

TRAINING MANUAL

GOOD LABORATORY PRACTICE (GLP)

TRAINER



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

TDR/PRD/GLP/01.1A

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

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

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:

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ABOUT THIS TRAINING MANUAL

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.

As an instructor, you have been provided with the notes which accompany the PowerPoint slides. These will help you during your presentations, since the notes explain what the message of each slide is, and occasionally suggest when you could fruitfully engage in a group discussion. You should be familiar with the contents of the manual before starting the training. Try to imagine what questions are likely to be asked for each of the sections and prepare to answer them. It is important to use as many of your own personal anecdotes or real life situations as possible to render the presentations lively and pertinent.

When you are running the workshop sessions, it is important to distribute the material only when it is needed – do not give it all out in advance. The amount of time needed for the workshops is estimated in the instructions, but you will have to adapt to the circumstances of each workshop. The most important part of the workshops is to ensure that there is sufficient time for discussion within the group and during the plenary feedback sessions.

For each workshop you have instructions about how to perform the activities. You also have the main points to develop during the discussions. However, there are no hard and fast rules about the solutions to workshop issues and you will have to take each proposition from each group as a suggestion and point for discussion. You should always be positive – never dismiss as unacceptable the group response to the workshop tasks. Find out why they have decided to make the suggestion that they put forward. The reason may be well founded even if the response seems to be non-compliant. Finally, always try to relate what the groups have to say to the fundamental points of GLP.

Timing and Support Material

The GLP training course is designed to last for three full days. 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. However, the instructor will need to modify it according to the interest of the participants and the experience in the field that they might already have.

The protocols and the SOPs to be used in the workshops are provided with the training manual for the instructor

As you will see from the Instructor's Notes, the participants are asked to consult the OECD Principles and Consensus documents from time to time. The participants should have these documents available and it is best to include them in the course package.

1. INTRODUCTION TO THE OECD PRINCIPLES OF GLP

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.

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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.

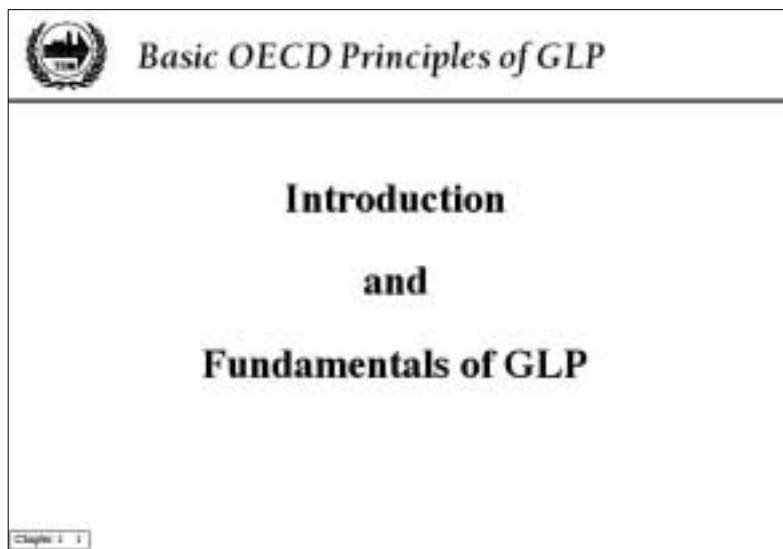
THE OECD GLP PRINCIPLES

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.

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



Instructor's notes

Explain

This short introduction explains why GLP was a necessary regulation.

The history of the development of the GLP regulations is explained and the five fundamental points of GLP are provided.

The participants should be told at this point that the training course is based upon the OECD Principles of GLP and the five fundamental points which will be dealt with in turn.

Day 1 of the training covers most of the basic points through a series of structured presentations. Day 2 focuses on protocols with workshop sessions. Day 3 deals with SOPs, again with workshop sessions. During the final part of the training, participants are asked to work on a series of practical case studies.

1. Introduction to the OECD Principles of GLP



Basic OECD Principles of GLP

The birth of GLP

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

Chapter 1 1

Instructor's notes

Explain


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

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

At the end of the investigation, the FDA published their findings. These are summarized on the next slide. Some cases of fraud were detected and the laboratories concerned were severely dealt with. One called Industrial Bio-Test was closed down and the directors were given long prison sentences.

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

1. Introduction to the OECD Principles of GLP

**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 8

11

Instructor's notes

Explain

The findings of the FDA were all available under the Freedom of Information Act. In this slide and the next one, a selection of the FDA findings are listed.

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

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

It is important to demonstrate that the need for quality management is not primarily to combat fraud, but to impose a sensible and documented organization of studies.

1. Introduction to the OECD Principles of GLP



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 8

Instructor's notes

Explain

This slide is a continuation of the list on the previous slide.

1. Introduction to the OECD Principles of GLP

**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 2

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Instructor's notes

Explain

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

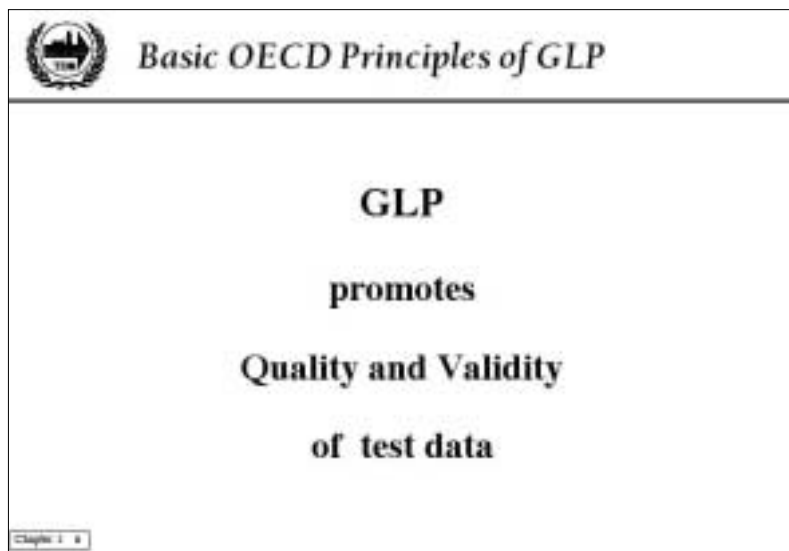
After the consultation period, the final regulation was published in 1978.

This came into force in 1979.

It is an American regulation, but had a wide impact world-wide because non-US companies wishing to register medicines in the USA now had to perform safety studies in compliance with FDA GLP. Don't forget that about 30% of the world's pharmaceutical trade occurs in the USA; it is a market that cannot be ignored!

Many countries introduced their own GLP regulations and the OECD produced GLP Principles in 1981 which have now become the international standard in the domain.

1. Introduction to the OECD Principles of GLP



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Instructor's notes

Explain

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

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

1. Introduction to the OECD Principles of GLP

**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

15

Instructor's notes

Explain


Studies which are organized under GLP promote reliability of test data because the study staff must carefully document any deviations from fixed standards and because the GLP organization encourages the scientist to document all variables.

GLP studies must be fully documented (methods, procedures, deviations), which means that they can be accurately repeated at any time in the future.

The full documentation of the studies, from planning activities right through to the production of reports, means that all the activities of the study are traceable and therefore the study may be audited by third parties.

Since GLP is an internationally accepted standard for the organization of studies, performing such experiments to GLP promotes their acceptance world-wide.

1. Introduction to the OECD Principles of GLP

**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 8

Instructor's notes


Explain

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

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

What GLP requires is that the scientists responsible for the organization of studies implement clear organizational structures in compliance with GLP so that the test data are more reliable.

1. Introduction to the OECD Principles of GLP

**Basic OECD Principles of GLP**

GLP Aim
To make the incidence of
False Negatives
more obvious
(e.g. Results demonstrate non-toxicity
of a toxic substance)

Chapter 1 8

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Instructor's notes

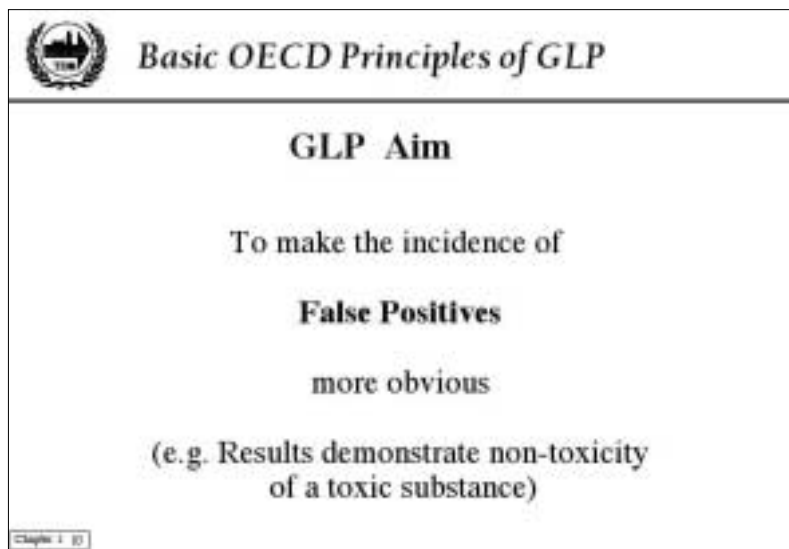
Explain

GLP will help scientists avoid getting false negatives from their studies because the studies are standardized where they can be and because the variables are well documented.

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

Taken to its extreme, this could be dangerous if the test item (believed wrongly to be inoffensive) is administered to man. However, such a situation rarely occurs because there are many studies to perform before getting to man and the chances of them all turning in false negative results is not great. BUT all false negative results are costly, time consuming and present ethical problems (animals used to no good purpose) and should, therefore, be avoided.

1. Introduction to the OECD Principles of GLP



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Instructor's notes

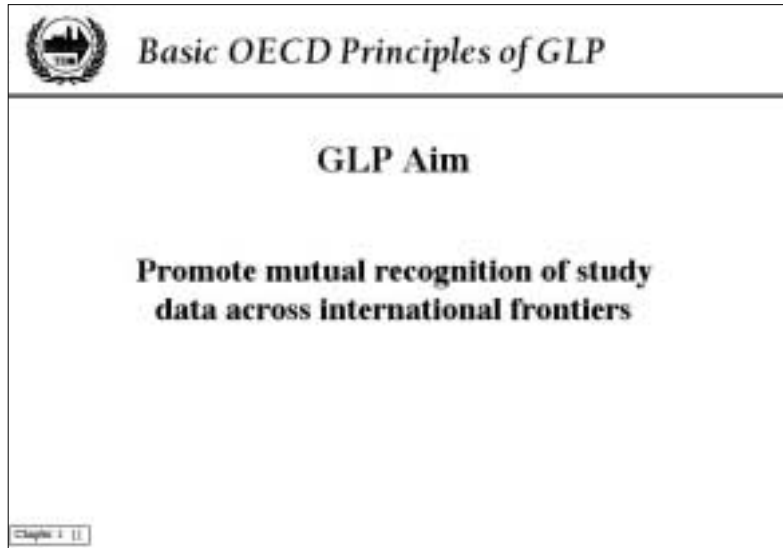
Explain

In the same way that GLP helps avoid false negatives, GLP also helps scientists avoid false positives.

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

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

1. Introduction to the OECD Principles of GLP



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Instructor's notes

Explain


GLP also promotes international recognition of study data.

When studies are performed to OECD GLP Principles, 30 countries of the world must recognize that the data have been generated under acceptable organizational standards.

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

For the purposes of the registration of studies in foreign countries, this is a fundamental advance over the time prior to GLP where many countries insisted that the studies from a foreign state be repeated in their own country because the confidence in the original data was very limited.

1. Introduction to the OECD Principles of GLP



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 11

Instructor's notes

Explain

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

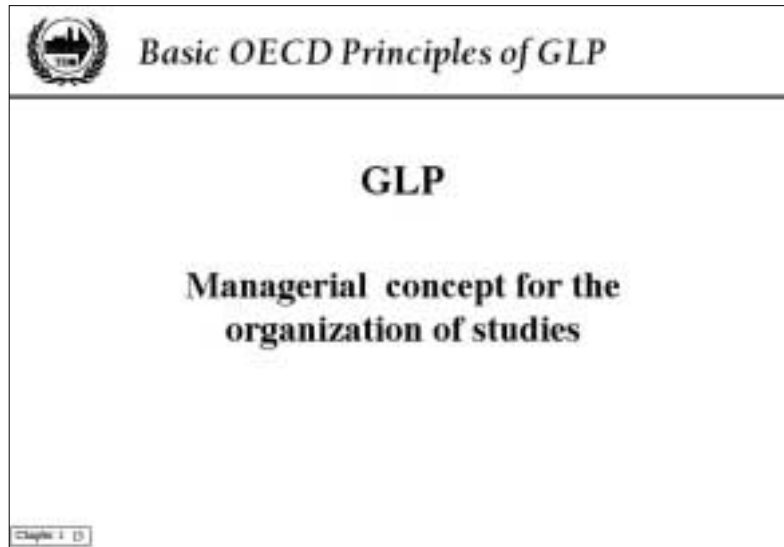
Limiting waste of resources is particularly aimed at limiting the use of animals.

Ensuring high quality of results concerns the validity of test data described above.

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

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

1. Introduction to the OECD Principles of GLP




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Instructor's notes

Explain

As outlined already, GLP stipulates the conditions for the organization of studies, not the scientific value of studies. As such, GLP is a quality system for the management of work.

1. Introduction to the OECD Principles of GLP



Basic OECD Principles of GLP

GLP

Defines conditions under which studies are

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

Chapter 1 16


Instructor's notes

Explain

This sentence is one of the key phrases which can be located in the introductory text to the OECD GLP Principles (upon which this course is based), GLP defines the working environment under which studies are:

- PLANNED – which is why great emphasis is given to the study plan (protocol) and to possible planned changes throughout the study.
- PERFORMED – this refers to the Standard Operating Procedures (SOPs) which are a GLP requirement.
- RECORDED – the collection of raw data and the recording of deviations during the study are dealt with in the regulations.
- REPORTED – one of the problems pre-GLP was that study reports did not always accurately reflect the study data, so assuring accuracy in the report has become an essential part of GLP.
- ARCHIVED – as studies may be inspected many years after their completion, it is important that the study data, specimens, samples and reports are correctly stored after the study.
- MONITORED – monitoring by study staff, quality assurance personnel and national inspectors helps assure GLP compliance.

1. Introduction to the OECD Principles of GLP



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 13

23

Instructor's notes

Explain

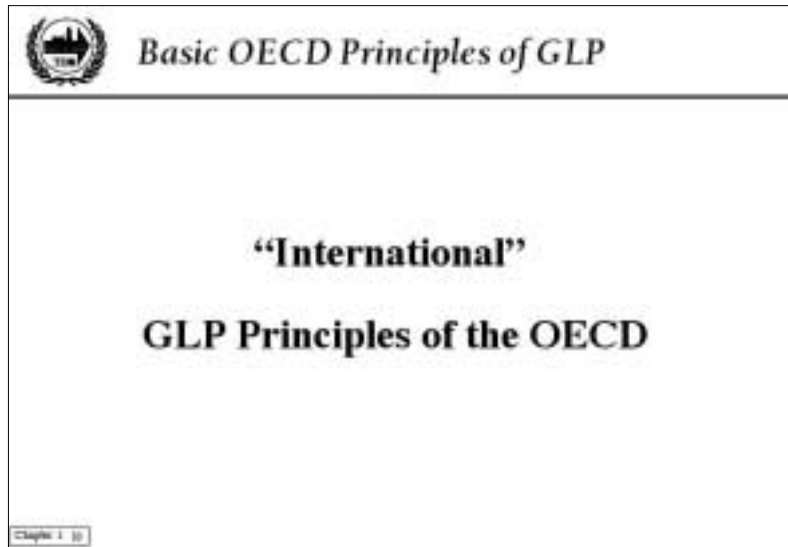
This slide shows the fundamental points of GLP. They are arranged under five convenient headings.

Take about 20 minutes to discuss this slide with the participants, providing basic information about the meaning of each of the five items.

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

You will find a brief summary of the importance of the 5 points in the introductory text accompanying these slides.

1. Introduction to the OECD Principles of GLP



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Instructor's notes

Explain

The OECD GLP Principles are the only truly international GLP texts.

This section explains that the OECD GLPs have been agreed to by all 30 member states of the OECD and as such they represent a single acceptable set of rules for performing GLP studies.

1. Introduction to the OECD Principles of GLP

**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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Instructor's notes

Explain

The first regulatory document about GLP was the USA-FDA regulation in 1978. This concerns safety studies performed in non-clinical studies on FDA regulated products.


The USA-EPA GLP regulations relate to pesticides used in the field and other substances which could be spread into the environment during, for example, agricultural practices.

The OECD GLP Principles were adopted as the GLP directives of the European Union and are, therefore, the same. They concern pharmaceuticals for human and veterinary use, cosmetics, food additives industrial chemicals and agrochemicals. Once again, the emphasis is on non-clinical safety tests.

The Japanese have developed separate GLP regulations which apply to different disciplines and are controlled by different ministries (health, industry, agriculture, employment...).

Fortunately there are very few differences between all these GLP regulations and the OECD Principles are accepted internationally.

1. Introduction to the OECD Principles of GLP



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 11

Instructor's notes


Explain

Experts from all member states represent the views of each state.

The member states agree to abide by the various rules and recommendations negotiated through the OECD.

Negotiated rules and agreements are binding on the signatories of the OECD.

1. Introduction to the OECD Principles of GLP

**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

27

Instructor's notes

Explain


All member states have signed up to the MAD agreement:

Mutual Acceptance of Data

Thus all the 30 member states agree to adopt OECD GLP Principles as a baseline for the conduct of Safety Studies.

The validity of data from studies which are OECD GLP compliant must be accepted by all member states. Of course, they may still be refused for scientific reasons.

1. Introduction to the OECD Principles of GLP



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 30

28

Instructor's notes

Explain


At the heart of the OECD GLP organization is the “GLP Group”.

This group is composed of the heads of each national GLP monitoring authority. There is obviously a minimum of 30 chief GLP inspectors (one for each state's monitoring authority). In actual fact there are many more than 30, as some states have divided their GLP monitoring activities between different organizations, e.g. USA FDA and USA EPA.

The group meets regularly and plans how to promote GLP compliance throughout all the OECD member states.

The GLP activities organized through the OECD include special training sessions for inspectors and the performance of joint inspections designed to help harmonize the inspection approach throughout the OECD member states.

1. Introduction to the OECD Principles of GLP

**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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Instructor's notes


Explain

The OECD GLP Principles have been completely revised since their first publication. This revision was in 1997 and the complete document was published in 1998.

The first part, and the part which interests us, is the GLP Principles.

The second part concerns the way in which the inspectors monitor GLP compliance.

1. Introduction to the OECD Principles of GLP

**Basic OECD Principles of GLP**

The OECD Consensus Documents

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


Chapter 1 22

Instructor's notes

Explain

This slide and the next lists the seven interpretative or consensus documents issued by the OECD to help people implement the GLP Principles.

1. Introduction to the OECD Principles of GLP

**Basic OECD Principles of GLP**

OECD Consensus Documents (continued)

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

Chapter 1 29

31

Instructor's notes

Explain


Same as previous slide.

The consensus documents are not strictly speaking part of the GLP Principles. But they are a considerable help to organizations wishing to set up GLP as they explain in more detail some GLP points which would otherwise be rather obscure.

The inspectors use these documents as references during their inspections. They are considered as “state of the art” in the domain covered by the document. Most people adhere to the advice given by these consensus documents as if they had the same status as the GLP Principles.

In this training course the OECD consensus documents are considered as serious recommendations on GLP implementation.

1. Introduction to the OECD Principles of GLP



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 24

Instructor's notes

Explain

Any member state can request the OECD to organize a consensus workshop on a subject of interest.

The OECD GLP Group decides whether or not the subject matter is of general interest and whether or not a consensus meeting should be held to debate the subject and produce an advisory document.


If the subject is chosen, the consensus workshop is organized over a short (three day) period.

Member states send representatives to the workshop, usually the head of the GLP inspectorate and representatives from industry.

A person is requested to write a position paper on the subject in hand (usually from the country that requested that the subject be dealt with in a consensus workshop).

The chairperson and the rapporteur put the first draft of the document together at the end of the consensus meeting.

1. Introduction to the OECD Principles of GLP

**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 25

33

Instructor's notes

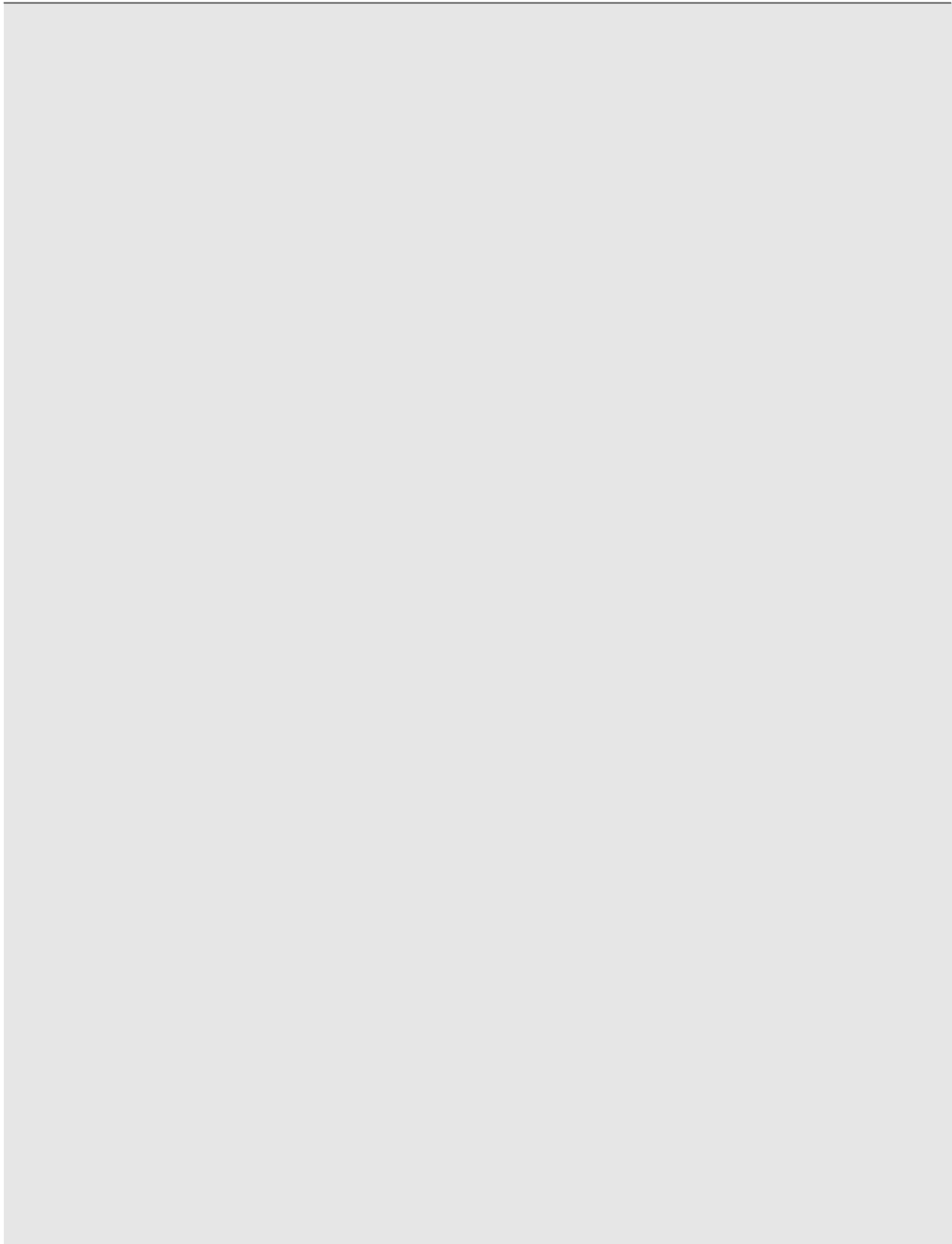
Explain

Once the first draft has been completed it is reviewed by the GLP Group of the OECD and a second draft prepared for the various committees of the OECD that will eventually approve the document.

