

HANDBOOK

GOOD LABORATORY PRACTICE (GLP)

Quality practices
for regulated non-clinical
research and development



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



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The Good Laboratory Practice (GLP) Handbook is designed to serve as an aid for those countries who wish to upgrade their laboratories to GLP status. It has been developed as part of a significant and wide-ranging technology transfer and capacity building programme in the area of pre-clinical product development for disease endemic countries.

The GLP Handbook has been produced by a Scientific Working Group (SWG) on GLP issues, convened by the UNDP / World Bank / WHO Special Programme for Research & Training in Tropical Diseases (TDR), which consisted of independent scientific specialists from around the world. The Handbook is broadly based on the Organisation for Economic Cooperation and Development (OECD) principles of GLP. The Handbook will provide laboratories in disease endemic countries, and trainers throughout these nations, with the necessary technical aid for implementing GLP programmes.

TDR gratefully acknowledges the participation and support of all those involved in the production of this Handbook and, in particular, the OECD who also kindly permitted reprint of both the OECD Principles of Good Laboratory Practice and the related documents.

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FOREWORD

To enjoy the advantages of new or improved methods for the control of tropical diseases, the countries in which these diseases are endemic will need to rely to a large extent on their own research activities. It is necessary to strengthen the capacity of these countries to perform research and drug product development studies at a level comparable with that demonstrated in other parts of the world. Good practice rules govern drug product development activities in many parts of the world. World Health Organization (WHO), which has published documents on good manufacturing practices (GMP) and good clinical practices (GCP), has not previously recommended or endorsed any quality standard governing the non-clinical phases of drug product development. Good laboratory practices (GLP) are recognized rules governing the conduct of non-clinical safety studies, ensuring the quality, integrity and reliability of their data. To introduce the concepts of GLP to scientists in developing countries, workshops on GLP have been organized in these regions. As an outcome of the workshops, it became apparent that some formal guidance would be needed for the successful implementation of the GLP standards.

The first scientific working group on GLP issues was convened on 25 November, 1999, in Geneva, to discuss quality issues in general and the necessity for a WHO guidance document on GLP in particular. The working group concluded that it was important to avoid the co-existence of two GLP standards, the Principles of Good Laboratory Practice of the Organization for Economic Cooperation and Development (OECD) being the internationally recognized and accepted standard, and recommended that the OECD Principles be adopted by WHO/TDR as the basis of this guidance document. The experts also recognized the need to address quality issues in areas other than the strictly regulated safety studies for regulatory submission, and recommended that some explanation be included in this guidance document. The working group further recommended that:

- WHO/TDR should request OECD's permission to publish the existing OECD GLP text with a WHO endorsement, and to supplement it with an explanatory introduction.

- WHO/TDR should promote/participate in GLP training in various regions of the world.
- WHO/TDR should prepare a guideline on the practical implementation of GLP in laboratories.
- WHO/TDR should prepare a volume containing:
 - Explanatory text to GLP.
 - OECD Principles of GLP.
 - Important issues in the performance of studies that fall outside of the GLP remit.
 - Need for, and development of, compliance monitoring systems.
 - Financial considerations of GLP implementation.
 - Training and education package(s).
 - Guide to stepwise implementation of GLP.

At its second meeting (Geneva, 4-6 September, 2000), the scientific working group on GLP issues discussed the material which had been prepared in the meantime. It concluded that it was not possible to address issues of quality both within and outside of the regulated sector of drug development and testing, in one and the same document. It therefore recommended that:

- Two documents should be developed from the proceedings of the meeting. These documents would address the quality of research data but at different levels, i.e. non-regulatory and regulatory (GLP).
- The first document should contain all sections dealing with GLP and should be published as soon as ready.
- A second document, addressing quality issues in biomedical research in general, should be produced as a draft and be circulated for comments.

The present WHO Handbook on GLP is the result of these deliberations, and it addresses aspects of regulatory safety studies which are covered and governed by the OECD Principles of GLP. The quality aspects of studies outside this regulated area (e.g. basic research, early development) will be discussed on a broader basis and are therefore not included here.

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1. INTRODUCTION TO THE TDR HANDBOOK ON GLP

GENERAL INTRODUCTION

The need for application of quality standards in drug research, development and testing: the situation of developing countries and the role of TDR

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Tropical diseases are a major public health problem in developing countries. For many of these diseases there are no new, effective and affordable medicines, while older therapeutic agents are beginning to lose ground on account of the emergence of resistance against them. The multinational pharmaceutical companies have not traditionally focused on these indications in their development programmes, which is why WHO has created research and development programmes in a number of priority areas such as malaria. WHO's Special Programme for Research and Training in Tropical Diseases (TDR) commissions studies to be conducted in the areas most affected by such diseases. If such programmes are to be successful – that is to say, result in the successful registration of effective and safe new drug products – it is evident that the component studies must comply with current quality standards in order to ensure the quality, reliability and integrity of data and to protect public health. National regulations require therefore that internationally accepted rules, i.e. good manufacturing practice, good laboratory practice, and good clinical practice, are followed in the respective stages of the development and life cycle of a drug product (see the diagram on product development, page 7).

WHO has already published standards for good manufacturing practices (GMP)¹ (covering the manufacture of drug product) and for good clinical practices (GCP)²

¹ *Quality assurance of pharmaceuticals: A compendium of guidelines and related materials. Volume 2, Good Manufacturing Practices and Inspection.* Geneva, World Health Organization, 1999.

² *Guidelines for Good Clinical Practices (GCP) for trials on pharmaceutical products.* Geneva, World Health Organization, 1995.

(covering clinical trials in human, to establish efficacy and safety). However WHO has not yet addressed quality standards for non-clinical testing for the safety of potential products, good laboratory practice (GLP).

Since the introduction of GLP quality standards in test facilities of developing countries was seen as an urgent issue, TDR set up a working party (Scientific Working Group on GLP issues), which convened in 1999 and 2000 to discuss how to present the WHO position on GLP.

During the discussions on this issue, it became first of all clear that, for test facilities in developing countries, the introduction of GLP quality measures may be impeded by the difficulty of obtaining adequate resources (e.g. facilities, equipment, trained personnel) or the instability of the infrastructure (e.g. water or electricity supply), either within the testing laboratory itself or in the community as a whole. On the other hand, investments in GLP quality standards would result in tangible returns in the number of studies placed with research organizations within these developing countries, resulting in an increase in funding. Conversely, it is clear that, where money is scarce, sponsors will not invest in studies if the reliability of results cannot be assured. Specifically, WHO/TDR would be reluctant to allocate its limited funding to non-clinical safety studies unless the results could be depended on to support decisions taken concerning future progress of a particular compound through the clinical stages to eventual registration.

From the deliberations of the Scientific Working Group on GLP issues, it further became clear that:

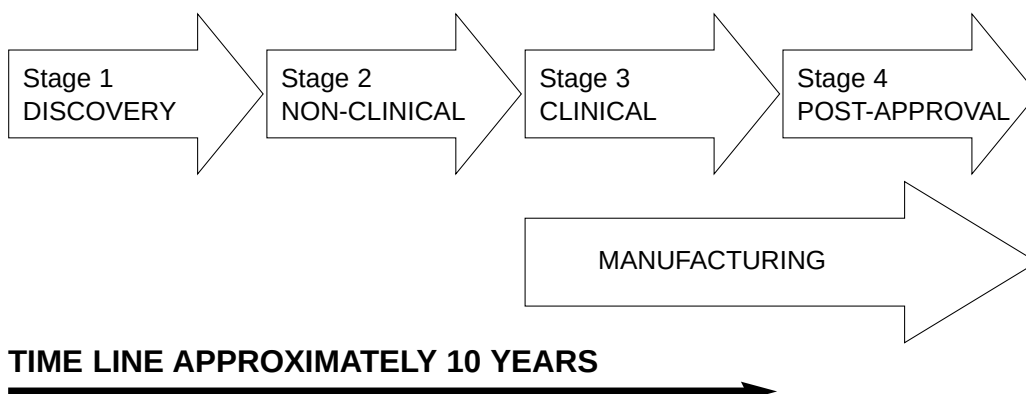
- Demonstrating compliance with GLP will become a prerequisite for clinical testing and drug registration in developing countries, and certainly if drug products are to be exported to countries other than the country of origin.
- It is essential to avoid the co-existence of two or more international regulatory GLP standards for non-clinical safety testing.
- Guidance is needed for the implementation of GLP.

With such considerations in mind, to adopt the revised Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice as the officially endorsed WHO/TDR regulation in the area of non-clinical safety testing was seen as the most rational way forward. In this handbook, these Principles are presented in their original text, supplemented by a training section and a guideline for implementing GLP.

The drug development process and the non-regulated vs. regulated areas

The drug development process can be divided into a number of distinct phases, which may overlap in time (e.g. clinical Phase 1 studies will be started before the toxicology studies of longer duration will have been finished; carcinogenicity studies may not even have been started at this time point).

Usually, drug research starts with basic research, the results of which may then be used to define efficacy targets for the potential drug. In established pharmaceutical companies, the discovery phase often involves testing thousands or even tens of thousands of compounds in screening assays for the desired pharmacological effect. The ten or twenty “survivors” would then be checked for potential toxic effects again in screening-type tests, reducing further the number of potential drug substances to be taken into full development. In countries without an established pharmaceutical industry, the discovery process may take a different form. In this case, the initial identification of potential compounds is likely to come from a medical or scientific research institution, possibly attached to a university or centre of learning. For example, a population may traditionally use a botanical remedy for certain indications. After observational studies to ascertain whether the practice is sound, one could set out chemical studies to find the active Principles, and perhaps prepare a set of chemical analogues. The number of starting compounds would, in this case, be much more modest, but this does not fundamentally alter the process as such, since the need for rigorous testing further along in the development will remain the same. Any work conducted after this selection process and further along the development pathway will finally contribute to the overall assessment of safety and efficacy of the candidate compound, and therefore,



the investigations to be performed during these subsequent stages are regulated by internationally accepted guidelines and quality requirements.

Classical drug development (drug life cycle) is characterized by four well-defined stages, summarized in the diagram on page 7.

STAGE 1

The first stage, the discovery of potential new drug products, is not covered by a regulatory standard, nor are studies demonstrating proof of concept. This area may well require some international standards or guidance documents in the future.

STAGE 2

The position of GLP studies within the drug development process is specific to the second stage. These studies are termed “non-clinical” as they are not performed in human. Their primary purpose is safety testing. Toxicology and safety pharmacology studies, with a potential extension to pharmacokinetics and bioavailability, are those studies where the compliance with GLP is required. From the diagram above, the rather restricted scope of GLP is evident.

STAGE 3

The third stage, following on from safety studies, encompasses the clinical studies in human. Here, GCP is the basis for quality standards, ethical conduct and regulatory compliance. GCP must be instituted in all clinical trials from Phase I (to demonstrate tolerance of the test drug and to define human pharmacokinetics), through Phase II (where the dose-effect relationship is confirmed), to Phase III (full-scale, often multi-centre, clinical efficacy trials in hundreds of patients).

STAGE 4

The fourth stage is post-approval. Here the drug is registered and available on the market. However, even after marketing, the use of the drug is monitored through formalized pharmacovigilance procedures³. Any subsequent clinical trials (Phase IV) must also comply with GCP.

³ WHO Programme for International Drug Monitoring. Uppsala, Sweden.

GOOD MANUFACTURING PRACTICE (GMP)

From stage 3 of development and continuing throughout the rest of the drug's lifetime, GMP applies to all manufacturing of bulk and formulated product.

This handbook on GLP is clearly restricted to dealing with the regulated area (stage 2 of the above diagram) of “...the non-clinical safety testing of test items contained in pharmaceutical products ... required by regulations for the purpose of registering or licensing ... The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment.” (OECD Principles of GLP).

INTRODUCTION TO GLP AND ITS APPLICATION

The history of GLP

The formal concept of ‘good laboratory practice’ first evolved in the USA in the 1970s because of concerns about the validity of preclinical safety data submitted to the Food and Drug Administration (FDA) in the context of new drug applications (NDA). The inspection of studies and test facilities had yielded indications for, and instances of, inadequate planning and incompetent execution of studies, insufficient documentation of methods and results, and even fraud. For example, replacing animals which died during a study by new ones (which had not been treated appropriately with the test compound) without documenting this fact; taking haematology data for control animals from control groups not connected with the study; deleting necropsy observations because the histopathologist received no specimens of lesions; or re-correcting discrepancies in raw data and final report tables by juggling around the raw data in order to ‘fit the results tables’ to the final report. These deficiencies were made public in the so-called Kennedy Hearings of the US Congress, and the political outcome of these subsequently led to the publication, by the FDA, of Proposed Regulations on GLP in 1976, with the respective Final Rule coming into effect in June 1979 (21 CFR 58). These regulations were intended to provide the regulatory basis for assurance that reports on studies submitted to the FDA would reflect faithfully and completely the experimental work carried out. In the chemical and pesticide field, the US

Environmental Protection Agency (EPA) had encountered similar problems with study quality and issued its own draft GLP regulations in 1979 and 1980, publishing the Final Rules in two separate parts (40 CFR 160 and 40 CFR 792, reflecting the different legal bases) in 1983.

On the international level, the OECD, in order to avoid non-tariff barriers to trade in chemicals, to promote mutual acceptance of non-clinical safety test data, and to eliminate unnecessary duplication of experiments, followed suit by assembling an expert group who formulated the first OECD Principles of GLP. Their proposals were subsequently adopted by the OECD Council in 1981 through its “Decision Concerning the Mutual Acceptance of Data in the Assessment of Chemicals” [C(81)30(Final)], in which they were included as Annex II. In this document, the Council decided that data generated in the testing of chemicals in an OECD member country in accordance with the applicable OECD Test Guidelines and with the OECD Principles of Good Laboratory Practice shall be accepted in other member countries for purposes of assessment and other uses relating to the protection of man and the environment. It was soon recognized that these Principles needed explanation and interpretation, as well as further development, and a number of consensus workshops dealt with various issues in subsequent years. The outcome of these workshops was then published by OECD in the form of consensus documents. After some 15 years of successful application, the OECD Principles were revised by an international group of experts and were adopted by the OECD Council on 26th November 1997 [C(97)186/Final] by a formal amendment of Annex II of the 1981 Council Decision.

These revised OECD Principles of Good Laboratory Practice, as well as the pertinent consensus documents, are reprinted as Annexes of this handbook.

A number of OECD member countries have adopted these Principles in their national legislation, notably the amendment of the European Union in Commission Directive 1999/11/EC of 8 March, 1999 to the Council Directive 87/18/EEC of 18 December, 1986, where GLP had first been introduced formally into the European legislation.

Internationally, the observance of GLP has thus been defined as a prerequisite for the mutual acceptance of data, which means that different countries or regulatory authorities accept laboratory studies from other countries as long as they follow the internationally accepted GLP Principles. This mutual acceptance of safety test data will also prevent the unnecessary repetition of studies carried out in order to comply with any

single country's regulations. In order to facilitate further the mutual acceptance of data and to extend this possibility to outside countries, the OECD Council adopted, on 26 November 1997, the 'Council Decision concerning the Adherence of Non-member Countries to the Council Acts related to the Mutual Acceptance of Data in the Assessment of Chemicals' [C(81)30(Final) and C(89)87(Final)] [C(97)114/Final], wherein interested non-member countries are given the possibility of voluntarily adhering to the standards set by the different OECD Council Acts and thus, after satisfactory implementation, to join the corresponding part of the OECD Chemicals Programme. Mutual acceptance of conformity of test facilities and studies with respect to their adherence to GLP, on the other hand, necessitated the establishment of national procedures for monitoring compliance. According to the OECD Council 'Decision-Recommendation on Compliance with Principles of Good Laboratory Practice' of 2 October 1989 [C(89)87(Final)], these procedures should be based on nationally performed laboratory inspections and study audits. The respective national compliance monitoring authorities should exchange not only information on the compliance of test facilities inspected, but should also provide relevant information concerning the countries' procedures for monitoring compliance. Although devoid of such officially recognized national compliance monitoring authorities, some developing countries do have an important pharmaceutical industry, where preclinical safety data are already developed under GLP. In these cases, individual studies are – whenever necessary – audited by foreign GLP inspectors (e.g. of FDA, the Netherlands or Germany).

What is GLP?

Good Laboratory Practice is defined in the OECD Principles as: "...a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported." The purpose of these Principles of Good Laboratory Practice is thus to promote the development of quality test data and to provide a managerial tool to ensure a sound approach to the management, including conduct, reporting and archiving, of laboratory studies. The Principles may be considered as a set of criteria to be satisfied as a basis for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions, and the traceability of data. Consequently the Principles require institutions to allocate roles and responsibilities in order to improve the operational management of each study, and to focus on those aspects of study execution (planning, monitoring, recording, reporting, archiving) which are

of special importance for the reconstructability of the whole study. Since all these aspects are of equal importance for compliance with the Principles of GLP, there cannot be any possibility of using only a choice of requirements and still claiming GLP compliance. No test facility may thus rightfully claim GLP compliance if it has not implemented, and if it does not comply with, the full array of GLP rules.

The GLP Principles in their strict, regulatory sense apply only to such studies on pharmaceuticals which:

- Are non-clinical, i.e. are mostly conducted in animals or in vitro, and include analytical aspects.
- Are conceived to obtain data on the properties and/or safety with respect to human health and/or the environment of the tested substances.
- Are intended to be submitted to a national registration authority for the purposes of registering or licensing the tested substance or any product derived from it.

In general, and depending on national legal requirements, the GLP requirements for non-clinical laboratory studies conducted for safety evaluation in the field of drug safety testing cover the following classes of studies:

- Single dose toxicity.
- Repeated dose toxicity (sub-acute and chronic).
- Reproductive toxicity (fertility, embryo-foetal toxicity and teratogenicity, peri-/post-natal toxicity).
- Mutagenic potential.
- Carcinogenic potential.
- Toxicokinetics (pharmacokinetic studies which provide systemic exposure data for the above studies).
- Pharmacodynamic studies designed to test the potential for adverse effects (safety pharmacology).
- Local tolerance studies, including phototoxicity, irritation and sensitization studies, and testing for suspected addictivity and/or withdrawal effects of drugs.

Irrespective of the place of study conduct, the GLP Principles generally apply to the relevant studies planned and conducted in a manufacturer's laboratories, at a contract or subcontract facility or in a university or governmental laboratory.

GLP is not directly concerned with the scientific design of a study. The scientific design of a study (i.e. with regard to the test system used and the scientific state-of-the-art of its conduct) is governed by the applicable testing guidelines and its scientific

value is judged by the (drug) regulatory authority; it is not a goal of GLP. Nevertheless, strict adherence to GLP will remove many sources of error and uncertainty. Through the application of 'technically valid' and approved standard operating procedures, many sources of systematic errors and artefacts can be avoided. The requirement to formulate a study plan with a defined (scientific) purpose of study will prevent false starts and diminish the incidence of incomplete or inconclusive studies. Respecting the GLP Principles will thus indirectly optimize the scientific yield of such studies.

It has to be reiterated that, in introducing GLP in a test facility, and in the training for its application, it is important to clearly differentiate between the formal, regulatory use of the term "good laboratory practice", as opposed to the general application of "good practices" in scientific investigations. Since the term "good laboratory practice" is not a trade-mark protected term, any laboratory which may consider itself to be following good practices in its daily work might be tempted to describe its adherence to these (possibly even self-defined) quality standards by this terminology.

It has to be clearly stated, however, that only adherence to, and compliance with, all the requirements set forth in the OECD Principles will constitute real compliance with GLP, and that therefore any use of similar terminology for the description of quality practices outside of the scope of GLP proper should be emphatically discouraged.

2. GOOD LABORATORY PRACTICE TRAINING

INTRODUCTION

The history, scope of and the reasons for, GLP are described in the Part 1. This part of the Handbook should be used in conjunction with the detailed TDR's GLP Training Manuals. It may be useful, however, to repeat here a few facts on GLP which may help in understanding the requirements and their use in safety related studies.

