QAU plans the inspections and audits considered necessary to support the study, if necessary, with input from the study director. There are arguments for and against performing unannounced QA inspections but usually inspections and audits are planned with the study director or his representative.

The QAU maintains its own inspection and audit plans study by study. These study specific inspection targets are entered onto a planning system in the QAU department along with facility/system and process inspections. This is to allow for overall planning and the most efficient organization of QAU resources.

### *Audits and Inspections*

An audit or an inspection is a methodical evaluation that should be performed in cooperation with the people concerned. The internal audit is not an inquisition or a punitive exercise.

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

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

QA may also inspect contractors and suppliers.

#### **Study-based Inspections/Audits**

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

Some general points:

- SOPs for inspections and for audit reports should ideally be prepared in dialogue with the operational staff.
- The inspector should prepare for the inspection. Usually this means reviewing the protocol, applicable SOPs and past inspections 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 or may not be used as considered necessary. Adherence to a checklist is no guarantee of completeness but it is useful for training and as a memory aide. Also checklists enable management to approve QAU methods and coverage and provide technical staff with a means of auto-control. Checklists are usually established formally and are updated as needed. However, the checklist may engender the risk that an unexpected finding might be missed.
- Logically and out of consideration, at the close of the inspection or at least before a report is generated, the inspector should discuss all problems with the persons inspected. Any error (e.g. dosing error, animal identification [ID]) should, obviously, be pointed out immediately.
- Comments should be clear and specific
- Comments should be constructive. The best means to ensure 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 with or without a separate report in summary form to management. 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 QAU inspections and audits target events and organization, not people. The more problems uncovered and resolved the better the level of quality.

### **System or Facility-based Inspections/Audits**

These are performed independently of studies. Frequency should be justifiable in terms of efficiency vs. costs. The results of a system/facility inspection are reported to the appropriate manager of the test facility rather than to a study director. The follow-up procedure will, however, be exactly the same as for a study specific inspection.

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

- Personnel records.
- Archives.
- Animal receipt.
- Cleaning computer operations and security.
- Access and security.
- SOP management.
- Water supply.
- Metrology.
- Etc.

### 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. Frequency is justified by efficiency and costs. These process-based inspections are performed because it is considered inefficient or inappropriate to conduct study-based inspections on repetitive phases. It is worth noting that the OECD at least 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

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

## QUALITY ASSURANCE STATEMENT

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

The QAU statement is *not* a GLP compliance statement. The study director provides this.

However, recommendations of the OECD with regard to the QAU statement should be remembered:

*“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 QAU statement becomes a sort of “Release” document that assures that:

- The study report is complete and accurately reflects the conduct and data of the study.
- The study was performed to GLP.
- That all audit comments have been satisfactorily resolved.

## QAU INSPECTIONS OF SUPPLIERS AND CONTRACTORS

Most QAU organizations also inspect/audit suppliers of major materials (animals, feed, etc.).

In the same manner, QAU may also inspect contract facilities before contracting out work. This applies whether the work concerned is a whole study, or part of a study (e.g. analytical work).

For pivotal studies, QAU may programme periodic visits to the contract facility to ensure that the contractor is in compliance throughout the duration of the study and/or audits the final report independently.

## THE DISTRIBUTION AND ARCHIVING OF QAU FILES AND REPORTS

The QAU has a dual role as an internal control and as the public guarantee that pre-clinical studies are performed in a way intended to provide valid data.

QAU reports are distributed to the study director and to management and are absolutely to be regarded as internal working documents. They are particularly valuable if important findings are picked up during the QAU activities, reported accurately, discussed and acted on.

Therefore, the provision that the QAU audit reports are not normally available to regulatory authorities will encourage the QAU to report findings honestly, without tactical fears that the facility will be damaged in the eyes of the outside world.

It follows that the QAU 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 by mistake during inspections.