The consensus document is reviewed again by a number of OECD officials before being ratified and signed at the highest level.

The process does not normally take longer than 9-12 months.

CHAPTER 1 • PERSONAL NOTES



2. RESOURCES

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

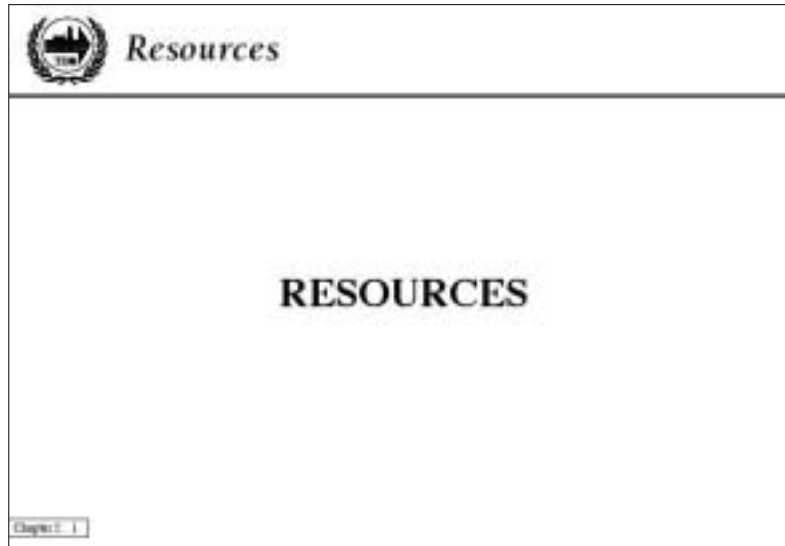
The planning of routine maintenance mentioned above should be documented in such a way that users of the equipment can ensure that it has been adequately maintained and is not outside its service interval. A “sticker” attached to equipment, or provision of a clear service plan, may do this.

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



Instructor's notes


This module first examines management responsibilities and then looks at the topic of personnel. Physical resources have been divided into buildings and equipment.

Explain

Any scientific inquiry requires proper resources.

GLP regulations state that management must provide proper resources. These are either personnel resources (people) or physical resources such as buildings and equipment. GLP requires that all resources are adequate for the task in hand.

2. Resources



Resources

RESOURCES

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

- Personnel
 - Study Director
 - Quality Assurance
 - Archivist
- Facilities / Equipment

Chapter 2

45

Instructor's notes

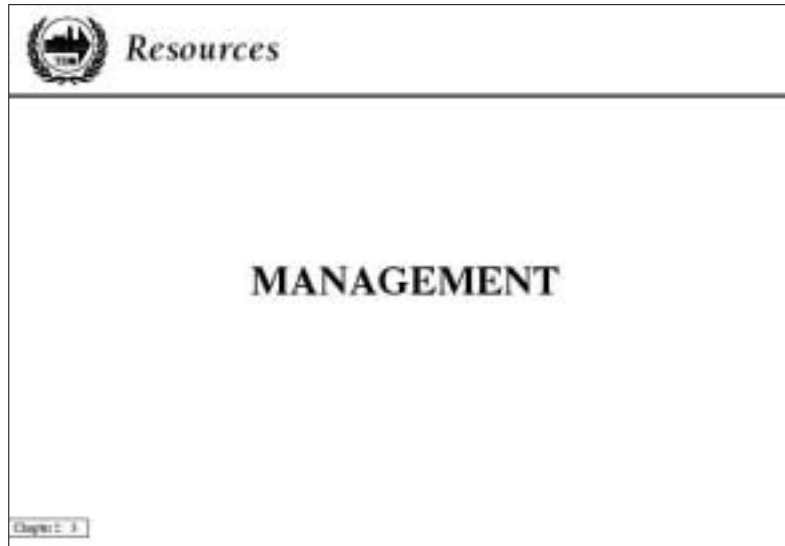
Explain

Management must demonstrate, in whatever way is fitting, that the resources provided are *appropriate*.

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

(We shall return to these responsibilities later on.)

2. Resources



Instructor's notes


Explain

Each research site must produce a document which identifies individuals with management responsibilities.

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

GLP requires that each facility has a document identifying individuals with management responsibilities.

2. Resources

**Resources**

MANAGEMENT

- Good science
- Good organization

Chapter 4

47

Instructor's notes

Explain


Management takes overall responsibility for both the conduct and interpretation of the study.

This means that management has a responsibility for both the scientific and organizational aspects of the study.

Activity

As the participants are scientists, ask them to list the points which are covered by good science on the one hand, and good organization on the other hand (about 10-15 minutes).

2. Resources

**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 2: 1


Instructor's notes

Activity

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

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

2. Resources



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 2: 6

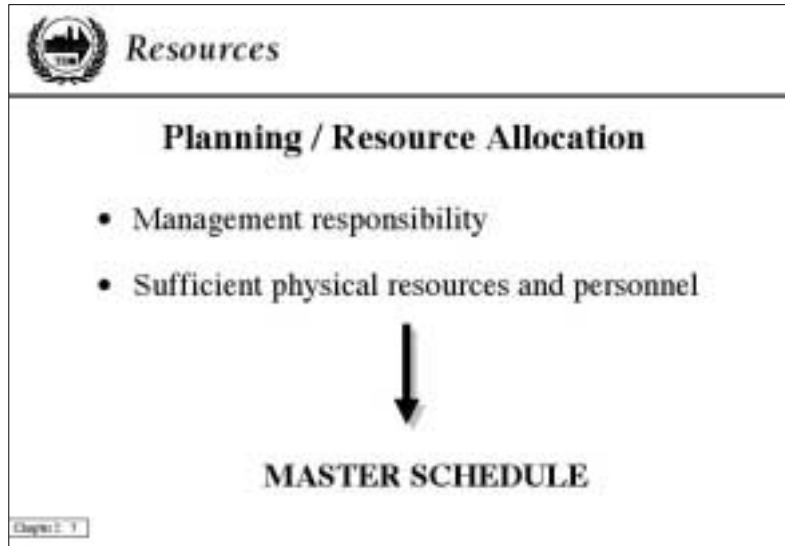
Instructor's notes

Activity

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

Good organisation is about (but may well not be limited to) the items listed in this slide.

2. Resources



Instructor's notes

Explain

The Master schedule is a document that is used to record the planning of the studies performed on a site, or in a department.

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

2. Resources

Resources

Master Schedule

- All studies should be included
- Keep up-dated & have a change control procedure
- Include actions such as protocol review and report preparation
- Have only one official schedule
- Define the system in an SOP
- Decide who should maintain this document
- Archive-off as necessary
- Distribute to those who need it

Chapter 2: 8

51

Instructor's notes

Explain


The master schedule should contain information which is useful for the planning aspects of studies performed in your institution. There are no hard and fast rules about the form the schedule should take. The information included should be used by management to assure the appropriate use of resources and as a document that demonstrates (for example at the time of an inspection by an authority) that sufficient resources were (are) available at all times that studies were (are) being performed.

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

Management is the ultimate author of the master schedule, but the task of authorship is often delegated to a specialist group like project management. Your quality assurance team must be provided with a current copy of the schedule.

Other GLP points are outlined on the slide.

2. Resources

**Resources**

Master Schedule

Test Item : XYZ 1234

STUDY INFORMATION				DATES						
Study ID*	Study Director	Title	Location	Protocol Review	Start Date	End In-Win	Draft Report Audit	Final Report Review	Archive	Comments


Chapter : 5

Instructor's notes

Explain

This slide is an example of the way in which many organizations present their master schedules. But there is no hard and fast rule for doing presentation.


2. Resources

*Resources*

PERSONNEL

Chapter 10

2. Resources

**Resources**

PERSONNEL

Organisation shown in standard documents

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


Chapter 11

Instructor's notes

Explain

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

2. Resources



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

Instructor's notes

Explain


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

This is used to explain very rapidly to any non-member of the institution where you work, the way in which you are organized and who reports to whom.

Many facilities add the number of staff present in each department or service unit as a way of illustrating the size of the organization.

In very small organizations it is common to find the names of all staff on the organizational chart.

2. Resources

 **Resources**

Job Descriptions

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

Chapter 2: 16

Instructor's notes

Explain


Everyone needs a job description.

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

Many laboratories include the relevant part of the organizational chart.

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

2. Resources

 **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 2: JH


57

Instructor's notes

Explain

These are the kind of sections that one often sees in job descriptions, but the actual content is left to the discretion of management.

2. Resources



Resources

Curriculum Vitae

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

Chapter : 11

Instructor's notes

Activity


Draw a list on the board of the topics you would expect to see in a CV
It is usual to put the following information in CVs:

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

Even a member of staff without formal qualifications needs to have a CV. This will contain details of the professional experience which qualifies them for their task.

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

2. Resources

 **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 2: 16

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Instructor's notes

Explain

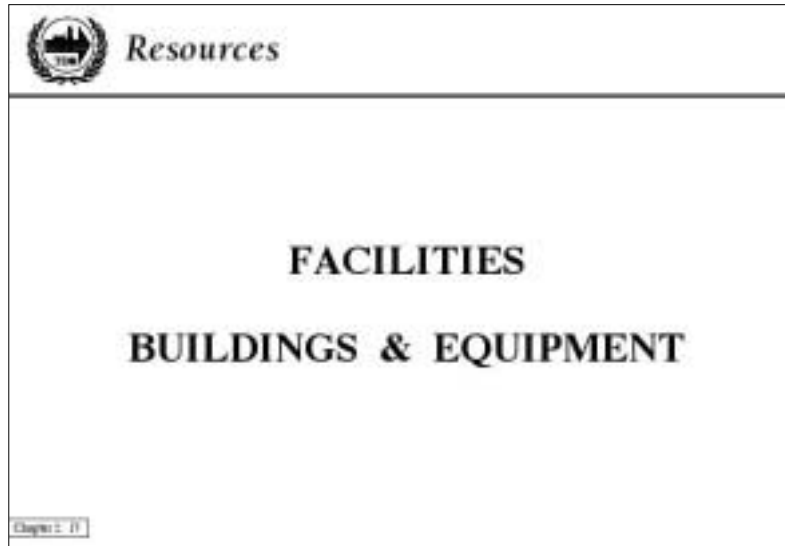
Training records should include information of all training not included in the CV. (There is no need to repeat here the formal education and qualifications of personnel.)

Include systematic training which qualifies you for the job you are doing. This should be based on the laboratory SOPs and on practice.

Include all courses attended both internal to your laboratory and those attended outside your institution. (Include this course!)

You may include attendance to seminars and congresses.

2. Resources




Instructor's notes

Explain

Facilities have been divided into two parts:

1. Buildings – which we will deal with first
2. Equipment


2. Resources

*Resources*

BUILDINGS

Chapter 11

2. Resources

**Resources**

BUILDINGS

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

Chapter 2: IV

Instructor's notes

Explain

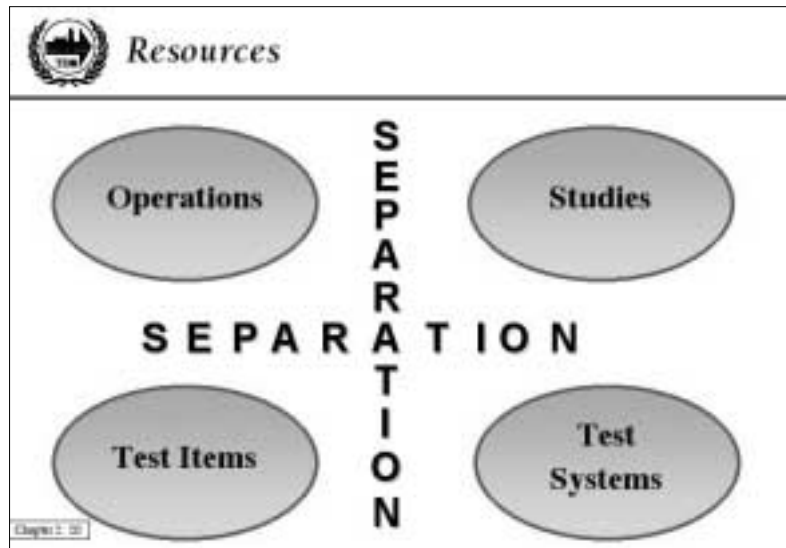
The GLP regulations do not stipulate exactly how buildings should be constructed. It is up to management and study staff to satisfy the authorities that the buildings are of adequate design and that they function properly.

Obviously the exact type of structure depends upon the kind of work to be performed in the building. However, it is required that buildings are adequate for the study, with particular assurance that studies are free from interference, disturbance and contamination.

Activity

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

2. Resources




Instructor's notes

Explain

The key point to prevent studies from contamination, disturbance or interference is to ensure separation between studies, test systems, operations and test items.

2. Resources

 *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

Instructor's notes

Explain

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


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

Activity

Lead a discussion with the group on contamination other than study-to-study (10 minutes maximum).

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

2. Resources

**Resources**

BUILDINGS : Factors to consider

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


Chapter 2 21

Instructor's notes

Explain

The points indicated here are some of the factors which would be taken into consideration either when judging whether or not a particular building is adequate for the job, or when designing a new building.

2. Resources

**Resources**

BUILDINGS : Adequate for Study

Examples :

- Pharmacy & dose mixing unit
- Animal facilities


Chapter 2: 24

Instructor's notes

Explain

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

2. Resources



Resources

Pharmacy and Dose Mixing unit

Deals with test and control items and their :

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

Chapter 1: 1+

67

Instructor's notes

Activity

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

Compare their thoughts to the list on this slide.

Now ask the participants to jot down on paper what they think are the important points to consider when evaluating the physical adequacy of a dose Mixing Unit.

Get the participants to group their thoughts under the headings:

1. Size
2. Construction
3. Location/separation

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

2. Resources




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 2: 22

2. Resources

**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 1: 56

Instructor's notes

Explain

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

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 2: 21

Instructor's notes

Explain

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

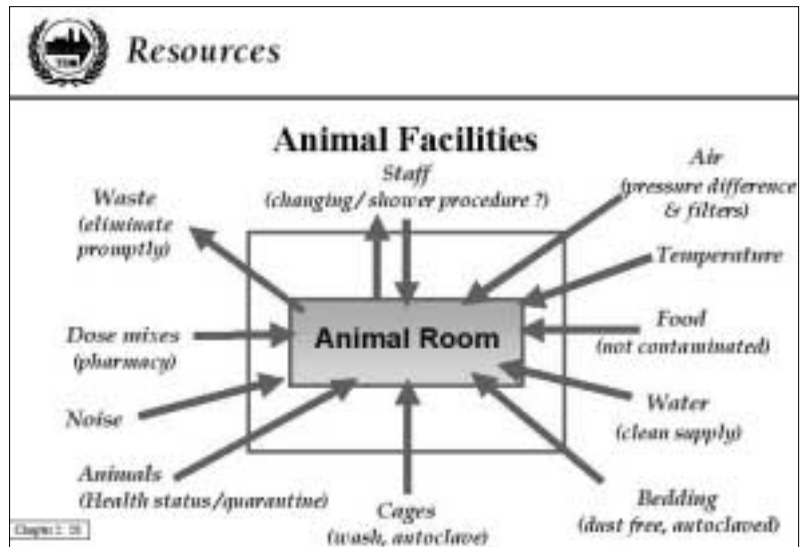
Barrier systems are often promoted as the best answer to ensuring minimal disturbance. But this “state of the art” situation is very costly and by no means always necessary.

Activity

Participants are asked here to list the important variables which need to be controlled to prevent disturbance of studies or contamination.

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

2. Resources



2. Resources



Resources

Animal Facilities

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

Chapter 2: 24

2. Resources




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 10

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

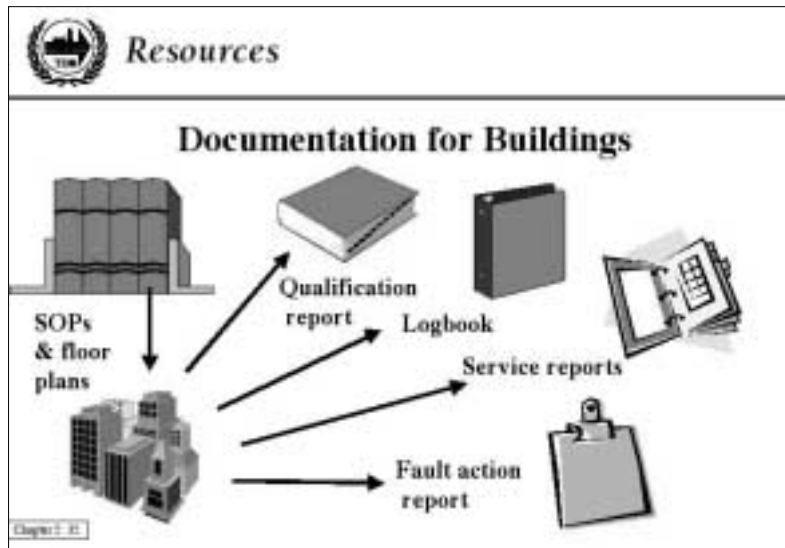
Instructor's notes

Explain

There are a number of procedures that can be implemented to help keep contamination and other interference at a minimum even if you don't have a barrier system.

Some of these procedures are indicated on this slide.

2. Resources



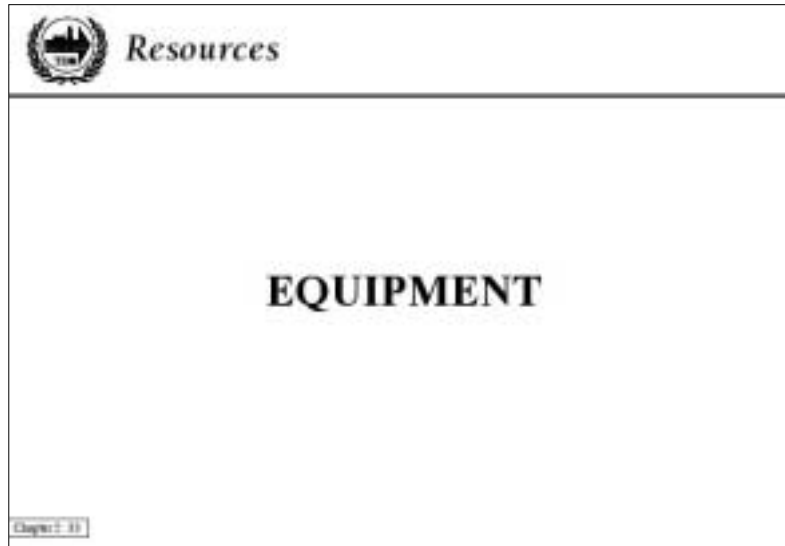
75

Instructor's notes

Explain

This slide summarizes in diagrammatic form the different sorts of document that you would expect to have if you wish to claim GLP compliance for the buildings at your facility.

2. Resources




Instructor's notes

Explain

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

2. Resources

**Resources**

EQUIPMENT

- Suitability
- Calibration
- Maintenance
- Documentation

Chapter 2 34


Instructor's notes

Explain

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

1. is suitable for the task in hand,
2. is properly calibrated and maintained, and
3. has good documentation relating to each piece of equipment.

2. Resources

**Resources**

EQUIPMENT : Suitability

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

Chapter 15

Instructor's notes


Explain

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

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

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

2. Resources

**Resources**

EQUIPMENT : Calibration

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

Chapter : 36

Instructor's notes


Explain

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

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

The scientist must decide what is the appropriate frequency of calibration for each instrument and this should be documented, normally in an SOP.

2. Resources

**Resources**

EQUIPMENT : Maintenance

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

Chapter 2.11

Instructor's notes

Explain


Maintenance is necessary for all equipment. This is usually divided into maintenance that is performed as a preventive measure (e.g. changing the ultra violet lamps in some equipment as their efficiency is known to decline over time) and curative maintenance which consists of repair work on broken apparatus.

In the case of equipment that breaks, it is necessary to have either back-up equipment or a back-up procedure so that the work can continue. This is the case when a computer system goes down but you still have to collect data.

Most institutions also have maintenance contracts with external service companies (sometimes the vendors of specific pieces of equipment). This work should be described in detail and traceable (contract, date, equipment number, technician...).

If your equipment requires an alarm, make sure that it is in working order, that it is regularly checked (part of the maintenance plan) and that, when the alarm operates, there is an emergency procedure for dealing with the problem.

2. Resources

**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 10

Instructor's notes

Explain

This slide reminds us of the need for Standard Operating Procedures (SOP) for all equipment.

Records must be kept for all interventions involving equipment.

2. Resources

Resources

EQUIPMENT : Service Plan

Plan title

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

Chapter 10

Instructor's notes

Explain

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

It concerns the planned interventions on an air conditioning system.

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

Letters change to UPPER CASE when the actions have been completed.

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

2. Resources

	<i>Resources</i>
EQUIPMENT : Service Label	
INSTRUMENT N° _____	
DATE OF LAST SERVICE _____	
NEXT SERVICE DUE _____	
NAME RESPONSIBLE METROLOGIST _____	
Signature / date _____	
<small>Chapter 1 - 40</small>	


Instructor's notes

Explain

This is the kind of information needed to show that the equipment has been properly serviced. Often the information is on a label attached to the equipment.

It is important not to use a piece of equipment if it is no longer covered by the service. This is why the information "Next service due" is important.

2. Resources

**Resources**

EQUIPMENT : Fault Action Report

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

Chapter 2

Instructor's notes

Explain

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

This is called a fault action report.

It is important that, after repair, a responsible person signs to state that the equipment can be used again.