Regulatory GLP started when the US Food and Drug Administration (FDA) issued mandatory requirements, which came into force on 20 June, 1979, reacting to instances of malpractice and fraud in the non-clinical testing of drugs by some pharmaceutical companies and contract research organizations. Subsequently, the FDA has revised these regulations a number of times but has never changed the basics, i.e. the scope of the regulations still applies to non-clinical studies used to evaluate safety only. Preliminary pharmacological studies and pharmacokinetic studies not designed to test safety are thus exempt from GLP requirements. A little later, the OECD issued Principles for GLP concerning the testing of any chemical substances; these were revised in 1997 to reflect developments. Since the OECD member states have agreed to accept studies which are conducted in compliance with these Principles in any other member state, the Principles have dominated GLP world wide. The world wide acceptance of the OECD Principles was even more accentuated when the OECD issued a council decision on the voluntary adherence of non-member states. This fact is the reason why these GLP Principles have been published as an Annex to this handbook, and are used as the basic rules for the WHO/TDR training programme.

In the WHO/TDR efforts to promote development of therapeutic substances against various tropical diseases, the conduct of studies in developing countries is a matter of high priority. In order that such studies are readily accepted by regulatory authorities world wide, the introduction of GLP in laboratories conducting non-clinical safety studies is of major importance. To achieve this goal in regions where there is limited knowledge of, and experience with, formal quality concepts like GLP, efforts have to be undertaken to instruct and train people to enable them to work according to these

standards. Therefore, TDR is actively promoting this kind of 'technology' or 'knowledge transfer' by means of training courses which are intended to provide a basis for understanding the concept of GLP and the practical application of the Principles.

The training course has, however, a two-fold purpose. On the one hand, it aims to transmit increased awareness for quality in the conduct of scientific studies, which could benefit all kinds of investigations in research and development. The introduction of the notion of quality in non-regulated environments should thus be encouraged. On the other hand, it aims to ensure full compliance with GLP when this quality system is introduced in a laboratory.

THE FUNDAMENTAL POINTS OF GLP

While the regulations fix the rules for good laboratory practices in a managerial, administrative way, they also help the researcher to perform his work in compliance with his/her own pre-established plan, and they standardize planning, recording, reporting and archiving procedures. The regulations are not concerned with the scientific or technical content of the studies conducted in compliance with them, and they do not aim to evaluate the scientific value of the studies, as this latter task is reserved for the registration authorities. However, the requirements for proper planning, for the faithful recording of all observations and for the complete archiving of all raw data obtained, will serve to eliminate many sources of error in the studies conducted in compliance with these regulations.

Good laboratory practice, applied in whatever the industry targeted, stresses the importance of the following main points:

- Resources: Organization, personnel, facilities, equipment.
- Rules: Protocols, Standard Operating Procedures, concept of the Study Director as the pivotal point of study control.
- Characterization: Test items, test systems.
- Documentation: Raw data, final report, archives.
- Quality assurance: Independence from study conduct.

The WHO/TDR training programme takes each of these five fundamental points in turn and explains the rules of GLP in each case. The major points are summarized below and are further detailed in the following sections.

Resources

ORGANIZATION AND PERSONNEL

GLP regulations require the structure of the research organization and the responsibilities of the research personnel to be clearly defined. This means that the organizational chart should reflect the reality and be kept up-to-date. The organizational chart and job descriptions give an immediate idea of the way in which the laboratory functions, and of the relationships between the different posts.

GLP stresses that the number of personnel must be sufficient to perform the tasks required in a timely and GLP-compliant way. The responsibilities of all personnel should be defined and recorded in job descriptions, and their qualifications and competence defined in training and education records. GLP attaches considerable importance to the qualifications of staff, and to both internal and external training given to personnel, in order to maintain levels of excellence.

A point of major importance in GLP is the position of the Study Director, who is the pivotal point of control for the whole study. This individual will have to assume full responsibility for the GLP compliance of all activities within the study, and he will have to assert this at the end of the study in a dated and signed compliance statement. She/he has therefore to be aware of all occurrences that may influence the quality and integrity of the study, to judge their impact and to institute corrective actions, as necessary.

FACILITIES AND EQUIPMENT

The GLP Principles emphasize the adequacy of facilities and equipment, which have to be sufficient to perform the studies. The facilities should be spacious enough to avoid problems such as overcrowding, cross contamination, confusion between projects and cramped working conditions. Utilities (water, electricity, etc.) must be adequate and stable.

All equipment must be in working order. A strict programme of validation, qualification, calibration and maintenance attains this. Keeping records of use and maintenance is essential in order to know, at any point in time, the precise state of the equipment.

Rules

PROTOCOLS

The principal steps of studies conducted in compliance with GLP have to be described in the study protocol. Thus the Study Plan or Protocol serves to outline the conduct of the study demonstrating at the same time that adequate planning is provided. The Protocol has therefore to be adopted by the Study Director through dated signature before the study starts, and alterations to the study design cannot be made unless by formal amendment procedures. All this will ensure the reconstructability of the study at a later point in time.

WRITTEN PROCEDURES

It will not be possible to describe in the protocol all the technical details of the study. Since the possibility for exact reconstruction of studies is a *sine qua non* for the mutual acceptance of data, 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.

But procedures cannot be fixed for all time, since this would lead to the use of out-dated methods and procedures; they have to be adapted to developments in knowledge and technical progress. They must, therefore, be reviewed regularly, and modified, if necessary, so that they reflect the actual 'state of the art'. Finally, it is important that, for ease of consultation, SOPs are available directly at the work place, and in the current version only.

THE STUDY DIRECTOR

This is the single most important individual in a GLP study, as he/she represents the pivotal point of study control. The Study Director is the person fully responsible for GLP compliance in a study: is responsible for the adequacy of the protocol, and the GLP compliant conduct of the study. The Study Director has to formally accept responsibility for GLP compliance by signing the compliance statement.

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 intended to evaluate the safety-related properties of pharmaceutical compounds during the preclinical phase, it is a prerequi-

site to have detailed knowledge about the properties of the test item, and of the test system (often an animal or plant) to which it is administered.

Characteristics such as identity, purity, composition, stability, impurity profile, should be known for the test item, for the vehicle, and for any reference material.

If the test system is an animal (which is very often the case), it is essential to know such details as its strain, health status, and normal biological values.

Documentation

RAW DATA

All studies generate raw data which are, on the one hand, the results of the investigations and represent the basis of the conclusions, but which, on the other hand, also document the procedures and circumstances under which the study was conducted. Some of the study results will be treated statistically, while others may be used directly. Whatever the case, the results and their interpretation provided by the scientist in the study report must be a true and accurate reflection of the raw data.

STUDY 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

Since a study may have to be reconstructed after many years, and the records must be stored for long periods of time but be available for prompt retrieval, the safekeeping of all records must be ensured. Archiving of the raw data and other essential documents must be such that data are kept in an integer state and can neither be lost nor altered; to achieve this goal, it is usual practice to restrict access to archives to a limited number of people and to maintain records of log-in and log-out for both documents and people.

Quality assurance

Quality assurance (QA), as defined by GLP, is a team of persons charged with assuring the management that GLP compliance has been attained in a test facility as a whole as

well as within each study. QA has to be independent of the operational conduct of the studies, and it functions as witness to the whole preclinical research process.

RESOURCES

Facilities: buildings and equipment

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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 does mean careful consideration of the objectives and how to achieve them.

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, e.g. by 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, maintaining separation of staff, or 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 work flow: receipt, storage, dispensing, weighing, mixing, dispatch to the animal house and waste disposal.

Size

The laboratory should be 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 of mixing up different materials.

Each operator should have a workstation sufficiently large to enable him/her to carry out the operation efficiently. There should also be 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 compound by another.

Construction

The laboratory has to be built of materials that allow easy cleaning but do not allow test materials to accumulate and cross-contaminate others. There should be a ventilation system that provides air-flow away from the operator through filters which both protect personnel and prevent cross-contamination. Most modern dose mixing areas are now designed in a 'box' fashion, each box having an independent air system.

Arrangement

There should be separate areas for:

- Storage of test items under different conditions.
- Storage of control items.
- Handling of volatile materials.
- Weighing.
- Mixing of different dose formulations, e.g. in the diet or as solutions or suspensions.
- Storage of prepared doses.
- Cleaning equipment.
- Offices and refreshment rooms.
- Changing rooms.

ANIMAL FACILITY

To minimize the effects of environmental variables on the animal, the facility should be designed and operated so as to prevent the animals coming into contact with disease, or with a test item other than the one under investigation.

Requirements will differ depending upon the nature and duration of the studies being performed in the facilities.

The risks of contamination can be reduced by a 'barrier' system, where all supplies, staff and services cross the barrier in a controlled way, as well as by providing 'clean' and 'dirty' corridors for the movement of new and used supplies.

A typical animal house would therefore have this required 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 at control system should maintain the temperature, humidity and airflow constantly at the defined levels for the species concerned.

The surfaces of walls, doors, floors and ceilings should be easy to clean completely, with no gaps or ledges where dirt and dust can build up, or no uneven floors where water can build up.

Whatever the capabilities or needs of your laboratory, sensible working procedures reduce the 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, if the construction of the facility does not permit other solutions, with corridors being cleaned between these times.
- Requiring staff to put on different clothing for different zones within the animal facility.
- Ensuring that rooms are cleaned and sanitized, if necessary, between studies.

EQUIPMENT

Appropriate equipment of adequate capacity should be available for the proper conduct of the study. All equipment should be suitable for its intended use, and it should be properly calibrated and maintained to ensure accurate performance. Records of repairs and routine maintenance, and of any non-routine work, should be retained.

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 tasks which the equipment is expected to perform. 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, a balance of this precision may well be required in the analytical laboratory. Adequate capacity is also needed to perform the tasks in a timely manner.

Calibration

Equipment that is performing to specification, whether it is used to generate data (e.g. analytical equipment or balances) or to maintain standard conditions (e.g. refrigerators 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 calibrated 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 and provides a basis from which to calculate the final result. Other equipment, such as air conditioning systems for animal housing or constant temperature storage rooms, 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 operating out of specification limits.

Maintenance

The GLP requirement that equipment should be maintained, ensures that equipment performs constantly to specification and reduces the likelihood of 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 is undertaken 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.
- For equipment, such as modern computer driven analysers or electronic balances, that does not easily lend itself to routine maintenance of this sort, a better approach may be to check it regularly and ensure that suitable contingencies are available should a problem occur. These contingencies may include having equipment duplicated or having 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 carrying out animal studies, for example, 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, as mentioned above, should be documented in such a way that users of the equipment can be assured that it is adequately maintained and is not outside its service interval. A 'sticker' attached to equipment, or provision of a clear service plan, may ensure this.

Records of equipment calibration, checking and maintenance, demonstrate that the respective SOPs have been followed and that the equipment used was adequate for the task and was operating within its specifications.

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 all relevant staff knew about, and took, appropriate action when parameters exceeded acceptable limits.

Personnel

Although laboratory management and organizational requirements occupy about 15% of GLP texts, unfortunately they are still seen by regulators and QA as one of the principal sources of non-compliance with the letter, if not the spirit, 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. Management and organizational systems therefore are a critical element of setting up GLP in a laboratory.

The management of a test facility, of course, has overall responsibility for the implementation of both good science and good organization, including compliance with GLP.

GOOD SCIENCE

- Careful definition of experimental design and parameters.
- 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' when their project activities have been modified but without adequate allowance made for needed resources 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 systems 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 activities such as protocol review and report preparation are allocated sufficient time.
- The system is the 'official' one (i.e. there are no competing systems for the same purpose).
- The system is described in an approved SOP.
- Responsibility for maintenance and updating of the master schedule 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. Once the protocol is signed and distributed, the study is entered into the master schedule. This may or may not be a QA function in a laboratory. 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 for 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 personnel to have the competence (education, experience, training) necessary to perform their functions. Personnel competence is reflected in job descriptions, curricula vitae (CVs) and training records.

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

Definition of tasks and responsibilities / job descriptions

Any quality system is based on making people responsible for their actions. This responsibility may be described in the two sentences below:

- 'Don't do something where you don't understand the reason, the context and the consequences.'
- 'Each person signs her/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 and by at least one appropriate member of management supervising the post.

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.

A review of all job descriptions annually, or in the event of any reorganization, helps a facility's management to ensure that their organization is coherent.

Curriculum vitae

A procedure should ensure that CVs:

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

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

Training

Finally, training records complement 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 will be formal, approved, documented to a standard format, described in a Standard Operating Procedure, and with historical reconstruction possible through the archive.

RULES FOR THE CONDUCT OF STUDIES

General aspects

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

- State general policies, decisions and principles.
- Inform staff as to the correct performance of operations.
- Provide retrospective documentation of what was planned.

The document types range from general policy statements, through standard operating procedures describing routine activities, to the study plan or protocol 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 study plan or protocol

The protocol is the central document whereby the Study Director communicates the planned organization and development of the study to the staff, and by which she/he informs third parties involved, such as the quality assurance unit (QAU) or, if the study is contracted to a contract research organization, the sponsor. The protocol may also function as the basis for a contract in the latter situation. The Protocol contains the overall plan of the study, and describes the methods and materials that will be used, thus demonstrating the adequacy of advance planning.

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

CONTENT OF THE PROTOCOL

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

IDENTIFICATION

The study number provides a means of uniquely identifying all records of the laboratory connected to a particular study 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 are only utilized for purposes for which they are suited. 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 and its stability, 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 planned to be used. The name of the sponsor should also be included.

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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 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 final report is signed by the Study Director) and the experimental dates. The latter 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 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.
 - Dosing route.
 - 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 power.
- Data to be retained after the study.
- Quality Assurance. Frequently, the Protocol outlines the proposed QA programme but this is not mandatory.

APPROVAL OF THE PROTOCOL

A GLP study cannot be started before the Protocol is approved. This is done by dated signature of the Study Director. The draft Protocol should also be controlled by QA in order to assess its compliance with GLP requirements. It is good practice also that the sponsor should have agreed to the design of the study before it begins. Protocol approval should be early enough before the study starts to ensure that all staff know their scheduled duties. Also, QA should receive a copy of the approved Study Plan in order to allow them to plan their inspection activities.

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.

DISTRIBUTION OF THE PROTOCOL

All involved staff should receive a copy of the Protocol. In order to ensure that everybody does get a copy, a distribution list should be prepared, and it is often worthwhile to obtain a signature from each person and to hold 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 has to be 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, this needs to be recorded, and a protocol amendment is issued as soon as possible afterwards.

It is not acceptable practice to use the amendment to retrospectively legalize omissions or errors that occurred during the study. Such unplanned 'one off' occurrences should be documented in a file note as 'deviations' and be 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 revised 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 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 required extremely urgently by study staff, this review is often performed retrospectively.

The original signed protocol and all amendments must be lodged in 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

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

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

Remember the Deming quote: “Use standards [i.e. SOPs] as the liberator that relegates the problems that have already been solved to the field of routine, and leaves the creative faculties free for the problems that are still unsolved” (W. Edwards Deming).

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, equipment, etc.

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 ease of use, a two-tier system of SOPs 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). 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. All alterations to SOPs have to be made through formal revisions; notes and changes as handwritten margin comments are not admissible.

Understanding. Staff must fully understand the SOP and follow it rigorously. If deviations are expected or occur, easy communication with the Study Director and ma-

nagement must be allowed to ensure respect of GLP requirements and to preserve the credibility of the system.

Responsibility. 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.

Change control. A formal system should be in place 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 updating should be easy and rapid, and authorization should not involve too many signatures.

Centralized organization. This concerns issues of reporting such as formatting, numbering, issuance, modification and withdrawal, incoherence, delays, lack of traceability and incomplete distribution. Centralized organization avoids duplication of effort.

Availability. SOPs should be made immediately available to the person doing the work.

Archiving. All withdrawn SOPs, whether no longer used or superseded by a revised version, 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.
- Technical and administrative improvements.
- Demonstration of management commitment to quality as part of the SOP approval process.
- Ease of documenting complicated techniques in study protocols and reports (a simple reference to the procedure should often suffice).
- Continuity in case of personnel turnover.
- Use as training manual.
- A means of study reconstruction after the event, also after a lapse of years.

- A 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 QA review.
- Formal approval by at least two people:
 - a designated author.
 - an appropriate member of test facility management.
- A formal change control system, coordinated by a designated person/group.

During the course of the study, a general SOP (tier 1) requires all deliberate deviations to operational SOPs to 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 (e.g. no impact on the study nor, if so, the extent of impact on the study), are maintained as raw data in the study file for audit and consideration when writing the final report.

CHARACTERIZATION

The test item

The identity, activity, stability 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 by preparation of detailed records which document every stage of the test item's 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 the 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 record the receipt, identity, issue, retention (taking back), and final disposal of the test item, but in small facilities the designated person may be an authorized technician or the Study Director. The 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 study conducted by a contract laboratory (CRO), the sponsor should provide this information, as well as other details which may help in the preparation of the dose formulation, to the CRO. A standard form on which to provide this information is helpful. During development of the protocol, the sponsor fills it out to give the testing facility the essential information necessary for safe and adequate handling of the test item.

The sponsor will either supply, or indicate that he has obtained, the necessary data on chemical characterization and stability 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, e.g. 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 the 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.

The 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 the laboratory.
- Condition of goods on arrival.

Storage of the test item

Test items must be stored under closely controlled conditions, particularly with respect to access and environment. The construction of the store should ensure that only designated staff has access to the material. The stores are kept locked when not in use. Separate areas should be available for storage at ambient temperature, +4° C, and –20° C.

The storage of the 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 information will be retained by the test facility in the compound archive for the same duration as are the study raw data and specimens. Normally this sample will not be used unless some test item is required, for example for confirmatory analysis.

Test item use

Documenting each use of test item on a record form allows a running check to be kept. Not only does this provide a complete trail of all the test item used, 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 out the weighing are 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 the 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 the test item should be disposed of in an environmentally acceptable way. This final event must again be documented 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, it will be necessary to adjust the amounts to be weighed out (and to investigate what impact the impurities may have on the validity of the study).
 - Concentration of the dose, amount or volume required. The volume required will vary throughout the study with the animals' weight, 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, analysis of the documentation and data required, and operation of all equipment.
 - The method of preparation of the dose form should be tested prior to starting the study. 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 clearly recording 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 this stock concentration to obtain 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 not react with either test item or 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, as 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.

It may be useful to colour code the label for each dose, with the same colours as those on the cage labels.

Sampling and quality control of dose formulation

Analysis of the formulation is required by the protocol to fulfil GLP requirements and to ensure 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, however, to conduct some of these analyses before the study starts, to prevent waste of time and resources as well as unnecessary dosing of test system by 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 dosing is to deliver the required amount of test material to the animal accurately and consistently. Therefore, the procedure must be very conscientiously carried out and the records must confirm 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 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 kept under appropriate conditions (e.g. placed on a magnetic stirrer, on ice, etc.) 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.
- Only one dose container is open at any one time, and each dose level has its own catheter and syringe.
- All cages from one group are 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 animals are individually housed, each is returned to its 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 should identify:

- The staff involved in dosing.
- The dose given to each animal. This acts both as a confirmation of dosing of each individual and as 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

INTRODUCTION

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 the laboratory and its procedures.

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 obtain 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.

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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 QA group and the person responsible for animal care will 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) compromise the 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 the quality of a study. A documented dialogue should be established and maintained with principal suppliers. The suppliers should provide certificates of animal health, freedom from parasites, etc.

Animal order forms, transport certificates and suppliers' invoices are part of the raw data. On arrival, the animals are inspected as 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) should then be completed and joined to 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 the general SOPs on animal handling.

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 of any other activity during this and the subsequent period should be maintained.

ANIMAL IDENTIFICATION

Identification of animals must be maintained throughout the study. Most laboratories use a system of cage cards, which may be temporary before group assignment, but change to permanent status afterwards; this should be done as described in the protocol. The animal management department should use consecutive temporary numbers to ensure animal accountability. Permanent cage-cards (as for dosing materials etc.) often follow a standard internal colour code. Animal numbers should be unique within the study, and they have to 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 jar at the end of the study (after histological processing) and is archived with the wet tissues.

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 randomization tables should be included in the raw data, along with a table listing the temporary and permanent animal numbers. Rack and cage locations should be documented from this point onwards. Special attention must be given to fully documenting 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 as per SOP and should be documented in the logbook or other appropriate system. Any relevant observations made at this time (e.g. empty feeder, blood in litter) 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 in the GLP Principles that the study report has to include:

‘A description of all circumstances that may have affected the quality or integrity of the data’.

Awareness of such ‘circumstances’ depends largely on the 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 heating ventilation air conditioning (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 efficiency 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, e.g.: 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; 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 and incidence, etc.) with which control group parameters can be compared. Significant departures from the norm would then trigger review of animal care and environmental control data and procedures.