## 6. Quality Assurance Unit

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*Quality Assurance Unit*

**QUALITY ASSURANCE  
UNIT**

Chapter 1



*Quality Assurance Unit*

**QUALITY ASSURANCE  
UNIT**

Chapter 1

## 6. Quality Assurance Unit

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### *Quality Assurance Unit*

**GLP :**

**Define conditions under which studies are:**

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

Chapter 3



### *Quality Assurance Unit*

#### **QA PROGRAMME / PERSONNEL**

**GLP requires:**

- **Documented QA programme**
- **Personnel who are familiar with studies**
- **QAU independent from study staff**
- **QAU report to management**
- **That the Master Schedule be supplied to QAU**

Chapter 4

## 6. Quality Assurance Unit

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### *Quality Assurance Unit*

#### **QA RESPONSIBILITIES (from GLP)**

- **Assure study plan & SOPs are available**
- **Ensure study plan & SOPs are followed**
  - **by inspection**
  - **by audit**

Chapter 3

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### *Quality Assurance Unit*

#### **QA RESPONSIBILITIES**

- **Report findings in writing**
- **Review final reports**
- **Prepare/sign QA statement**

Chapter 4

## 6. Quality Assurance Unit

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### *Quality Assurance Unit*

#### QA RESPONSIBILITIES

- Review study plan
- Review SOPs

Chapter 1



### *Quality Assurance Unit*

#### QA INSPECTION / AUDIT


##### 3 Types:

- Study-based
- Facility / system-based
- Process-based

Chapter 2

## 6. Quality Assurance Unit

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 *Quality Assurance Unit*


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**QA INSPECTION / AUDIT**

**Study-based**

- Protocol (Study plan)
- On-going
- Report

Chapter 6 - 1

 *Quality Assurance Unit*

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**QA INSPECTIONS / AUDITS**

**Facility / Systems-based**

- installations / equipment / metrology
- support services
- computer systems
- personnel training / documentation
- etc...

Chapter 6 - 2

## 6. Quality Assurance Unit

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### *Quality Assurance Unit*

#### QA INSPECTIONS / AUDITS

##### **Process-based**

- **Process inspections which occur frequently, e.g.**
  - slide preparation
  - reading Ames tests

Chapter 6 11



### *Quality Assurance Unit*


#### QA INSPECTIONS / AUDIT

- **Suppliers**
- **Sub-contractors**


Chapter 6 12

## 6. Quality Assurance Unit

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 <i>Quality Assurance Unit</i>			
<b>QA INSPECTION REPORT</b>			
<b>Header</b>			
<b>Phase audited</b>	<b>QA comments</b>	<b>Responses/corrective action planned</b>	
	<b>Signature    Date</b>	<b>Signature</b>	<b>Date</b>

Chapter 15

 <i>Quality Assurance Unit</i>	
<b>QUALITY ASSURANCE STATEMENT</b>	
<ul style="list-style-type: none"><li>• Dates of inspections</li><li>• Dates of findings to Study Director &amp; Management Plus</li><li>• Phases audited</li><li>• Confirmation that report reflects methods used and data generated</li><li>• Any exceptions</li><li>• Sign only if GLP compliance statement from Study</li><li>• Director is considered justifiable and all corrective actions completed</li></ul>	

Chapter 14

## CHAPTER 6 • PERSONAL NOTES

## 7. WORKSHOPS – STUDY PLANS / PROTOCOLS

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There are two workshops dealing with protocols:

### WORKSHOP 1

The first workshop is based on the protocol review. The protocol concerns a 13-week intravenous study in the rat.

**Task 1** – is to perform a protocol review.

The instructor will provide you with the protocol which has been prepared by a junior study director. As the head of department you are asked to comment on his protocol and to suggest improvements. There are some situations in the protocol that are frankly wrong. The inexperience of the author is evident, and you should be able to correct the protocol where it is deficient and suggest ways in which it can be improved, even in those parts of the document that are compliant

**Task 2** – is to draw up a fishbone (or Ishikawa) diagram that illustrates the processes of the 13-week study and determines the domains of the major SOPs that apply to the study.

Your instructor will explain the Ishikawa model to you before starting the workshop.

Your group is asked to report back to a plenary session at the end of the workshop, so it is important to choose a spokesperson(s) at the beginning of the session.

The instructor will be available during the workshop to answer your questions and help you if necessary.

### WORKSHOP 2

The second is based on a different protocol, a study performed in marmosets.

The instructor will provide you with the protocol that has certain GLP sections deliberately missing.