2. Resources



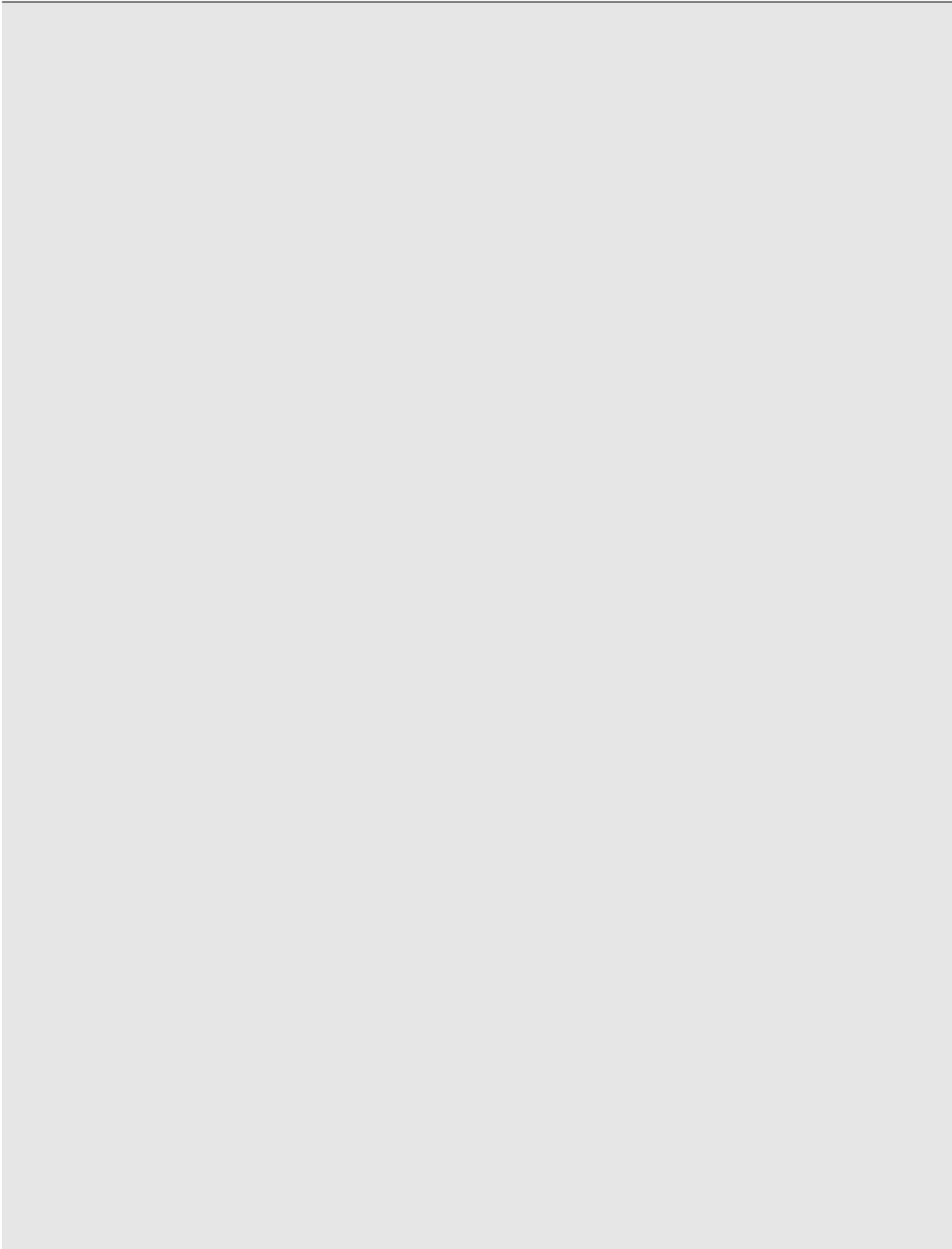
85

Instructor's notes

Explain

This slide summarises in diagrammatic form the different sorts of document that you would expect to have if you wish to claim GLP compliance for the equipment at your facility.

CHAPTER 2 • PERSONAL NOTES



3. RULES

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.

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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

*Rules*


RULES

Part I

PROTOCOL or STUDY PLAN

Chapter 3 | 1

3. Rules

 *Rules*

RULES

- **Guidelines**
- **Protocol / Study Plan**
- **Standard Operating Procedures (SOPs)**

Chapter 3 2


Instructor's notes

Explain

It is important to distinguish between these three types of rules.

In GLP, the Study Plan or protocol and the SOPs are the most important documents and will form the major part of this section.

3. Rules

 *Rules*

GUIDELINES

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

Chapter 3

97

Instructor's notes


Explain

Guidelines provide information on the scientific methods which are recommended for specific studies. They define the scientific methods which are recommended for certain studies.

The OECD has published a large number of scientific guidelines for the performance of specific studies, ranging from toxicology to physico-chemical analyses. All these tests can be performed in compliance with GLP.

GLP studies do not have to be performed to guidelines. However, when guidelines are used they should be referenced in the protocol.

3. Rules

**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

Instructor's notes

Explain


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

The protocol need not follow international guidelines where this is inappropriate.

The protocol provides a description of the important parameters of the study and the timelines. In this sense, the protocol is a Master Plan for the study.

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

3. Rules

**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 3

99

Instructor's notes

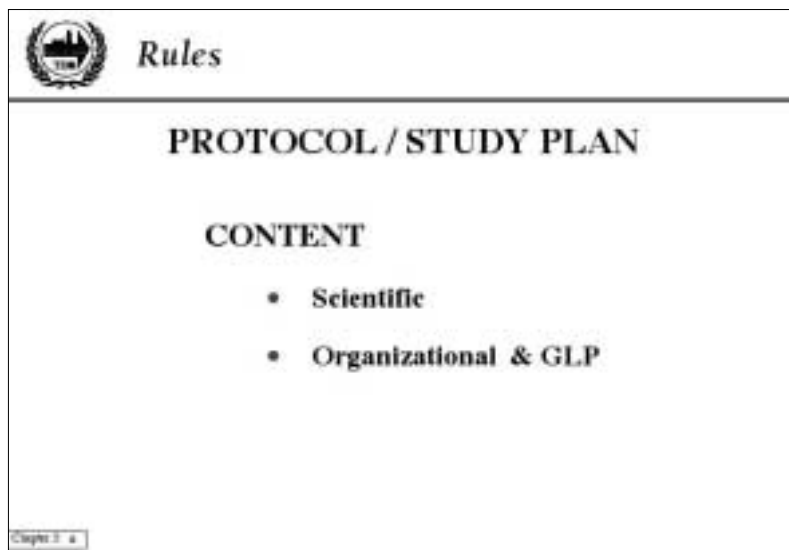
Explain

The importance of the protocol as a formal document for communication or for contractual reasons is explained drawing on examples from the instructor's experience to illustrate the importance of this communication document.

Activity

Ask the participants to discuss the problems they have had in the design, approval and use of protocols or similar non-GLP study plans.

3. Rules



Instructor's notes

Explain


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

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

Activity

Ask a few of the participants which scientific aspects they consider should be included in the kind of studies they perform.

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

101

Instructor's notes


Explain

The protocol is a multi-function document. Some of the functions are mentioned here.

Activity

Ask the participants for other possible functions of the protocol.

3. Rules

 *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 8


Instructor's notes

Explain

GLP requires that each study has a separate protocol, individually identified.

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

3. Rules

**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. 8

103

Instructor's notes

Explain

GLP requires a clear title and statement of purpose for each study. The points that it is usual to address are those in the slide.

However, very often the title is sufficiently explicit to indicate the purpose of the study too:

e.g. study of the short-term toxicity of compound XXX when administered orally to the rat as a single administration, followed by a two-week observation period.

3. Rules

Rules

PROTOCOL / STUDY PLAN
GLP REQUIREMENTS

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

Chapter 3 40

Instructor's notes


Explain

GLP requires that the test & control items be identified, and any reference items too. Usually, test items are identified by the points shown in the slide. The test item may only be identified by a code number or name. This is often the case when a CRO is performing the studies on behalf of a sponsor.

It is preferable to use a single batch throughout the study as this eliminates possible batch to batch variability.

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

3. Rules

**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


105

Instructor's notes

Explain

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

3. Rules

**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 22

Instructor's notes


Explain

Although GLP only requires you to identify the study director in a protocol (and principal investigators if it is a multi-site study) it is highly recommended to identify other significant personnel here.

This is good for communications and to clarify responsibilities.

The study monitor is the person who will follow the study on behalf of the Sponsor when the study is being performed by a contract research organisation (CRO).

3. Rules

**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 23

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Instructor's notes

Explain

The dates required by the GLP regulations are:


- The date of approval and signature of the study director (and management and the sponsor if required by individual national regulatory authorities)
- The proposed start and finish dates for the study
 - Start = date study director signs the protocol
 - Finish = date study director signs the final report

Activity

Discuss with participants that a good protocol will include a more extensive time plan for the whole study. It is useful to include dates that will help the scientists working in different areas to co-ordinate various activities.

The instructor should underline the importance of using the draft protocol with its draft proposed dates as a planning document so that all scientists involved in the study can agree to the overall time plan. For instance, it is important that the Study Director has the agreement of the clinical pathologist concerning the dates of sending blood samples to that laboratory for analysis.

3. Rules

 *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 28

Instructor's notes


Explain

This slide indicates the information required for the adequate description of a test system. In this case, as the most usual example, the test system is a mammal.

Activity

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

3. Rules

**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 23

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Instructor's notes

Explain

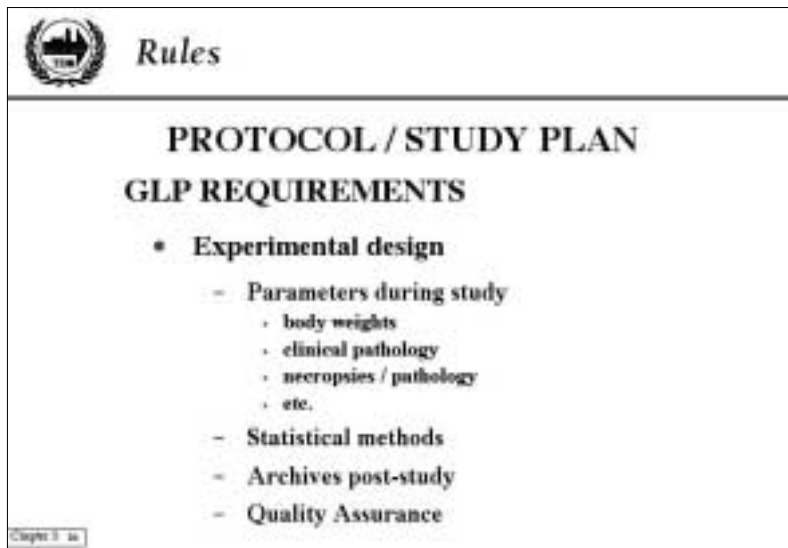
This slide and the next give some of the points that would normally be mentioned in a typical animal toxicity study.

The experimental design depends on the kind of study being performed. The items listed are given as examples only. The participants will be faced with the detailed examination of a protocol later in the course.

Points which could be commented on include:

- The preparation of the dose mix will be covered in more detail in the SOPs for the study and need not be given in detail in the protocol.
- It is usual in a long-term toxicology study to perform analytical work on the dose mix (QC) at the start of the study, often in the first week, to make sure that the desired concentrations are being correctly prepared, and at the end of the study to ensure that there has been no deviation of preparation during the study. For very long studies, it is customary to do QC every three months at least.
- The method of randomization of animals is important since it reduces group-to-group variability. You should also distribute the animals in the cages/racks in a way which reduces the effect of environmental variables.

3. Rules



The slide features a header with a circular logo on the left and the word "Rules" on the right. Below the header, the text "PROTOCOL / STUDY PLAN" and "GLP REQUIREMENTS" is centered. A bulleted list follows, starting with "Experimental design" and containing four sub-points: "Parameters during study" (with further sub-points: "body weights", "clinical pathology", "necropsies / pathology", "etc."), "Statistical methods", "Archives post-study", and "Quality Assurance". A small box in the bottom left corner of the slide content area contains the text "Chapter 3.1a".

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 3.1a

Instructor's notes

Explain

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

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

Mention where the archives of the study will be kept.

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

Activity

After this slide, participants should all read sections 8.1 and 8.2 of the OECD regulations where the full list of GLP protocol requirements are. If the instructor prefers, this reading can be done immediately prior to the workshop on protocols.

3. Rules

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

Instructor's notes


Explain

As stated earlier, the study director signs and dates the protocol to approve it. In some countries, the protocol must also be signed by management. It is also often a requirement that the sponsor signs the protocol to indicate his approval.

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

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

3. Rules

 *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 22

Instructor's notes

Explain

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

The amendment must be signed by the study director. The amendment will be reviewed, but as some of the changes need to be immediate, it is accepted that the review may be retrospective.

Under no circumstances must amendments be issued for "unplanned changes" which are deviations to the study plan. These are noted in the study file and reported in the final report.

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 3.21

113


Instructor's notes

Explain

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

All personnel having received the original protocol should get all the amendments even if they are not directly concerned.

3. Rules

**Rules**

PROTOCOL / STUDY PLAN

PROTOCOL CIRCULATION LIST

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

Chapter 3 114

Instructor's notes

Explain

To ensure that all staff concerned receive the protocol and to provide traceability of that distribution, most laboratories implement a protocol distribution list like the one in this example. Staff sign to indicate that they have received the protocol.

The same kind of distribution/receipt form is used for the amendments to protocols.

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		
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	
Food consumption				X								X																						X		
Body weights				X		X		X			X		X		X																				X	
Ophthalmoscopy		X																																		X
Haematology																																				X
Blood chemistry																																				X
Urinalysis																																			X	
Necropsy																																				X

Page 3 of 21

Instructor's notes

Explain

This document is not a GLP requirement but is a very useful document for the persons actually performing the operations that are detailed in the protocol or study plan shown here. It is quite simply a time plan showing, day by day, what phase of the study is to be performed.

3. Rules



Rules


RULES

Part II

Standard Operating Procedures

Chapter 3 22

3. Rules

*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 22

117

Instructor's notes


Explain

Standard Operating Procedures (SOPs) describe in detail the routine operations of your laboratory. They are a necessary addition to the protocol if you wish to exactly repeat a study.

In most cases you will find SOPs reply to the following questions:

- Who performs the operation?
- What is the operation being performed?
- When is it being performed?
- Where is it done?
- How is it being done?

3. Rules

 *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


Instructor's notes

Explain

This famous quote from one of the “gurus” of the Total Quality Movement illustrates the importance given to the idea that SOPs standardize routine procedures.

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

3. Rules

**Rules**

STANDARD OPERATING PROCEDURES

For successful SOP implementation:

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

Chapter 3 22

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Instructor's notes


Explain

It is pointless trying to implement GLP if there is no management support. As SOPs are an integral part of GLP, they too must have full management support. Management must be convinced of the advantages that a good SOP system can bring to the institution.

SOPs should be used as a tool for education and training of staff. People who perform a technique for a GLP study must do so in compliance with the SOP. There must be good correspondence between what the SOP says and what actually happens on the ground.

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

3. Rules

 *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 3.1a

Instructor's notes

Explain

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


You will need to write SOPs to cover all the technical aspects of your studies. These are probably the most important SOPs.

But in addition, you will need SOPs on some administrative aspects of your activities, especially where the activity impinges on the conduct of the study (e.g. SOP on the transfer of data to the archives, SOP on the management of documents such as SOPs), and you will need to have SOPs covering aspects of safety and hygiene (e.g. SOP on the handling of dangerous chemicals, SOP on the elimination of waste, SOP on the protective clothing needed for entry into an animal room).

It is pointless having SOPs which are not easy to understand or easy to read. This is one reason why an independent, but informed, person from Quality Assurance will review the SOP before it is distributed for use.

The SOP must be followed, otherwise there is increased test-to-test variability, no traceability and no possibility to audit. This is one reason why quality assurance will inspect certain activities of the study to ensure that SOPs are complied with.

3. Rules

**Rules**

STANDARD OPERATING PROCEDURES

SYSTEM CHARACTERISTICS

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

Chapter 3 21

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Instructor's notes


Explain

To facilitate the management of SOPs, particularly updating, it is a good idea to nominate a person responsible for each SOP. This person ensures that the SOP corresponds to the needs of the laboratory, that it is kept up to date, and that persons using it are trained to use it.

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

A central organization dealing with the management of SOPs is helpful, but not mandatory – each department or unit can control their own SOPs – since this makes sure that the SOPs used on a site are harmonized. In some laboratories, the QAU undertakes this responsibility.

3. Rules

**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 3 122

Instructor's notes

Explain

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

3. Rules

*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

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Instructor's notes

Activity

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

Compare with the points in these next 2 slides.

3. Rules



Rules


STANDARD OPERATING PROCEDURES

BENEFITS FROM GOOD SOP SYSTEM

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

Chapter 3: 82

3. Rules



Rules

STANDARD OPERATING PROCEDURES

DEPARTMENT:		GROUP:	
TITLE: STANDARD OPERATING PROCEDURES			
(Writing, Reviewing, Approval, Distribution, Use and Modifications)			
N°: ABC/223.001		PAGE 1 OF 5	
Approval / Date:			
Author/Responsible		Management	Quality
<div></div>		<div></div>	<div></div>
Name		Name	Name
Signature		Signature	Signature
Date applicable:		Revision period:	
The following SOPs are cited in the text of this SOP ABC/110, CDE/420, ABC/224			


Graphs 3-01

Instructor's notes

Explain

- This is the kind of header you usually see on organizations' SOPs.
- There is no mandatory way for the presentation of SOPs.
- It is important to stipulate which is the date when the SOP came into force. This is necessary for traceability of operations.
- There is no need for the QAU to sign SOPs. But this is frequently done in Europe to signify that the SOP has been reviewed. It is not a way of under-writing the technical aspects of the SOP.
- If you can avoid it, it is recommended not to refer to other SOPs in the SOP concerned. This is because when you change the number of one you have to change the reference in the other.

3. Rules

 *Rules*

STANDARD OPERATING PROCEDURES
Sections in SOPs should be standardised e.g.

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

Chapter 3: 42

Instructor's notes

Explain

Most organizations have a standard approach as to how to deal with the various chapters that should be included in SOPs. This is one example.

4. CHARACTERIZATION

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.

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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



Test Item

CHARACTERIZATION

Part I

TEST ITEM

Chapter 4 - I

4. Characterization

Test Item

TEST ITEM

- **Bulk Test Item**
- **Preparation of dose-form**
- **Chemical analysis**

Chapter 4 2

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Instructor's notes


Explain

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

The trainer should ask the participants to suggest test items other than chemical substances that might be tested preclinically. However, most are chemical compounds and this example is the one chosen for consideration here.

The GLP regulations consider the above three topics related to the test items used in studies.

4. Characterization

 *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

Chapter 4.4

Instructor's notes

Explain


There is often confusion about whether or not good manufacturing practice (GMP) is needed for the production of batches used in GLP studies.

GMP is only required for clinical studies performed in man.

But authorities do require that you demonstrate that your test item is of a constant quality and fit for use.

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

4. Characterization

*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

Chapter 4

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Instructor's notes

Activity

Discuss with the participants the points they consider to be important for their studies with regard to the quality of the BULK or ACTIVE INGREDIENT.

What difficulties do they have when it comes to the characterization of the active ingredient?

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


Instructor's notes

Explain

GLP requires you to put procedures into place that guarantee that the dose-form is made up with the right test item, in the right concentration and in the same way each time.

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

4. Characterization

 *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

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Instructor's notes

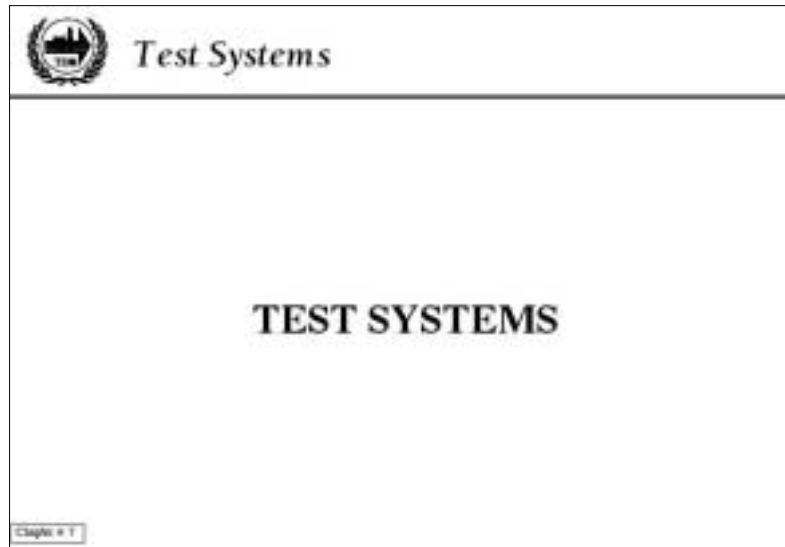
Explain

The analytical laboratory provides results that are used to demonstrate that the correct dose level of the correct test item has reached the test system.


Unless these results are reliable, the whole study is worthless.

This is why the GLP regulations require that these data be generated under GLP.

4. Characterization



4. Characterization



Test Systems

What are Test Systems ?

- Animals
- Bacteria
- Cells
- Organs
- Plants

or can also be

- Analytical equipment

Chapter 4.1

147

Instructor's notes


Explain

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

Activity

Here is a list of various test systems. Ask the participants to complete the list from their own studies.

4. Characterization

 *Test Systems*

TEST SYSTEMS : Animals

- GLP compliance
- Compliance with animal welfare legislation

Chapter 4.9

Instructor's notes


Explain

Because it is impossible to deal with all kinds of test systems, and because it is the most common situation, the case of animals is chosen here.

The way in which the test system is dealt with must comply with the GLP regulations and also with the national animal welfare rules.

You could be asked to show that you do respect welfare legislation during a GLP inspection.

4. Characterization

**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 18

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Instructor's notes

Explain

It is the responsibility of the study director to select the right animal for his/her study.

There are many reasons for choosing one type or strain of animal rather than another. These reasons may depend on the kind of things listed in this slide.

Remember that the quantity of animals put on a study, neither too few nor too many, is also a responsibility of the study director.

GLP requires you to explain why the particular test system has been chosen for the particular study in hand; this should be set out in the protocol.

4. Characterization




Test Systems

ANIMALS

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

Chapter 4.1.1

4. Characterization

**Test Systems**

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

151

Instructor's notes

Explain


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

Many organizations have separate units that keep track of environmental factors in the animal rooms. These data are often supplied to the study director when he/she is writing the final report for his/her study.

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

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

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


Instructor's notes

Explain

The items shown on this slide are some of the documents you will need to keep to show how the animals were assigned to groups. It is important to be able to demonstrate that no bias was introduced in the study by the way the animals are divided into groups and the way that they are caged and their location in the animal room.

Any animal eliminated from the groups for whatever reason must be accounted for and the reason for elimination recorded. It should be remembered that one of the reasons that GLP came into existence was the malpractice of replacing ill animals for healthy ones during an experiment. Inspectors are, therefore, very sensitive about this kind of issue.

4. Characterization

**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 14

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Instructor's notes

Activity

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


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

Explain

All data referring to animals should contain full animal identity.

Even though it is always necessary to identify animals at the moment of dosing, it is also good practice to have regular identity checks on the animals in a given room to make sure that there is no problem of identity.

4. Characterization

 **Test Systems**

ANIMALS - Acclimatization

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

Chapter 4 15

Instructor's notes


Explain

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

During the acclimatization period it is necessary to maintain full documentation on the procedures performed and on the identity of the animals.

Usually when the animals are ready for the study, the study room is prepared (cleaned, disinfected, supplied with feed etc.) these activities should also be recorded.

4. Characterization

 **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 14

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Instructor's notes

Explain

Animal receipt is an important phase in the activity of the laboratory.

Organizations must have SOPs covering this part of the laboratory activity as shown in this slide.

4. Characterization

 **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 9 17

Instructor's notes

Explain


It is important to build up a "partnership" relationship with the animal supplier.

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

In some countries the national QA society performs regular audits.

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

4. Characterization

**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

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Instructor's notes

Explain

When the study director writes the final report he/she must take into account the environmental conditions, particularly deviations from target values, that the animals have been kept in.

Deviations from specifications should be reported and in some cases commented on in the study report.