DOCUMENTATION – RAW DATA AND DATA COLLECTION

This section relates to the collection of experimental data.

Carrying out procedures and recording observations

PROCEDURES

Before embarking on any procedure, 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 at the site of the procedures.
- SOPs are written, and are available in the work areas.
- Necessary equipment and supplies are available.
- Data recording forms are available in the work area.

Before starting any procedure requiring equipment of any kind, the operator should check the equipment for correct function. 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 logbook or an equipment label.

Records and recording

Making a record is essential for 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, the study validity is compromised.

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

The data should therefore indicate:

WHAT was done

Description of what was done, demonstrating that the actions required by the protocol were carried out and including the results of the observation or measurement.

HOW it was done

It should be indicated in the data that they were collected and recorded in accordance with the methods set out in the SOPs and protocol, or, where there were deviations from these instructions, this should be indicated also.

WHEN the work was performed

Demonstration of compliance with the timings laid down in the protocol. This should be done by recording the date, and, if necessary, the time. For certain procedures

(e.g. sampling in a toxicokinetic study), very exact timing is necessary and the data must demonstrate that the schedule has been followed.

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, along with a description of the responsibilities of each.

The records are therefore a great deal more than a list of figures. All data generated during the conduct of a study should be identified and recorded directly, promptly, accurately, legibly and indelibly by the person entering them, 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. The person making the change must sign and date it.

Example:

The person making the change must sign and date it. sig. Jane Smith, 08-11-2000.

Explanation of above terms:

‘Identified’: Study number, animal number, etc., must be recorded with data in order to ensure that data mix-up does not occur. The parameter must be identified.

‘Directly’: Since the first written records are considered to constitute the raw data and must be retained, records should not be made on scraps of paper and then transcribed into a final form. When data are recorded directly by computer, the raw data are either considered to be the magnetic medium or an immediate, direct printout. Similarly, for data derived from equipment, the raw data may be a direct printout 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 accuracy determines the integrity of the study.

‘Legibly’: Data that cannot be read are useless and records that are difficult to decipher raise doubts in the minds of the reader as to 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 evident. Use indelible and waterproof ink: ballpoint pens are well suited for the purpose. Check the robustness of machine printout: some print disappears quickly as is the case with light-sensitive printouts from thermo-printers. In this case, take an authorized (signed and dated) photocopy for storage.

'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, when and by whom.

Data should be recorded and organized in such a way that supports both recording and also subsequent processes (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. A clear structure for the study file, defined up-front, helps to organize and archive the documents as they are produced in real-time, preventing loss and facilitating reference to earlier records.

QUALITY ASSURANCE UNIT

GLP defines the minimum quality assurance requirements necessary to ensure the integrity of the study and thus the validity of the 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 GLP regulations, the mandated role of the QAU in GLP is that of an 'independent' control service.

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

Study-based inspections target specific 'critical' phases of the study. 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 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 be missed.
- Logically, and out of consideration for study staff, 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 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.
- Utilities supply (water, electricity).
- Metrology.

PROCESS-BASED INSPECTIONS

Process-based inspections are also performed independently of specific studies. They are conducted to monitor procedures or processes of a repetitive nature. 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 of authenticity and GLP compliance in the data i.e. signatures, dates, handling of corrections and deviations, consistency, etc.

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

- Contents.
- Data completeness.
- Protocol compliance.
- Animal environment records.
- Test item QC/accountability.
- Dose preparation/dosing/QC records.
- Individual tables versus raw data (sample basis).
- Summary tables.
- Appendices.
- Conclusions.

Whatever the audit plan, it should exist in writing as part of the audit file.

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 statement – that the study had been conducted in compliance with the applicable Principles of GLP.

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.
- 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.

3. STEPWISE IMPLEMENTATION OF GLP

INTRODUCTION

The implementation of the OECD Principles of Good Laboratory Practice (GLP) presents problems to novice organizations not because it necessarily requires a large financial investment, but because it represents an organizational challenge.

TDR requisitioned the compilation of this document as part of an initiative to encourage laboratories working in the field of product development to comply with GLP. The aim of the document is to provide a sequential framework for implementation. Although there are many ways to achieve GLP compliance, the steps recommended here are based upon the practical experience of scientists who have already implemented GLP.

The implementation of GLP must be a collaborative effort, preferably enthusiastically supported by top management, and involving personnel practising a multitude of disciplines such as research, quality assurance, maintenance, metrology, human resources, documentation, archives. Implementation is best organized in the form of a project, with a team of persons deriving their authority directly from upper management.

It is important to remember that the whole effort depends on management setting the scope of GLP implementation by giving the project team its mandate. Management support is essential if the project is to move forward at the agreed pace. Top management should not become directly involved in the day-to-day business of the implementation process so as to retain some measure of impartiality for conflict resolution. The project team members will need to have the explicit support of their immediate superiors, since they will need relief from their usual duties, and they will need a mandate from their superiors when attending team meetings. Finally, the project team leader must have immediate access to all levels of management in all departments concerned.

IMPLEMENTATION AS A PROJECT

The project team should draw up the list of steps to be achieved within an agreed timeframe. In order not to disturb the regular work of the organization, it is unwise to be too ambitious when setting the overall time allotted to implement GLP. Experience shows that allowing 24 months for implementation is reasonable. However, it is possible to do some tasks in parallel and ‘overlapping’. These would reduce the implementation time to 18 months. This schedule will allow staff to continue their other work, albeit at a slightly reduced pace, and yet requires that a momentum be maintained in order to reach the goal of implementation.

One can maintain the momentum by setting up the main, high level steps for the project, and identifying individual tasks within each step. Each task has a responsible person and a finishing date. In addition to the person responsible for the task in question, it is advisable to appoint a second person (not necessarily senior to the first) who will critically review the work of the first person. This process of verification during the life of the project assures timely completion of each task, and helps coordinate implementation.

The project team should meet regularly (monthly) and review progress. Someone who is well versed in GLP should manage the project team. This person should be appointed by, and report directly to, upper management. The project manager must, in addition to a scientific profile, have excellent management and communication skills. If the necessary skills do not appear to be available from within the organization, it would be appropriate to request aid from external sources.

Table 1 describes the generic stages for the establishment and completion of the project.

TABLE I Approach for establishing the project

No.	Stage	Description
1	Appoint GLP implementation Project team	• Upper management appoints a project team leader. • Project team leader draws up a formal document to inform personnel of the missions and objectives of the team. • Upper management circulates the formal document to all staff and holds a project launch meeting to explain the importance of the project. • Project objectives include an overall time plan for completion of the project. • The project team leader appoints a multidisciplinary team. • Calendar dates are set for the project team meetings.
2	Establish table of tasks to be achieved during the life of the project	• An expert (internal or external to the organization) should evaluate the shortfall in meeting GLP compliance (gap analysis). The gap analysis is based on an audit of the organization over a 4-5 day period. • The essential steps for GLP implementation are suggested in Table 2. • The project team will then jointly agree on the priorities and details of the tasks necessary to achieve GLP compliance. These will be assembled in the project task table. To achieve this, the first project meetings will be held more frequently than during the rest of the project life span. • Table 3 below is a model of this type of table.

No.	Stage	Description
3	Project review meetings	• The team reviews project progress monthly. • The project task table is updated at each meeting. • The team should investigate tasks not completed on time and find solutions.
4	Project progress	• Communicate progress with all staff at regular intervals. • Communication could be organized in the form of attractive wall charts or short meetings that describe progress. • At strategic points in the project, for example when major milestones or key documents have been implemented (protocols, final reports, change control SOP, established archives, validation of major computer systems, etc.), a meeting of the whole project team with upper management should be arranged to explain progress.
5	Task implementation	• As the various tasks are completed, they are progressively implemented and become part of the routine processes of the organization. • At some stage in project implementation, a quality assurance unit (QAU) will be appointed. Once implemented, this QAU will be responsible for verifying the good functioning of all processes implemented.

No.	Stage	Description
6	Project close-out	• When all the tasks indicated in the project task table have been implemented, the project is closed out by a formal audit (4-5 days) conducted by a third party (could be the same as performed the gap analysis). • The formal close-out audit will establish the degree of GLP compliance. • Any outstanding actions required by the audit are implemented. The laboratory can then claim GLP compliance and add this to the Study Director's statement in the final reports.

STEPWISE IMPLEMENTATION OF GLP REQUIREMENTS

Table 2 shows one way forward to the full implementation of GLP over a 24-month period. The assumption is that the laboratory in question has no GLP systems or documentation in place. The stepwise process is designed to tackle the implementation in a structured way so that progress is evident. The early successes in implementation of relatively simple systems (like the system for personnel documents) will encourage personnel to continue with more difficult parts of the process. The project team will construct a very detailed project task table (shown in table 3) on the basis of the steps shown below.

TABLE II Part 1 (3 month)

Step	Content	Comments
1.1	Arrange general GLP training for all staff.	Training of 1-2 days will underline the fundamental points of GLP and the importance of GLP for the organization. There is particular emphasis on the way in which data are collected and handled.

Step	Content	Comments
1.2	Construct an organizational chart for the organization.	Ensure that the chart is signed and dated by management. Ensure that the persons responsible for the studies (future study directors), and those responsible for the quality assurance unit, are independent from each other.
1.3	Management appoints: • Project manager for GLP implementation. • Study directors. • Quality assurance personnel. • Archivist.	Management should write a formal memo of appointment in all cases, underlining the role to be played by each group of staff and the significance of each role for GLP compliance.
1.4	Prepare a standard format for the personnel documents: • Curricula vitae. • Job descriptions. • Training records.	Obtain management agreement for this format.
1.5	Compile the personnel documents for all staff using the formats agreed upon in 1.4 above.	Ensure that the persons concerned sign the CVs and training records, and that the person concerned, and his/her immediate superior, sign the job descriptions.
1.6	Write an SOP on the establishment, review and revision of organizational charts and personnel documents.	

Step	Content	Comments
1.7	Decide who will be responsible for the management of the organization's SOP system. Define the system in an SOP. All the new SOPs will be managed through the defined system.	In small organizations, the management of SOPs may be the responsibility of the QA group. It is a non-trivial task that needs careful planning. The definition should cover the way in which SOPs are written, signed off, identified, reviewed, revised, archived, issued and withdrawn.
1.8	Establish archives. Write archive SOPs.	Ensure that access to archives is restricted to as few people as practically possible. Make sure that visits by staff to archives are recorded. Make sure that no records are moved in or out of the archives without the transaction being recorded. Ensure that environmental conditions for archives are adequate, depending on the nature of the archival material. Establish security arrangements.

TABLE II Part 2 (3 months)

Step	Content	Comments
2.1	Write SOP for content, layout and format, or prepare template protocols for the studies performed by the organization.	The templates will act as detailed guidance documents for Study Directors who will be faced with the problem of constructing GLP compliant protocols in the future. Consider the approach suggested in the OECD consensus document on short-term studies. This may well be suitable for your organization.

Step	Content	Comments
2.2	Train study directors for their special roles and responsibilities in GLP.	External courses exist for this training, but if there are many staff to be trained it is worth considering internal training courses (2-3 days).
2.3	Write an SOP on the workflow (writing, review, approval, amendment, distribution and archiving) of protocols.	Do not forget to include QA review in the circuit of protocol review.
2.4	Put the template protocol to the test by using it in all studies of this type. Review problems which the use of the template reveals. Decide which other documents are necessary to support the protocol (could need methods documents or detailed SOPs for certain techniques)	
2.5	Prepare SOP for content, layout and format, or template reports for the studies performed by the organization.	The templates will act as detailed guidance documents for study directors who will be faced with the problem of writing GLP compliant reports in the future. Consider the approach suggested in the OECD consensus document on short-term studies. This may well be suitable for your organization.
2.6	Write an SOP on the workflow (writing, review, approval, amendment, distribution, archiving) of reports.	Do not forget to include QA review in the circuit of report review.

TABLE II Part 3 (6 months)

Step	Content	Comments
3.1	Agree on a system between all interested parties regarding the identification of the equipment and instruments listed above. • Write an SOP explaining the system used for the identification of equipment and instruments.	The important point is to ensure that each piece of equipment is uniquely identified. The identification numbers will be used later when acquiring raw data and to ensure traceability to operations such as calibration and maintenance.
3.2	Make master list template. List all the equipment and instruments used in the laboratory. It is best to do this sector by sector, for example: • Clinical pathology. • Analytical laboratory. • Animal house. • Microbiology. • Histology. • Pharmacy and dose preparation.	The list should include balances, pH meters, HPLC system components, and all measuring instruments that will require maintenance and/or calibration. It is not sensible to list consumable items such as glassware, nor basic equipment such as cages, desks, etc.
3.3	Physically identify all listed equipment/instruments according to the system.	
3.4	Write an SOP on the equipment logbook, its importance and use.	

Step	Content	Comments
3.5	Open a logbook for each piece of equipment.	The logbook will be used, throughout the life of the equipment, to note down all maintenance operations, all anomalies and corrective actions, etc. Once the logbook has been established, management must insist on its use.
3.6	Decide the method of maintenance and metrology for each piece of equipment (including creation of maintenance and metrology unit – maintenance responsibilities stay with operational units). Define, in SOPs, the maintenance schedule for all listed equipment.	The way in which you organize maintenance for the laboratory's equipment will depend on the amount of GLP activity and the size of the equipment park. Only large organizations will need to establish separate maintenance units, though it is a good idea to appoint a person responsible for managing the system once it has been established.
3.7	Consider which large-scale equipment or installations need to be formally qualified*. (*Qualification means collecting documentation for the installation and testing of the equipment to prove that it functions according to specification).	At facilities where animals are used in preclinical studies, it is usual to qualify the Heating Ventilation Air Conditioning (HVAC) systems in animal rooms. Equally, in microbiology laboratories, the laminar flow systems may also need qualifying. Other installations may require qualification.

Step	Content	Comments
3.8	Qualify the systems chosen for qualification.	Specialized contractors can be used to qualify systems, but in small units it is practical and cost effective to do this oneself. Qualification work needs a formal qualification protocol and a formal report after completion.
3.9	Decide which maintenance or qualification operations require external contracts. Sign contracts with contractors. The contract should contain a documentation plan to ensure traceability of the contract work.	

TABLE II Part 4 (2 months)

Step	Content	Comments
4.1	Establish quality assurance unit.	In small organizations, this unit may well only consist of one person. Upper management should issue a formal memo to define the roles and responsibilities of the QAU and the reporting line. This is well explained in the OECD Principles of GLP and in the OECD consensus document on GLP.

Step	Content	Comments
4.2	Train the QAU personnel in audit/inspection techniques.	External training programmes exist in these techniques. Preferably, pick a course which is specifically oriented to GLP. The course will be a 2-3 day session.
4.3	Write the QA programme, based on the three inspection approaches described by OECD GLP. Implement QA inspections/ audits and start the process of reporting to study directors and management.	

TABLE II Part 5 (2 months)

Step	Content	Comments
5.1	Define rules for the receipt, identification, handling and storage of all test items, reagents and reference items.	Remember that all test items need to be uniquely identified and characterized. With regard to the handling of test items and other chemicals, consider safety issues and issues relating to the stability of the items and the need to ensure that there is no cross contamination between items.
5.2	Establish how to determine the expiry of reagents and reference items. Write SOPs for the labelling of all test items, solutions, reagents and reference items.	Most laboratories fix rules regarding the dates written on bottles of common reagents. This is based on the date indicated by the manufacturer in combination with the actual date of opening the container.

Step	Content	Comments
5.3	Define rules and write SOPs for the preparation of solutions, etc. used for dose formulations.	Although each formulation will be prepared in its own way, the SOPs should clearly describe how the preparation process is to be documented, why the test is necessary (e.g. homogeneity tests, stability tests), and the manner in which the formulations will be kept and distributed to their point of use.
5.4	Define rules for the receipt, identification, handling, quarantine and husbandry of all test systems.	If the test system is an animal, the local laws on care and welfare of animals must be respected. All animals must be identified. In the case where test systems are not whole animals, definitions concerning the characterization of the system (cell line, bacterial expression, genotyping, etc.) should be established.

TABLE II Part 6 (2 months)

Step	Content	Comments
6.1	Define raw data in all operational units, and how to record the raw data.	Some raw data will be hand written. Define the way to record these data, e.g. in laboratory notebooks or on pre-established forms.
	Define the rules for the acquisition, modification and approval of raw data.	Some will be printed from equipment (e.g. balance printouts). Some raw data will be directly acquired through computerized systems. Such systems will require validation. The method for signing and storing such data will need to be established. The organization should have a single rule for how corrections to data are effected (signed, dated, etc.), justified and authorized. The system chosen must ensure a complete audit trail of the modifications.
6.2	Define the process of verification of raw data in all operational units, and all transfer and further handling of data. Define the QC steps conducted on data and reports prior to requesting QA audit.	Verification of data by someone in authority within operational units is essential. There should be defined quality control steps for the checking of data before handing on any data or study report to QA for audit. It is not the job of QA to perform 100% audits of all data supplied to them.
	Write SOPs on this verification and QC work.	These QC steps should be defined in SOPs and followed by the staff of the operational units.

TABLE II Part 7 (3 months)

Step	Content	Comments
7.1	List all computer systems used within the organization.	
7.2	Define which systems require formal validation.	Systems which require validation are those which have an impact on the quality and integrity of the preclinical studies. Use the OECD consensus document on the validation of computerized systems to help you.
7.3	Write an SOP for the validation process and its generic documents. Write formal validation protocols for the systems requiring validation.	For very complex systems it may be worthwhile seeking external help in the validation process. It will be helpful to appoint a validation team to be responsible for the validation for each system selected. QA and IS personnel must assist in writing the protocol, but the responsibility lies with the user of the system. The supplier or vendor of the system may be prepared to supply a template protocol for the system you have acquired. Remember to include validation tests to ensure that the back-up systems function and that access security (by passwords, etc.) is adequate.
7.4	Conduct the validation testing following the validation protocols.	Remember that final responsibility lies with the user, who should ensure the systems he/she uses are validated. So the user should perform the bulk of the validation protocol.

Step	Content	Comments
7.5	Write formal validation reports for the validated systems.	These should be signed off by the validators and reviewed by QA.
7.6	Formally train all staff in the use of the computer systems they need.	Keep records of the training programme. Add training to the records of all individuals.
7.7	List and then write all necessary SOPs for the use and maintenance of the system.	
7.8	Proceed to a formal 'release for use' of the system once validation and training are completed and the system SOPs have been approved.	Define who is responsible for the release.
7.9	Define the organizational rules for access rights and passwords and write an SOP for this process.	It is usual to have a centrally organized unit (normally within the IS department) responsible for the issuance of access rights. Passwords should be of a defined length and should be changed at a defined frequency.

TABLE II Part 8 (3 months)

Step	Content	Comments
8.1	Review existing SOPs and list all outstanding SOP needs.	The newly established QA group will be able to assist in establishing the list of SOPs which are still required.
8.2	Draw up a schedule to complete these SOPs. Add the names of authors and allow time for proper review prior to signature.	
8.3	Establish a master schedule for all ongoing studies in the organization. Decide who should manage this schedule, and complete SOPs regarding its management and maintenance.	
8.4	Perform a thorough 'mock inspection' to determine any remaining shortfall for GLP compliance. Draw up an action plan to address these issues.	The mock inspection is best performed by someone independent of the implementation team. Once these issues have been successfully addressed, it is possible to declare GLP compliance in your study reports.

The project is articulated around the development of a project task table. This is a very detailed table of the tasks identified to bring the organization to the level of GLP compliance. It is subsequently used as the basis for follow-up during project team meetings. This extract is simply an example of the kind of table that should be drawn up.

TABLE III Project task table for GLP implementation

Task	Person responsible	Follow-up by	Due	Status
List of all equipment.	Mr A	Mr D	02	A
Production of a master list template:				
– Analytical laboratory.	Mr B	Mr E	03	C
– Clinical pathology laboratory.	Mr C	Mr F	03	C
– Histology laboratory.	Mr L	Ms G	04	
Set up calibration records/logbooks.	Ms T	Ms Z	02	C
Production of standard logbook format:				
– Resistance meter	Ms U	Mr G	05	A
– Balances	Ms V	Ms Y	03	C
– PH meters	Ms W	Mr B	07	A
– Manometers	Ms X	Mr F	08	A
– Thermometers	Ms Y	Ms U	03	C
– Micropipettes	Mr L	Ms G	04	
Etc.	Etc.	Etc.	Etc.	Etc.