As study director you are asked to complete the missing parts.

Your group is asked to report back to a plenary session at the end of the workshop, so it is important to choose a spokesperson(s) at the beginning of the session.

The instructor will be available during the workshop to answer your questions and help you if necessary.

## 8. WORKSHOP – STANDARD OPERATING PROCEDURES

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### FOR THE PARTICIPANTS

The workshop is based on 6 SOPs which deal with the same problem: waste disposal. Different departments, all on the same research site and all part of the same overall organization, have written these SOPs.

Participants will be expected to do the following:

#### *Review the SOPs*

- Read the SOPs and note down any criticisms of the way the SOPs have been written. Comments should be made page by page to simplify reporting back later on.

#### *Draw a Flowchart*

- From the information contained in the SOPs, **construct a single flowchart** of waste disposal at this research centre.

#### *Comment*

- Make recommendations to improve the situation.

Your instructor will explain the general situation to you and will comment on flow charts before you start the workshop.

You will be divided into groups, each of which will be asked to report back to a plenary session at the end of the workshop. So it is important to choose a spokesperson(s) at the beginning of the session.

The instructor will be available during the workshop to answer your questions and help you if necessary.

## GLP WORKSHOP ON CASE STUDIES

### *Workshop instructions*

Below are 11 case studies that have actually arisen during GLP investigations. With your group, please discuss what you would do if faced with these situations, and be ready to report back to the whole group.

You have about 90 minutes to consider what you would do in these cases. Be as thorough as you can. Sometimes you may feel that you lack some information to reply fully. If this is the case, say what extra information you would like and how you would go about collecting it. Remember that there will be many ways of resolving these situations. Therefore, if your group comes up with more than one way of dealing with the problem, please let us know.

When reporting back your group will need a spokesperson. Since each case will be dealt with separately, you may, if you wish, nominate a separate person for each case.

1. You are the study director of a study being conducted to determine the blood levels of a compound. When the analytical results are reported, it is shown that the control group of animals has been exposed to the test article at some time during the study. What should you do?
2. During a long-term study, the environmental parameters that are measured on a daily basis (temperature, humidity, light intensity) have, at various times, been out of specification. How should a study director deal with this?
3. The drinking water provided to animals is monitored for quality on a three monthly basis in your laboratory. In January, the results were satisfactory and within specifications. In March, the results were out of specifications for total germ count. What consequence does this have on the studies conducted between January and March? What should happen?
4. A contract laboratory is performing a GLP study for a sponsor. Part of the study consists of a hormone analysis for which the contract laboratory has neither the expertise nor the equipment. A university department close to the contract lab has the required expert knowledge and equipment. What policy should the contract lab adopt in this situation?

5. During a routine quality assurance audit of an analytical laboratory, the auditor requests the technician to stop his work because he believes that samples are incorrectly labelled. What should happen in this case?
6. A computer system has been used in your laboratory for the acquisition of body weight data for many years. It has, however, never been validated. A regulatory inspection is expected in about three weeks time. What should you do about this computerized system?
7. An inspector from your national regulatory authority calls you on the telephone to say that he will be inspecting your laboratory in two weeks time. How should you prepare for this “visit”?
8. During a QA audit performed at the week-end on a three-month iv mouse study, it is noted that there are no records of training, for intravenous injections into the tail vein of mice, relating to one of the technicians who has performed this task. What should QA do?
9. A final report, already signed by the study director, is found to contain some erroneous data (miscalculation means that one outlying animal was not eliminated from the calculations when it should have been). What should happen now?
10. During an inspection of the dosing of dogs, several cases of rejection of formulation (dogs vomiting when replaced in their cages) were observed. However this was not recorded in the raw data by the technician. How serious is this? What should be done about this?
11. In the histology laboratory, staff have the habit of sticking non-controlled photocopies of SOPs useful for their techniques on the walls. What should you do about this?

## CHAPTER 8 • PERSONAL NOTES

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## 9. SELF ASSESSMENT QUESTIONNAIRE

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When answering this questionnaire, please remember that the reference documents are the OECD GLP Principles and the relevant OECD Consensus documents on GLP.