CHAPTER 4 • PERSONAL NOTES

5. DOCUMENTATION

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:

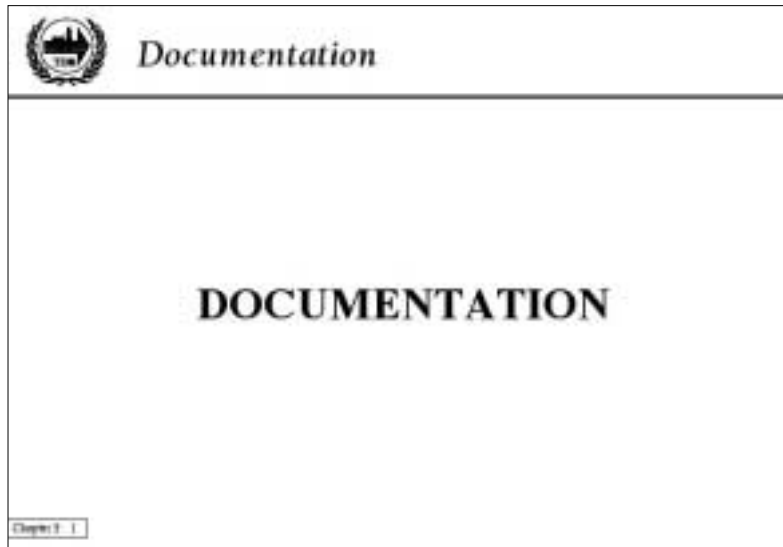
- Project or study number.
- Test article/reference article and lot numbers for bulk and formulated material, if appropriate (tie-in with product accountability records).
- Protocol number (may be same as study number).
- Testing facility.
- Key word retrieval from study title (route, species, etc.).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

Retrieval from Archives

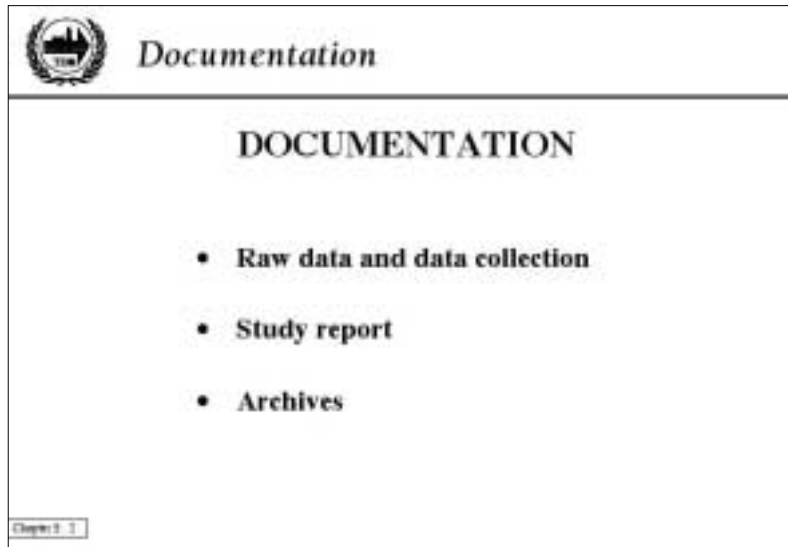
Once an item has become an official central archives holding, the original should be subject to restricted access. It should be examined in situ with verbal authorization but only within the central archives area, and in the presence of the archivist. Photocopies should be provided upon request.

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



5. Documentation



Instructor's notes

Explain

This section deals with raw data collection.

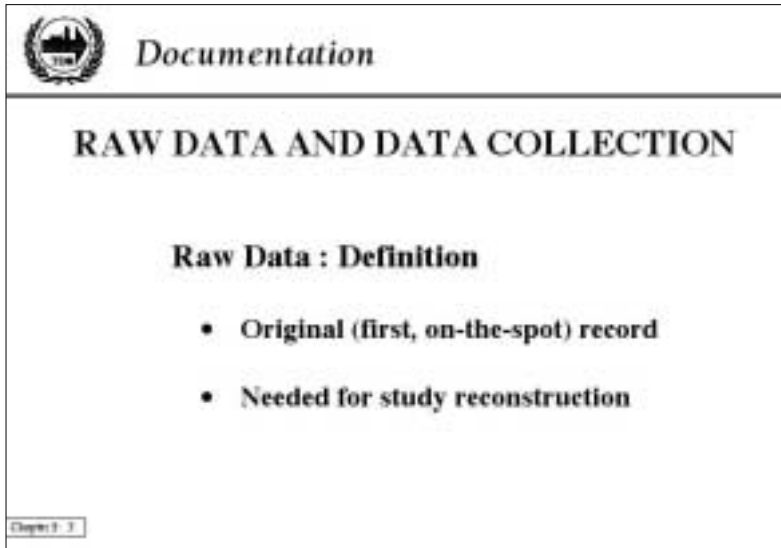
Stress the importance of data as being "WHAT IS LEFT AT THE END OF THE STUDY". In a sense it is the only tangible result of the scientific inquiry.

The data will be reported in a FINAL REPORT.

The FINAL REPORT and the DATA will be removed to the archives for safe-keeping at the end of the study.

For some long-term studies it is wise to archive bit-by-bit during the course of the study.

5. Documentation



The slide features a logo in the top left corner, a title 'Documentation' in a serif font, and a subtitle 'RAW DATA AND DATA COLLECTION' in a bold, all-caps serif font. Below the subtitle, the text 'Raw Data : Definition' is followed by a bulleted list. A small box in the bottom left corner contains the text 'Chapter 3 3'.

Documentation

RAW DATA AND DATA COLLECTION

Raw Data : Definition

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

Chapter 3 3

169

Instructor's notes

Explain


The GLP definition of RAW DATA is two-fold, as shown in this slide.

It is useful to explain the way in which raw data are defined by using the image of a set of individual values recorded from a series of weights, and the mean value.

Each individual weight is a raw datum, needed to reconstruct the weighing series.

The mean is not a raw datum (though important) ; it can be regenerated by a simple calculation.

5. Documentation



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 5 4

Instructor's notes


Explain

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

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

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

5. Documentation



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

171

Instructor's notes

Activity

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

You can use the analogy of the series of weights to underline the fact that one piece of lost data (a weight) can never be regenerated.


Explain

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

This is called auditability.

Having data which can survive an audit gives the study credibility and makes the acceptance of data by other scientists or authorities much easier. The reputation of your organization depends in great part on the auditability of your data.

5. Documentation

**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 5: 6

Instructor's notes

Explain

The collected data, on data sheets or in a laboratory notebook, should clearly identify **WHAT** the process was and that it was performed according to plans (protocol) and procedures (SOPs).

5. Documentation

**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 5 T

173


Instructor's notes

Explain

Not all procedures will go exactly according to plan. All deviations from the planned method should be recorded carefully in the raw data.

The impact of deviations must be assessed by the study director and will be commented on in the study report.

5. Documentation

**Documentation**

RAW DATA AND DATA COLLECTION

WHEN

Data should show:

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

Chapter 5 8


Instructor's notes

Explain

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

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

5. Documentation

*Documentation*

RAW DATA AND DATA COLLECTION

WHO

Data should show:

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

Chapter 5.5


175

Instructor's notes

Explain

Everyone who is concerned with the collection, recording or verification of the data should be identified and the dates (at least) of their interventions, and what they did, should also be recorded.

5. Documentation

**Documentation**

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 5 ID

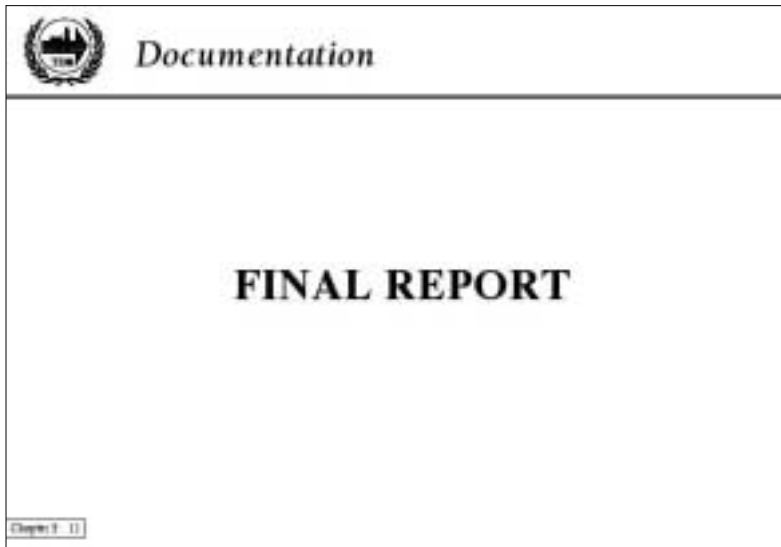
Instructor's notes

Explain

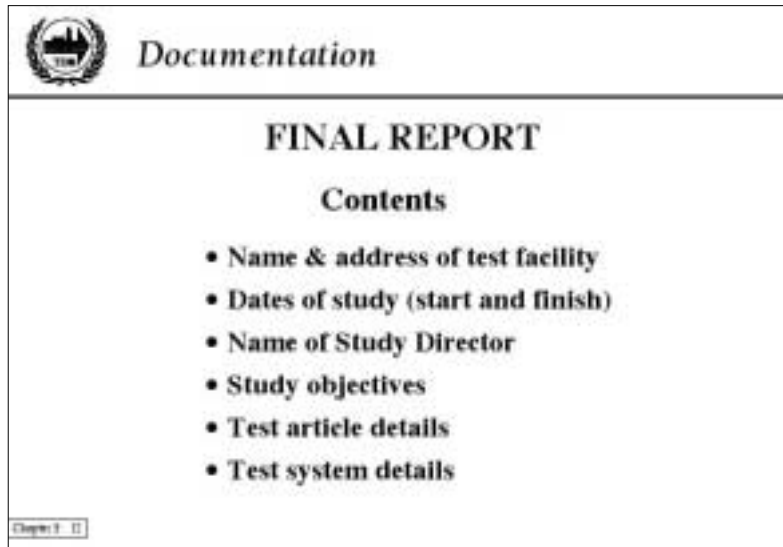
These are the general rules for data collection.

Never use pencil, never use “white out”, never correct data if you do not explain why, and sign and date every change. This correction method applies also to computerized data. It is called leaving an AUDIT TRAIL.

5. Documentation



5. Documentation



Instructor's notes

Activity


Ask the participants to look at the GLP regulations concerning the requirements for final reports (section 9.2 of the OECD GLP Principles, page 28).

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

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

Discuss what should be considered as the "Experimental start and completion dates".

5. Documentation



Documentation

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 3 13

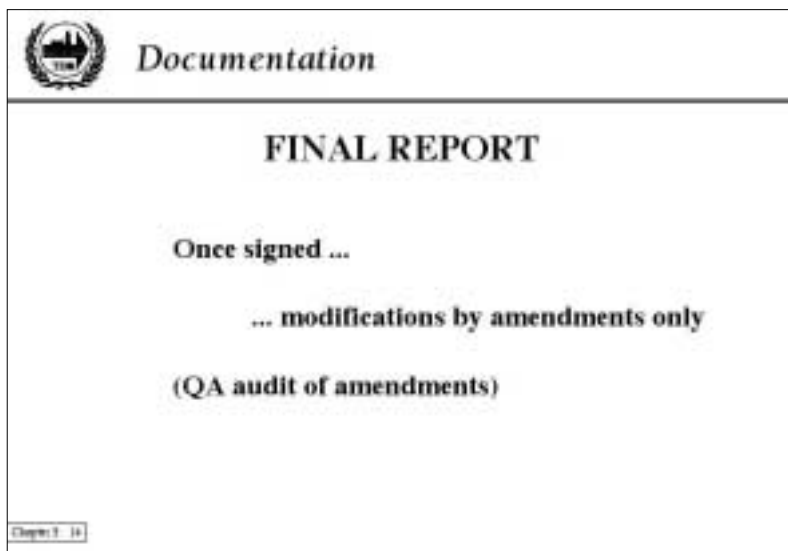
179

Instructor's notes

Activity

Activity as above.

5. Documentation



Instructor's notes

Explain

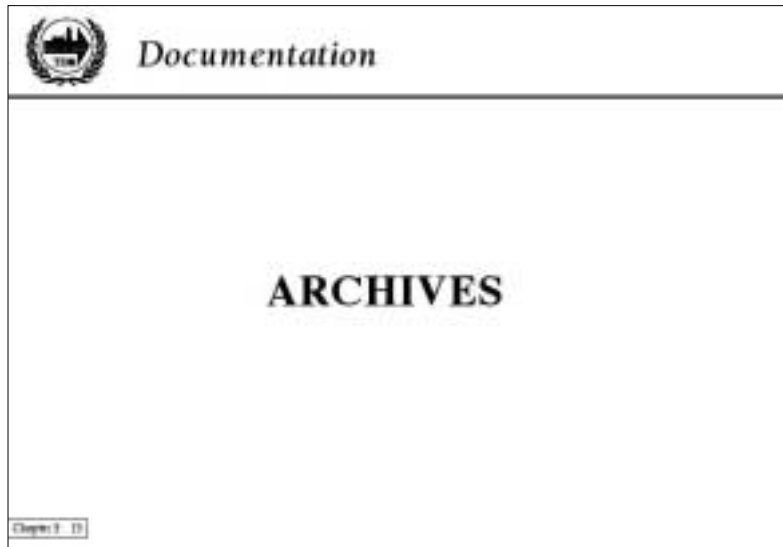
Once a final report has been signed by the study director, it cannot be changed. If there is a need to correct or amplify the report, this has to be done by issuing a separate amendment to the report.

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


Activity

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

5. Documentation



5. Documentation



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

182

Instructor's notes


Explain

All that is left at the end of the study is needed to demonstrate the validity and traceability of the scientific results. This is why the archives are so important. The kind of things that you would find in the archives are listed here, but there may be other things to archive, depending on the type of study performed.

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

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

5. Documentation

**Documentation**

ARCHIVES : Function

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

Chapter 5 17


183

Instructor's notes

Explain

The function of the archive is to store important items over a long period under secure conditions.

5. Documentation



Documentation

ARCHIVES : Submission form

DEPT./GROUP :
PROJECT :
STUDY N° :

Holding number :

QUANTITY	DESCRIPTION	COMMENTS
Date	Signature submitter	Signature archivist

Chapter 5 10


Instructor's notes

Explain

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

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

5. Documentation

 Documentation		
ARCHIVES : History		
DATE	EVENT	AUTHORIZATIONS

Chapter 3 19

185


Instructor's notes

Explain

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

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

5. Documentation



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 8 30

Instructor's notes

Explain

The archived materials must be protected from interference (particularly unauthorized removal that will lead to loss) and from disasters like fire and flooding and also deliberate vandalism.

This is why entry to the archives should be restricted. You need an SOP to describe the conditions of entry (sign in and out) and a list of persons who are allowed access.

If possible, do not let anybody remove articles from the archives, allow them instead to consult the documents in the archives and if necessary give them a photocopy if they need to have the data with them.

5. Documentation

The logo of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals in Human Use (ICH) is located in the top left corner of the slide. It features a circular emblem with a building and the text "ICH" inside.

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 9 11

187

Instructor's notes


Explain

The GLP regulations require you to store archives under conditions which minimize possible damage and loss.

Activity

These are some of the conditions that might be applicable in the organizations where the participants work. You should discuss with the participants other possible archive conditions applicable in their studies.

5. Documentation



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 5 11

Instructor's notes

Explain

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

Most organizations use a combination of the criteria listed in this slide.

6. QUALITY ASSURANCE UNIT

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



195

Instructor's notes

Explain

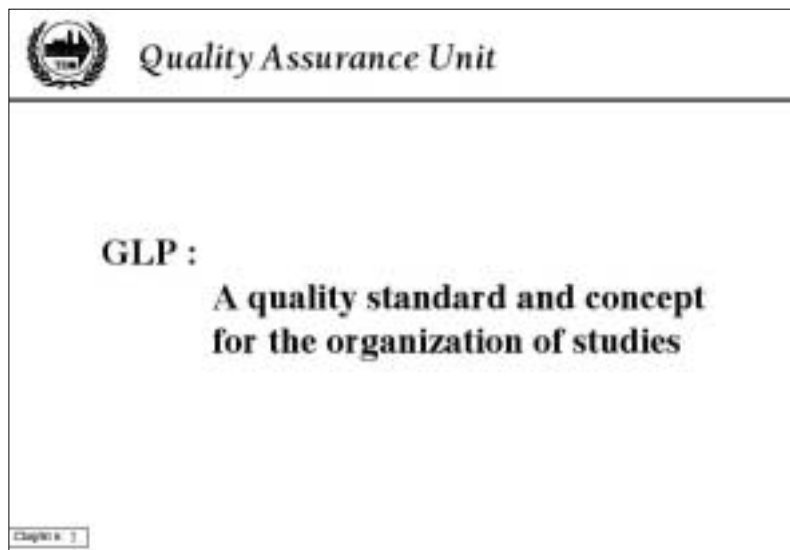
This is the last of the five Fundamental Points of GLP.

The Quality Assurance Unit (QAU) is the subject of an important chapter of GLP regulations and the OECD has published a consensus document to help the interpretation of the QAU section in the main text.

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

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

6. Quality Assurance Unit



Instructor's notes


Explain

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

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

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

6. Quality Assurance Unit

 *Quality Assurance Unit*

GLP :
Define conditions under which studies are:

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

Chapter 6 3

197


Instructor's notes

Explain

GLP is concerned with the organization of studies and, in particular, the way in which they are:

- PLANNED – This is why the protocol is important
- PERFORMED – This is why respecting SOPs is important
- RECORDED – This is why GLP gives such importance to raw data
- REPORTED – This is why the study director is requested to make a final report including his scientific judgement
- MONITORED – Continuous monitoring of the study is done by the study director and his team, and also by the QAU

6. Quality Assurance Unit

**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

Instructor's notes

Activity

Read with the participants the section on “Qualifications of QA personnel” from the OECD Consensus document “Quality Assurance and GLP” page 7. Discuss with the group.

Explain


The GLP regulations require that the QAU has a documented programme. This means that the QAU must have its own SOPs on how it operates, and must record what it does.

QAU personnel must be familiar with the studies they are auditing. Note that the GLP regulations do not require QAU personnel to be scientific experts in these studies, the expert is the study director. QAU personnel should, however, be experts in their own field, which is GLP, quality and organisational issues.

QAU personnel must be independent of the study personnel. They report directly to the facility management, never to the study staff. This allows them to be as objective as possible during audits and inspections.

The QAU must have a copy of the Master Schedule. They need this to plan their own inspection/audit programmes.

6. Quality Assurance Unit

**Quality Assurance Unit**

QA RESPONSIBILITIES (from GLP)

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

Chapter 6 3

199

Instructor's notes

Activity

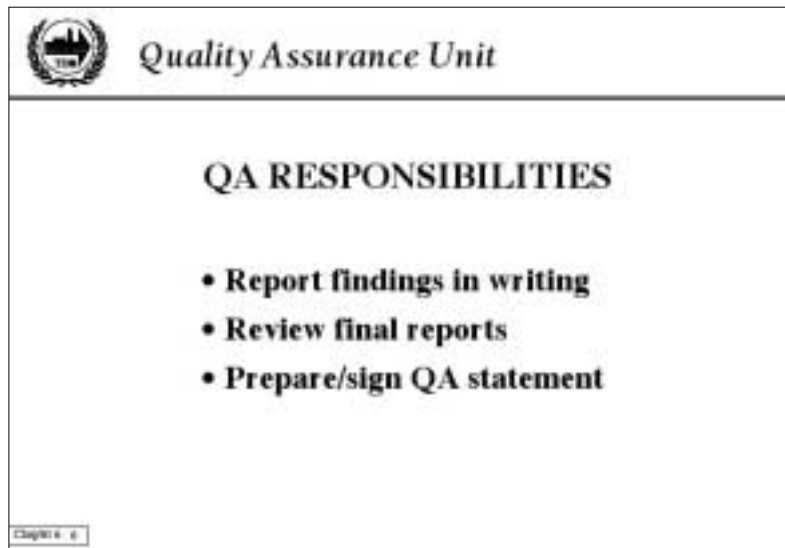
Ask all the participants to read Section 2 of the OECD GLG Principles.
What follows highlights some of the aspects that are detailed in this section.

Explain

The GLP Principles require QAU to check that all personnel have protocols and SOPs available for their work and that these documents are followed during the performance of their work.

This is achieved by audit or inspection. It is this programme of audits/inspection that should be defined in the QAU SOPs.

6. Quality Assurance Unit



Instructor's notes

Explain


When the QAU performs an audit/inspection it must be recorded in writing.

Any findings resulting from the investigation must be reported to the appropriate person in management and the study director if the finding is about a specific study.

QAU responsibilities with respect to the final report are to audit it against raw data and make sure that the results in the report represent exactly the raw data.

QAU will add a statement to the study report detailing the dates and the nature of the investigations performed during the study.

6. Quality Assurance Unit

**Quality Assurance Unit**

QA RESPONSIBILITIES

- **Review study plan**
- **Review SOPs**

Chapter 1

201


Instructor's notes

Explain

Although the OECD GLP Principles clearly state that the QAU must verify (review) the protocol, the same is not clearly stated for SOPs.

However, the OECD Consensus document on QAU responsibilities recommends this.

6. Quality Assurance Unit

**Quality Assurance Unit**

QA INSPECTION / AUDIT

3 Types:

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

Chapter 6


Instructor's notes

Explain

The OECD GLP Principles recommend that the QAU performs three types of inspections/audit.

These are explained in the following slides.

6. Quality Assurance Unit

 **Quality Assurance Unit**

QA INSPECTION / AUDIT

Study-based

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

Chapter 6 5

Instructor's notes

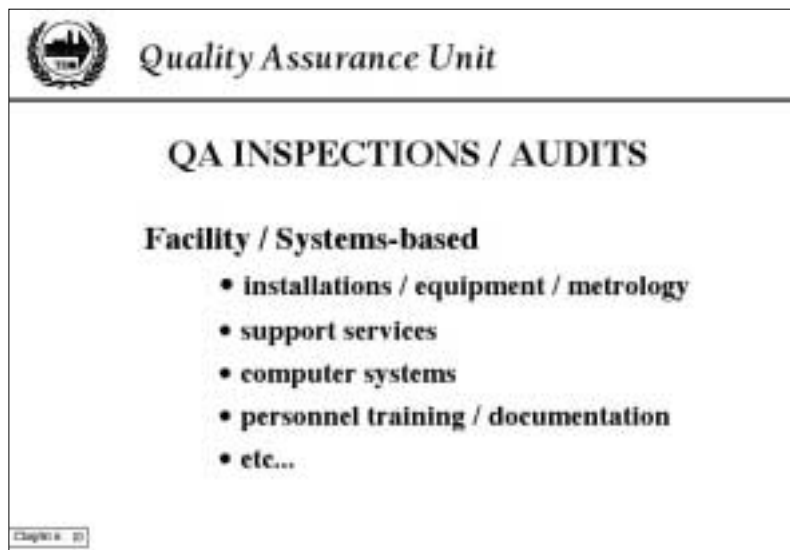
Explain

Study-based inspections are those that investigate specific studies.

They are performed on the protocol, the phases of the study that are in process or on going, and on the final report.

Typically, the QAU identifies important study phases known as critical phases, which are then inspected during the actual performance of operations by study staff.

6. Quality Assurance Unit



Instructor's notes

Explain


Facility-based inspections cover wider aspects of the laboratory's operations than those relating to a single study.

The slide shows some examples of the type of facility inspections that QAU could do within a laboratory.

Activity

Read the definition of facility inspections, in the OECD consensus document "Quality Assurance and GLP": Section on QA inspections, page 8.

6. Quality Assurance Unit

**Quality Assurance Unit**

QA INSPECTIONS / AUDITS

Process-based

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

Chapter 6 11

205

Instructor's notes

Activity

Read to participants the paragraph in the OECD consensus document "Quality Assurance and GLP" relating to Process inspections, and explain what it means. Section "QA inspections" page 8.

Examples of process-based inspections are given in this slide.

6. Quality Assurance Unit



Instructor's notes

Explain

The QAU also performs inspections of important suppliers (like suppliers of animals) and work contracted out to a third party.

6. Quality Assurance Unit

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

Chapter 6 19

Instructor's notes


Explain

This is an example of the kind of report the QAU will make to management and the study director.

What is important is that the QAU clearly explains the finding recorded during the inspection/audit and that the study director responds with a plan of action for correcting the problem found.

Of course the study director may not agree with the QAU finding, in which case, he/she should say so here.