Dates due are defined as last day of month, i.e. 06 is 30th June of the year concerned
A = Awaited (the task is not yet complete) C = Completed

At the start of the project, all tasks have the status ‘Awaited’. As they are completed, the status is revised.

It is unlikely that the table will contain all tasks from the outset. It will require modifications and additions as the project progresses. The project team should authorize and include changes during regular meetings.

For a laboratory that has not implemented any GLP, the project task table is likely to run to 15-20 pages.

ANNEXES

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE MONITORING

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77

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE
AND COMPLIANCE MONITORING
Number 1

**OECD principles on Good Laboratory Practice
(as revised in 1997)**

61011

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ABOUT THE OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 29 industrialised countries in North America, Europe and the Pacific, as well as the European Commission, meet to co-ordinate and harmonize policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised Committees and subsidiary groups composed of Member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's Workshops and other meetings. Committees and subsidiary groups are served by the OECD Secretariat, located in Paris, France, which is organised into Directorates and Divisions.

The work of the OECD related to chemical safety is carried out in the Environmental Health and Safety Division. The Environmental Health and Safety Division publishes free-of-charge documents in six different series: **Testing and Assessment; Principles on Good Laboratory Practice and Compliance Monitoring; Pesticides; Risk Management; Chemical Accidents and Harmonization of Regulatory Oversight in Biotechnology.** More information about the Environmental Health and Safety Programme and EHS publications is available on OECD's World Wide Web site (see next page).

This publication was produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC).

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, FAO, WHO, UNIDO and the OECD (the Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international coordination in the field of chemical safety. UNITAR joined the IOMC in 1997 to become the seventh Participating Organization. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

This publication is available electronically, at no charge.

For the complete text of this and many other Environmental Health and Safety publications, consult the OECD's World Wide Web site (<http://www.oecd.org/ehs/>)

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FOREWORD

Chemicals control legislation in OECD Member countries is founded in a proactive philosophy of preventing risk by testing and assessing chemicals to determine their potential hazards. The requirement that evaluations of chemicals be based on safety test data of sufficient quality, rigour and reproducibility is a basic principle in this legislation. The Principles of Good Laboratory Practice (GLP) have been developed to promote the quality and validity of test data used for determining the safety of chemicals and chemicals products. It is a managerial concept covering the organisational process and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported. Its principles are required to be followed by test facilities carrying out studies to be submitted to national authorities for the purposes of assessment of chemicals and other uses relating to the protection of man and the environment.

The issue of data quality has an important international dimension. If regulatory authorities in countries can rely on safety test data developed abroad, duplicative testing can be avoided and costs saved to government and industry. Moreover, common principles for GLP facilitate the exchange of information and prevent the emergence of non-tariff barriers to trade, while contributing to the protection of human health and the environment.

The OECD Principles of Good Laboratory Practice were first developed by an Expert Group on GLP established in 1978 under the Special Programme on the Control of Chemicals. The GLP regulations for non-clinical laboratory studies published by the US Food and Drug Administration in 1976 provided the basis for the work of the Expert Group, which was led by the United States and comprised experts from the following countries and organisations: Australia, Austria, Belgium, Canada, Denmark, France, the Federal Republic of Germany, Greece, Italy, Japan, the Netherlands, New Zealand, Norway, Sweden, Switzerland, the United Kingdom, the United States, the Commission of the European Communities, the World Health Organisation and the International Organisation for Standardisation.

Those Principles of GLP were formally recommended for use in Member countries by the OECD Council in 1981. They were set out (in Annex II) as an integral part of the Council Decision on Mutual Acceptance of Data in the Assessment of Chemicals, which states that “data generated in the testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines* and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment” [C(81)30(Final)].

After a decade and half of use, Member countries considered that there was a need to review and update the Principles of GLP to account for scientific and technical progress in the field of safety testing and the fact that safety testing was currently required in many more areas than was the case at the end of the 1970’s. On the proposal of the Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals, another Expert Group was therefore established in 1995 to develop a proposal to revise the Principles of GLP. The Expert Group, which completed its work in 1996, was led by Germany and comprised experts from Australia, Austria, Belgium, Canada, the Czech

* *OECD Guidelines for the Testing of Chemicals, 1981 and continuing series.*

Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Korea, the Netherlands, Norway, Poland, Portugal, the Slovak Republic, Spain, Sweden, Switzerland, the United Kingdom, the United States and the International Organisation for Standardisation.

The Revised OECD Principles of GLP were reviewed in the relevant policy bodies of the Organisation and were adopted by Council on 26th November, 1997 [C(97)186/Final], which formally amended Annex II of the 1981 Council Decision. This publication, the first in the OECD series on Principles of Good Laboratory Practice and Compliance Monitoring, contains the Principles of GLP as revised in 1997 and, in Part Two, the three OECD Council Acts related to the Mutual Acceptance of Data.

This document cancels and replaces
the Environment Monograph No. 45 entitled
“The OECD Principles of Good Laboratory Practice”,
published in 1992

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PART ONE :**OECD PRINCIPLES OF GOOD LABORATORY PRACTICE*
(as revised in 1997)****SECTION I: INTRODUCTION****Preface**

Government and industry are concerned about the quality of non-clinical health and environmental safety studies upon which hazard assessments are based. As a consequence, OECD Member countries have established criteria for the performance of these studies.

To avoid different schemes of implementation that could impede international trade in chemicals, OECD Member countries have pursued international harmonisation of test methods and good laboratory practice. In 1979 and 1980, an international group of experts established under the Special Programme on the Control of Chemicals developed the “OECD Principles of Good Laboratory Practice” (GLP), utilising common managerial and scientific practices and experience from various national and international sources. These Principles of GLP were adopted by the OECD Council in 1981, as an Annex to the Council Decision on the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)].

In 1995 and 1996, a new group of experts was formed to revise and update the Principles. The current document is the result of the consensus reached by that group. It cancels and replaces the original Principles adopted in 1981.

The purpose of these Principles of Good Laboratory Practice is to promote the development of quality test data. Comparable quality of test data forms the basis for the mutual acceptance of data among countries. If individual countries can confidently rely on test data developed in other countries, duplicative testing can be avoided, thereby saving time and resources. The application of these Principles should help to avoid the creation of technical barriers to trade, and further improve the protection of human health and the environment.

1. Scope

These Principles of Good Laboratory Practice should be applied to the non-clinical safety testing of test items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives, and industrial chemicals. These test items are frequently synthetic

* The OECD Principles of Good Laboratory Practice are contained in Annex II of the Decision of the Council concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)] (See Part Two of this document for the text of that Council Decision). The 1981 Council Decision was amended in 1997, at which time Annex II was replaced by the revised Principles of GLP [C(97)186/Final].

chemicals, but may be of natural or biological origin and, in some circumstances, may be living organisms. The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment.

Non-clinical health and environmental safety studies covered by the Principles of Good Laboratory Practice include work conducted in the laboratory, in greenhouses, and in the field.

Unless specifically exempted by national legislation, these Principles of Good Laboratory Practice apply to all non-clinical health and environmental safety studies required by regulations for the purpose of registering or licensing pharmaceuticals, pesticides, food and feed additives, cosmetic products, veterinary drug products and similar products, and for the regulation of industrial chemicals.

2. Definitions of Terms

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2.1 *Good Laboratory Practice*

1. Good Laboratory Practice (GLP) is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

2.2 *Terms Concerning the Organisation of a Test Facility*

1. *Test facility* means the persons, premises and operational unit(s) that are necessary for conducting the non-clinical health and environmental safety study. For multi-site studies, those which are conducted at more than one site, the test facility comprises the site at which the Study Director is located and all individual test sites, which individually or collectively can be considered to be test facilities.
2. *Test site* means the location(s) at which a phase(s) of a study is conducted.
3. *Test facility management* means the person(s) who has the authority and formal responsibility for the organisation and functioning of the test facility according to these Principles of Good Laboratory Practice.
4. *Test site management* (if appointed) means the person(s) responsible for ensuring that the phase(s) of the study, for which he is responsible, are conducted according to these Principles of Good Laboratory Practice.
5. *Sponsor* means an entity which commissions, supports and/or submits a non-clinical health and environmental safety study.
6. *Study Director* means the individual responsible for the overall conduct of the nonclinical health and environmental safety study.
7. *Principal Investigator* means an individual who, for a multi-site study, acts on behalf of the Study Director and has defined responsibility for delegated phases of the study. The Study Director's responsibility for the overall conduct of the study cannot be delegated to

the Principal Investigator(s); this includes approval of the study plan and its amendments, approval of the final report, and ensuring that all applicable Principles of Good Laboratory Practice are followed.

8. *Quality Assurance Programme* means a defined system, including personnel, which is independent of study conduct and is designed to assure test facility management of compliance with these Principles of Good Laboratory Practice.
9. *Standard Operating Procedures (SOPs)* means documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines.
10. *Master schedule* means a compilation of information to assist in the assessment of workload and for the tracking of studies at a test facility.

2.3 Terms Concerning the Non-Clinical Health and Environmental Safety Study

1. *Non-clinical health and environmental safety study*, henceforth referred to simply as “study”, means an experiment or set of experiments in which a test item is examined under laboratory conditions or in the environment to obtain data on its properties and/or its safety, intended for submission to appropriate regulatory authorities.
2. *Short-term study* means a study of short duration with widely used, routine techniques.
3. *Study plan* means a document which defines the objectives and experimental design for the conduct of the study, and includes any amendments.
4. *Study plan amendment* means an intended change to the study plan after the study initiation date.
5. *Study plan deviation* means an unintended departure from the study plan after the study initiation date.
6. *Test system* means any biological, chemical or physical system or a combination thereof used in a study.
7. *Raw data* means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognised as capable of providing secure storage of information for a time period as stated in section 10, below.
8. *Specimen* means any material derived from a test system for examination, analysis, or retention.
9. *Experimental starting date* means the date on which the first study specific data are collected.
10. *Experimental completion date* means the last date on which data are collected from the study.

11. *Study initiation date* means the date the Study Director signs the study plan.
12. *Study completion date* means the date the Study Director signs the final report.

2.4 *Terms Concerning the Test Item*

1. *Test item* means an article that is the subject of a study.
2. *Reference item* (“control item”) means any article used to provide a basis for comparison with the test item.
3. *Batch* means a specific quantity or lot of a test item or reference item produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character and should be designated as such.
4. *Vehicle* means any agent which serves as a carrier used to mix, disperse, or solubilise the test item or reference item to facilitate the administration/application to the test system.

SECTION II: GOOD LABORATORY PRACTICE PRINCIPLES

1. Test Facility Organisation and Personnel

1.1 *Test Facility Management’s Responsibilities*

1. Each test facility management should ensure that these Principles of Good Laboratory Practice are complied with, in its test facility.
2. At a minimum it should:
 - a) ensure that a statement exists which identifies the individual(s) within a test facility who fulfil the responsibilities of management as defined by these Principles of Good Laboratory Practice;
 - b) ensure that a sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the study;
 - c) ensure the maintenance of a record of the qualifications, training, experience and job description for each professional and technical individual;
 - d) ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions;
 - e) ensure that appropriate and technically valid Standard Operating Procedures are established and followed, and approve all original and revised Standard Operating Procedures;
 - f) ensure that there is a Quality Assurance Programme with designated personnel and assure that the quality assurance responsibility is being performed in accordance with these Principles of Good Laboratory Practice;

- g) ensure that for each study an individual with the appropriate qualifications, training, and experience is designated by the management as the Study Director before the study is initiated. Replacement of a Study Director should be done according to established procedures, and should be documented;
 - h) ensure, in the event of a multi-site study, that, if needed, a Principal Investigator is designated, who is appropriately trained, qualified and experienced to supervise the delegated phase(s) of the study. Replacement of a Principal Investigator should be done according to established procedures, and should be documented;
 - i) ensure documented approval of the study plan by the Study Director;
 - j) ensure that the Study Director has made the approved study plan available to the Quality Assurance personnel;
 - k) ensure the maintenance of an historical file of all Standard Operating Procedures;
 - l) ensure that an individual is identified as responsible for the management of the archive(s);
 - m) ensure the maintenance of a master schedule;
 - n) ensure that test facility supplies meet requirements appropriate to their use in a study;
 - o) ensure for a multi-site study that clear lines of communication exist between the Study Director, Principal Investigator(s), the Quality Assurance Programme(s) and study personnel;
 - p) ensure that test and reference items are appropriately characterised;
 - q) establish procedures to ensure that computerised systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with these Principles of Good Laboratory Practice.
3. When a phase(s) of a study is conducted at a test site, test site management (if appointed) will have the responsibilities as defined above with the following exceptions: 1.1.2 g), i), j) and o).

1.2 *Study Director's Responsibilities*

1. The Study Director is the single point of study control and has the responsibility for the overall conduct of the study and for its final report.
2. These responsibilities should include, but not be limited to, the following functions. The Study Director should:
 - a) approve the study plan and any amendments to the study plan by dated signature;
 - b) ensure that the Quality Assurance personnel have a copy of the study plan and any amendments in a timely manner and communicate effectively with the Quality Assurance personnel as required during the conduct of the study;

- c) ensure that study plans and amendments and Standard Operating Procedures are available to study personnel;
- d) ensure that the study plan and the final report for a multi-site study identify and define the role of any Principal Investigator(s) and any test facilities and test sites involved in the conduct of the study;
- e) ensure that the procedures specified in the study plan are followed, and assess and document the impact of any deviations from the study plan on the quality and integrity of the study, and take appropriate corrective action if necessary; acknowledge deviations from Standard Operating Procedures during the conduct of the study;
- f) ensure that all raw data generated are fully documented and recorded;
- g) ensure that computerised systems used in the study have been validated;
- h) sign and date the final report to indicate acceptance of responsibility for the validity of the data and to indicate the extent to which the study complies with these Principles of Good Laboratory Practice;
- i) ensure that after completion (including termination) of the study, the study plan, the final report, raw data and supporting material are archived.

1.3 *Principal Investigator's Responsibilities*

The Principal Investigator will ensure that the delegated phases of the study are conducted in accordance with the applicable Principles of Good Laboratory Practice.

1.4 *Study Personnel's Responsibilities*

1. All personnel involved in the conduct of the study must be knowledgeable in those parts of the Principles of Good Laboratory Practice which are applicable to their involvement in the study.
2. Study personnel will have access to the study plan and appropriate Standard Operating Procedures applicable to their involvement in the study. It is their responsibility to comply with the instructions given in these documents. Any deviation from these instructions should be documented and communicated directly to the Study Director, and/or if appropriate, the Principal Investigator(s).
3. All study personnel are responsible for recording raw data promptly and accurately and in compliance with these Principles of Good Laboratory Practice, and are responsible for the quality of their data.
4. Study personnel should exercise health precautions to minimise risk to themselves and to ensure the integrity of the study. They should communicate to the appropriate person any relevant known health or medical condition in order that they can be excluded from operations that may affect the study.

2. Quality Assurance Programme

2.1 General

1. The test facility should have a documented Quality Assurance Programme to assure that studies performed are in compliance with these Principles of Good Laboratory Practice.
2. The Quality Assurance Programme should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.
3. This individual(s) should not be involved in the conduct of the study being assured.

2.2 Responsibilities of the Quality Assurance Personnel

1. The responsibilities of the Quality Assurance personnel include, but are not limited to, the following functions. They should:
 - a) maintain copies of all approved study plans and Standard Operating Procedures in use in the test facility and have access to an up-to-date copy of the master schedule;
 - b) verify that the study plan contains the information required for compliance with these Principles of Good Laboratory Practice. This verification should be documented;
 - c) conduct inspections to determine if all studies are conducted in accordance with these Principles of Good Laboratory Practice. Inspections should also determine that study plans and Standard Operating Procedures have been made available to study personnel and are being followed.

Inspections can be of three types as specified by Quality Assurance Programme Standard Operating Procedures:

- Study-based inspections,
- Facility-based inspections,
- Process-based inspections.

Records of such inspections should be retained.

- d) inspect the final reports to confirm that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the studies;
- e) promptly report any inspection results in writing to management and to the Study Director, and to the Principal Investigator(s) and the respective management, when applicable;
- f) prepare and sign a statement, to be included with the final report, which specifies types of inspections and their dates, including the phase(s) of the study inspected, and the dates inspection results were reported to management and the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

3. Facilities

3.1 *General*

1. The test facility should be of suitable size, construction and location to meet the requirements of the study and to minimise disturbance that would interfere with the validity of the study.
2. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study.

3.2 *Test System Facilities*

1. The test facility should have a sufficient number of rooms or areas to assure the isolation of test systems and the isolation of individual projects, involving substances or organisms known to be or suspected of being biohazardous.
2. Suitable rooms or areas should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems.
3. There should be storage rooms or areas as needed for supplies and equipment. Storage rooms or areas should be separated from rooms or areas housing the test systems and should provide adequate protection against infestation, contamination, and/or deterioration.

3.3 *Facilities for Handling Test and Reference Items*

1. To prevent contamination or mix-ups, there should be separate rooms or areas for receipt and storage of the test and reference items, and mixing of the test items with a vehicle.
2. Storage rooms or areas for the test items should be separate from rooms or areas containing the test systems. They should be adequate to preserve identity, concentration, purity, and stability, and ensure safe storage for hazardous substances.

3.4 *Archive Facilities*

Archive facilities should be provided for the secure storage and retrieval of study plans, raw data, final reports, samples of test items and specimens. Archive design and archive conditions should protect contents from untimely deterioration.

3.5 *Waste Disposal*

Handling and disposal of wastes should be carried out in such a way as not to jeopardise the integrity of studies. This includes provision for appropriate collection, storage and disposal facilities, and decontamination and transportation procedures.

4. Apparatus, Material, and Reagents

1. Apparatus, including validated computerised systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.
2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement.
3. Apparatus and materials used in a study should not interfere adversely with the test systems.
4. Chemicals, reagents, and solutions should be labelled to indicate identity (with concentration if appropriate), expiry date and specific storage instructions. Information concerning source, preparation date and stability should be available. The expiry date may be extended on the basis of documented evaluation or analysis.

5. Test Systems

5.1 *Physical/Chemical*

1. Apparatus used for the generation of physical/chemical data should be suitably located and of appropriate design and adequate capacity.
2. The integrity of the physical/chemical test systems should be ensured.

5.2 *Biological*

1. Proper conditions should be established and maintained for the storage, housing, handling and care of biological test systems, in order to ensure the quality of the data.
2. Newly received animal and plant test systems should be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, this lot should not be used in studies and, when appropriate, should be humanely destroyed. At the experimental starting date of a study, test systems should be free of any disease or condition that might interfere with the purpose or conduct of the study. Test systems that become diseased or injured during the course of a study should be isolated and treated, if necessary to maintain the integrity of the study. Any diagnosis and treatment of any disease before or during a study should be recorded.
3. Records of source, date of arrival, and arrival condition of test systems should be maintained.
4. Biological test systems should be acclimatised to the test environment for an adequate period before the first administration/application of the test or reference item.

5. All information needed to properly identify the test systems should appear on their housing or containers. Individual test systems that are to be removed from their housing or containers during the conduct of the study should bear appropriate identification, wherever possible.
6. During use, housing or containers for test systems should be cleaned and sanitised at appropriate intervals. Any material that comes into contact with the test system should be free of contaminants at levels that would interfere with the study. Bedding for animals should be changed as required by sound husbandry practice. Use of pest control agents should be documented.
7. Test systems used in field studies should be located so as to avoid interference in the study from spray drift and from past usage of pesticides.

6. Test and Reference Items

6.1 *Receipt, Handling, Sampling and Storage*

1. Records including test item and reference item characterisation, date of receipt, expiry date, quantities received and used in studies should be maintained.
2. Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured to the degree possible and contamination or mixup are precluded.
3. Storage container(s) should carry identification information, expiry date, and specific storage instructions.

6.2 *Characterisation*

1. Each test and reference item should be appropriately identified (e.g., code, Chemical Abstracts Service Registry Number [CAS number], name, biological parameters).
2. For each study, the identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test or reference items should be known.
3. In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation between the sponsor and the test facility, to verify the identity of the test item subject to the study.
4. The stability of test and reference items under storage and test conditions should be known for all studies.
5. If the test item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined. For test items used in field studies (e.g., tank mixes), these may be determined through separate laboratory experiments.
6. A sample for analytical purposes from each batch of test item should be retained for all studies except short-term studies.