1. One of the essential roles of GLP is to promote the mutual recognition of test data between countries:

True / False

2. For each particular study report, a statement of GLP compliance is signed by:

- a) Quality assurance
- b) Study director
- c) Company management

3. It is mandatory to archive study data as the study progresses:

True / False

4. All copies of SOPs should be destroyed once they are revised or cancelled:

True / False

5. The archivist must be named within the laboratory:

True / False

6. Retrospective validation of newly acquired software is recommended good practice:

True / False

7. Study Directors should liaise with quality assurance:

- a) Before the study starts
- b) At the end of the study
- c) Throughout the study

8. OECD GLP Principles require QA to review study protocols:

True / False

9. Which of the following is not a QA responsibility?
  - a) Keeping a copy of all ongoing study protocols
  - b) Reporting the findings of audits to management
  - c) Signing a statement of GLP compliance for inclusion in the final report
  - d) Verifying that SOPs are available to staff
  
10. One of the aims of GLP is to help reduce the incidence of false positive results:  
True / False
  
11. GLP monitoring authorities routinely consult QA inspection findings as part of their inspections:  
True / False
  
12. Which of the following is unsuitable for archiving data:
  - a) Paper records written in ink
  - b) Magnetic tapes
  - c) Thermographic printouts
  - d) Data on CD-ROM
  
13. GLP regulations include scientific “guidelines”:  
True / False
  
14. Computer held raw data should have all the attributes of hand written raw data:  
True / False
  
15. The GLP compliance statement is:
  - a) A list of known deviations during the study
  - b) A report on QA involvement during the study
  - c) An authentication of the conclusion of the study
  - d) All of the above / None of the above
  
16. Only computer applications used for the direct acquisition of raw data require validation:  
True / False

17. Quality assurance should never write SOPs:  
True / False
18. OECD recommends that quality assurance should only sign the QA statement for inclusion in the study report if the study director's claim to GLP compliance can be substantiated:  
True / False
19. When auditing a contractor, QA should investigate whether or not the contractor has passed work onto a third party without the prior agreement of the sponsor:  
True / False
20. All amendments to final reports should be audited by QA:  
True / False
21. Before signing the QA statement for inclusion in a final study report, QA should check that all issues raised in inspection reports have been adequately addressed:  
True / False
22. It is legitimate for QA to request outside assistance from consultants when internal resources are inadequate:  
True / False
23. Which of the following would not normally be archived at the end of a study?  
a) Histological blocks  
b) Stained foetuses  
c) Haematological slides  
d) Blood samples
24. The OECD GLP regulations are binding on all member states of the OECD including Japan and the USA:  
True / False
25. According to the OECD recommendations for short term studies, it is acceptable to design generic protocols which may then be used for several studies of the same type:  
True / False

26. Which of the following is not a responsibility of QA?
- a) Give technical assistance during a study
  - b) Report unauthorized deviations from SOPs
  - c) Prepare a statement for inclusion in the final report
27. It is acceptable practice to make reference to SOPs in the study protocol:  
True / False
28. The OECD recommends that, for short-term studies, it is acceptable practice to have generic reports which may be supplemented by study specific information:  
True / False
29. When reviewing computer validation protocols, verifications should be made to ensure that the protocol contains:
- a) Approval signatures
  - b) Objectives of the protocol
  - c) Tests to be performed
  - d) Acceptance criteria
  - e) All of the above / None of the above
30. GLP regulations do not require facilities to document and retain the training of QA personnel:  
True / False

**Correct responses**

Now check your answers with the correct responses which are given below:

1	True
2	b
3	False
4	False
5	True
6	False
7	c
8	True
9	c
10	True
11	False
12	c
13	False
14	True
15	d – None
16	False
17	False
18	True
19	True
20	True
21	True
22	True
23	d
24	True
25	True
26	a
27	True
28	True
29	e – All
30	False

## CHAPTER 9 • PERSONAL NOTES

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WHO/TDR  
Avenue Appia 20  
1211 Geneva 27 – Switzerland  
Tel: (+41-22) 791-3725  
Fax: (+41-22) 791-4854  
E-mail: [tdr@who.int](mailto:tdr@who.int)  
Web: [www.who.int/tdr](http://www.who.int/tdr)