6. Quality Assurance Unit

**Quality Assurance Unit**

QUALITY ASSURANCE STATEMENT

- Dates of inspections
- Dates of findings to Study Director & Management Plus
- Phases audited
- Confirmation that report reflects methods used and data generated
- Any exceptions
- Sign only if GLP compliance statement from Study
- Director is considered justifiable and all corrective actions completed

Chapter 16

Instructor's notes

Activity

Read the section on “Audits of data and final reports” in the consensus document (page 9) and the section on “The QA statement” (page 10).

Discuss the points raised in these sections.

This slide summarizes what the requirements are with respect to the QA statement.

It is a good idea here to reiterate the difference between :

1. the QA statement from the QAU and
2. the GLP compliance statement from the study director.

Both of these appear in the final report.

7. WORKSHOPS – STUDY PLANS / PROTOCOLS

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.

FOR THE INSTRUCTOR

You have at your disposal two different study plans or protocols (see Appendices 1 and 2). These should not be provided to the participants before the start of this workshop.

You should deal with each study plan separately so that there are two different workshops, one after the other.

WORKSHOP 1

Allow about 2 hours for the work in groups and
15-20 minutes for each group to report back

This workshop uses the study plan entitled:

“Protocol EEC 31

Study: 461 0B

A 13-week intravenous toxicity study in the rat

Study number: 13/001”

Before setting the task for the participants, show them an Ishikawa diagram and explain what this kind of diagram is used for.

To test their understanding of the Ishikawa process, draw up an Ishikawa diagram together (through a technique of brainstorming with the whole group), dealing with the factors involved when deciding upon a holiday abroad.

You may want to consider the following points:

- **Locality** / country / language / traditions / cuisine / ticket price
- **Time of year** / season / temperature / school holidays / interesting activities
- **Hotel** / price / quality / space / restaurant / menus / politeness of staff / cleanliness / room service
- **Tourist attractions** / sea and beach / mountains & countryside / monuments / interesting culture / art / folklore

You can only use the above as a guide. Each time you do this exercise it turns out differently; that is to be expected. The point of this is to get the participants to understand that the Ishikawa system can be used as a means of sorting out (categorizing) complicated issues into their component parts. The purists will say that this is not what Ishikawa was intended for in the first place. Tell them they are right, but it doesn't matter for the workshop you are about to do.

1. Make the participants work in small groups of 5-8.
2. Hand out the protocol.
3. The tasks are:

Task 1 – Review the study plan and comment upon anything that you find unacceptable for a GLP study. The participants should imagine that they are the managers of a new study director who has produced one of his first protocols and passed it on to the manager for detailed review. Ask the participants to concentrate on issues that are concerned with GLP, general organization and clarity, rather than the science behind the study. This is a classical 13-week rat toxicity study by the intravenous route.

They should elect a spokesperson to report back to the plenary session later on. They will need transparencies and pens to do this. Ask them to organize their finding page by page so that reporting back is easier to control and follow.

Task 2 – Draw up an Ishikawa diagram of the standard operating procedures (SOPs) they would expect to find in the laboratory in order to perform this kind of study. The Ishikawa is used so that SOPs dealing with the same phases of studies are grouped together.

Reporting back can either be done using a transparency or by using flip charts, whatever is available on site.

The group should appoint a spokesperson to report back to a plenary session of the participants when the task is completed.

The instructor should provide transparencies and pens so that the important points can be shown by overhead projection.

The instructor will regularly visit each group to answer any questions about the task and to monitor progress.

Allow one and a half to two hours for the group work. Some groups work faster than others, so stop all groups working, even if not all the groups have finished, before any one group gets bored.

WORKSHOP 2

Allow about 45 minutes for the work in groups and
15 minutes for each group to report back

This workshop uses the study plan entitled:

“Study Number 102 P 99

A 2-week toxicity study of Ro 10-1000/02 (Prodrug of 10-1000/01) via intravenous infusion in male common marmosets followed by a 4-week recovery period”

The protocol / study plan is supplied in a version which has parts missing. These blank parts are labelled A to N.

On the front sheet attached to the study plan, there are instructions concerning the sections A to N, which should be filled in by the participants.

REPORTING BACK ON WORKSHOPS

Workshop 1

Task 1 – The Review

During the plenary session, the spokespersons from each group present their groups comments.

Listen first to the comments on the protocol contents. The protocol is full of points that need clarification. The instructor should listen to the findings of each group, but to avoid repetition, the instructor should ask each group to report on separate parts, or take the comments page by page, a few pages per group. The instructor should comment on the points brought out by the groups and always attempt to underline the cardinal points of GLP. As a minimum the groups should find the major deficiencies in the protocol, as listed below. However they will find many, many minor deficiencies and will have many comments about clarity. These should all be discussed with the group, or explained by the instructor. Remember not to be negative about any of the comments. There is NO right way of writing a study plan. There are many ways of improving the present plan – it has been chosen so that discussion will be stimulated. The group should consult the OECD GLP Principles where there is a list of what all study plans must contain as a minimum for compliance. The instructor should point this out to the groups during the feedback session, but not before the workshop has started.

Major Deficiencies

1. **Page 1 of 16**

The numbers used on this page are inconsistent with the rest of the report. The test item is wrongly identified.

2. **Page 2 of 16**

Same problems with the numbers identifying the study and test item.
Need definition by job title of Mr Crown and Arthur Sixpence.

3. **Page 3 of 16**

Expiry date of test item is BEFORE the end of the study!
Stability, expiry date and batch number of vehicle not provided.
This is NOT a suspension... i.v. route!

4. **Page 4 of 16**

The species and strain of the animal used should be justified.

5. **Page 6 of 16**

The route of administration should be justified.

6. **Page 9 of 16**

Professor C Dracula should be identified as a principal investigator.

7. **Page 12 of 16**

Spleen is not listed as an organ to be preserved and cut though it is a target organ and is listed as an organ to collect.

8. Page 13 of 16

Do not need reference to GLP regulations other than the OECD Principles.

9. Page 14 of 16

How long will blood and bone marrow smears be kept?

Remember that this is ONLY the list of the glaringly obvious errors. The participants will have lots of other things to comment on.

Task 2 – The Ishikawa Diagrams

When the diagrams are shown, let the spokespersons explain them as fully as they wish. The instructor should ask questions about them but not make any negative comments.

The point of this exercise is to prime the situation in preparation for the presentations concerning SOPs.

What the participants will realize is that the Ishikawa diagram can be used as a means of planning what SOPs need to be written with reference to a particular study. It is also a good method for deciding which category SOPs fit into. Many organizations use a suffix to SOPs as a first part of the identifier for the SOP.

Workshop 2

After the groups have reconvened, the instructor should ask representatives of each group to report on what they think would be satisfactory texts for the blanks A to N.

The instructor should comment on all the suggestions, bringing out the important points in GLP terms.

A complete protocol, with parts A to N filled in, is available to the instructor. This complete study plan is provided to the participants at the end of the feedback plenary session.

8. WORKSHOP – STANDARD OPERATING PROCEDURES

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. (See Appendix 4.)

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.

FOR THE INSTRUCTOR

Introduction to the Workshop

You have at your disposal two different types of flow chart. These should be shown to the participants and commented on, but do not take more than 15 minutes to do this. The flowcharts can be distributed to the participants, but underline the fact that they are *just examples* of the different types of flowcharts that one sees habitually (see Appendix 3):

- The first is a structured chart showing the major steps in the production of a report. Each major step is subdivided into its constituent parts.
- The second is a “question and answer” flowchart. This one deals with the arrival and receipt of stock at a factory site.

Show the flowcharts and comment upon the usefulness of each. ***The most important point is that the flowcharts replace what would otherwise be a long conversation with someone or a long descriptive text.***

Distribute to each participant a copy of each of the six different standard operating procedures (SOPs) (see Appendix 4). These SOPs are from the same research centre but written by a variety of departments. They all deal with the same kind of problem, that of waste disposal.

Tell the participants that these SOPs reflect a real life situation where a manager was asked to help sort out the problem of waste disposal because the staff responsible for the collection and disposal of waste found the SOPs difficult or impossible to use.

The Task

Divide the participants into groups. Try not to have more than six people per group. The groups should be provided a space to work in which is relatively free of interference from the other groups.

Tell the groups that their workshop tasks are as follows:

- Read the SOPs and note any criticisms they have of the way the SOPs have been written. Comments should be made page by page to simplify reporting back later on.
- From the information contained in the SOPs, construct a single flowchart of waste disposal at this research centre.
- Make recommendations to improve the situation.

The group should appoint a spokesperson to report back to a plenary session of the participants when the task is completed.

The instructor should provide transparencies and pens so that the flowcharts can be shown by overhead projection.

The instructor will regularly visit each group to answer any questions about the task and to monitor progress.

Allow two hours for the group work. Some groups work faster than others so stop all groups working, even if not all the groups have finished, before any one group gets bored.

Reporting

During the plenary session, the spokespersons from each group present their groups' comments. **Allow 15-20 minutes for each spokesperson to present their group's conclusions.**

1. Listen first to the comments on the SOP contents. The SOPs are full of mistakes, they lack coherence, have missing parts, etc. The instructor should listen to the findings of each group, but to avoid repetition, should ask each group to report on separate parts, or take the comments page by page, a few pages per group. The instructor should comment on the points brought out by the groups and always attempt to underline the cardinal points of GLP. It is likely that the general comments will deal with the necessity to separate out different subjects and make separate SOPs for them. These SOPs cover two main areas: waste disposal and medical considerations. They are best dealt with in separate SOPs.
2. When the flowcharts are shown, let the spokespersons explain them as fully as they wish. The instructor should ask questions about the charts but not make any negative comments. The points that are important to develop during the discussion are:
 - a) before writing an SOP it is useful to draw up a flowchart of the procedure because this will help you write the SOP in a coherent manner.
 - b) a good flowchart can replace a wordy SOP; you do not always need text in an SOP.
 - c) flowcharting is a useful tool when reviewing SOPs.

3. The spokesperson should also present what could be done to improve the situation. Most comments will probably be based on the need to get the authors of the individual SOPs together so that they can rework their six SOPs into one or two. The importance of a transverse review of SOPs (usually by QA) should underlined.

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.

Instructor's notes

This workshop session requires groups of participants to discuss actual case studies that may well occur in GLP studies.

As before, the instructor should designate groups, and after each group has discussed each case study, the groups should report back in a plenary session where the ideas of everyone can be aired. So, remind the groups to choose a spokesperson for each case study and provide transparencies and pens.

You should allow 90 minutes for the groups to decide on their responses to the cases, and reporting back will take another hour.

Once again, the important point to underline is that there are no “absolute answers” just ways of approaching these issues, based on the GLP Principles and common sense.

When the groups report back, the instructor should constantly encourage discussion by posing relevant questions and give his/her own point of view based on a complete understanding of GLP.

To help the instructor, notes for discussion have been added after each case study.

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?

Discussion ideas

Is it possible that the analytical results are not correct, that samples have been contaminated in the analytical laboratory? Is the analytical laboratory GLP compliant?

How bad is the exposure of control animals? The study director should decide and document the impact on the study. If the study is now invalid, who has to be informed?

Is it possible to trace from the raw data the source of exposure? Have the animals been wrongly dosed or has there been a mistake when making up the dosing solutions or in labelling?

Can an individual(s) be identified as responsible; in which case there may well be a need for additional training? Review of the whole training programme may be required.

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?

Discussion ideas

How extreme are the variations? As it is a long-term study, there may be no impact on study validity. The study director must record his/her view of the impact on the study.

The final study report must contain a record of this deviation from specifications.

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?

Discussion ideas

How extreme are the results? The study director must record his/her view of the impact on the study.

It is essential to try and find out when and where the contamination started and why, but this may not be possible. It is possible that the contamination has affected all the other studies where the animals drink the same water, in which case all the studies will have to be evaluated for the effect that this contamination has had.

Possible actions include: disinfecting the system; performing more monitoring of the system to ensure that the contamination has been eliminated; monitoring on a schedule that is more frequent than three monthly until you are confident that the contamination has been completely eliminated.

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?

Discussion ideas

Is the university laboratory performing to GLP compliance? If so, no problem.

If the university is not GLP compliant, the contract laboratory and the sponsor must decide whether or not the data are the pivotal part of the study. If so, then there could be an attempt to render the laboratory as GLP compliant for this assay in the short term, say in 3-6 months.

If making the laboratory GLP compliant is not a possibility, the university laboratory can still perform the assay, but the contract laboratory or the sponsor will have to monitor very closely the conduct of the assay. The university laboratory could use some of the contract laboratories SOPs for example, and the university laboratory could provide its raw data for verification to the contract laboratory QA group, etc.

The contract laboratory QA group could also inspect the university laboratory in an on-going phase.

The study director must state the non-GLP status of the university in the final report. The receiving authority could reject the study if it believes that the hormone assay was not sufficiently controlled by the contract laboratory or the sponsor, but this would depend on the importance of the data coming from the assay.

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?

Discussion ideas

The question that arises is whether or not it is legitimate for QA to interrupt the normal work of study staff. There will be different views on this point.

Remember that if the QA person says nothing, the study may be invalidated because of this possible error in manipulation. As a general rule it is worth calling in a member of staff superior to the technician to confirm that there is no mistake, or to confirm that there is a mistake.

QA should be regarded as helping in these situations, not as a hindrance to normal operations.

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?

Discussion ideas

Three weeks is probably too short to do a complete validation.

Try to write a validation protocol and show this to the inspector (if he requests it) and ask his opinion on its content. This will show that at least you have decided to validate and have started the process of validation.

Collect as much evidence from the past that the computer system has been performing correctly.

Be ready to describe to the inspector the systems you have in place for secured access to the system (passwords, access levels) if he asks for it. The same applies to the procedure you have for backing up and archiving data.

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”?

Discussion ideas

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You are lucky to be informed beforehand.

There is no way, in two weeks, of transforming a non-GLP laboratory into a GLP compliant laboratory.

What you can do is:

- Check that the organizational chart is up to date.
- Verify the exactness of personnel documentation.
- Make sure that any SOPs which are still being reviewed or revised pass quickly through the system and are available for the inspector.
- Make sure that the archives are in good order.
- Make sure that personnel are aware of the inspection. Brief them on how to behave with the inspector.
- Reserve a meeting room to receive the inspector.
- Clear up any obvious mess!
- Find out from him why he is coming. Is he/she coming for a general inspection of the facilities, for a specific compound and study(ies), or at the request of a foreign authority, etc.?

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?

Discussion ideas

During the weekends, persons are sometimes found to be performing work they have not been trained for. In this case, QA should determine whether or not the person has really been trained. It may be that the training record is incomplete.

The study director must be informed. He/she should determine whether there is an impact on the study.

QA would do well to inspect all the training records for all personnel working at weekends to find out whether this is a general problem or not.

If there is a general training issue this should be reported to management so that all necessary training can be undertaken.

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?

Discussion ideas

This is unfortunate, as you cannot ever change a final report.

The correction will have to be made by sending an amendment to all the people who received the original final report.

The amendment will contain all the new calculations and should also explain where in the original report these calculations supersede what has already been reported.

The study director must sign the amendment.

The amendment must be audited by QA to ensure its accuracy. QA must also provide a QA statement to accompany the report amendment.

This unfortunate incident underlines the importance of quality control which should be conducted by the study staff prior to the release of draft reports and the importance of a QA review prior to the release of the final report.

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?

Discussion ideas

This is very serious indeed as it could invalidate the study since we no longer have any reliable idea as to how much of the test item has been administered to the animals. It is not an infrequent problem, particularly at the start of studies.

You cannot stop the dogs rejecting material, but the study director must be aware of this, otherwise he/she will not be able to interpret the data correctly.

The SOP for dose administration should be reviewed. It may not indicate that the dogs must be watched carefully for a period after dosing.

The training of the technicians should be reviewed; it may be that they are not aware of their role in this case.

Some attempt should be made to find out if this was a “one-off” incident. Have there been records of this in the data during the study so far?

In the worst case scenario, it may be necessary to abandon the study and start again.

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?

Discussion ideas

This practice should be discouraged if the SOPs in question are not controlled copies. This is because it is possible that they will continue to use these “on the wall instructions” even after the real SOP has been revised.

It may be possible to replace the SOP on the wall with a proper, controlled version. If so do not forget to ensure that the distribution of this wall copy is recorded, as usual, in the management system. Remember it will have to be collected in, destroyed and replaced when any revisions are made to it.

9. SELF ASSESSMENT QUESTIONNAIRE

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 fetuses
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

A large, empty gray rectangular area intended for personal notes, occupying the majority of the page below the chapter title.

APPENDIX 1

WORKSHOP 1

Protocol: EEC 31

Study: 461 0B

A 13-Week intravenous toxicity study in the rat

Study number: 13/001

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Study Sponsor
SHILLING LABORATORIES
PENNY LANE
DOLLARVILLE
ENGLAND

THE CONTENT OF THIS PROTOCOL REPRESENTS OUR INTERPRETATION OF
THE STUDY OBJECTIVES AND THE REQUIREMENTS OF THE REGULATORY
GUIDELINES

ALL PROCEDURES DESCRIBED IN THIS PROTOCOL ARE THE SUBJECT OF
DETAILED DEPARTMENTAL STANDARD OPERATING PROCEDURES.

1. GENERAL POINTS

TEST ARTICLE: RM-0087

AIM OF THE STUDY: to determine the toxicity of the test article in the rat following daily intravenous administration for 13 weeks.

PROTOCOL: EEC 31 -IV

STUDY NUMBER: 13/001

GUIDELINES: this study will be conducted in general compliance with OECD 408 and directive 91/507/EEC.

STUDY SPONSOR:

SHILLING LABORATORIES

PENNY LANE

DOLLARVILLE

ENGLAND

Study Monitor: Mr. CROWN

TESTING FACILITY:

QUALITY SOCIETY

3, rue de l'Arnaque

75024 PARIS

FRANCE

Study Director: Joseph Bloggs Ph.D.

Deputy Study Director: Josephine Untelle B.Sc.

SCHEDULE OF THE STUDY (week beginning):

Start of treatment: 30 November 2000

Necropsy: 22 February 2001

Draft report: 26 June 2001

Signature Date

Issued by the study Director: Joseph Bloggs

Accepted by the study Sponsor: Arthur Sixpence

2. TEST ARTICLE INFORMATION

2.1 Test article

(See Sponsor documentation, if supplied)

- Denomination: RM-0087
- Supplier: THE MESNIL INSTITUTE
- Appearance: white powder
- Batch number: LS 01 004
- Purity: assumed to be 100 %
- Quantity required: 3 kg
- Storage: at room temperature, protected from light
- Expiry date: January 2001

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2.2 VEHICLE

- Denomination: saline for injection (0.9% NaCl)
- Supplier: Rolls-Royce Laboratory, 205 Peugeot Street, Austin, Oxford UK
- Batch number: to be defined in the report
- Quantity required: 10 liters
- Storage: at room temperature, refrigerated after opening

2.3 CONTROL ARTICLE

- Denomination: saline for injection
- Supplier: Rolls-Royce Laboratory, 205 Peugeot Street, Austin, Oxford UK

2.4 FORMULATION OF THE TEST ARTICLE

- Preparation: the test article will be prepared as a suspension in the vehicle at different concentrations.
- Storage: at room temperature (20°C - 25°C) and protected from light.
- Frequency of preparations: daily (to be confirmed); the suspensions will be administered to the animals within 4 hours of preparation

3. EXPERIMENTAL PROCEDURE

3.1 TEST SYSTEM AND ENVIRONMENT

3.1.1 SPECIES, STRAIN, SUPPLIER AND SPECIFICATIONS

- Species: Strain: rat abc: SPF-SD
- Supplier: DARWIN Laboratories, Claude Bernard Street, Newton, USA
- Number of animals in the study: 100 (50 males and 50 females)
- Age at initiation of treatment: 6 weeks
- Body weight range at initiation of treatment:
 - males: 170 to 220 g
 - females: 140 to 190 g

3.1.2 ENVIRONMENT AND HUSBANDRY

- Housing: one room for the study in an air-conditioned building (x barrier protected unit)
- Temperature: 22° (2°C (target range)
- Relative humidity: 55 (15% (target range)
- Air changes: minimum 15 air changes per hour
- Light cycle: 12 hours light (artificial) 12 hours dark
- Caging: animals housed singly in stainless steel mesh cages (260×350×200 mm)

3.1.3 DIET AND WATER

- Diet: pelleted complete diet *ad libitum* (Diet reference AU41, National Feeders Ltd., 999 Pudding Lane, Kellogsville, Belgium), sterilised by irradiation and analysed for the absence of chemical and bacteriological contaminants. Animals will be fasted overnight before blood and urine sampling and before necropsy.
- Water: filtered (0.2 µm) mains drinking water, *ad libitum* analysed twice a year for chemical and bacterial contaminants (Oasis Laboratory, 2 Dessert Lane, Bordeaux, France).

3.2 PRE-TREATMENT PROCEDURES

- Animal health procedure: clinical inspection for ill-health on arrival
- Acclimatisation period: 7 days minimum between animal arrival and start of treatment.
- Allocation to treatment group: performed during the acclimatization period, using a computer generated randomization programme.

Mean body weights of each group at randomization will not be statistically significantly different from each other (analysis of variance), each sex being considered separately.

- Identification of the animals: ear tattoo
- Identification numbers

Group number	Colour code	Males	Females
1	White	01 to 10	41 to 50
2	Green	11 to 20	51 to 60
3	Blue	21 to 30	61 to 70
4	Red	31 to 40	71 to 80

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- Identification of the cages: group-related coloured card with study number, group number, sex and animal.

3.3 TREATMENT

3.3.1 EXPERIMENTAL DESIGN

Group number	Group designation	Number of animals	
		Males	Females
1	White	01 to 10	41 to 50
2	Green	11 to 20	51 to 60
3	Blue	21 to 30	61 to 70
4	Red	31 to 40	71 to 80

Group number	Dose level (mg/kg/day)	Doses volume (ml/kg/day)	Dose concentration (mg/ml)
1	White	01 to 10	41 to 50
2	Green	11 to 20	51 to 60
3	Blue	21 to 30	61 to 70
4	Red	31 to 40	71 to 80

- Group 1 animals (control) will receive the control article.

- **Rationale for the dose selection:** based on previous toxicity studies with the test article.

3.3.2 ROUTE AND METHOD OF ADMINISTRATION

- Route: intravenous
- Method: intravenous injection using a microflex infusion set introduced into a tail vein
- Rate of dosing: 1 ml/minute
- Volume administered: 2 ml/kg/day. Individual dose volumes will be calculated weekly using the most recent body weight.

3.3.3 FREQUENCY AND DURATION OF TREATMENT

- Frequency: once daily
- Number of administration: 91 administrations minimum.

At the end of the treatment period, animals will be killed the day after the last administration.

3.4 EXAMINATIONS PERFORMED

3.4.1 MORBIDITY/MORTALITY

Animals observed twice daily, at the beginning and at the end of the working day. Moribund animals will be killed and submitted to necropsy. Animals found dead will be submitted to necropsy.

3.4.2 CLINICAL SIGNS

Animals observed daily, before and at least once after dosing to detect any clinical signs or reaction to treatment. A full clinical examination will be performed weekly.

3.4.3 BODY WEIGHT

Recorded weekly for each animal during the treatment period

3.4.4 FOOD CONSUMPTION

Recorded weekly for each animal during the treatment period.

3.4.5 OPHTHALMOLOGY

- Animals examined and frequency:
 - all animals pretest.

- all animals in groups 1 and 4 during week 13.

If there are treatment-related changes examination will be performed in groups 2 and 3.
(Amendment to protocol – cost not included.)

- Method: examination of adnexa, optic media and fundus will be performed by indirect ophthalmoscopy. If necessary an examination using a slit lamp will be performed in order to investigate abnormalities of the anterior segment of the eye; a mydriatic agent (Tropicamide) will be instilled into the eyes before examination.