7. Standard Operating Procedures

- 7.1. A test facility should have written Standard Operating Procedures approved by test facility management that are intended to ensure the quality and integrity of the data generated by that test facility. Revisions to Standard Operating Procedures should be approved by test facility management.
- 7.2. Each separate test facility unit or area should have immediately available current Standard Operating Procedures relevant to the activities being performed therein. Published text books, analytical methods, articles and manuals may be used as supplements to these Standard Operating Procedures.
- 7.3. Deviations from Standard Operating Procedures related to the study should be documented and should be acknowledged by the Study Director and the Principal Investigator(s), as applicable.
- 7.4. Standard Operating Procedures should be available for, but not be limited to, the following categories of test facility activities. The details given under each heading are to be considered as illustrative examples.

1. *Test and Reference Items*

Receipt, identification, labelling, handling, sampling and storage.

2. *Apparatus, Materials and Reagents*

- a) *Apparatus*

Use, maintenance, cleaning and calibration.

- b) *Computerised Systems*

Validation, operation, maintenance, security, change control and back-up.

- c) *Materials, Reagents and Solutions*

Preparation and labelling.

3. *Record Keeping, Reporting, Storage, and Retrieval*

Coding of studies, data collection, preparation of reports, indexing systems, handling of data, including the use of computerised systems.

4. *Test System (where appropriate)*

- a) Room preparation and environmental room conditions for the test system.

- b) Procedures for receipt, transfer, proper placement, characterisation, identification and care of the test system.

- c) Test system preparation, observations and examinations, before, during and at the conclusion of the study.

- d) Handling of test system individuals found moribund or dead during the study.

- e) Collection, identification and handling of specimens including necropsy and histopathology.
- f) Siting and placement of test systems in test plots.

5. *Quality Assurance Procedures*

Operation of Quality Assurance personnel in planning, scheduling, performing, documenting and reporting inspections.

8. Performance of the Study

8.1 Study Plan

1. For each study, a written plan should exist prior to the initiation of the study. The study plan should be approved by dated signature of the Study Director and verified for GLP compliance by Quality Assurance personnel as specified in Section 2.2.1.b., above. The study plan should also be approved by the test facility management and the sponsor, if required by national regulation or legislation in the country where the study is being performed.
2.
 - a) Amendments to the study plan should be justified and approved by dated signature of the Study Director and maintained with the study plan.
 - b) Deviations from the study plan should be described, explained, acknowledged and dated in a timely fashion by the Study Director and/or Principal Investigator(s) and maintained with the study raw data.
3. For short-term studies, a general study plan accompanied by a study specific supplement may be used.

8.2 Content of the Study Plan

The study plan should contain, but not be limited to the following information:

1. *Identification of the Study, the Test Item and Reference Item*
 - a) A descriptive title;
 - b) A statement which reveals the nature and purpose of the study;
 - c) Identification of the test item by code or name (IUPAC; CAS number, biological parameters, etc.);
 - d) The reference item to be used.
2. *Information Concerning the Sponsor and the Test Facility*
 - a) Name and address of the sponsor;
 - b) Name and address of any test facilities and test sites involved;

- c) Name and address of the Study Director;
- d) Name and address of the Principal Investigator(s), and the phase(s) of the study delegated by the Study Director and under the responsibility of the Principal Investigator(s).

3. *Dates*

- a) The date of approval of the study plan by signature of the Study Director. The date of approval of the study plan by signature of the test facility management and sponsor if required by national regulation or legislation in the country where the study is being performed.
- b) The proposed experimental starting and completion dates.

4. *Test Methods*

Reference to the OECD Test Guideline or other test guideline or method to be used.

5. *Issues (where applicable)*

- a) The justification for selection of the test system;
- b) Characterisation of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age and other pertinent information;
- c) The method of administration and the reason for its choice;
- d) The dose levels and/or concentration(s), frequency, and duration of administration/application;
- e) Detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed, and statistical methods to be used (if any).

6. *Records*

A list of records to be retained.

8.3 *Conduct of the Study*

- 1. A unique identification should be given to each study. All items concerning this study should carry this identification. Specimens from the study should be identified to confirm their origin. Such identification should enable traceability, as appropriate for the specimen and study.
- 2. The study should be conducted in accordance with the study plan.
- 3. All data generated during the conduct of the study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialled and dated.

4. Any change in the raw data should be made so as not to obscure the previous entry, should indicate the reason for change and should be dated and signed or initialled by the individual making the change.
5. Data generated as a direct computer input should be identified at the time of data input by the individual(s) responsible for direct data entries. Computerised system design should always provide for the retention of full audit trails to show all changes to the data without obscuring the original data. It should be possible to associate all changes to data with the persons having made those changes, for example, by use of timed and dated (electronic) signatures. Reason for changes should be given.

9. Reporting of Study Results

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9.1 *General*

1. A final report should be prepared for each study. In the case of short term studies, a standardised final report accompanied by a study specific extension may be prepared.
2. Reports of Principal Investigators or scientists involved in the study should be signed and dated by them.
3. The final report should be signed and dated by the Study Director to indicate acceptance of responsibility for the validity of the data. The extent of compliance with these Principles of Good Laboratory Practice should be indicated.
4. Corrections and additions to a final report should be in the form of amendments. Amendments should clearly specify the reason for the corrections or additions and should be signed and dated by the Study Director.
5. Reformatting of the final report to comply with the submission requirements of a national registration or regulatory authority does not constitute a correction, addition or amendment to the final report.

9.2 *Content of the Final Report*

The final report should include, but not be limited to, the following information:

1. *Identification of the Study, the Test Item and Reference Item*
 - a) A descriptive title;
 - b) Identification of the test item by code or name (IUPAC, CAS number, biological parameters, etc.);

- c) Identification of the reference item by name;
- d) Characterisation of the test item including purity, stability and homogeneity.

2. *Information Concerning the Sponsor and the Test Facility*

- a) Name and address of the sponsor;
- b) Name and address of any test facilities and test sites involved;
- c) Name and address of the Study Director;
- d) Name and address of the Principal Investigator(s) and the phase(s) of the study delegated, if applicable;
- e) Name and address of scientists having contributed reports to the final report.

3. *Dates*

Experimental starting and completion dates.

4. *Statement*

A Quality Assurance Programme statement listing the types of inspections made and their dates, including the phase(s) inspected, and the dates any inspection results were reported to management and to the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

5. *Description of Materials and Test Methods*

- a) Description of methods and materials used;
- b) Reference to OECD Test Guideline or other test guideline or method.

6. *Results*

- a) A summary of results;
- b) All information and data required by the study plan;
- c) A presentation of the results, including calculations and determinations of statistical significance;
- d) An evaluation and discussion of the results and, where appropriate, conclusions.

7. *Storage*

The location(s) where the study plan, samples of test and reference items, specimens, raw data and the final report are to be stored.

10. Storage and Retention of Records and Materials

10.1 The following should be retained in the archives for the period specified by the appropriate authorities:

- a) The study plan, raw data, samples of test and reference items, specimens, and the final report of each study;
- b) Records of all inspections performed by the Quality Assurance Programme, as well as master schedules;
- c) Records of qualifications, training, experience and job descriptions of personnel;
- d) Records and reports of the maintenance and calibration of apparatus;
- e) Validation documentation for computerised systems;
- f) The historical file of all Standard Operating Procedures;
- g) Environmental monitoring records.

In the absence of a required retention period, the final disposition of any study materials should be documented. When samples of test and reference items and specimens are disposed of before the expiry of the required retention period for any reason, this should be justified and documented. Samples of test and reference items and specimens should be retained only as long as the quality of the preparation permits evaluation.

10.2 Material retained in the archives should be indexed so as to facilitate orderly storage and retrieval.

10.3 Only personnel authorised by management should have access to the archives. Movement of material in and out of the archives should be properly recorded.

10.4 If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archives of the sponsor(s) of the study(s).

PART TWO:**OECD COUNCIL ACTS RELATED TO GLP PRINCIPLES
AND COMPLIANCE MONITORING****DECISION OF THE COUNCIL: Concerning the Mutual Acceptance of Data in the
Assessment of Chemicals [C(81)30(Final)]**

(Adopted by the Council at its 535th Meeting on 12th May, 1981)

The Council,

Having regard to Articles 2(a), 2(d), 3, 5(a) and 5(b) of the Convention on the Organisation for Economic Co-operation and Development of 14th December, 1960;

Having regard to the Recommendation of the Council of 26th May, 1972, on Guiding Principles concerning International Economic Aspects of Environmental Policies [C(72)128];

Having regard to the Recommendation of the Council of 14th November, 1974, on the Assessment of the Potential Environmental Effects of Chemicals [C(74)215];

Having regard to the Recommendation of the Council of 26th August, 1976, concerning Safety Controls over Cosmetics and Household Products [C(76)144(Final)];

Having regard to the Recommendation of the Council of 7th July, 1977, establishing Guidelines in respect of Procedure and Requirements for Anticipating the Effects of Chemicals on Man and in the Environment [C(77)97(Final)];

Having regard to the Decision of the Council of 21st September, 1978, concerning a Special Programme on the Control of Chemicals and the Programme of Work established therein [C(78)127(Final)];

Having regard to the Conclusions of the First High Level Meeting of the Chemicals Group of 19th May, 1980, dealing with the control of health and environmental effects of chemicals [ENV/ CHEM/ HLM/80.M/1];

Considering the need for concerted action amongst OECD Member countries to protect man and his environment from exposure to hazardous chemicals;

Considering the importance of international production and trade in chemicals and the mutual economic and trade advantages which accrue to OECD Member countries from harmonization of policies for chemicals control;

Considering the need to minimise the cost burden associated with testing chemicals and the need to utilise more effectively scarce test facilities and specialist manpower in Member countries;

Considering the need to encourage the generation of valid and high quality test data and noting the significant actions taken in this regard by OECD Member countries through provisional application of OECD Test Guidelines and OECD Principles of Good Laboratory Practice;

Considering the need for and benefits of mutual acceptance in OECD countries of test data used in the assessment of chemicals and other uses relating to protection of man and the environment;

On the proposal of the High Level Meeting of the Chemicals Group, endorsed by the Environment Committee;

PART I

1. DECIDES that data generated in the testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment.
2. DECIDES that for the purposes of this decision and other Council actions the terms OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall mean guidelines and principles adopted by the Council.
3. INSTRUCTS the Environment Committee to review action taken by Member countries in pursuance of this Decision and to report periodically thereon to the Council.
4. INSTRUCTS the Environment Committee to pursue a programme of work designed to facilitate implementation of this Decision with a view to establishing further agreement on assessment and control of chemicals within Member countries.

PART II

To implement the Decision set forth in Part I:

1. RECOMMENDS that Member countries, in the testing of chemicals, apply the OECD Test Guidelines and the OECD Principles of Good Laboratory Practice, set forth respectively in Annexes I and II* which are integral parts of this text.
2. INSTRUCTS the Management Committee of the Special Programme on the Control of Chemicals in conjunction with the Chemicals Group of the Environment Committee to establish an updating mechanism to ensure that the aforementioned test guidelines are modified from time to time as required through the revision of existing Guidelines or the development of new Guidelines.
3. INSTRUCTS the Management Committee of the Special Programme on the Control of Chemicals to pursue its programme of work in such a manner as to facilitate internationally-harmonized approaches to assuring compliance with the OECD Principles of Good Laboratory Practice and to report periodically thereon to the Council.

* Annex I to the Council Decision (the OECD Test Guidelines) was published separately. Annex II (the OECD Principles of Good Laboratory Practice) can be found in Part One of this publication.

**COUNCIL DECISION-RECOMMENDATION
on Compliance with Principles of Good Laboratory Practice
[C(89)87(Final)]**

(Adopted by the Council at its 717th Meeting on 2nd October 1989)

The Council,

Having regard to Articles 5 a) and 5 b) of the Convention on the Organisation for Economic Co-operation and Development of 14th December, 1960;

Having regard to the Recommendation of the Council of 7th July, 1977 Establishing Guidelines in Respect of Procedure and Requirements for Anticipating the Effects of Chemicals on Man and in the Environment [C(77)97(Final)];

Having regard to the Decision of the Council of 12th May, 1981 concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)] and, in particular, the Recommendation that Member countries, in the testing of chemicals, apply the OECD Principles of Good Laboratory Practice, set forth in Annex 2 of that Decision;

Having regard to the Recommendation of the Council of 26th July, 1983 concerning the Mutual Recognition of Compliance with Good Laboratory [C(83)95(Final)];

Having regard to the conclusions of the Third High Level Meeting of the Chemicals Group (OECD, Paris, 1988);

Considering the need to ensure that test data on chemicals provided to regulatory authorities for purposes of assessment and other uses related to the protection of human health and the environment are of high quality, valid and reliable;

Considering the need to minimise duplicative testing of chemicals, and thereby to utilise more effectively scarce test facilities and specialist manpower, and to reduce the number of animals used in testing;

Considering that recognition of procedures for monitoring compliance with good laboratory practice will facilitate mutual acceptance of data and thereby reduce duplicative testing of chemicals; Considering that a basis for recognition of compliance monitoring procedures is an understanding of, and confidence in, the procedures in the Member country where the data are generated;

Considering that harmonized approaches to procedures for monitoring compliance with good laboratory practice would greatly facilitate the development of the necessary confidence in other countries' procedures;

On the proposal of the Joint Meeting of the Management Committee of the Special Programme on the Control of Chemicals and the Chemicals Group, endorsed by the Environment Committee;

PART I

GLP Principles and Compliance Monitoring

1. DECIDES that Member countries in which testing of chemicals for purposes of assessment related to the protection of health and the environment is being carried out pursuant to principles of good laboratory practice that are consistent with the OECD Principles of Good Laboratory Practice as set out in Annex 2 of the Council Decision [C(81)30(Final)] (hereafter called “GLP Principles”) shall:

- i) establish national procedures for monitoring compliance with GLP Principles, based on laboratory inspections and study audits;
- ii) designate an authority or authorities to discharge the functions required by the procedures for monitoring compliance; and
- iii) require that the management of test facilities issue a declaration, where applicable, that a study was carried out in accordance with GLP Principles and pursuant to any other provisions established by national legislation or administrative procedures dealing with good laboratory practice.

2. RECOMMENDS that, in developing and implementing national procedures for monitoring compliance with GLP Principles, Member countries apply the “Guides for Compliance Monitoring Procedures for Good Laboratory Practice” and the “Guidance for the Conduct of Laboratory Inspections and Study Audits,” set out respectively in Annexes I and II* which are an integral part of this Decision-Recommendation.

PART II

Recognition of GLP Compliance among Member countries

1. DECIDES that Member countries shall recognise the assurance by another Member country that test data have been generated in accordance with GLP Principles if such other Member country complies with Part I above and Part II paragraph 2 below.

2. DECIDES that, for purposes of the recognition of the assurance in paragraph 1 above, Member countries shall:

- i) designate an authority or authorities for international liaison and for discharging other functions relevant to the recognition as set out in this Part and in the Annexes to this Decision-Recommendation;

* Annexes I and II of the Council Act as revised in 1995 can be found in Numbers 2 and 3, respectively, of this OECD-series on Principles of GLP and Compliance Monitoring (Environment Monographs No. 110 and No. 111).

- ii) exchange with other Member countries relevant information concerning their procedures for monitoring compliance, in accordance with the guidance set out in Annex III* which is an integral part of this Decision-Recommendation, and
 - iii) implement procedures whereby, where good reason exists, information concerning GLP compliance of a test facility (including information focusing on a particular study) within their jurisdiction can be sought by another Member country.
3. DECIDES that the Council Recommendation concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95(Final)] shall be repealed.

PART III

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Future OECD Activities

1. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to ensure that the “Guides for Compliance Monitoring Procedures for Good Laboratory Practice” and the “Guidance for the Conduct of Laboratory Inspections and Study Audits” set out in Annexes I and II** are updated and expanded, as necessary, in light of developments and experience of Member countries and relevant work in other international organisations.
2. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to pursue a programme of work designed to facilitate the implementation of this Decision-Recommendation, and to ensure continuing exchange of information and experience on technical and administrative matters related to the application of GLP Principles and the implementation of procedures for monitoring compliance with good laboratory practice.
3. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to review actions taken by Member countries in pursuance of this Decision-Recommendation.

* Annex III of the Council Act as revised in 1995 will be found in Number 2 of this OECD series on Principles of GLP and Compliance Monitoring (Environment Monograph No. 110).

** See footnote on previous page.

**COUNCIL DECISION concerning the Adherence of Non-member Countries
to the Council Acts related to the Mutual Acceptance
of Data in the Assessment of Chemicals [C(81)30(FINAL) AND C(89)87(FINAL)]
[C(97)114/Final]**

(Adopted by the Council at its 912th meeting on 26th November, 1997)

The Council,

Having regard to Articles 5(a) and 5(c) of the Convention on the Organisation for Economic Co-operation and Development of 14th December, 1960;

Having regard to the Decision of the Council of 12th May, 1981, concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)];

Having regard to the Decision of the Council of 26th July, 1983, concerning the Protection of Proprietary Rights to Data submitted in Notification of New Chemicals [C(83)96(Final)] and the Recommendations of the same date concerning the Exchange of Confidential Data on Chemicals [C(83)97(Final)] and the OECD List of Non-Confidential Data on Chemicals [C(83)98(Final)];

Having regard to the Decision Recommendation of the Council of 2nd October, 1989 on Compliance with Principles of Good Laboratory Practice [C(89)87(Final)] as amended;

Considering that effective implementation of the OECD Council Acts [C(81)30(Final)] and [C(89)87(Final)] is essential in view of the extension of these acts to adherence by non-member countries;

Recognising that the conclusion of agreements among Members and with non-member countries constitutes a means for effective implementation of these Council Acts;

Recognising that adherence to the OECD Council Acts does not preclude use or acceptance of test data obtained in accordance with other scientifically valid and specified test methods, as developed for specific chemical product areas;

Considering that on 14th June, 1992 the United Nations Conference on Environment and Development in Chapter 19, section E of Agenda 21, recommended that governments and international organisations should co-operate, particularly with developing countries, to develop appropriate tools for management of chemicals;

Considering the commitments made by Ministers at the meeting of the Council at Ministerial level of 23rd and 24th May, 1995 to support the integration of developing countries and economies in transition into the world economic system, and to pursue further progress toward a better environment;

Considering that Member countries and non-member countries would derive both economic and environmental benefits from enlarged participation in the OECD Council Acts related to mutual acceptance of data in the assessment of chemicals;

Considering that non-member countries are increasingly demonstrating an interest in participating in the OECD Council Acts related to mutual acceptance of data in the assessment of chemicals;

Considering that the chemical industries in all nations have an interest in harmonized testing requirements and will benefit from the elimination of costly, duplicative testing and the avoidance of nontariff barriers to trade;

Considering that expanded international co-operation to reduce duplicative testing would, in the process, diminish the use of animals for safety testing;

Considering, therefore, that it is appropriate and timely to pursue broadened international participation in the OECD programme on mutual acceptance of data in the assessment of chemicals, specifically by opening up the relevant OECD Council Acts to adherence by non-member countries and that a clear administrative procedure is required to facilitate this process;

On the proposal of the Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals, endorsed by the Environment Policy Committee;

1. DECIDES to open the OECD Council Acts related to the mutual acceptance of data in the assessment of chemicals* to adherence by non-member countries which express their willingness and demonstrate their ability to participate therein.
2. DECIDES that non-member countries adhering to the Council Acts shall be entitled to join the part of the OECD Chemicals Programme involving the mutual acceptance of data, with the same rights and obligations as Member countries.
3. DECIDES that adherence to the Council Acts and participation in the part of the OECD Chemicals Programme related to the mutual acceptance of data shall be governed by the procedure set out in the Appendix to this Decision, of which it forms an integral part.
4. RECOMMENDS that Member countries, with a view to facilitating the extension of the Council Acts to non-member countries, take or pursue all available means to ensure the most effective implementation of the Council Acts. Pending this effective implementation of the Council Acts by nonmembers, Member countries shall be free to establish mutual acceptance of data with non-member countries on a bilateral basis.
5. INSTRUCTS the Management Committee of the Special Programme on the Control of Chemicals to assume responsibility for promoting international awareness of the Council Acts, with a view to informing, advising and otherwise encouraging non-member countries to participate in the programmes and activities that have been established by OECD countries pursuant to these Council Acts. Further, the Management Committee should monitor closely the technical aspects of implementation of the procedure set out in the Appendix, review the implementation of this Decision, and report thereon to Council within three years.