3.4.6 CLINICAL PATHOLOGY

- Animals examined and frequency
 - all animals in groups 1 and 4 after 4 weeks of treatment
 - all animals in all groups after 13 weeks of treatment.
- Samples taken:
 - blood: withdrawn from the retro-orbital sinus following light ether anaesthesia of animals fasted overnight (about 16 hours). Samples will also be taken from moribund animals where possible.

Collection of samples (before the daily dosing where applicable):

Haematology parameters:

Prothrombin time and activated partial thromboplastin time: trisodium citrate,

Clinical chemistry parameters: no anticoagulant

Urine: collected in metabolism cages (about 16 hours) from animals deprived of food and water but receiving a gavage of 20 ml/kg of tap water before the beginning of the collection period.

- Parameters:

Haematology

Haemoglobin

Mean corpuscular haemoglobin

Mean corpuscular haemoglobin concentration

Packed cell volume

Red blood cell count

Mean corpuscular volume

Reticulocyte count (if signs of anaemia are observed)

Platelet count

Total white blood cell count

Differential white blood cell count

Bone marrow smears will be prepared at the scheduled necropsy for all animals.

They will be examined at the discretion of the Study Sponsor (amendment to protocol – reporting time and cost implications to be negotiated).

Examinations will be performed by

Professor C. Dracula

National Vampire School of Veterinary Medicine

1000 Corpuscule Road

Belfry

UK

Blood clinical chemistry

Sodium

Potassium

Calcium

Glucose

Blood urea nitrogen

Total cholesterol

Total bilirubin

Total Protein

Albumin

Globulin (calculated)

Albumin/Globulin ratioCreatinine

Alkaline phosphatase

Aspartate aminotransferase

Alanine aminotranferase

Urine analysis

Volume

Specific gravity

Appearance

Semi-quantitative estimation:

pH

protein

glucose

ketones
urobilinogen
bilirubin
blood
reducing substances

Microscopic examination of spun deposit

3.4.7 PATHOLOGY

3.4.7.1 NECROPSY

- After week 13, all designated animals will be necropsied in a random order
- Animals will be weighed before necropsy (except found dead/moribund animals)
- Animals will be killed by carbon dioxide inhalation and exsanguination

- All animals (including found dead/moribund animals) will be submitted to full necropsy procedures including an examination of:
 - the external surface
 - all orifices
 - the cranial cavity
 - the external surface of the brain and samples of the spinal cord (spinal cord will be examined at the time of tissue processing)
 - the thoracic and abdominal cavities and organs
 - the cervical tissues and organs
 - the carcass
 - the injection site

3.4.7.2 ORGAN WEIGHTS

The following organs will be weighed at scheduled necropsy for all animals (organs from found dead/moribund animals will not be weighed):

adrenals
brain
epididymides
heart
kidneys
liver
ovaries

pituitary
prostate
spleen
testes
thyroids

Paired organs will be weighed together (except if a difference in size is observed macroscopically). Organs will be weighed after dissection of fat and other contiguous tissues. Organ weights will be expressed as absolute values (g) and relative values (g per 100 g of body weight and g per g of brain weight).

3.4.7.3 ORGAN/TISSUE PRESERVATION AND HISTOPATHOLOGY

The following organs/tissues will be sampled for all animals:

adrenals
bone (sternum) with bone marrow
bone marrow smears (cf. section 3.4.6.)
bronchi (mainstream)
brain
caecum
colon
duodenum
epididymides
eyes
heart
ileum
injection site
jejunum
kidneys
liver
lungs
lymph node (submaxillary)
lymph node (mesenteric)
mammary gland
oesophagus
optic nerves
ovaries

pancreas
parathyroids
pituitary
prostate
salivary gland (submaxillary)
skin
spinal cord (cervical, thoracic, lumbar)
stomach
testes
thymus(where identified)
thyroids
trachea
urinary bladder
uterus (horn + cervix)
all gross lesions.

Fixatives

All organs/tissues sampled will be fixed and preserved in 10% neutral formalin with the following exceptions:

- bone marrow smears fixed in methanol
- eyes and optic nerves fixed and preserved in Davidson's fluid

Slide staining: haematoxylin and eosin (except bone marrow smears)

Histopathology

Histopathological examinations will be performed for all organs/tissues:

- for all animals found dead or killed moribund during the study (cost not included)
- for all animals in groups 1 (control) and 4 (high dose) killed after 13 weeks of treatment.

Liver, lungs and spleen will be examined in the animals from groups 2 and 3 killed after 13 weeks of treatment, each sex being considered separately.

In each group, histopathological examination will be performed for all gross lesions, except those for which the diagnosis is judged unnecessary for the outcome of the study by the pathologist.

4. DATA EVALUATION

Data from concurrent controls and historical data from control rats will be used to assess effects.

Statistical analysis will be performed where appropriate using the following currently accepted methods:

Levene's test for homogeneity of variance followed by parametric tests (ANOVA followed by Dunnett's t-test) or non parametric tests (Kruskal Wallis ANOVA followed by Wilcoxon rank sun test).

Non standard statistical analysis can be performed: such analysis could influence the reporting time and will result in additional cost.

5. QUALITY ASSURANCE

This study will be subjected to quality assurance procedures in compliance with:

- "OECD Principles of Good Laboratory Practice" concerning Mutual Acceptance of Data in the Assessment of Chemicals dated 12 May 1981 (C (81) 30 Final).
- "Good Laboratory Practice" described in the US Federal Register (Food and Drug Administration) dated 22 December 1978 with subsequent revisions, of which the last is dated 15 July 1991.
- "Good Laboratory Practice standards for Safety Studies on Drugs" described by the Japanese Minister of Health and Welfare dated "& March 1982 (Notification No 313) with subsequent revisions which the last is dated 5 October 1988 (Notification No 870)".

The protocol will be inspected. Specific procedures and data from this study will be inspected. Other relevant procedures and data are also inspected periodically. The final report will be reviewed to assure that it accurately describes the methods and procedures and that the results accurately reflect the raw data. Reports on these activities will be made to the Study Director and to Management.

6. REPORTS

Incidental reports

The Study Sponsor will be informed promptly of any significant findings at any time of the study.

Draft report

A complete draft report in English, audited by the Quality Assurance Unit and containing all procedures and results will be issued for discussion with the Study Sponsor (see Reports on next page).

Final Report

After reciprocal agreement the final report will be issued and 3 copies (bound and one unbound) in English sent to the Study Sponsor.

7. ARCHIVES

The following materials will be maintained in the archives of the testing facility for the periods indicated.

Description of material	Duration
Original protocol and (if applicable) amendment(s)	5 years
Raw data and final report	5 years
Labile specimens (blood urine)	Until acceptance of final report then disposed of
Wet tissues	2 years
Blood and bone marrow smears	
Blocks and histology slides	5 years
Test article (samples)	2 years

Duration of archiving starts after dispatch of the final report.
Once the period of archiving is over, at the request of the testing facility, the Study Sponsor can (cost not included) :

- ask to continue the archiving
- ask for the material to be returned
- ask for destruction of the material.

REPORTS

1. DRAFT REPORT

A complete draft report will be issued for the Study Sponsor's comments. The report will contain the following information:

- 1.1 The objectives and procedures stated in the approved protocol including any changes made to the original protocol;
- 1.2 The identity of the test/control articles (by name or code number) and their strength (quality/purity)
- 1.3 The test system: species, strain and sex of the animals used
- 1.4 Procedure for identification of the test system.
- 1.5 The dose levels used, the dosage regimen, route of administration and duration of treatment.
- 1.6 Any unforeseen circumstances which may have affected the quality or integrity of the study.
- 1.7 The report of the individual scientists involved in the study, e.g. pathologist
- 1.8 The location of all raw data and final report
- 1.9 The name and address of the testing facility, start and completion dates of the study.
- 1.10 The following items of data will be presented:
 - experimental design
 - analysis of dose formulations (if performed)
 - morbidity and mortality
 - clinical observations (toxic and pharmacological effects, condition and behaviour)
 - effects on body weight and food consumption

ophthalmology
laboratory findings
organ weights, absolute and relative value
macroscopic and microscopic pathological findings

2. FINAL REPORT

The final report will be issued following Quality Assurance Evaluation of the complete draft report. This report will include all the details described in section 1 above with the following additions:

- 2.1 The signature of the Study Director and other scientists involved in the study as authentication of the report.
- 2.2 A statement that the report has been subjected to Quality Assurance Evaluation.

APPENDIX 2

WORKSHOP 2 (A)

You have been provided with a partially written protocol for toxicity study of compound by the i.v. route to marmosets. Some sections are missing.

Please write suitable material to fill in the sections A to N of the subsequent protocol by answering the following questions:

A	What information would you give to describe the study objectives?
B	What would you write to complete this section on GLP compliance?
C	Suggest a reasonable study calendar.
D	What would you expect to find in this section on stability?
E	What would you expect to find in this section on “Confirmation of concentrations of the preparations”?
F	What would you expect to find in this section on “Confirmation of stability”?
G	What might be good justification for the choice of the route of administration?
H	How many animals would you put on acclimation?
I	How would you justify the selection of the study species?
J	What would be suitable parameters to follow during the period of acclimation?
K	Suggest animal numbers for this table.
L	Suggest a suitable sentence to cover peer reviews.
M	The urine analysis cannot be performed to GLP standard in this laboratory. Suggest a sentence to put in the protocol here.
N	Suggest a sentence to cover the requirements for archiving.

Study Number 102 P 99

A 2-WEEK TOXICITY STUDY OF Ro 10-1000/002 (PRODRUG OF 10-1000/001)
VIA INTRAVENOUS INFUSION IN MALE COMMON MARMOSETS
FOLLOWED BY A 4-WEEK RECOVERY PERIOD

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PROTOCOL

July, 1999

Health Investment Ltd.
Toxicology Department, Paradise City

I. STUDY TITLE

A 2-Week Toxicity Study of Ro 10-1000/002 (Prodrug of 10-1000/001) via Intravenous Infusion in Male Common Marmosets Followed by a 4-Week Recovery Period

II. **A:**

III. COMPLIANCE WITH GLP

B:

IV. TESTING FACILITY

Toxicology Department
Pharma Research, Nonclinical Development
Health Investment Ltd.
Paradise City

V. PERSONNEL ENGAGED IN THE STUDY

Management Director:	A. B., D.V.M., Ph.D.
Study Director:	B. B., D.V.M., Ph.D.
Study Director Deputy:	C. C., D.V.M., Ph.D. M.S.
Pathologist:	D. D., D.V.M., Ph.D.
Test Article Controller:	E. E., B.S.

VII. STUDY SCHEDULE

Date of Initiation of Study:	August 5, 1999
Date of Initiation of Acclimation:	C:
Date of Operation:	
Date of Initiation of Dosing:	
Date of End of Dosing:	

Date of End of Recovery period:
Date of Necropsy
At the End of the Dosing period:
At the End of the Recovery period:
Date of Presentation of Final Report:
Date of End of Study:

VIII. TEST AND CONTROL ARTICLES

A. Test Article

Chemical Name: Ro 10-1000/002 (prodrug of Ro 10-1000/001)
Supplier: Chemistry Department, Kilo laboratory, Health Investment Ltd.
Lot Number: G GP 0186 (6.25 mg/ml Ro 10-1000/001), G GP 0187 (12.5 mg/ml Ro 10-1000/001), G GP 0188 (31.25 mg/ml Ro 10-1000/001)
Purity: will be determined from each batch by the Principal Investigator (Pharmacy Department) and a certificate of analysis will be included in the Final Report.
Physical State: Amorphous solid
Stability: **D:**

Arrival Date of Test Article: August 11, 1999
Amount of Test Article: 30 vials per group
Storage Conditions: -80°C and protected from light
Storage Facility: Deep freezer in the test article control room of the test facility
Handling Instructions: Wear gloves, mask and cap, and protect the test article from light.

Disposal of Remaining**Test Article:**

All remaining test article will be discarded at the end of each infusion cycle.

B. Control**Chemical Name:**

Placebo to Ro 10-1000/002

Lot Number:

G GP 0185

Storage Conditions:

2-8°C and protected from light

Storage Facility:

The refrigeration room in the Test Article Depository of the test facility

C. Vehicle**Chemical Name:**

Reconstitution solution

Lot Number:

will be known prior to the initiation of the study and will be included in the Final Report.

Storage Conditions:

2-8°C and protected from light

Storage Facility:

The refrigeration room in the Test Article Depository of the test facility

IX. PREPARATION AND ADMINISTRATION OF TEST ARTICLE**Preparation Method:**

According to instructions by Pharmacy R&D, Health Investment Ltd., the test article will be dissolved in a reconstitution solution. Reconstituted solutions will be passed through a sterile filter prior to infusion.

Conversion Factor

1 g of Ro 10-1000/001 corresponds to 1.45 g of Ro 10-1000/002.

Confirmation of concentration of the preparations:

E:

Confirmation of stability
of the preparations:

F:

Administration Route:

Intravenous (infusion)

Justification for the
Administration Route:

G:

Administration Method:

The test article will be administered twice daily for 4 hours (with a 12-hour interval) into the Vena Cava (inferior) through a catheter inserted into the femoral vein. During the non-test article administration period, 0.9% NaCl will be administered.

Justification for the
Administration Method:

For accurate administration of the intended dose.

Administration Volume:
Administration Frequency:

2 mL/kg/h
Twice daily for 14 days
(i.e. total of 28 administrations)

Justification for the
Administration Frequency:

In accordance with the expected clinical administration frequency.

Initiation Time of the First
Test Article Administration:

09:00-10:00 (at a predetermined hour). Each individual dosing time will be recorded.

X. STUDY ANIMALS

Species:	Common marmosets
Sex:	Male
Body Weight:	250-400 g (at the initiation of acclimation)
Age:	At least 12 months old (at the initiation of dosing)
Name and Address of Supplier:	Happy Primates Inc, Banana Republic
Date of Receipt of Animals:	April 24, 1998, October 29, 1998 and April 23, 1999

Number of Animals for Acclimation: **H:**

253

Number of Animals for Study: 15

Justification for Selection of the Study Species: **I:**

XI. MAINTENANCE CONDITIONS

Room Number:	Marmoset Facility, room no. 44
Temperature:	$28 \pm 2^{\circ}\text{C}$
Humidity:	$50 \pm 10\%$
Frequency of Ventilation:	15 times/hour
Illumination:	Artificial lighting for 12 hours (08:00 - 20:00)
Animal Cage and Size:	Stainless steel, 44 cm (D) \times 44 cm (W) \times 60 cm (H)
Number of Animals per Cage:	One animal per cage
Food:	Approximately 40 g of solid food (CMS-1, Happy Primates Inc, Banana Republic) will be provided to each animal daily at approximately 15:00,

and on the following day, uneaten food will be withdrawn at approximately 09:00. On the day before blood sampling and necropsy, uneaten food will be collected at approximately 17:00.

Water: Water will be available *ad libitum* from water bottles obtained as tap water from municipal water sources; twice a week, they will contain vitamin C (Health Investment Ltd, Vitamin Division) at a concentration of 2 %. The water is certified to meet the Water Quality Standards required by the National Water Supply Law.

Cleaning:

Rooms: To be washed with water daily

Cages: Soiled trays to be washed with water daily

Food Containers and Water Bottles: To be washed with water daily

XII. IDENTIFICATION OF ANIMALS AND CAGES

Identification of Individual Animals: The animals will be identified by the fitting of individual identification collars as well as writing an individual animal number on each jacket using an oil-type felt-tip pen.

Identification of Cages: Color-coded cage cards indicating the study number, group number, dose level and animal number.

XIII. QUARANTINE AND ACCLIMATION

Male animals will be selected for this study from amongst the quarantined animals, and weighed. The animals will be acclimated for 2 weeks prior to the initiation of dosing.

J:

At the end of the first week the animals will undergo a surgical procedure for the insertion of a catheter.

XIV. CATHETER INSERTION OPERATION

The animals will be restrained in a supine position under anesthesia (ketamine chloride, Sigma Chemical Co.), and an incision made (under sterile conditions). A polyurethane tube for continuous infusion will be inserted from the femoral vein to the posterior large vein near the right atrium. The tube will exit subcutaneously through the back and will be connected to a swivel and tether sewn into a jacket. The animals will be observed thereafter, during which time they will be routinely administered physiological saline so as to avoid any blockage forming in the catheter.

XV. GROUPING OF ANIMALS

On the day prior to the initiation of dosing, 15 healthy animals will be selected for the study and assigned to each group by stratified randomization, according to body weight, so as to achieve approximately equal mean body weights among the groups.

XVI. STUDY DESIGN

Group	Test Article	Dose Level*	Dose Volume (mL/kg/h)	No. of Animals (Animal No.)
1	Control**	0 mg/kg/4h twice/d	2	3 K: ()
2	Ro 10-1000/002	50 mg/kg/4h twice/d	2	3 ()
3	Ro 10-1000/002	100 mg/kg/4h twice/d	2	3 ()
4	Ro 10-1000/002	250 mg/kg/4h twice/d	2	3+3 () ***

* Dose level calculated as Ro 10-1000/001. The test article will be administered as the pro-drug Ro 10-1000/002.

** The control group animals will receive placebo to Ro 10-1000/002, in the same manner as the test article groups.

*** Animals for 4-week recovery test (animal nos.???).

XVII. JUSTIFICATION FOR SELECTION OF THE DOSE LEVEL

The 50 mg/kg/4h twice/day and 100 mg/kg/4h twice/day should provide a no-effect level regarding the deposition of precipitates in the distal renal tubules and kidney tissue reaction. The high dose should confirm borderline changes as seen in the previous study and provide information on the reversibility of these changes (4-week recovery period).

XVIII. OBSERVATIONS AND EXAMINATIONS

The first days of the dosing and recovery periods will be designated as Day 0 of the dosing or recovery period.

A. Mortality and Clinical Signs

All animals will be observed at least 7 times daily during the dosing period. Daily observations will be conducted just prior to each dosing, once during each dosing, immediately after the end of each dosing, 3-4 hours after the end of the 1st dosing, or more frequently as necessary.
(SOP/GTX/151)

B. Food Consumption

Food consumption per animal will be calculated daily from the amount of food supplied and the amount left over, once prior to the initiation of dosing

during the pre-dosing period, and daily during the dosing and recovery periods.
(SOP/GTX/213)

C. **Body Weight**

Body weight for each animal will be measured using an electronic balance (EP-41KA, A&D Co., Ltd.), once prior to the initiation of dosing (before surgical operation), once on the day prior to the initiation of dosing, once weekly during the dosing and recovery periods, and once on the day of necropsy.
(SOP/GTX/211)

D. **Urinalysis**

Frequency: Once prior to the initiation of dosing (last week of acclimation), on Day 12 (prior to the beginning of the first administration) and on Day 12 of the recovery period.

Number of Animals: All animals
Urine sediment will be examined on all animals as possible.

Collection Method: Fresh urine (2-hr sample) will be collected.

Parameter	Method	Apparatus
Color	Visual	—
pH	Test paper	Clinitek 200+*
Glucose	Test paper	Clinitek 200+*
Ketone body	Test paper	Clinitek 200+*
Bilirubin	Test paper	Clinitek 200+*
Urine occult blood	Test paper	Clinitek 200+*
Urobilinogen	Test paper	Clinitek 200+*
NAG	M-cresol purple method	U-3200**
Urine sediment	Microscopic examination of urine sediments stained with Sternheimer-Malbin after centrifugation (1500 rpm, 5 minutes)	

* Automatic urine analyzer (Clinitek 200+ type, Miles Labs. Inc., USA)

** Spectrophotometer (U3200, Hitachi Co., Ltd.).

(SOP/HTL/012, 114, 120)

- E. Hematology
- Frequency:

Once prior to the initiation of dosing (last week of the acclimation period), on Day 13 of the dosing period and on Day 13 of the recovery period.
- Number of Animals:

All animals
- Sampling Volume:

Approximately 0.8 mL
- Blood Sampling Method:

Blood samples will be drawn from the femoral vein. EDTA-2K will be used as an anticoagulant.

Parameter	Method	Apparatus
Erythrocyte count (RBC)	Detection system by electric resistance	E-4000 *
Leukocyte count (WBC)	Detection system by electric resistance	E-4000 *
Hematocrit value	Detection by pulse method	E-4000 *
Hemoglobin concentration	Sodium lauryl sulfate hemoglobin method	E-4000 *
Blood platelet count	Detection system by electric resistance	E-4000 *
Mean corpuscular volume (MCV)	Calculation	E-4000 *
Mean corpuscular hemoglobin (MCH)	Calculation	E-4000 *
Mean corpuscular hemoglobin concentration (MCHC)	Calculation	E-4000 *
Reticulocyte count	Brecher method	MICROX HEG-120A **
Differential leukocyte	Wright staining method	MICROX HEG-120A **

* Multipurpose automatic cell counter (E-4000, Sysmex Co.)

** Blood cell autoanalyzer (MICROX HEG-120A, Omron, Co.)

E Serum Biochemistry

Frequency:	Once prior to the initiation of dosing (last week of the acclimation period), on Day 13 of the dosing period and on Day 13 of the recovery period.
Number of Animals:	All animals
Sampling Volume:	Approximately 2.5 mL
Blood Sampling Method:	Blood samples will be drawn from the femoral vein. After 40 to 60 minutes of stabilization at room temperature, sera will be obtained by centrifugation (3000 rpm, 15 min.).

Parameter	Method	Apparatus
Aspartate aminotransferase (AST)	Modified JSCC method	RX-10 *
Alanine aminotransferase (ALT)	Modified JSCC method	RX-10 *
Alkaline phosphatase (ALP)	p-nitrophenyl phosphoric acid substrate method	RX-10 *
Lactate dehydrogenase (LDH)	UV Rate assay	RX-10 *
Total bilirubin	Alkaline azo bilirubin method	RX-10 *
Total protein	Biuret method	RX-10 *
Albumin**	BCG method	RX-10 *
Total cholesterol	COD-DAOS method	RX-10 *
Triglyceride	GPO-DAOS method	RX-10 *
Glucose	GlcK . G-6-PDH method	RX-10 *
Blood urea nitrogen (BUN)	Urease-GlDH method	RX-10 *
Creatinine	Jaffé method	RX-10 *
Inorganic phosphorus	Molybdc acid direct method	RX-10 *
Calcium	OCPC method	RX-10 *
Sodium	Electrode method	RX-10 *
Potassium	Electrode method	RX-10 *
Chloride	Coulometric titration method	RX-10 *

* Clinalyzer (RX-10, JEOL, Ltd.)

** Including a calculation of the A/G ratio.

(SOP/HTL/050)

G. Gross Pathology

Animals that die will be weighed, and necropsied as soon as possible after death (within 1-2 hours after death, or as early as possible if death occurs overnight) and macroscopic observation of the organs and tissues will be performed.

Moribund animals will be weighed, and euthanized by exsanguination under anesthesia, by an intravenous injection of sodium pentobarbital (64.8 mg/mL, 0.4 mL/kg, Health Investment Ltd.) into the cephalic vein of the forearm. Organs and tissues will be weighed, observed macroscopically, and prepared for subsequent histopathology examinations. If the condition of the moribund animal allows, blood samples will be drawn for terminal hematology, serum biochemistry and toxicokinetic examinations prior to euthanization. Immediately after removal samples of brain tissue will be frozen in liquid nitrogen and stored thereafter at -80°C . Brain tissue will be sent on dry ice to the Principle Investigator Dr. H. Smart (see under Toxicokinetics) together with plasma samples.

On the day following the end of the dosing or recovery period, all surviving animals will be weighed, and euthanized by exsanguination under anesthesia, by an intravenous injection of sodium pentobarbital into the cephalic vein of the forearm. The organs and tissues will be weighed and observed macroscopically. Immediately after removal, samples of brain tissue will be frozen in liquid nitrogen and stored thereafter at -80°C . Brain tissue will be sent on dry ice to the Principle Investigator Dr. H. Smart (see under Toxicokinetics) together with plasma samples. Photographs of abnormalities will be taken as necessary.

(SOP/PAT/007)

H. Organ Weight (absolute and relative organ weights)

Number of Animals:	All animals
Organs to be Weighed:	Brain (including cerebellum and brain stem), thyroids* (including para-thyroid), heart, liver, adrenals, kidneys, spleen, testes

*Thyroids will be weighed after fixation.

(SOP/PAT/011)

I. Histopathology (light microscopy)

Number of Animals:	All animals
Fixation:	10% neutral buffered formalin (testes will be fixed in Bouin's solution, and eye balls and optic nerves will be fixed in a mixture solution of formaldehyde and glutaraldehyde)
Staining:	Hematoxylin-Eosin stain (and other stains as necessary, following consultation with the Sponsor; Kidneys: PAS)
Organs to be Examined:	All the organs listed below and any organs with macroscopic abnormalities.

Heart, thoracic aorta, spleen, thymus, bone marrow (femur without decalcifying, sternum after decalcification) and bone (femur and sternum as decalcified specimens), submandibular lymph nodes, mesenteric lymph node, lungs, bronchus, trachea, tongue, esophagus, stomach (fundus, pylorus), small intestine (duodenum, jejunum, ileum), large intestine (cecum, colon, rectum), pancreas, liver, gall bladder, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicle, pituitary, thyroids, parathyroid (as much as possible), adrenals, cerebrum, cerebellum, brain stem, lumbar spinal cord, sciatic nerve, eye balls (with optic nerve), lachrymal glands, skin (gluteal area), ovaries, vagina, uterus (corpus), submandibular glands, quadriceps muscle of thigh and gross lesions.

Peer Review: **L:**

Storage: The above organs and tissues will be stored after vacuum packing.

(SOP/PAT/032)

J. Toxicokinetics in the Urine

Frequency:

Once prior to the initiation of dosing (6-hour sample in the morning), and the first and last administrations (0-6 and 6-12 hours after the initiation of each infusion).

Number of Animals:

All animals as possible

Urine Sampling Method:

Urine samples will be collected. Prior to the initiation of urine sampling, 30 μ L of 2 mol/L citric acid will be added to each sampling tube. During sampling, urine samples will be cooled in ice-water. At the end of the collection period, the urine volume will be measured and the samples will be frozen at -80°C , and transferred on dry-ice to the Principle Investigator Dr. H. Smart.

For exposure assessment, urine concentrations of the active principle Ro 10-1000/002 will be analyzed under the responsibility of the Principle Investigator for Bioanalytics Dr. H. Smart using the validated HPLC/UV method DA-100/04. The toxicokinetic evaluation will be conducted by the Principle Investigator for Kinetics, Dr. W. Profile for the assessment of pharmacokinetic parameters (AUC, Cmax, Tmax).

K. Toxicokinetics in the Blood

Frequency:

4 hours after the beginning of the first and last administrations. The exact time of sampling will be recorded individually for each animal. In addition, terminal blood samples will be collected at necropsy.

Number of Animals:

All animals

Sampling Volume:

Approximately 1 mL

Blood Sampling Method:

Blood samples will be drawn from the femoral vein. EDTA/NaF will be used as the anticoagulant and 1 mol/L citric

acid at 10 µL/mL whole blood will be added. Plasma (approximately 0.4 mL) will be obtained by centrifugation (3000 rpm, 15 min.), stored frozen transferred to the Principle Investigator Dr. H. Smart.

For exposure assessment, urine concentrations of the active principle Ro 10-1000/002 will be analyzed under the responsibility of the Principle Investigator for Bioanalytics Dr. H. Smart using the validated HPLC/UV method DA-100/04. The toxicokinetic evaluation will be conducted by the Principle Investigator for Kinetics, Dr. W. Profile for the assessment of pharmacokinetic parameters (AUC, Cmax, Tmax).

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L. Metabolism in the Urine

Frequency:

At Week 1 of the dosing period.

Number of Animals:

All animals as possible

Urine Sampling Method:

0-6 and 6-12 hour urine samples will be collected. Urine samples will be adjusted to approximately pH 9.0 at the end of the collection period and frozen at –80°C (SOP/HTL/501).

M:

XIX. STATISTICAL ANALYSES

Food consumption, body weight, NAG, hematology, serum biochemistry and organ weight (absolute and relative) data will first be analyzed for homogeneity of variance by Bartlett's test. If homogeneity of variance exists, Dunnett's test will be applied to compare the means. If no homogeneity of variance exists by Bartlett's test, a non-parametric Dunnett's test will be applied to compare the mean ranks.

A computer (AlphaServer 1000, DEC Co., Ltd.) will be used for these statistical analyses. A risk percentage of $p < 0.05$ will be regarded as statistically significant. Clinical signs, and non-quantitative values from urinalysis, gross pathology and histopathology data and all data during the recovery period will not be analyzed statistically.

XX. FINAL REPORT

The Final Report will consist of summary, introduction, materials and methods, results, and discussion sections incorporating the results of the involved Principle Investigators in Pharmacy R&R and the Department of Pharmacokinetics and Metablism.

XXI. ARCHIVING

N:

SIGNATURES

STUDY DIRECTOR:

Dr. A. Master

.....
date:

DEPUTY STUDY DIRECTOR:

Dr. D. Simple

.....
date:

QAU MANAGER:

Dr. G. Nosy

.....
date:

MANAGEMENT:

Dr. T.R. King

.....
date:

PRINCIPLE INVESTIGATOR:
DMPK: Bioanalytics

Dr. H. Smart

PRINCIPLE INVESTIGATOR:
DMPK: Pharmacokinetics

Dr. W. Profile

PRINCIPLE INVESTIGATOR:
Pharmacy: Formulation Analytics

Dr. H. Galen

WORKSHOP 2 (B)

Study Number 102 P 99

A 2-WEEK TOXICITY STUDY OF Ro 10-1000/002 (PRODRUG OF 10-1000/001)
VIA INTRAVENOUS INFUSION IN MALE COMMON MARMOSETS
FOLLOWED BY A 4-WEEK RECOVERY PERIOD

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PROTOCOL

July, 1999

Health Investment Ltd.
Toxicology Department, Paradise City

- I. STUDY TITLE
A 2-Week Toxicity Study of Ro 10-1000/002 (Prodrug of 10-1000/001) via Intravenous Infusion in Male Common Marmosets Followed by a 4-Week Recovery Period
- II. PURPOSE OF THE STUDY
The purpose of this study is to evaluate the toxicity of Ro 10-1000/002 (pro-drug of 10-1000/001), when infused intravenously to male common mar-mosets for 2 weeks followed by a week recovery period.
- III. COMPLIANCE WITH GLP
This study will be performed in accordance with the Good Laboratory Practice Regulations (Ministry of Health and Welfare Ordinance No. 21, March 26, 1997) and the Guideline for Toxicity Studies Required for Applications for Approval to Manufacture (Import) Drugs (Notification No. 24 of Pharmaceu-tical Affairs Bureau, Ministry of Health and Welfare, Japan, September 11, 1989, Notification No. 316, partially amended as of April 14, 1997), and Note for Guidance on Toxicokinetics (The Assessment of Systemic Exposure in Tox-icity Studies, Notification No. 443 of the Pharmaceutical Affairs Bureau, Min-istry of Health and Welfare, Japan, July 2, 1996).
- IV. TESTING FACILITY
Toxicology Department
Pharma Research, Nonclinical Development
Health Investment Ltd.
Paradise City
- V. PERSONNEL ENGAGED IN THE STUDY
Management Director: A. B., D.V.M., Ph.D.
Study Director: B. B., D.V.M., Ph.D.
Study Director Deputy: C. C., D.V.M., Ph.D. M.S.
Pathologist: D. D., D.V.M., Ph.D.
Test Article Controller: E. E., B.S.

VII. STUDY SCHEDULE

Date of Initiation of Study:	August 5, 1999
Date of Initiation of Acclimation:	August 11, 1999
Date of Operation:	August 18-20, 1999
Date of Initiation of Dosing:	August 25, 1999
Date of End of Dosing:	September 7, 1999
Date of End of Recovery period:	October 5, 1999
Date of Necropsy	
At the End of the Dosing period:	September 8, 1999
At the End of the Recovery period:	October 6, 1999

Date of Presentation of Final Report: January 25, 2000

Date of End of Study: January 25, 2000

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VIII. TEST AND CONTROL ARTICLES

A. Test Article

Chemical Name:	Ro 10-1000/002 (prodrug of Ro 10-1000/001)
Supplier:	Chemistry Department, Kilo laboratory, Health Investment Ltd.
Lot Number:	G GP 0186 (6.25 mg/ml Ro 10-1000/001), G GP 0187 (12.5 mg/ml Ro 10-1000/001), G GP 0188 (31.25 mg/ml Ro 10-1000/001)
Purity:	will be determined from each batch by the Principal Investigator (Pharmacy Department) and a certificate of analysis will be included in the Final Report.
Physical State:	Amorphous solid
Stability:	will be determined of each batch by the Principal Investigator (Pharmacy Department) and a certificate of analysis will be included in the Final Report.

Arrival Date of Test Article: August 11, 1999
Amount of Test Article: 30 vials per group
Storage Conditions: –80°C and protected from light
Storage Facility: Deep freezer in the test article control room of the test facility
Handling Instructions: Wear gloves, mask and cap, and protect the test article from light.
Disposal of Remaining Test Article: All remaining test article will be discarded at the end of each infusion cycle.

B. **Control**

Chemical Name: Placebo to Ro 10-1000/002
Lot Number: G GP 0185
Storage Conditions: 2-8°C and protected from light
Storage Facility: The refrigeration room in the Test Article Depository of the test facility

C. **Vehicle**

Chemical Name: Reconstitution solution
Lot Number: will be known prior to the initiation of the study and will be included in the Final Report.
Storage Conditions: 2-8°C and protected from light
Storage Facility: The refrigeration room in the Test Article Depository of the test facility

IX. **PREPARATION AND ADMINISTRATION OF TEST ARTICLE**

Preparation Method: According to instructions by Pharmacy R&D, Health Investment Ltd., the test article will be dissolved in a reconstitution solution. Reconstituted solutions will be passed through a sterile filter prior to infusion.

Conversion Factor	1 g of Ro 10-1000/001 corresponds to 1.45 g of Ro 10-1000/002.
Confirmation of concentration of the preparations:	Confirmation of dosing solutions (by HPLC) will be performed by the Principle Investigator of Pharmacy R&D. Samples from the first dosing on Day 0, the first dosing on Day 7 and the last dosing solution will be frozen (–80°C) and transferred to the PI for subsequent analyses.
Confirmation of stability of the preparations:	The stability of the preparations will be determined by the PI of Pharmacy R&D prior to the initiation of the study.
Administration Route: Justification for the Administration Route:	Intravenous (infusion) In accordance with the expected clinical route
Administration Method:	The test article will be administered twice daily for 4 hours (with a 12-hour interval) into the Vena Cava (inferior) through a catheter inserted into the femoral vein. During the non-test article administration period, 0.9% NaCl will be administered.
Justification for the Administration Method:	For accurate administration of the intended dose.
Administration Volume: Administration Frequency:	2 mL/kg/h Twice daily for 14 days (i.e. total of 28 administrations)
Justification for the Administration Frequency:	In accordance with the expected clinical administration frequency.

Initiation Time of the First
Test Article Administration: 09:00-10:00 (at a predetermined
hour). Each individual dosing time
will be recorded.

X. STUDY ANIMALS

Species: Common marmosets
Sex: Male
Body Weight: 250-400 g (at the initiation of acclima-
tion)
Age: At least 12 months old (at the initia-
tion of dosing)
Name and Address of Supplier: Happy Primates Inc, Banana Republic
Date of Receipt of Animals: April 24, 1998, October 29, 1998 and
April 23, 1999
Number of Animals for Acclimation: 18
Number of Animals for Study: 15
Justification for Selection of the
Study Species: This species is often used in standard
toxicity programmes.

XI. MAINTENANCE CONDITIONS

Room Number: Marmoset Facility, room no. 44
Temperature: $28 \pm 2^{\circ}\text{C}$
Humidity: $50 \pm 10\%$
Frequency of Ventilation: 15 times/hour
Illumination: Artificial lighting for 12 hours
(08:00-20:00)
Animal Cage and Size: Stainless steel,
44 cm (D) \times 44 cm (W) \times 60 cm (H)
Number of Animals per Cage: One animal per cage
Food: Approximately 40 g of solid food
(CMS-1, Happy Primates Inc, Banana
Republic) will be provided to each

	animal daily at approximately 15:00, and on the following day, uneaten food will be withdrawn at approximately 09:00. On the day before blood sampling and necropsy, uneaten food will be collected at approximately 17:00.
Water:	Water will be available ad libitum from water bottles obtained as tap water from municipal water sources; twice a week, they will contain vitamin C (Health Investment Ltd, Vitamin Division) at a concentration of 2%. The water is certified to meet the Water Quality Standards required by the National Water Supply Law.
Cleaning:	
Rooms:	To be washed with water daily
Cages:	Soiled trays to be washed with water daily
Food Containers and Water Bottles:	To be washed with water daily

XII. IDENTIFICATION OF ANIMALS AND CAGES

Identification of Individual Animals:	The animals will be identified by the fitting of individual identification collars as well as writing an individual animal number on each jacket using an oil-type felt-tip pen.
Identification of Cages:	Color-coded cage cards indicating the study number, group number, dose level and animal number.

XIII. QUARANTINE AND ACCLIMATION

Eighteen male animals will be selected for this study from amongst the quarantined animals, and weighed. The animals will be acclimated for 2 weeks prior to the initiation of dosing. During this period, clinical signs will be observed daily; food consumption will be measured once prior to the initiation of dosing; body weight measured once on the final day of this period; and urinalysis, hematology and serum biochemistry will be examined once. At the end of the first week the animals will undergo a surgical procedure for the insertion of a catheter.

XIV. CATHETER INSERTION OPERATION

The animals will be restrained in a supine position under anesthesia (ketamine chloride, Sigma Chemical Co.), and an incision made (under sterile conditions). A polyurethane tube for continuous infusion will be inserted from the femoral vein to the posterior large vein near the right atrium. The tube will exit subcutaneously through the back and will be connected to a swivel and tether sewn into a jacket. The animals will be observed thereafter, during which time they will be routinely administered physiological saline so as to avoid any blockage forming in the catheter.

XV. GROUPING OF ANIMALS

On the day prior to the initiation of dosing, 15 healthy animals will be selected for the study and assigned to each group by stratified randomization, according to body weight, so as to achieve approximately equal mean body weights among the groups.

XVI. STUDY DESIGN

Group	Test Article	Dose Level*	Dose Volume (mL/kg/h)	No. of Animals (Animal No.)
1	Control**	0 mg/kg/4h twice/d	2	3 (1-3)
2	Ro 10-1000/002	50 mg/kg/4h twice/d	2	3 (4-6)
3	Ro 10-1000/002	100 mg/kg/4h twice/d	2	3 (7-9)
4	Ro 10-1000/002	250 mg/kg/4h twice/d	2	3+3 (10-15) ***

* Dose level calculated as Ro 10-1000/001. The test article will be administered as the pro-drug Ro 10-1000/002

** The control group animals will receive placebo to Ro 10-1000/002, in the same manner as the test article groups.

*** Animals for 4-week recovery test (animal nos.13-15)

XVII. JUSTIFICATION FOR SELECTION OF THE DOSE LEVEL

The 50 mg/kg/4h twice/day and 100 mg/kg/4h twice/day should provide a no-effect level regarding the deposition of precipitates in the distal renal tubules and kidney tissue reaction. The high dose should confirm borderline changes as seen in the previous study and provide information on the reversibility of these changes (4-week recovery period).

XVIII. OBSERVATIONS AND EXAMINATIONS

The first days of the dosing and recovery periods will be designated as Day 0 of the dosing or recovery period.

A. Mortality and Clinical Signs

All animals will be observed at least 7 times daily during the dosing period. Daily observations will be conducted just prior to each dosing, once during each dosing, immediately after the end of each dosing, 3-4 hours after the end of the 1st dosing, or more frequently as necessary.
(SOP/GTX/151)

B. Food Consumption

Food consumption per animal will be calculated daily from the amount of food supplied and the amount left over, once prior to the initiation of dosing

during the pre-dosing period, and daily during the dosing and recovery periods.
(SOP/GTX/213)

C. **Body Weight**

Body weight for each animal will be measured using an electronic balance (EP-41KA, A&D Co., Ltd.), once prior to the initiation of dosing (before surgical operation), once on the day prior to the initiation of dosing, once weekly during the dosing and recovery periods, and once on the day of necropsy.
(SOP/GTX/211)

D. **Urinalysis**

Frequency: Once prior to the initiation of dosing (last week of acclimation), on Day 12 (prior to the beginning of the first administration) and on Day 12 of the recovery period.

Number of Animals: All animals
Urine sediment will be examined on all animals as possible.

Collection Method: Fresh urine (2-hr sample) will be collected.

Parameter	Method	Apparatus
Color	Visual	—
pH	Test paper	Clinitek 200+*
Glucose	Test paper	Clinitek 200+*
Ketone body	Test paper	Clinitek 200+*
Bilirubin	Test paper	Clinitek 200+*
Urine occult blood	Test paper	Clinitek 200+*
Urobilinogen	Test paper	Clinitek 200+*
NAG	M-cresol purple method	U-3200**
Urine sediment	Microscopic examination of urine sediments stained with Sternheimer-Malbin after centrifugation (1500 r.p.m., 5 minutes)	

* Automatic urine analyzer (Clinitek 200+ type, Miles Labs. Inc., USA)

** Spectrophotometer (U3200, Hitachi Co., Ltd.)

(SOP/HTL/012, 114, 120)

E. Hematology

Frequency:

Once prior to the initiation of dosing (last week of the acclimation period), on Day 13 of the dosing period and on Day 13 of the recovery period.

Number of Animals:

All animals

Sampling Volume:

Approximately 0.8 mL

Blood Sampling Method:

Blood samples will be drawn from the femoral vein. EDTA-2K will be used as an anticoagulant.

Parameter	Method	Apparatus
Erythrocyte count (RBC)	Detection system by electric resistance	E-4000 *
Leukocyte count (WBC)	Detection system by electric resistance	E-4000 *
Hematocrit value	Detection by pulse method	E-4000 *
Hemoglobin concentration	Sodium lauryl sulfate hemoglobin method	E-4000 *
Blood platelet count	Detection system by electric resistance	E-4000 *
Mean corpuscular volume (MCV)	Calculation	E-4000 *
Mean corpuscular hemoglobin (MCH)	Calculation	E-4000 *
Mean corpuscular hemoglobin concentration (MCHC)	Calculation	E-4000 *
Reticulocyte count	Brecher method	MICROX HEG-120A **
Differential leukocyte	Wright staining method	MICROX HEG-120A **

* Multipurpose automatic cell counter (E-4000, Sysmex Co.)
** Blood cell autoanalyzer (MICROX HEG-120A, Omron, Co.).
(SOP/HTL/124, 142)

E Serum Biochemistry

Frequency:	Once prior to the initiation of dosing (last week of the acclimation period), on Day 13 of the dosing period and on Day 13 of the recovery period.
Number of Animals:	All animals
Sampling Volume:	Approximately 2.5 mL
Blood Sampling Method:	Blood samples will be drawn from the femoral vein. After 40 to 60 minutes of stabilization at room temperature, sera will be obtained by centrifugation (3000 rpm, 15 min.).

Parameter	Method	Apparatus
Aspartate aminotransferase (AST)	Modified JSCC method	RX-10 *
Alanine aminotransferase (ALT)	Modified JSCC method	RX-10 *
Alkaline phosphatase (ALP)	p-nitrophenyl phosphoric acid substrate method	RX-10 *
Lactate dehydrogenase (LDH)	UV Rate assay	RX-10 *
Total bilirubin	Alkaline azo bilirubin method	RX-10 *
Total protein	Biuret method	RX-10 *
Albumin**	BCG method	RX-10 *
Total cholesterol	COD-DAOS method	RX-10 *
Triglyceride	GPO-DAOS method	RX-10 *
Glucose	GlcK . G-6-PDH method	RX-10 *
Blood urea nitrogen (BUN)	Urease-GIDH method	RX-10 *
Creatinine	Jaffé method	RX-10 *
Inorganic phosphorus	Molybdic acid direct method	RX-10 *
Calcium	OCPC method	RX-10 *
Sodium	Electrode method	RX-10 *
Potassium	Electrode method	RX-10 *
Chloride	Coulometric titration method	RX-10 *

* Clinalyzer (RX-10, JEOL, Ltd.)
 ** Including a calculation of the A/G ratio.
 (SOP/HTL/050)

G. Gross Pathology

Animals that die will be weighed, and necropsied as soon as possible after death (within 1-2 hours after death, or as early as possible if death occurs overnight) and macroscopic observation of the organs and tissues will be performed.

Moribund animals will be weighed, and euthanized by exsanguination under anesthesia, by an intravenous injection of sodium pentobarbital (64.8 mg/mL, 0.4 mL/kg, Health Investment Ltd.) into the cephalic vein of the forearm. Organs and tissues will be weighed, observed macroscopically, and prepared for subsequent histopathology examinations. If the condition of the moribund animal allows, blood samples will be drawn for terminal hematology, serum biochemistry and toxicokinetic examinations prior to euthanization. Immediately after removal samples of brain tissue will be frozen in liquid nitrogen and stored thereafter at -80°C . Brain tissue will be sent on dry ice to the Principle Investigator Dr. H. Smart (see under Toxicokinetics) together with plasma samples.

On the day following the end of the dosing or recovery period, all surviving animals will be weighed, and euthanized by exsanguination under anesthesia, by an intravenous injection of sodium pentobarbital into the cephalic vein of the forearm. The organs and tissues will be weighed and observed macroscopically. Immediately after removal, samples of brain tissue will be frozen in liquid nitrogen and stored thereafter at -80°C . Brain tissue will be sent on dry ice to the Principle Investigator Dr. H. Smart (see under Toxicokinetics) together with plasma samples. Photographs of abnormalities will be taken as necessary.

(SOP/PAT/007)

H. Organ Weight (absolute and relative organ weights)

Number of Animals:	All animals
Organs to be Weighed:	Brain (including cerebellum and brain stem), thyroids* (including parathyroid), heart, liver, adrenals, kidneys, spleen, testes

* Thyroids will be weighed after fixation.

(SOP/PAT/011)

I. Histopathology (light microscopy)

Number of Animals:

All animals

Fixation:

10% neutral buffered formalin (testes will be fixed in Bouin's solution, and eye balls and optic nerves will be fixed in a mixture solution of formaldehyde and glutaraldehyde)

Staining:

Hematoxylin-Eosin stain (and other stains as necessary, following consultation with the Sponsor; Kidneys: PAS)

Organs to be Examined:

All the organs listed below and any organs with macroscopic abnormalities.

Heart, thoracic aorta, spleen, thymus, bone marrow (femur without decalcifying, sternum after decalcification) and bone (femur and sternum as decalcified specimens), submandibular lymph nodes, mesenteric lymph node, lungs, bronchus, trachea, tongue, esophagus, stomach (fundus, pylorus), small intestine (duodenum, jejunum, ileum), large intestine (cecum, colon, rectum), pancreas, liver, gall bladder, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicle, pituitary, thyroids, parathyroid (as much as possible), adrenals, cerebrum, cerebellum, brain stem, lumbar spinal cord, sciatic nerve, eye balls (with optic nerve), lachrymal glands, skin (gluteal area), ovaries, vagina, uterus (corpus), submandibular glands, quadriceps muscle of thigh and gross lesions.