* These Council Acts are: the 1981 Council Decision concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)] as amended, together with the OECD Guidelines for the Testing of Chemicals and the OECD Principles of Good Laboratory Practice, and the 1989 Council Decision- Recommendation on Compliance with Principles of Good Laboratory Practice [C(89)87(Final)] as amended and are hereafter referred to as “the Council Acts”.

ANNEX

PROCEDURE FOR ADHERENCE OF NON-MEMBER COUNTRIES TO THE COUNCIL ACTS RELATED TO THE MUTUAL ACCEPTANCE OF DATA IN THE ASSESSMENT OF CHEMICALS

- i) The OECD Secretariat should ensure that an interested non-member country is provided with full information on the rights and obligations associated with adhering to the OECD Council Acts related to mutual acceptance of data in the assessment of chemicals.
- ii) At the invitation of the Council, the interested non-member country would confirm, at an appropriate level, that it would agree to provisionally adhere to the Council Acts and to accept, for purposes of assessment and other uses relating to the protection of man and the environment, data generated in the testing of chemicals with OECD Test Guidelines and OECD Principles of Good Laboratory Practice.
- iii) Following such invitation, confirmation and provisional adherence, the Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals (Joint Meeting) would organise, in consultation with the non-member country, technical support that might assist in the implementation of the Council Acts.
- iv) The non-member country would be invited by the Joint Meeting to nominate a Test Guideline Co-ordinator and to take part in the activities and meetings related to the development and updating of OECD Test Guidelines and to take part in technical meetings related to GLP and, if recommended by the OECD Panel on GLP, to attend as an observer meetings of the Panel. Such an invitation would be for a maximum of three years and could be renewed by the Joint Meeting.
- v) Once the non-member country has fully implemented the Council Acts, and taking account of the recommendation of the Joint Meeting in this respect, the non-member country may be invited by the Council to adhere to the Council Acts and to join the part of the OECD Chemicals Programme involving the mutual acceptance of data as a full member; this would require the non-member country to contribute to the resource costs of implementing this part of the Chemicals Programme.
- vi) Participation may be terminated by either party upon one year advance notice. The Council may set any further terms and conditions to the invitation.



PARIS

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OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE
AND COMPLIANCE MONITORING
Number 2 (Revised)

109

GUIDANCE FOR GLP MONITORING AUTHORITIES

**Revised guides for compliance monitoring procedures
for Good Laboratory Practice**

Environment Monograph No. 110

Paris 1995

FOREWORD

The 1981 Council Decision on Mutual Acceptance of Data [C(81)30(Final)], of which the OECD Principles of Good Laboratory Practice¹ are an integral part, includes an instruction for OECD to undertake activities “to facilitate internationally-harmonized approaches to assuring compliance” with the GLP Principles. Consequently, in order to promote the implementation of comparable compliance monitoring procedures, and international acceptance, among Member countries the Council adopted in 1983 the Recommendation concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95(Final)], which set out basic characteristics of the procedures for monitoring compliance.

A Working Group on Mutual Recognition of Compliance with GLP was established in 1985, under the chairmanship of Professor V. Silano (Italy), to facilitate the practical implementation of the Council acts on GLP, develop common approaches to the technical and administrative problems related to GLP compliance and its monitoring, and develop arrangements for the mutual recognition of compliance monitoring procedures. The following countries and organisations participated in the Working Group: Australia, Belgium, Canada, Denmark, the Federal Republic of Germany, Finland, France, Italy, Japan, Norway, the Netherlands, Portugal, Spain, Sweden, Switzerland, the United Kingdom, the United States, the Commission of the European Communities, the International Organization for Standardization, the Pharmaceuticals Inspections Convention, and the World Health Organization.

The Working Group developed, *inter alia*, Guides for Compliance Monitoring Procedures for Good Laboratory Practice, which concern the requisites of administration, personnel and GLP compliance monitoring programmes. These were first published in 1988 in the Final Report of the Working Group². A slightly abridged version was annexed to the 1989 Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practice [C(89)87(Final)], which superseded and replaced the 1983 Council Act.

In adopting that Decision-Recommendation, the Council in Part III.1 instructed the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to ensure that the “Guides for Compliance Monitoring Procedures for Good Laboratory Practice” and the “Guidance for the Conduct of Laboratory Inspections and Study Audits” set out in Annexes I and II thereto were updated and expanded, as necessary, in light of developments and experience of Member countries and relevant work in other international organisations.

¹ See *The OECD Principles of Good Laboratory Practice*, No. 1 in this OECD series on Principles of GLP and Compliance Monitoring.

² *Final Report of the Working Group on Mutual Recognition of Compliance with Good Laboratory Practice*, OECD Environment Monograph No. 15, March 1988.

The OECD Panel on Good Laboratory Practice developed proposals for amendments to these Annexes, as well as to Annex III which provides “Guidance for the Exchange of Information concerning National Programmes for Monitoring of Compliance with the Principles of Good Laboratory Practice” and which was amended essentially to include an appendix on “Guidance for Good Laboratory Practice Monitoring Authorities for the Preparation of Annual Overviews of Test Facilities Inspected”. These revised Annexes were approved by the Council in a Decision “Amending the Annexes to the Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practice on 9th March, 1995” [C(95)8(Final)].

Part I of this Publication consists of the Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice, as annexed to the 1989 Council Act [C(89)87(Final)] and revised by Council in 1995 [C(95)8(Final)]. The text of that Council Act will be found in Part Two, together with revised Annex III.

This document cancels and replaces
the Environment Monograph No. 46 entitled
“Guides for Compliance Monitoring Procedures
for Good Laboratory Practice”,
published in 1992.

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PART ONE :**REVISED GUIDES FOR COMPLIANCE MONITORING PROCEDURES FOR
GOOD LABORATORY PRACTICE³**

(As revised by the Council, on 9th March, 1995)

To facilitate the mutual acceptance of test data generated for submission to Regulatory Authorities of OECD Member countries, harmonization of the procedures adopted to monitor good laboratory practice compliance, as well as comparability of their quality and rigour, are essential. The aim of this document is to provide detailed practical guidance to OECD Member countries on the structure, mechanisms and procedures they should adopt when establishing national Good Laboratory Practice compliance monitoring programmes so that these programmes may be internationally acceptable.

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It is recognised that Member countries will adopt GLP Principles and establish compliance monitoring procedures according to national legal and administrative practices, and according to priorities they give to, e.g., the scope of initial and subsequent coverage concerning categories of chemicals and types of testing. Since Member countries may establish more than one Good Laboratory Practice Monitoring Authority due to their legal framework for chemicals control, more than one Good Laboratory Practice Compliance Programme may be established. The guidance set forth in the following paragraphs concerns each of these Authorities and Compliance Programmes, as appropriate.

DEFINITIONS OF TERMS

The definitions of terms in the “OECD Principles of Good Laboratory Practice” [Annex 2 to Council Decision C(81)30(Final)] are applicable to this document. In addition, the following definitions apply:

GLP Principles: Principles of good laboratory practice that are consistent with the OECD Principles of Good Laboratory Practice as set out in Annex 2 of Council Decision C(81)30(Final)⁴.

GLP Compliance Monitoring: The periodic inspection of test facilities and/or auditing of studies for the purpose of verifying adherence to GLP Principles.

³ The *Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice* are contained in the revision of Annex I to the Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practice [C(89)87(Final)] and [C(95)8(Final)]. For the text of C(89)87(Final), see page 15 of this publication.

⁴ See *The OECD Principles of Good Laboratory Practice*, No. 1 in this OECD series on Principles of GLP and Compliance Monitoring.

(National) GLP Compliance Programme: The particular scheme established by a Member country to monitor good laboratory practice compliance by test facilities within its territories, by means of inspections and study audits.

(National) GLP Monitoring Authority: A body established within a Member country with responsibility for monitoring the good laboratory practice compliance of test facilities within its territories and for discharging other such functions related to good laboratory practice as may be nationally determined. It is understood that more than one such body may be established in a Member country.

Test Facility Inspection: An on-site examination of the test facility's procedures and practices to assess the degree of compliance with GLP Principles. During inspections, the management structures and operational procedures of the test facility are examined, key technical personnel are interviewed, and the quality and integrity of data generated by the facility are assessed and reported.

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Study Audit: A comparison of raw data and associated records with the interim or final report in order to determine whether the raw data have been accurately reported, to determine whether testing was carried out in accordance with the study plan and Standard Operating Procedures, to obtain additional information not provided in the report, and to establish whether practices were employed in the development of data that would impair their validity.

Inspector: A person who performs the test facility inspections and study audits on behalf of the (National) GLP Monitoring Authority.

GLP Compliance Status: The level of adherence of a test facility to the GLP Principles as assessed by the (National) GLP Monitoring Authority.

Regulatory Authority: A national body with legal responsibility for aspects of the control of chemicals.

COMPONENTS OF GOOD LABORATORY PRACTICE COMPLIANCE MONITORING PROCEDURES

Administration

A (National) GLP Compliance Programme should be the responsibility of a properly constituted, legally identifiable body adequately staffed and working within a defined administrative framework.

Member countries should:

- ensure that the (National) GLP Monitoring Authority is directly responsible for an adequate “team” of inspectors having the necessary technical/scientific expertise or is ultimately responsible for such a “team”;
- publish documents relating to the adoption of GLP Principles within their territories;
- publish documents providing details of the (National) GLP Compliance Programme, including information on the legal or administrative framework within which the programme operates and

references to published acts, normative documents (e.g., regulations, codes of practice), inspection manuals, guidance notes, periodicity of inspections and/or criteria for inspection schedules, etc.;

- maintain records of test facilities inspected (and their GLP Compliance Status) and of studies audited for both national and international purposes.

Confidentiality

(National) GLP Monitoring Authorities will have access to commercially valuable information and, on occasion, may even need to remove commercially sensitive documents from a test facility or refer to them in detail in their reports.

Member countries should:

- make provision for the maintenance of confidentiality, not only by Inspectors but also by any other persons who gain access to confidential information as a result of GLP Compliance Monitoring activities;
- ensure that, unless all commercially sensitive and confidential information has been excised, reports of Test Facility Inspections and Study Audits are made available only to Regulatory Authorities and, where appropriate, to the test facilities inspected or concerned with Study Audits and/or to study sponsors.

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Personnel and Training

(National) GLP Monitoring Authorities should:

- *ensure that an adequate number of Inspectors is available*

The number of Inspectors required will depend upon:

- i) the number of test facilities involved in the (National) GLP Compliance Programme;
 - ii) the frequency with which the GLP Compliance Status of the test facilities is to be assessed;
 - iii) the number and complexity of the studies undertaken by those test facilities;
 - iv) the number of special inspections or audits requested by Regulatory Authorities.
- *ensure that Inspectors are adequately qualified and trained*

Inspectors should have qualifications and practical experience in the range of scientific disciplines relevant to the testing of chemicals. (National) GLP Monitoring Authorities should:

- i) ensure that arrangements are made for the appropriate training of GLP Inspectors, having regard to their individual qualifications and experience;
- ii) encourage consultations, including joint training activities where necessary, with the staff of (National) GLP Monitoring Authorities in other Member countries in order to promote interna-

tional harmonization in the interpretation and application of GLP Principles, and in the monitoring of compliance with such Principles.

- *ensure that inspectorate personnel, including experts under contract, have no financial or other interests in the test facilities inspected, the studies audited or the firms sponsoring such studies*
- *provide Inspectors with a suitable means of identification (e.g., an identity card).*

Inspectors may be:

- on the permanent staff of the (National) GLP Monitoring Authority;
- on the permanent staff of a body separate from the (National) GLP Monitoring Authority; or
- employed on contract, or in another way, by the (National) GLP Monitoring Authority to perform Test Facility Inspections or Study Audits.

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In the latter two cases, the (National) GLP Monitoring Authority should have ultimate responsibility for determining the GLP Compliance Status of test facilities and the quality/acceptability of a Study Audit, and for taking any action based on the results of Test Facility Inspections or Study Audits which may be necessary.

(National) GLP Compliance Programmes

GLP Compliance Monitoring is intended to ascertain whether test facilities have implemented GLP Principles for the conduct of studies and are capable of assuring that the resulting data are of adequate quality. As indicated above, Member countries should publish the details of their (National) GLP Compliance Programmes. Such information should, *inter alia*:

- *define the scope and extent of the Programme*
A (National) GLP Compliance Programme may cover only a limited range of chemicals, e.g., industrial chemicals, pesticides, pharmaceuticals, etc., or may include all chemicals. The scope of the monitoring for compliance should be defined, both with respect to the categories of chemicals and to the types of tests subject to it, e.g., physical, chemical, toxicological and/or ecotoxicological.
- *provide an indication as to the mechanism whereby test facilities enter the Programme*
The application of GLP Principles to health and environmental safety data generated for regulatory purposes may be mandatory. A mechanism should be available whereby test facilities may have their compliance with GLP Principles monitored by the appropriate (National) GLP Monitoring Authority.
- *provide information on categories of Test Facility Inspections/Study Audits*

A (National) GLP Compliance Programme should include:

- i) provision for Test Facility Inspections. These inspections include both a general Test Facility Inspection and a Study Audit of one or more on-going or completed studies;

- ii) provision for special Test Facility Inspections/Study Audits at the request of a Regulatory Authority – e.g., prompted by a query arising from the submission of data to a Regulatory Authority.
- *define the powers of Inspectors for entry into test facilities and their access to data held by test facilities (including specimens, SOP's, other documentation, etc.)*

While Inspectors will not normally wish to enter test facilities against the will of the facility's management, circumstances may arise where test facility entry and access to data are essential to protect public health or the environment. The powers available to the (National) GLP Monitoring Authority in such cases should be defined.

- *describe the Test Facility Inspection and Study Audit procedures for verification of GLP compliance*

The documentation should indicate the procedures which will be used to examine both the organisational processes and the conditions under which studies are planned, performed, monitored and recorded. Guidance for such procedures is available in *Guidance for the Conduct of Test Facility Inspections and Study Audits* (No. 3 in the OECD series on Principles of GLP and Compliance Monitoring).

- *describe actions that may be taken as follow-up to Test Facility Inspections and Study Audits.*

Follow-up to Test Facility Inspections and Study Audits

When a Test Facility Inspection or Study Audit has been completed, the Inspector should prepare a written report of the findings.

Member countries should take action where deviations from GLP Principles are found during or after a Test Facility Inspection or Study Audit. The appropriate actions should be described in documents from the (National) GLP Monitoring Authority.

If a Test Facility Inspection or Study Audit reveals only minor deviations from GLP Principles, the facility should be required to correct such minor deviations. The Inspector may need, at an appropriate time, to return to the facility to verify that corrections have been introduced.

Where no or where only minor deviations have been found, the (National) GLP Monitoring Authority may:

- issue a statement that the test facility has been inspected and found to be operating in compliance with GLP Principles. The date of the inspections and, if appropriate, the categories of test inspected in the test facility at that time should be included. Such statements may be used to provide information to (National) GLP Monitoring Authorities in other Member countries;

and/or

- provide the Regulatory Authority which requested a Study Audit with a detailed report of the findings.

Where serious deviations are found, the action taken by (National) GLP Monitoring Authorities will depend upon the particular circumstances of each case and the legal or administrative provisions under which GLP Compliance Monitoring has been established within their countries. Actions which may be taken include, but are not limited to, the following:

- issuance of a statement, giving details of the inadequacies or faults found which might affect the validity of studies conducted in the test facility;
- issuance of a recommendation to a Regulatory Authority that a study be rejected;
- suspension of Test Facility Inspections or Study Audits of a test facility and, for example and where administratively possible, removal of the test facility from the (National) GLP Compliance Programme or from any existing list or register of test facilities subject to GLP Test Facility Inspections;
- requiring that a statement detailing the deviations be attached to specific study reports;
- action through the courts, where warranted by circumstances and where legal/administrative procedures so permit.

Appeals Procedures

Problems, or differences of opinion, between Inspectors and test facility management will normally be resolved during the course of a Test Facility Inspection or Study Audit. However, it may not always be possible for agreement to be reached. A procedure should exist whereby a test facility may make representations relating to the outcome of a Test Facility Inspection or Study Audit for GLP Compliance Monitoring and/or relating to the action the GLP Monitoring Authority proposes to take thereon.

PART TWO:**COUNCIL DECISION-RECOMMENDATION
on Compliance with Principles of Good Laboratory Practice
[C(89)87(Final)]**

(Adopted by the Council at its 717th Session on 2nd October 1989)

The Council,

Having regard to Articles 5 a) and 5 b) of the Convention on the Organisation for Economic Cooperation and Development of 14th December 1960;

Having regard to the Recommendation of the Council of 7th July 1977 Establishing Guidelines in Respect of Procedure and Requirements for Anticipating the Effects of Chemicals on Man and in the Environment [C(77)97(Final)];

Having regard to the Decision of the Council of 12th May 1981 concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)] and, in particular, the Recommendation that Member countries, in the testing of chemicals, apply the OECD Principles of Good Laboratory Practice, set forth in Annex 2 of that Decision;

Having regard to the Recommendation of the Council of 26th July 1983 concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95(Final)];

Having regard to the conclusions of the Third High Level Meeting of the Chemicals Group (OECD, Paris, 1988);

Considering the need to ensure that test data on chemicals provided to regulatory authorities for purposes of assessment and other uses related to the protection of human health and the environment are of high quality, valid and reliable;

Considering the need to minimise duplicative testing of chemicals, and thereby to utilise more effectively scarce test facilities and specialist manpower, and to reduce the number of animals used in testing;

Considering that recognition of procedures for monitoring compliance with good laboratory practice will facilitate mutual acceptance of data and thereby reduce duplicative testing of chemicals;

Considering that a basis for recognition of compliance monitoring procedures is an understanding of, and confidence in, the procedures in the Member country where the data are generated;

Considering that harmonized approaches to procedures for monitoring compliance with good laboratory practice would greatly facilitate the development of the necessary confidence in other countries' procedures;

On the proposal of the Joint Meeting of the Management Committee of the Special Programme on the Control of Chemicals and the Chemicals Group, endorsed by the Environment Committee;

PART I

GLP Principles and Compliance Monitoring

1. DECIDES that Member countries in which testing of chemicals for purposes of assessment related to the protection of health and the environment is being carried out pursuant to principles of good laboratory practice that are consistent with the OECD Principles of Good Laboratory Practice as set out in Annex 2 of the Council Decision C(81)30(Final) (hereafter called “GLP Principles”) shall:

- i) establish national procedures for monitoring compliance with GLP Principles, based on laboratory inspections and study audits;
- ii) designate an authority or authorities to discharge the functions required by the procedures for monitoring compliance; and
- iii) require that the management of test facilities issue a declaration, where applicable, that a study was carried out in accordance with GLP Principles and pursuant to any other provisions established by national legislation or administrative procedures dealing with good laboratory practice.

2. RECOMMENDS that, in developing and implementing national procedures for monitoring compliance with GLP Principles, Member countries apply the “Guides for Compliance Monitoring Procedures for Good Laboratory Practice” and the “Guidance for the Conduct of Laboratory Inspections and Study Audits”, set out respectively in Annexes I and II which are an integral part of this Decision-Recommendation⁵.

PART II

Recognition of GLP Compliance among Member countries

1. DECIDES that Member countries shall recognise the assurance by another Member country that test data have been generated in accordance with GLP Principles if such other Member country complies with Part I above and Part II paragraph 2 below.

2. DECIDES that, for purposes of the recognition of the assurance in paragraph 1 above, Member countries shall:

- i) designate an authority or authorities for international liaison and for discharging other functions relevant to the recognition as set out in this Part and in the Annexes to this Decision-Recommendation;

⁵ The revision of Annex I of the Council Act [set out in C(95)8(Final)] is Part One (pages 9-14) of this publication. Annex II will be found in No. 3 (Revised) in this OECD series on Principles of GLP and Compliance Monitoring (Environment Monograph No. 111).