Peer Review:

Peer review will be performed by another veterinarian pathologist within the toxicology department.

Storage:

The above organs and tissues will be stored after vacuum packing.

(SOP/PAT/032)

J. Toxicokinetics in the Urine

Frequency:

Once prior to the initiation of dosing (6-hour sample in the morning), and the first and last administrations (0-6 and 6-12 hours after the initiation of each infusion).

Number of Animals:	All animals as possible
Urine Sampling Method:	Urine samples will be collected. Prior to the initiation of urine sampling, 30 μ L of 2 mol/L citric acid will be added to each sampling tube. During sampling, urine samples will be cooled in ice-water. At the end of the collection period, the urine volume will be measured and the samples will be frozen at -80°C , and transferred on dry-ice to the Principle Investigator Dr. H. Smart.

For exposure assessment, urine concentrations of the active principle Ro 10-1000/002 will be analyzed under the responsibility of the Principle Investigator for Bioanalytics Dr. H. Smart using the validated HPLC/UV method DA-100/04. The toxicokinetic evaluation will be conducted by the Principle Investigator for Kinetics, Dr. W. Profile for the assessment of pharmacokinetic parameters (AUC, Cmax, Tmax).

K. Toxicokinetics in the Blood

Frequency:	4 hours after the beginning of the first and last administrations. The exact time of sampling will be recorded individually for each animal. In addition, terminal blood samples will be collected at necropsy.
------------	---

Number of Animals:	All animals
Sampling Volume:	Approximately 1 mL
Blood Sampling Method:	Blood samples will be drawn from the femoral vein. EDTA/NaF will be used as the anticoagulant and 1 mol/L citric acid at 10 μ L/mL whole blood will be added. Plasma (approximately 0.4 mL) will be obtained by centrifugation (3000 rpm, 15 min.), stored frozen transferred to the Principle Investigator Dr. H. Smart.

For exposure assessment, urine concentrations of the active principle Ro 10-1000/002 will be analyzed under the responsibility of the Principle Investigator for Bioanalytics Dr. H. Smart using the validated HPLC/UV method DA-100/04. The toxicokinetic evaluation will be conducted by the Principle Investigator for Kinetics, Dr. W. Profile for the assessment of pharmacokinetic parameters (AUC, Cmax, Tmax).

L. Metabolism in the Urine

Frequency:

At Week 1 of the dosing period.

Number of Animals:

All animals as possible

Urine Sampling Method:

0-6 and 6-12 hour urine samples will be collected. Urine samples will be adjusted to approximately pH 9.0 at the end of the collection period and frozen at -80°C (SOP/HTL/501).

Analysis of urine samples for metabolites and reporting of these results will not be done as part of this study and will not be performed according to GLP.

XIX. STATISTICAL ANALYSES

Food consumption, body weight, NAG, hematology, serum biochemistry and organ weight (absolute and relative) data will first be analyzed for homogeneity of variance by Bartlett's test. If homogeneity of variance exists, Dunnett's test will be applied to compare the means. If no homogeneity of variance exists by Bartlett's test, a non-parametric Dunnett's test will be applied to compare the mean ranks.

A computer (AlphaServer 1000, DEC Co., Ltd.) will be used for these statistical analyses. A risk percentage of $p < 0.05$ will be regarded as statistically significant. Clinical signs, and non-quantitative values from urinalysis, gross pathology and histopathology data and all data during the recovery period will not be analyzed statistically.

XX. FINAL REPORT

The Final Report will consist of summary, introduction, materials and methods, results, and discussion sections incorporating the results of the involved Principle Investigators in Pharmacy R&R and the Department of Pharmacokinetics and Metablism.

XXI. ARCHIVING

Protocol, report, all specimens, all raw data and reference samples of the test article pertaining to this study including the raw data obtained by the investigations of the Principle Investigators will be stored in the archives of the toxicology department.

SIGNATURES

STUDY DIRECTOR:

Dr. A. Master

.....
date:

DEPUTY STUDY DIRECTOR:

Dr. D. Simple

.....
date:

QAU MANAGER:

Dr. G. Nosy

.....
date:

MANAGEMENT:

Dr. T.R. King

.....
date:

PRINCIPLE INVESTIGATOR:
DMPK: Bioanalytics

Dr. H. Smart

PRINCIPLE INVESTIGATOR:
DMPK: Pharmacokinetics

Dr. W. Profile

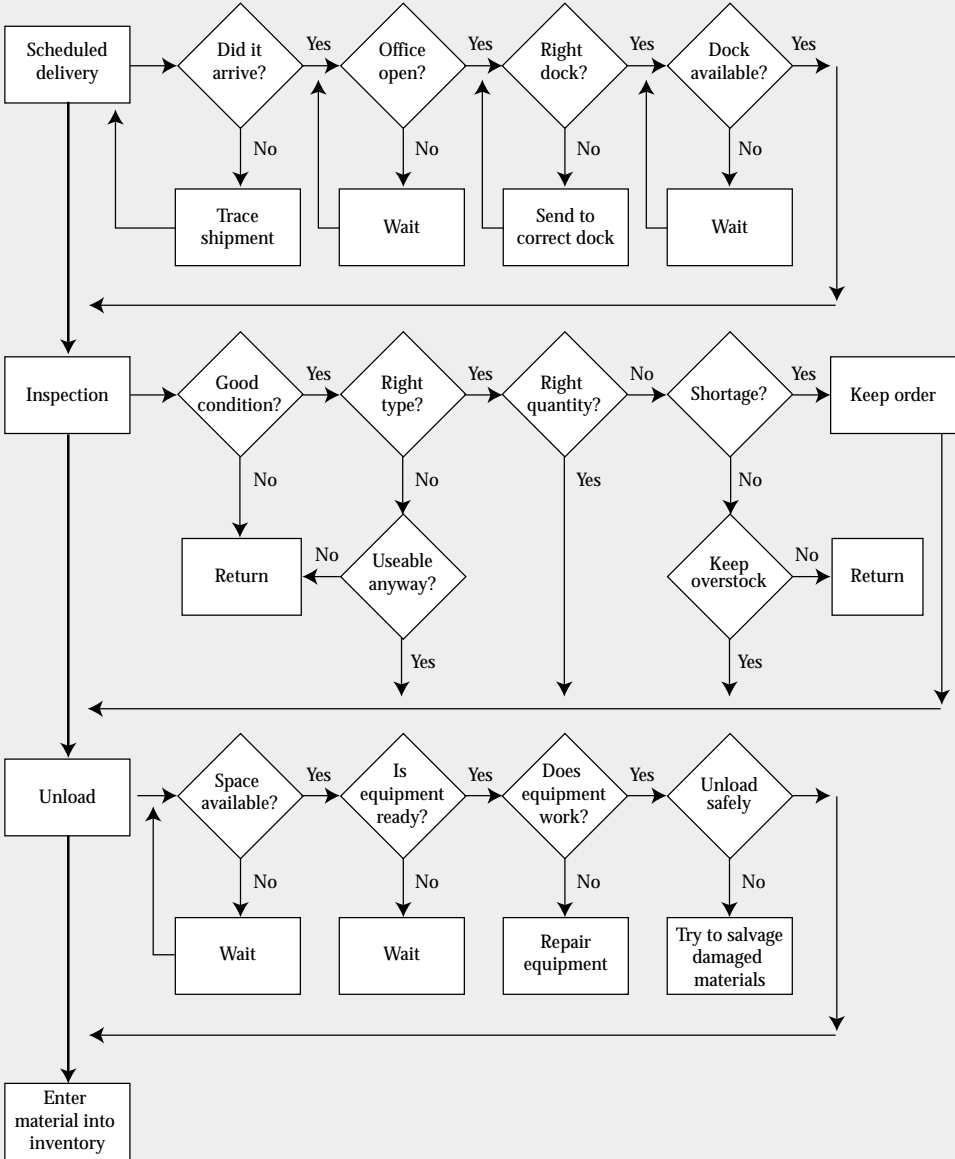
PRINCIPLE INVESTIGATOR:
Pharmacy: Formulation Analytics

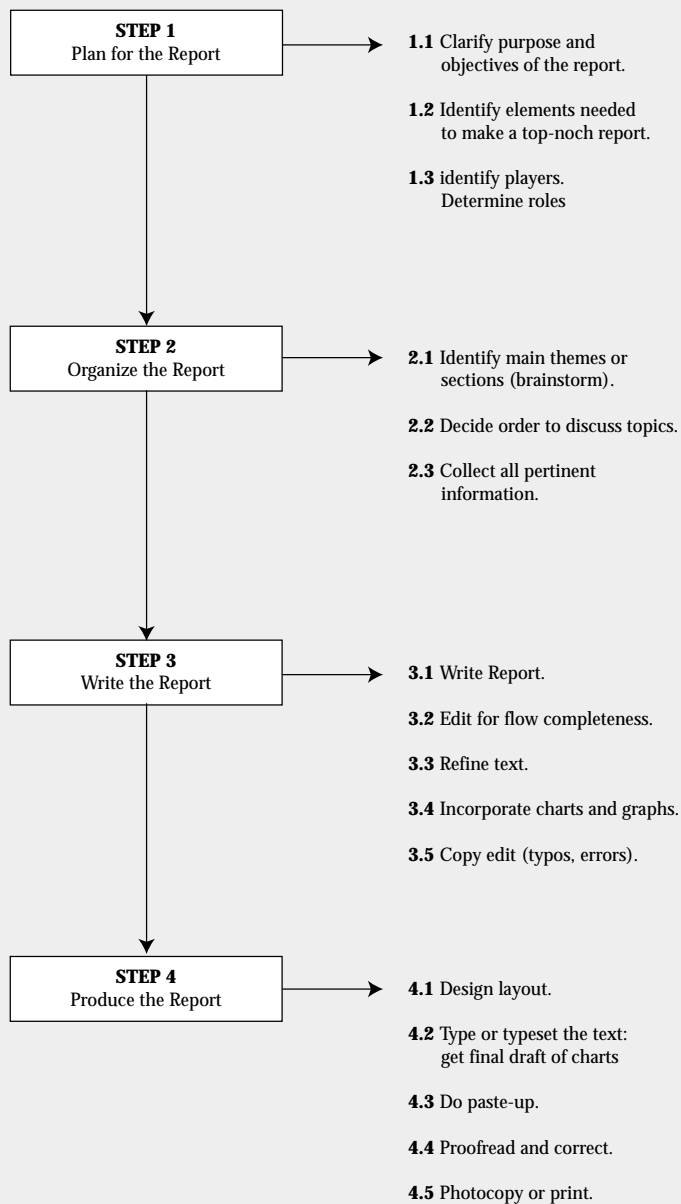
Dr. H. Galen

APPENDIX 3

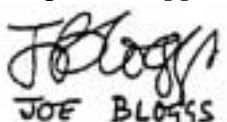
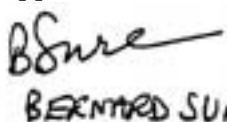
FLOWCHARTS

DETAILED FLOWCHART
OF SUPPLIES RECEIVING PROCESS





APPENDIX 4
EXAMPLES OF SOPs

QUALITY SOCIETY	
SOP No: 00104/002	Date:
Revision frequency: 12 months	
Management Approval:  JOE BLOSS	QA Approval:  BERNARD SURE

HEALTH AND SAFETY DURING WASTE INCINERATION

I INTRODUCTION

The incineration area is a “Classified Zone”. All operations within the area are therefore to be performed in compliance with the regulations concerning classified zones. This regulation is attached to this SOP.

II INDIVIDUAL PROTECTION

Personnel working in the incineration area must wear at all times:

- a single-use work suit
- protective gloves.

When removing ashes from the incinerator, the following must also be worn:

- rubber boots
- protective, heavy-duty apron
- single-use head covering
- mask with filtering cartridge.

III HYGIENE

- Paper tissues must be available in the area at all times.
- The personnel must shower after a day's work and before going to lunch. Time is allowed for this procedure.
- The wash area must always be equipped with liquid soap and single-use paper towels.

IV SAFETY

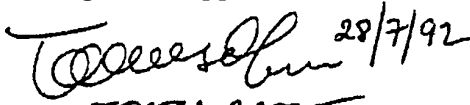
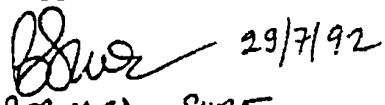
On a regular basis, the single-use clothing and other material used in the incineration area must be incinerated. If the operator has doubts about having been in contact with any radioactive material the clothing should be changed and the soiled material incinerated immediately.

At least once a day, preferably at the end of the working day, each operator should verify that he/she has not been contaminated by radioactivity. Use the -CB+C counter for this operation (SOP SAF 2002/01).

Under no circumstances should the operators leave the incineration area wearing their work clothes.

V EMERGENCIES

In case of emergency, call the company doctor: ext 1234 and the company safety officer: ext. 4321.

QUALITY SOCIETY	
SOP No: 00539/002	Date:
Revision frequency: 12 months	
Management Approval:  28/7/92 TERESA GREENE	QA Approval:  29/7/92 BERNARD SURE

REMOVAL OF CONTAMINATED WASTE FROM TOXICOLOGY BUILDING

I ANIMAL CADAVERS

Animal remains which are to be removed from the building are stored temporarily on the ground floor of the building. The remains are placed in black plastic bags, which are in turn placed in rigid plastic bins. Each weekday between 14.00h and 15.00h the LAR personnel places these bins outside the building in the designated area (East door). Each bag is individually sealed and labelled. Labels will include the wording Contaminated Waste, and will be completed with the origin of the material and the date.

II PAPER FOR URINE/FAECES COLLECTION

The paper which is used to collect the urine and the faeces and which is regularly removed from under the animals' cages, is placed in transparent plastic bags. It is placed outside the building (East door) in the designated area.

The bags must be closed using the plastic tie-band and labelled using a label with the wording, **Contaminated Waste**, which will be completed with the origin (room number) of the paper and the date.

III OTHER CONTAMINATED, NON-RADIOACTIVE, WASTE

The waste of this type is mostly:

- Residue of feed materials
- Plastic material and broken glassware
- Petri dishes
- Waste from microbiological labs
- Waste from pathology labs

This waste must be placed in plastic bags which are in turn placed in transparent plastic bags and labelled with the wording **Contaminated Waste**, dated and identified with the origin of the material. These bags are transferred to the outside of the building (East door) and placed in the area designated. This operation must occur between 14.00h and 15.00h and is performed by the LAR personnel.

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IV DISPOSAL OF CONTAMINATED RADIOACTIVE WASTE

This waste is placed in a black plastic bag which is then placed in a second transparent plastic bag. The bag is sealed and identified using a special label with the wording, **Radioactive Waste**. The technician who bags-up the waste transfers it him/herself directly to the incineration area.

V COLLECTION OF NON-RADIOACTIVE WASTE

The black bags and the bins of waste which are temporarily placed outside the Toxicology building (East door) are collected the same day between 15.00h and 16.00h by the personnel in charge of incineration.

QUALITY SOCIETY	
SOP No: 00192/002	Date: 21/10/93
Revision frequency: 12 months	
Management Approval: BENCE POLITE	QA Approval: COLIN THURMAN

COLLECTION AND INCINERATION OF CONTAMINATED WASTE

I PERSONNEL IN CHARGE OF COLLECTION AND INCINERATION

All contaminated waste is incinerated on site, as well as some non-contaminated waste. The technician in charge of the incinerator is also responsible for the collection of contaminated waste.

Waste should be incinerated on the day of the collection. In the event of the incinerator personnel being indisposed, temporary staff will be employed.

II COLLECTION OF CONTAMINATED WASTE

Contaminated waste, adequately packed (see SOP BIOL 00101/002), is placed in bins specially intended for this purpose at places indicated by the marks on the ground (Toxicology, east door; Biology, doors A and B).

The bins should be placed in the designated areas between 10.00h and 11.00h in the morning, each day. Collection will start at 11.30h.

Before the collection process, which is effected using a electric Fenwick, the technician must check that the bins are correctly labelled and are closed.

Should there be a defective label or defective closure, this will be reported to the foremen in charge of the relevant building who will take the necessary action.

The bins are then fork-lifted onto the vehicle and taken to the incinerator area.

III INCINERATION OF WASTE

Correctly containered contaminated waste is placed in an area designated to this effect on the sidewalk adjacent to the incinerator.

The incinerator operated every weekday.

In principle, all waste should be incinerated the day of its collection.

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IV INCINERATION LOG BOOK



All waste which is incinerated must be recorded in the log book. The log books should be verified periodically by the technician in charge of the area. They are archived in the department.

Non-radioactive waste

All incineration of non-radioactive waste is recorded in the same log book. On each occasion, the following is noted: date, origin of the material, weight incinerated, any observations (see attachment 1).

Radio-active waste

All incineration of radioactive waste is recorded in a separate log book. On each occasion, the following is noted: the date of receipt in the area, the date of incineration, the origin of the material, the label i.d. number, the nature of the material, the radioactivity at the time of incineration in MBq. The total radioactivity incinerated per day must not exceed 37 MBq in equivalents of group 4 (i.e. 1mCi).

QUALITY SOCIETY	
SOP No: 000101/001	Date:
Revision frequency: 12 months	
Management Approval:  2/5/93 NORMAN COMMITTAL	QA Approval:  3/5/93 BERNAD SURE

MEDICAL SUPERVISION OF PERSONNEL WORKING IN THE INCINERATION AREA

I GENERAL POINTS

No person under the age of 18 and no woman will be allowed to work within this area. Under no circumstances, even on a temporary basis, will non-company personnel or students etc. be allowed to work in this area.

II DECLARATION OF RISKS

Since the incineration area is a part of the research centre which will contain radioactive material for a short time, the area is considered as a controlled zone and is, therefore, subject to a weekly declaration of radioactive exposure.

III MEDICAL SUPERVISION

Radioactivity dose-meter badges

Personnel working within the incinerator area must wear a radioactivity dose-meter badge at all times. These badges are to be renewed on a monthly basis. The senior responsible technician is in charge of ensuring that the badges are changed regularly as required.

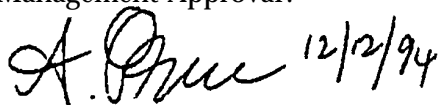
Urine examination

All personnel working in this area will undergo regular examinations concerning the radioactive level in 24-hour urine. The required container, necessary for the collection of the 24-hour urine sample, is obtained from the company medical service. The request for containers must be made 3 weeks prior to the day of the collection.

The urine should be transferred to the company medical service as soon as collection is complete. The container should be accompanied by the form, correctly filled out, which is attached to this SOP.

Haematological examinations

At the discretion of the company medical service, blood samples will be drawn from personnel working in this area on a regular basis. Samples will be examined for the following parameters: Blood cell count, Differential white cell count, Platelets.

QUALITY SOCIETY	
SOP No: 00101/002	Date:
Revision frequency: 12 months	
Management Approval:  12/2/94 ANATOLE PRICE	QA Approval: S. GONZALEZ

NON-RADIOACTIVE WASTE – CLASSIFICATION, PACKAGING AND DESTRUCTION

I CLASSIFICATION

This waste is classified into two types:

- Non-contaminated waste
- Contaminated waste

II DEFINITION AND TREATMENT OF NON-CONTAMINATED WASTE

Definition

Non-contaminated waste can be assimilated with household waste. It includes used objects in current use such as office materials, paper, documents, archives, broken glass, used pens etc. Remember that any object liable to cut must be placed in a container to protect personnel.

Disposal/destruction

Non-contaminated waste is placed in regular bins which are distributed all over the research site. Confidential documents and sensitive archives should be incinerated.

III DEFINITION AND TREATMENT OF CONTAMINATED WASTE

Definition

This kind of waste is a result of normal research activities in biomedical sciences and in chemistry. Principally, the following are considered as contaminated:

- waste including animal bodies, or parts thereof, litter from cages and any other material soiled by biological liquids
- feed waste, used culture media, single-use towels or swabs, Petri dishes, bench-coats etc., any material that may be contaminated by use in a microbiology laboratory.

Packaging

Waste including animal cadavers and waste from autopsies is placed in black polyethylene bags (60-100 microns thick).

If necessary these bags may then be placed in rigid containers.



Waste other than anatomical waste is placed in transparent polyethylene bags of 100 micro thickness.

Storage and disposal

These bags are placed in 50L bins and transferred to the incinerator area by the technician of the service having produced them. The bags are then placed in a cold store for a period not longer than 48 hours prior to incineration.

Destruction

Any contaminated waste must be destroyed by incineration within 48 hours. The management of this turnover in the cold store is in the hands of the technician responsible for the incineration area. If for any reason this is not possible (incinerator maintenance or repair) the bags must be placed in the freezer located in the incineration area while awaiting incineration.

QUALITY SOCIETY	
SOP No: 00102/001	Date:
Revision frequency: 12 months	
Management Approval:  I.N. COMPITENT 5/12/94	QA Approval:  S. GONZALEZ 6/12/94

**RADIOACTIVE WASTE – CLASSIFICATION, PACKAGING,
LABELLING, DESTRUCTION OR REMOVAL**

I CLASSIFICATION

Because the radioactivity, this type of waste should be classified as contaminated or dangerous. There are 3 types of radioactive waste:

- 1) Waste which should be incinerated immediately.
- 2) Solid waste which must be stored for a period so that radioactive decay occurs before incineration or removal by an outside contractor.

II PACKAGING

- A) All liquid waste is placed in black polyethylene bags, 60-100 microns thick, and sealed. The contents may be mixed with sawdust.
- B) Waste that is to subjected to a period of decay and is therefore stored before destruction, is also placed in metal bins which are also sealed. The bins are then placed in the appropriate locality awaiting the moment to perform the incineration.
- C) Liquid radioactive waste is evacuated into holding tanks with a constant measurement of radioactive levels. This is addressed in a separate SOP.

III LABELLING

A) In accordance with the legislation in force, all radioactive waste must be identified clearly with an appropriate label. Only labels issued and managed by the “Safety Department” are to be used.

B) Three types of labels are in use:

***Radioactive Waste**
Immediate incineration

These labels are beige in colour and should be used on bags containing radioactive waste for immediate destruction by incineration.

***Radioactive Waste**
For decay

These labels are red in colour and are to be used only on these bags which contain material for delayed destruction, i.e. after decay.

***Liquid Radioactive Waste**

These labels are applied to the holding tanks.

C) The following information should be recorded on the labels which are to be applied to the bags:

- date
- the radio element concerned and the group to which it is attributed in terms of its activity
- the total activity of the contents in (Ci.

Labels which are to be applied to holding tanks should have the following information on them:

- tank number
- date of sealing the tank
- the radioelement, group and total activity in (Ci
- the residual activity in (Ci at the date of incineration (or release)).

IV DESTRUCTION OF REMOVAL

A) Waste for immediate incineration

Waste that is correctly bagged and labelled must be immediately taken to the incinerator block by the personnel of the departments which produced the waste.

The bags are placed in the identified containers in the incinerator block.

The technician responsible for the operation of the incinerator should ensure that the waste is incinerated as soon as possible, taking into consideration the total daily quantity of radioactivity which can be incinerated.

B) Waste after decay-period

This waste, properly bagged and identified, is also transferred to the incinerator block by the personnel responsible for its production, and who are equally responsible for ensuring that the material has undergone the correct length of time for decay.

The technician responsible for the incinerator will incinerate this waste as soon as possible, taking into account the total daily quantity of radioactivity which can be incinerated.

C) Waste collected by a specialized service

The waste concerned here is generally animal cadavers and waste such as faeces and sawdust from the cages. The volumes are such that incineration may not be possible on-site. Or the high level of radioactivity is such that it is preferable to request the intervention of a specialized service.

This waste is stored in freezers until removed by the outside contractors. The frequency and manner of removal by the contractor is the subject of a separate SOP.



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