- ii) exchange with other Member countries relevant information concerning their procedures for monitoring compliance, in accordance with the guidance set out in Annex III⁶ which is an integral part of this Decision-Recommendation; and
 - iii) implement procedures whereby, where good reason exists, information concerning GLP compliance of a test facility (including information focussing on a particular study) within their jurisdiction can be sought by another Member country.
3. DECIDES that the Council Recommendation concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95(Final)] shall be repealed.

PART III

Future OECD Activities

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1. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to ensure that the “Guides for Compliance Monitoring Procedures for Good Laboratory Practice” and the “Guidance for the Conduct of Laboratory Inspections and Study Audits” set out in Annexes I and II⁷ are updated and expanded, as necessary, in light of developments and experience of Member countries and relevant work in other international organisations.
2. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to pursue a programme of work designed to facilitate the implementation of this Decision-Recommendation, and to ensure continuing exchange of information and experience on technical and administrative matters related to the application of GLP Principles and the implementation of procedures for monitoring compliance with good laboratory practice.
3. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to review actions taken by Member countries in pursuance of this Decision-Recommendation.

⁶ For the revision of Annex III of the Council Act [*Revised Guidance for the Exchange of Information concerning National Procedures for Monitoring of Compliance with Principles of Good Laboratory Practice*, set out in C(95)8(Final)], see page 21 of this publication.

⁷ See note 5, page 16.

Annex I to C(89)87(Final)/Revised in C(95)8(Final)**REVISED GUIDES FOR COMPLIANCE MONITORING PROCEDURES
FOR GOOD LABORATORY PRACTICE**

See pages 9-14

Annex II to C(89)87(Final)/Revised in C(95)8(Final)**REVISED GUIDANCE FOR THE CONDUCT OF LABORATORY
INSPECTIONS AND STUDY AUDITS**

See OECD series on Principles of GLP and Compliance Monitoring, No. 3 (Revised)
(Environment Monograph No. 111)

Annex III to C(89)87(Final)/Revised in C(95)8(Final)**REVISED GUIDANCE FOR THE EXCHANGE OF INFORMATION
CONCERNING NATIONAL PROGRAMMES FOR MONITORING
OF COMPLIANCE WITH PRINCIPLES OF GOOD LABORATORY PRACTICES**

(As revised by the Council, on 9th March, 1995)

Part II, paragraph 2 of the Council Act contains a Decision that Member countries exchange information related to their programmes for monitoring of compliance with GLP Principles. This Annex provides guidance concerning the types of information which should be exchanged. While information concerning all of the aspects covered in the “Guides for Compliance Monitoring Programmes procedures for Good Laboratory Practice” (Annex I) are relevant to an understanding of other Member countries’ programmes for GLP Compliance Monitoring, certain types of information are of particular importance.

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These include:

- the GLP Principles adopted nationally;
- the scope of the national programme for monitoring compliance with GLP Principles in terms of the types of chemicals and tests covered;
- the identity, legal status, and organisational structure of the (National) GLP Monitoring Authority(ies);
- the procedures followed during Test Facility Inspections and Study Audits, and the periodicity of inspections and/or criteria for inspection schedules;
- the number and qualifications of Inspectors;
- the actions available to the (National) GLP Monitoring Authority(ies) in cases of noncompliance, including the ability to inform other Member countries, when necessary, of the results of Test Facility Inspections and Study Audits;
- the arrangements for protecting confidentiality of information;
- the procedures for initiating, conducting and reporting on Test Facility Inspections and Study Audits at the request of other Member countries;
- the procedures for obtaining information on test facilities which have been inspected by a (National) GLP Monitoring Authority of another Member country, including such facilities’ compliance status; and
- the nature of test facility certifications that studies were carried out following GLP Principles.

Where serious deviations which may have affected specific studies are found, the (National) GLP Monitoring Authority should consider the need to inform relevant (National) GLP Monitoring Authorities in other Member countries of their findings.

The names of test facilities subject to Test Facility Inspections within a (National) GLP Compliance Programme, their levels of compliance with the national GLP Principles and the date(s) the Inspections were conducted should be made available annually to (National) GLP Monitoring Authorities in other Member countries upon request (see “Guidance for GLP Monitoring Authorities for the Preparation of Annual Overviews of Test Facilities Inspected” set out in the Appendix to this Annex.)

Recognition of national programmes for monitoring compliance with GLP Principles may not be immediately forthcoming from other Member countries. Member countries should be prepared to meet genuine concerns in a co-operative way. It may be that a Member country is unable to judge the acceptability of the GLP Compliance Monitoring programmes of another solely on the basis of the exchange of written information. In such cases, Member countries may seek the assurance they require through consultation and discussion with relevant (National) GLP Monitoring Authorities. In this context, OECD provides a forum for the discussion and solving of problems relating to the international harmonization and acceptance of GLP Compliance Monitoring programmes.

To facilitate international liaison and the continuing exchange of information, the establishment of a single GLP Monitoring Authority covering all good laboratory practice activities within a Member country has obvious advantages. Where more than one Authority exists, a Member country should ensure that they operate in a consistent way, and have similar GLP Compliance Programmes. The Authority or Authorities with responsibilities for international contacts should be identified by Member countries.

Situations will arise where a national Regulatory Authority of a Member country will need to request information on the GLP Compliance Status of a test facility located in another Member country. On rare occasions, and where good reason exists, a particular Study Audit may be requested by a Regulatory Authority of another Member country. Arrangements should be provided whereby these requests may be fulfilled and the results reported back to the requesting Regulatory Authority.

Formal international contact should be established for the exchange of information between GLP Monitoring Authorities. However, this should not be understood to prevent informal contacts between Regulatory Authorities and the GLP Monitoring Authority in another Member country, to the extent that such contacts are accepted by the Member countries concerned.

National authorities should note that authorities from another Member country may wish to be present at a Test Facility Inspection or Study Audit that they have specifically requested; or they may wish that representative(s) from the Member country seeking a special Test Facility Inspection or Study Audit be present at that Inspection or Audit. In these cases, Member countries should enable Inspectors from another Member country to participate in facility inspections and Study Audits carried out by their GLP Monitoring Authority.

Appendix to Annex III to C(89)87(Final)/Revised in C(95)8(Final)

GUIDANCE FOR GOOD LABORATORY PRACTICE MONITORING AUTHORITIES FOR THE PREPARATION OF ANNUAL OVERVIEWS OF TEST FACILITIES INSPECTED

Overviews of GLP inspections should be circulated to Members of the OECD Panel on GLP and the OECD Secretariat annually before the end of March. The following minimum set of information should allow harmonisation of the overviews exchanged among national GLP monitoring authorities:

- 1. Identification of the facility inspected:** Sufficient information should be included to make the identification of the facility unequivocal, i.e. the name of the test facility the city and country in which it is located, including inspections abroad.
- 2. Dates of inspections and decisions:** month and year of inspection, and, if appropriate, date of final decision on GLP compliance status.
- 3. Nature of inspection:** A clear indication should be given of whether a full GLP inspection or only a study audit was carried out, as well as whether the inspection was routine or not and any other authorities which were involved.
- 4. Areas of expertise of the facility inspected:** Since GLP compliance is related to the tests performed by a facility, the area(s) of expertise of the test facilities inspected should be included in the annual overviews, using the following broad categories:
 - 1) physical-chemical testing
 - 2) toxicity studies
 - 3) mutagenicity studies
 - 4) environmental toxicity studies on aquatic and terrestrial organisms
 - 5) studies on behaviour in water, soil and air; bioaccumulation
 - 6) residue studies
 - 7) studies on effects on mesocosms and natural ecosystems
 - 8) analytical and clinical chemistry testing
 - 9) other studies, specify.

It is emphasised that these categories are to be used in a flexible manner on a case-by-case basis and that the aim is to provide information related to GLP compliance of test facilities that will be useful for other national monitoring authorities.

5. Compliance status: The three following categories should be used to report the compliance status of facilities:

- in compliance
- not in compliance
- pending (with explanation)

In light of the fact that “pending” is interpreted differently by Member countries and that the varying legal and administrative systems do not allow for harmonised use of the term, explanations must accompany the use of the “pending” status in the national overview of test facilities inspected. Such explanations could include, e.g., “pending reinspection”, “pending responses from test facility”, “pending completion of administrative procedures”. etc.

6. Comments: If appropriate, further comments can be made.

7. Major deficiencies: At a minimum, individual studies for which a study audit has revealed serious GLP deficiencies and which have consequently been rejected by receiving authorities should be reported in the annual overviews of test facilities inspected. Since many studies are submitted to authorities in several countries at the same time, however, it is recommended that this kind of information be circulated among national authorities as rapidly as possible on an *ad hoc* basis, when necessary in addition to the annual overviews.

8. Statements of compliance: When statements of compliance are provided to facilities by national monitoring authorities, they should use the same terminology and categories as the annual overviews.

9. Circulation of annual overviews: Overviews should be circulated annually before the end of March to the Members of the GLP Panel and the OECD Secretariat. This information can be released to the public on request.



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GUIDANCE FOR GLP MONITORING AUTHORITIES

**Revised guidance for the conduct of laboratory inspections
and study audits**

Environment Monograph No. 111

Paris 1995

FOREWORD

The 1981 Council Decision on Mutual Acceptance of Data [C(81)30(Final)], of which the OECD Principles of Good Laboratory Practice¹ are an integral part, includes an instruction for OECD to undertake activities “to facilitate internationally-harmonized approaches to assuring compliance” with the GLP Principles. Consequently, in order to promote the implementation of comparable compliance monitoring procedures, and international acceptance, among Member countries the Council adopted in 1983 the Recommendation concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95(Final)], which set out basic characteristics of the procedures for monitoring compliance.

A Working Group on Mutual Recognition of Compliance with GLP was established in 1985 under the chairmanship of Professor V. Silano (Italy) to facilitate the practical implementation of the Council acts on GLP, develop common approaches to the technical and administrative problems related to GLP compliance and its monitoring, and develop arrangements for the mutual recognition of compliance monitoring procedures. The following countries and organisations participated in the Working Group: Australia, Belgium, Canada, Denmark, the Federal Republic of Germany, Finland, France, Italy, Japan, Norway, the Netherlands, Portugal, Spain, Sweden, Switzerland, the United Kingdom, the United States, the Commission of the European Communities, the International Organization for Standardization, the Pharmaceutical Inspection Convention, and the World Health Organization.

The Working Group developed, *inter alia*, Guidance for the Conduct of Laboratory Inspections and Study Audits. The Guidance was based on a text developed by the Expert Group on GLP and presented as part of its Final Report in 1982². The current Guidance was first published in 1988 in the Final Report of the Working Group³. A slightly abridged version was annexed to the 1989 Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practice [C(89)87(Final)], which superseded and replaced the 1983 Council Act.

In adopting that Decision-Recommendation, the Council in Part III.1 instructed the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to ensure that the “Guides for Compliance Monitoring Procedures for Good Laboratory Practice” and the “Guidance for the Conduct of Laboratory Inspections and Study Audits” set out in Annexes I and II thereto were updated and expanded, as necessary, in light of developments and experience of Member countries and relevant work in other international organisations.

¹ See *The OECD Principles of Good Laboratory Practice* (No. 1 in this OECD series on Principles of GLP and Compliance Monitoring).

² *Good Laboratory Practice in the Testing of Chemicals*, OECD, 1982, out of print.

³ *Final Report of the Working Group on Mutual Recognition of Compliance with Good Laboratory Practice*, OECD Environment Monograph No. 15, March 1988.

The OECD Panel on Good Laboratory Practice developed proposals for amendments to these Annexes. These revised Annexes were approved by the Council in a Decision “Amending the Annexes to the Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practice” on 9th March, 1995 [C(95)8(Final)].

Part One of this document consists of the Revised Guidance for the Conduct of Laboratory Inspections and Study Audits as annexed to the 1989 Council Act [C(89)87(Final)] and revised by Council in 1995 [C(95)8(Final)]. The text of the 1989 Council Act will be found in Part Two.

This document cancels and replaces the Environment Monograph No. 47 entitled “Guides for Compliance Monitoring Procedures for Good Laboratory Practice”, published in 1992.

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PART ONE :**REVISED GUIDANCE FOR THE CONDUCT
OF TEST FACILITY INSPECTIONS AND STUDY AUDITS⁴**

(As revised by the Council, on 9th March, 1995)

INTRODUCTION

The purpose of this document is to provide guidance for the conduct of Test Facility Inspections and Study Audits which would be mutually acceptable to OECD Member countries. It is principally concerned with Test Facility Inspections, an activity which occupies much of the time of GLP Inspectors. A Test Facility Inspection will usually include a Study Audit or “review” as a part of the inspection, but Study Audits will also have to be conducted from time to time at the request, for example, of a Regulatory Authority. General guidance for the conduct of Study Audits will be found at the end of this document.

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Test Facility Inspections are conducted to determine the degree of conformity of test facilities and studies with GLP Principles and to determine the integrity of data to assure that resulting data are of adequate quality for assessment and decision-making by national Regulatory Authorities. They result in reports which describe the degree of adherence of a test facility to the GLP Principles. Test Facility Inspections should be conducted on a regular, routine basis to establish and maintain records of the GLP compliance status of test facilities.

Further clarification of many of the points in this document may be obtained by referring to the OECD Consensus Documents on GLP (on, e.g., the role and responsibilities of the Study Director).

DEFINITIONS OF TERMS

The definitions of terms in the “OECD Principles of Good Laboratory Practice”⁵ [Annex II to Council Decision C(81)30(Final)] and in the “Guides for Compliance Monitoring Procedures for Good Laboratory Practice”⁶ [Annex I to Council Decision-Recommendation C(89)87(Final)/revised in C(95)8(Final)] are applicable to this document.

⁴ The *Revised Guidance for the Conduct of Laboratory Inspections and Study Audits* is contained in the revision of Annex II to the Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practice [C(89)87(Final) and C(95)8(Final)]. For the text of C(89)87(Final), see page 21 of this publication.

⁵ See *The OECD Principles of Good Laboratory Practice* (No. 1 in this OECD series on Principles of GLP and Compliance Monitoring).

⁶ See *Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice* (No. 2 (Revised) in this OECD series on Principles of GLP and Compliance Monitoring).

TEST FACILITY INSPECTIONS

Inspections for compliance with GLP Principles may take place in any test facility generating health or environmental safety data for regulatory purposes. Inspectors may be required to audit data relating to the physical, chemical, toxicological or ecotoxicological properties of a substance or preparation. In some cases, Inspectors may need assistance from experts in particular disciplines.

The wide diversity of facilities (in terms both of physical layout and management structure), together with the variety of types of studies encountered by Inspectors, means that the Inspectors must use their own judgement to assess the degree and extent of compliance with GLP Principles. Nevertheless, Inspectors should strive for a consistent approach in evaluating whether, in the case of a particular test facility or study, an adequate level of compliance with each GLP Principle has been achieved.

In the following sections, guidance is provided on the various aspects of the testing facility, including its personnel and procedures, which are likely to be examined by Inspectors. In each section, there is a statement of purpose, as well as an illustrative list of specific items which could be considered during the course of a Test Facility Inspection. These lists are not meant to be comprehensive and should not be taken as such.

Inspectors should not concern themselves with the scientific design of the study or the interpretation of the findings of studies with respect to risks for human health or the environment. These aspects are the responsibility of those Regulatory Authorities to which the data are submitted for regulatory purposes.

Test Facility Inspections and Study Audits inevitably disturb the normal work in a facility. Inspectors should therefore carry out their work in a carefully planned way and, so far as practicable, respect the wishes of the management of the test facility as to the timing of visits to certain sections of the facility.

Inspectors will, while conducting Test Facility Inspections and Study Audits, have access to confidential, commercially valuable information. It is essential that they ensure that such information is seen by authorised personnel only. Their responsibilities in this respect will have been established within their (National) GLP Compliance Monitoring Programme.

INSPECTION PROCEDURES

Pre-Inspection

PURPOSE: To familiarise the Inspector with the facility which is about to be inspected in respect of management structure, physical layout of buildings and range of studies.

Prior to conducting a Test Facility Inspection or Study Audit, Inspectors should familiarise themselves with the facility which is to be visited. Any existing information on the facility should be reviewed. This may include previous inspection reports, the layout of the facility, organisation charts, study reports, protocols and curricula vitae (CVs) of personnel. Such documents would provide information on:

- the type, size and layout of the facility;
- the range of studies likely to be encountered during the inspection;

- the management structure of the facility.

Inspectors should note, in particular, any deficiencies from previous Test Facility Inspections. Where no previous Test Facility Inspections have been conducted, a pre-inspection visit can be made to obtain relevant information.

Test Facilities may be informed of the date and time of Inspector's arrival, the objective of their visit and the length of time they expect to be on the premises. This could allow the test facility to ensure that the appropriate personnel and documentation are available. In cases where particular documents or records are to be examined, it may be useful to identify these to the test facility in advance of the visit so that they will be immediately available during the Test Facility Inspection.

Starting Conference

PURPOSE: To inform the management and staff of the facility of the reason for the Test Facility Inspection or Study Audit that is about to take place, and to identify the facility areas, study(ies) selected for audit, documents and personnel likely to be involved.

The administrative and practical details of a Test Facility Inspection or Study Audit should be discussed with the management of the facility at the start of the visit. At the starting conference, Inspectors should:

- outline the purpose and scope of the visit;
- describe the documentation which will be required for the Test Facility Inspection, such as lists of on-going and completed studies, study plans, standard operating procedures, study reports, etc. Access to and, if necessary, arrangements for the copying of relevant documents should be agreed upon at this time;
- clarify or request information as to the management structure (organisation) and personnel of the facility;
- request information as to the conduct of studies not subject to GLP Principles in the areas of the test facility where GLP studies are being conducted;
- make an initial determination as to the parts of the facility to be covered during the Test Facility Inspection;
- describe the documents and specimens that will be needed for on-going or completed study(ies) selected for Study Audit;
- indicate that a closing conference will be held at the completion of the inspection.

Before proceeding further with a Test Facility Inspection, it is advisable for the Inspector(s) to establish contact with the facility's Quality Assurance (QA) Unit.

As a general rule, when inspecting a facility, Inspectors will find it helpful to be accompanied by a member of the QA unit.

Inspectors may wish to request that a room be set aside for examination of documents and other

activities.

Organisation and Personnel

PURPOSE: To determine whether: the test facility has sufficient qualified personnel, staff resources and support services for the variety and number of studies undertaken; the organisational structure is appropriate; and management has established a policy regarding training and staff health surveillance appropriate to the studies undertaken in the facility.

The management should be asked to produce certain documents, such as:

- floor plans;
- facility management and scientific organisation charts;
- CVs of personnel involved in the type(s) of studies selected for the Study Audit;
- list(s) of on-going and completed studies with information on the type of study, initiation/completion dates, test system, method of application of test substance and name of Study Director;
- staff health surveillance policies;
- staff job descriptions and staff training programmes and records;
- an index to the facility's Standard Operating Procedures (SOPs);
- specific SOPs as related to the studies or procedures being inspected or audited;
- list(s) of the Study Directors and sponsors associated with the study(ies) being audited.

The Inspector should check, in particular:

- lists of on-going and completed studies to ascertain the level of work being undertaken by the test facility;
- the identity and qualifications of the Study Director(s), the head of the Quality Assurance unit and other personnel;
- existence of SOPs for all relevant areas of testing.

Quality Assurance Programme

PURPOSE: To determine whether the mechanisms used to assure management that studies are conducted in accordance with GLP Principles are adequate.

The head of the Quality Assurance (QA) Unit should be asked to demonstrate the systems and methods for QA inspection and monitoring of studies, and the system for recording observations made during QA monitoring. Inspectors should check:

- the qualifications of the head of QA, and of all QA staff;
- that the QA unit functions independently from the staff involved in the studies;
- how the QA unit schedules and conducts inspections, how it monitors identified critical phases

- in a study, and what resources are available for QA inspections and monitoring activities;
- that where studies are of such short duration that monitoring of each study is impracticable, arrangements exist for monitoring on a sample basis;
- the extent and depth of QA monitoring during the practical phases of the study;
- the extent and depth of QA monitoring of routine test facility operation;
- the QA procedures for checking the final report to ensure its agreement with the raw data;
- that management receives reports from QA concerning problems likely to affect the quality or integrity of a study;
- the actions taken by QA when deviations are found;
- the QA role, if any, if studies or parts of studies are done in contract laboratories;
- the part played, if any, by QA in the review, revision and updating of SOPs.

Facilities

PURPOSE: To determine if the test facility, whether indoor or outdoor, is of suitable size, design and location to meet the demands of the studies being undertaken.

The Inspector should check that:

- the design enables an adequate degree of separation so that, e.g., test substances, animals, diets, pathological specimens, etc. of one study cannot be confused with those of another;
- environmental control and monitoring procedures exist and function adequately in critical areas, e.g., animal and other biological test systems rooms, test substance storage areas, laboratory areas;
- the general housekeeping is adequate for the various facilities and that there are, if necessary, pest control procedures.

Care, Housing and Containment of Biological Test Systems

PURPOSE: To determine whether the test facility, if engaged in studies using animals or other biological test systems, has support facilities and conditions for their care, housing and containment, adequate to prevent stress and other problems which could affect the test system and hence the quality of data.

A test facility may be carrying out studies which require a diversity of animal or plant species as well as microbial or other cellular or sub-cellular systems. The type of test systems being used will determine the aspects relating to care, housing or containment that the Inspector will monitor. Using his judgement, the Inspector will check, according to the test systems, that:

- there are facilities adequate for the test systems used and for testing needs;
- there are arrangements to quarantine animals and plants being introduced into the facility and

- that these arrangements are working satisfactorily;
- there are arrangements to isolate animals (or other elements of a test system, if necessary) known to be, or suspected of being, diseased or carriers of disease;
- there is adequate monitoring and record-keeping of health, behaviour or other aspects, as appropriate to the test system;
- the equipment for maintaining the environmental conditions required for each test system is adequate, well maintained, and effective;
- animal cages, racks, tanks and other containers, as well as accessory equipment, are kept sufficiently clean;
- analyses to check environmental conditions and support systems are carried out as required;
- facilities exist for removal and disposal of animal waste and refuse from the test systems and that these are operated so as to minimise vermin infestation, odours, disease hazards and environmental contamination;
- storage areas are provided for animal feed or equivalent materials for all test systems; that these areas are not used for the storage of other materials such as test substances, pest control chemicals or disinfectants, and that they are separate from areas in which animals are housed or other biological test systems are kept;
- stored feed and bedding are protected from deterioration by adverse environmental conditions, infestation or contamination.

Apparatus, Materials, Reagents and Specimens

PURPOSE: To determine whether the test facility has suitably located, operational apparatus in sufficient quantity and of adequate capacity to meet the requirements of the tests being conducted in the facility and that the materials, reagents and specimens are properly labelled, used and stored.

The Inspector should check that:

- apparatus is clean and in good working order;
- records have been kept of operation, maintenance, verification, calibration and validation of measuring equipment and apparatus (including computerised systems);
- materials and chemical reagents are properly labelled and stored at appropriate temperatures and that expiry dates are not being ignored. Labels for reagents should indicate their source, identity and concentration and/or other pertinent information;
- specimens are well identified by test system, study, nature and date of collection;
- apparatus and materials used do not alter to any appreciable extent the test systems.

Test Systems

PURPOSE: To determine whether adequate procedures exist for the handling and control of the variety of test systems required by the studies undertaken in the facility, e.g., chemical and physical systems, cellular and microbic systems, plants or animals.

Physical and Chemical Systems

The Inspector should check that:

- where required by study plans, the stability of test and reference substances was determined and that the reference substances specified in test plans were used;
- in automated systems, data generated as graphs, recorder traces or computer print-outs are documented as raw data and archived.

Biological Test Systems

Taking account of the relevant aspects referred to above relating to care, housing or containment of biological test systems, the Inspector should check that:

- test systems are as specified in study plans;
- test systems are adequately and, if necessary and appropriate, uniquely identified throughout the study; and that records exist regarding receipt of the test systems and document fully the number of test systems received, used, replaced or discarded;
- housing or containers of test systems are properly identified with all the necessary information;
- there is an adequate separation of studies being conducted on the same animal species (or the same biological test systems) but with different substances;
- there is an adequate separation of animal species (and other biological test systems) either in space or in time;
- the biological test system environment is as specified in the study plan or in SOPs for aspects such as temperature, or light/dark cycles;
- the recording of the receipt, handling, housing or containment, care and health evaluation is appropriate to the test systems;
- written records are kept of examination, quarantine, morbidity, mortality, behaviour, diagnosis and treatment of animal and plant test systems or other similar aspects as appropriate to each biological test system;
- there are provisions for the appropriate disposal of test systems at the end of tests.

Test and Reference Substances

PURPOSE: To determine whether the test facility has procedures designed (i) to ensure that the identify, potency, quantity and composition of test and reference substances are in accordance with their specifications, and (ii) to properly receive and store test and reference substances.

The Inspector should check that:

- there are written records on the receipt (including identification of the person responsible), and for the handling, sampling, usage and storage of tests and reference substances;
- test and reference substances containers are properly labelled;
- storage conditions are appropriate to preserve the concentration, purity and stability of the test and reference substances;
- there are written records on the determination of identity, purity, composition, stability, and for the prevention of contamination of test and reference substances, where applicable;
- there are procedures for the determination of the homogeneity and stability of mixtures containing test and reference substances, where applicable;
- containers holding mixtures (or dilutions) of the test and reference substances are labelled and that records are kept of the homogeneity and stability of their contents, where applicable;
- when the test is of longer than four weeks' duration, samples from each batch of test and reference substances have been taken for analytical purposes and that they have been retained for an appropriate time;
- procedures for mixing substances are designed to prevent errors in identification or crosscontamination.

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Standard Operating Procedures

PURPOSE: To determine whether the test facility has written SOPs relating to all the important aspects of its operations, considering that one of the most important management techniques for controlling facility operations is the use of written SOPs. These relate directly to the routine elements of tests conducted by the test facility.

The Inspector should check that:

- each test facility area has immediately available relevant, authorised copies of SOPs;
- procedures exist for revision and updating of SOPs;
- any amendments or changes to SOPs have been authorised and dated;
- historical files of SOPs are maintained;
- SOPs are available for, but not necessarily limited to, the following activities:
 - i) receipt; determination of identity, purity, composition and stability; labelling; handling; sampling; usage; and storage of test and reference substances;
 - ii) use, maintenance, cleaning, calibration and validation of measuring apparatus, computerised systems and environmental control equipment;

- iii) preparation of reagents and dosing formulations;
- iv) record-keeping, reporting, storage and retrieval of records and reports;
- v) preparation and environmental control of areas containing the test systems;
- vi) receipt, transfer, location, characterisation, identification and care of test systems;
- vii) handling of the test systems before, during and at the termination of the study;
- viii) disposal of test systems;
- xi) use of pest control and cleaning agents;
- x) Quality Assurance programme operations.

Performance of the Study

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PURPOSE: To verify that written study plans exist and that the plans and the conduct of the study are in accordance with GLP Principles.

The Inspector should check that:

- the study plan was signed by the Study Director;
- any amendments to the study plan were signed and dated by the Study Director;
- the date of the agreement to the study plan by the sponsor was recorded (where applicable);
- measurements, observations and examinations were in accordance with the study plan and relevant SOPs;
- the results of these measurements, observations and examinations were recorded directly, promptly, accurately and legibly and were signed (or initialled) and dated;
- any changes in the raw data, including data stored in computers, did not obscure previous entries, included the reason for the change and identified the person responsible for the change and the date it was made;
- computer-generated or stored data have been identified and that the procedures to protect them against unauthorised amendments or loss are adequate;
- the computerised systems used within the study are reliable, accurate and have been validated;
- any unforeseen events recorded in the raw data have been investigated and evaluated;
- the results presented in the reports of the study (interim or final) are consistent and complete and that they correctly reflect the raw data.

Reporting of Study Results

PURPOSE: To determine whether final reports are prepared in accordance with GLP Principles.

When examining a final report, the Inspector should check that:

- it is signed and dated by the Study Director to indicate acceptance of responsibility for the validity of the study and confirming that the study was conducted in accordance with GLP Principles;
- it is signed and dated by other principal scientists, if reports from co-operating disciplines are included;
- a Quality Assurance statement is included in the report and that it is signed and dated;
- any amendments were made by the responsible personnel;
- it lists the archive location of all samples, specimens and raw data.

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Storage and Retention of Records

PURPOSE: To determine whether the facility has generated adequate records and reports and whether adequate provision has been made for the safe storage and retention of records and materials.

The Inspector should check:

- that a person has been identified as responsible for the archive;
- the archive facilities for the storage of study plans, raw data (including that from discontinued GLP Studies), final reports, samples and specimens and records of education and training of personnel;
- the procedures for retrieval of archived materials;
- the procedures whereby access to the archives is limited to authorised personnel and records are kept of personnel given access to raw data, slides, etc.;
- that an inventory is maintained of materials removed from, and returned to, the archives;
- that records and materials are retained for the required or appropriate period of time and are protected from loss or damage by fire, adverse environmental conditions, etc.

STUDY AUDITS

Test Facility inspections will generally include, *inter alia*, Study Audits, which review on-going or completed studies. Specific Study Audits are also often requested by Regulatory Authorities, and can be conducted independently of Test Facility Inspections. Because of the wide variation in the types of studies which might be audited, only general guidance is appropriate, and Inspectors and others taking part in Study Audits will always need to exercise judgement as to the nature and extent of their examinations. The objective should be to reconstruct the study by comparing the final report with the study plan, relevant SOPs, raw data and other archived material.

In some cases, Inspectors may need assistance from other experts in order to conduct an effective Study Audit, e.g., where there is a need to examine tissue sections under the microscope.

When conducting a Study Audit, the Inspector should:

- obtain names, job descriptions and summaries of training and experience for selected personnel engaged in the study(ies) such as the Study Director and principal scientists;
- check that there is sufficient staff trained in relevant areas for the study(ies) undertaken;
- identify individual items of apparatus or special equipment used in the study and examine the calibration, maintenance and service records for the equipment;
- review the records relating to the stability of the test substances, analyses of test substance and formulations, analyses of feed, etc.;
- attempt to determine, through the interview process if possible, the work assignments of selected individuals participating in the study to ascertain if these individuals had the time to accomplish the tasks specified in the study plan or report;
- obtain copies of all documentation concerning control procedures or forming integral parts of the study, including:
 - i) the study plan;
 - ii) SOPs in use at the time the study was done;
 - iii) log books, laboratory notebooks, files, worksheets, print-outs of computer-stored data, etc.; check calculations, where appropriate;
 - iv) the final report.

In studies in which animals (i.e., rodents and other mammals) are used, the Inspectors should follow a certain percentage of individual animals from their arrival at the test facility to autopsy. They should pay particular attention to the records relating to:

- animal body weight, food/water intake, dose formulation and administration, etc.;
- clinical observations and autopsy findings;
- clinical chemistry;
- pathology.

COMPLETION OF INSPECTION OR STUDY AUDIT

When a Test Facility Inspection or Study Audit has been completed, the Inspector should be prepared to discuss his findings with representatives of the test facility at a Closing Conference and should prepare a written report, i.e., the Inspection Report.

A Test Facility Inspection of any large facility is likely to reveal a number of minor deviations from GLP Principles but, normally, these will not be sufficiently serious to affect the validity of studies emanating from that test facility. In such cases, it is reasonable for an Inspector to report that the facility is operating in compliance with GLP Principles according to the criteria established by the (National) GLP Monitoring Authority. Nevertheless, details of the inadequacies or faults detected should be provided to the test facility and assurances sought from its senior management that action will be taken to remedy them. The Inspector may need to revisit the facility after a period of time to verify that necessary action has been taken.

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If a serious deviation from the GLP Principles is identified during a Test Facility Inspection or Study Audit which, in the opinion of the Inspector, may have affected the validity of that study, or of other studies performed at the facility, the Inspector should report back to the (National) GLP Monitoring Authority. The action taken by that Authority and/or the regulatory authority, as appropriate, will depend upon the nature and extent of the non-compliance and the legal and/or administrative provisions within the GLP Compliance Programme.

Where a Study Audit has been conducted at the request of a Regulatory Authority, a full report of the findings should be prepared and sent via the relevant (National) GLP Monitoring Authority to the Regulatory Authority concerned.

PART TWO :**COUNCIL DECISION-RECOMMENDATION
on Compliance with Principles of Good Laboratory Practice
[C(89)87(Final)]**

(Adopted by the Council at its 717th Session on 2nd October 1989)

The Council,

Having regard to Articles 5 a) and 5 b) of the Convention on the Organisation for Economic Cooperation and Development of 14th December 1960;

Having regard to the Recommendation of the Council of 7th July 1977 Establishing Guidelines in Respect of Procedure and Requirements for Anticipating the Effects of Chemicals on Man and in the Environment [C(77)97(Final)];

Having regard to the Decision of the Council of 12th May 1981 concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)] and, in particular, the Recommendation that Member countries, in the testing of chemicals, apply the OECD Principles of Good Laboratory Practice, set forth in Annex 2 of that Decision;

Having regard to the Recommendation of the Council of 26th July 1983 concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95(Final)];

Having regard to the conclusions of the Third High Level Meeting of the Chemicals Group (OECD, Paris, 1988);

Considering the need to ensure that test data on chemicals provided to regulatory authorities for purposes of assessment and other uses related to the protection of human health and the environment are of high quality, valid and reliable;

Considering the need to minimise duplicative testing of chemicals, and thereby to utilise more effectively scarce test facilities and specialist manpower, and to reduce the number of animals used in testing;

Considering that recognition of procedures for monitoring compliance with good laboratory practice will facilitate mutual acceptance of data and thereby reduce duplicative testing of chemicals;

Considering that a basis for recognition of compliance monitoring procedures is an understanding of, and confidence in, the procedures in the Member country where the data are generated;

Considering that harmonized approaches to procedures for monitoring compliance with good laboratory practice would greatly facilitate the development of the necessary confidence in other countries' procedures;

On the proposal of the Joint Meeting of the Management Committee of the Special Programme on the Control of Chemicals and the Chemicals Group, endorsed by the Environment Committee;

PART I

GLP Principles and Compliance Monitoring

1. DECIDES that Member countries in which testing of chemicals for purposes of assessment related to the protection of health and the environment is being carried out pursuant to principles of good laboratory practice that are consistent with the OECD Principles of Good Laboratory Practice as set out in Annex 2 of the Council Decision C(81)30(Final) (hereafter called “GLP Principles”) shall:

- i) establish national procedures for monitoring compliance with GLP Principles, based on laboratory inspections and study audits;
- ii) designate an authority or authorities to discharge the functions required by the procedures for monitoring compliance; and
- iii) require that the management of test facilities issue a declaration, where applicable, that a study was carried out in accordance with GLP Principles and pursuant to any other provisions established by national legislation or administrative procedures dealing with good laboratory practice.

2. RECOMMENDS that, in developing and implementing national procedures for monitoring compliance with GLP Principles, Member countries apply the “Guides for Compliance Monitoring Procedures for Good Laboratory Practice” and the “Guidance for the Conduct of Laboratory Inspections and Study Audits,” set out respectively in Annexes I and II which are an integral part of this Decision- Recommendation⁷.

PART II

Recognition of GLP Compliance among Member countries

1. DECIDES that Member countries shall recognise the assurance by another Member country that test data have been generated in accordance with GLP Principles if such other Member country complies with Part I above and Part II paragraph 2 below.

2. DECIDES that, for purposes of the recognition of the assurance in paragraph 1 above, Member countries shall:

- i) designate an authority or authorities for international liaison and for discharging other functions relevant to the recognition as set out in this Part and in the Annexes to this Decision-Recommendation;

⁷ The revision of Annex I of the Council Act [set out in C(95)8](Final)] will be found in the *Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice*, No. 2 (Revised) in this OECD series on Principles of GLP and Compliance Monitoring (Environment Monograph No. 110). The revision of Annex II is Part One of this publication.

- ii) exchange with other Member countries relevant information concerning their procedures for monitoring compliance, in accordance with the guidance set out in Annex III⁸ which is an integral part of this Decision-Recommendation; and
 - iii) implement procedures whereby, where good reason exists, information concerning GLP compliance of a test facility (including information focussing on a particular study) within their jurisdiction can be sought by another Member country.
3. DECIDES that the Council Recommendation concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95(Final)] shall be repealed.

PART III

Future OECD Activities

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1. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to ensure that the “Guides for Compliance Monitoring Procedures for Good Laboratory Practice” and the “Guidance for the Conduct of Laboratory Inspections and Study Audits” set out in Annexes I and II⁹ are updated and expanded, as necessary, in light of developments and experience of Member countries and relevant work in other international organisations.
2. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to pursue a programme of work designed to facilitate the implementation of this Decision-Recommendation, and to ensure continuing exchange of information and experience on technical and administrative matters related to the application of GLP Principles and the implementation of procedures for monitoring compliance with good laboratory practice.
3. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to review actions taken by Member countries in pursuance of this Decision-Recommendation.

⁸ The revision of Annex III of the Council Act [*Guidance for the Exchange of Information concerning National Procedures for Monitoring of Compliance of Good Laboratory Practice*], set out in C(95)8(Final) will also be found in *Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice*, No. 2 (revised) in this OECD Series on Principles of GLP and Compliance Monitoring, pages 22-23 (Environment Monograph No. 110).

⁹ See note 7, page 22.



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Quality assurance and GLP

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FOREWORD

In the framework of the OECD Consensus Workshop on Good Laboratory Practice, held 16th-18th October 1990 in Bad Dürkheim, Germany, a Working Group met to discuss and arrive at consensus on Good Laboratory Practice and the role of quality assurance (QA). The Working Group was chaired by Dr. Hans Könemann (Head, GLP Compliance Monitoring Authority, the Netherlands). Participants were mainly members of national GLP compliance monitoring units or experienced QA managers from test facilities. The following countries were represented: Austria, Belgium, France, Germany, Ireland, the Netherlands, Norway, Spain, Sweden, Switzerland, and the United Kingdom.

The Working Group reached consensus on the role of QA as an important component of GLP. It identified major issues related to QA and GLP, but did not attempt to treat the subject exhaustively. One area not specifically addressed was the application of QA to field studies. This and some other aspects of QA will be addressed separately.

The draft consensus document developed by the Working Group was circulated to Member countries and revised, based on the comments received. It was subsequently endorsed by the OECD Panel on GLP, and the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals. The Environment Committee then recommended that this document be derestricted under the authority of the Secretary-General.

In light of the adoption of the Revised OECD Principles of GLP in 1997, this Consensus Document was reviewed by the Working Group on GLP and revised to make it consistent with modifications made to the Principles. It was endorsed by the Working Group in April 1999 and, subsequently by the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in August 1999. It too is declassified under the authority of the Secretary-General.

GLP CONSENSUS DOCUMENT

QUALITY ASSURANCE AND GLP

Background

The OECD Principles of GLP have been in force for over fifteen years (see No.1 in this OECD Series on Good Laboratory Practice and Compliance Monitoring, as revised in 1997). Valuable experience has been gained at test facilities where these principles have been applied, as well as by governmental bodies monitoring for compliance. In light of this experience, some additional guidance can be given on the role and operation of quality assurance programmes in test facilities.

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References to Quality Assurance in the OECD Principles of GLP

A quality assurance programme is defined in the Revised OECD Principles of Good Laboratory Practice as “a defined system, including personnel, which is independent of study conduct and is designed to assure test facility management of compliance with these Principles of Good Laboratory Practice” [Section I.2.2(8)]. The responsibilities of the management of a test facility include ensuring “that there is a Quality Assurance Programme with designated personnel and assure that the quality assurance responsibility is being performed in compliance with these Principles of Good Laboratory Practice” [Section II.1.1(2f)]. In addition the test facility management should ensure “that the Study Director has made the approved study plan available to the Quality Assurance personnel” [Section II.1.1(2j)] and the responsibility of the Study Director should include ensuring “that the Quality Assurance personnel have a copy of the study plan and any amendments in a timely manner and communicate effectively with the Quality Assurance personnel as required during the conduct of the study” [Section II.1.2(2b)]. The test facility management should also ensure that “for a multi-site study that clear lines” of communication exist between the Study Director, Principal Investigator(s), the Quality Assurance Programme(s) and study personnel [Section II.1.1(2o)].

In section II.2 (“Quality Assurance Programme”) the following requirements are listed:

2.1 *General*

1. The test facility should have a documented Quality Assurance Programme to assure that studies performed are in compliance with these Principles of Good Laboratory Practice.
2. The Quality Assurance Programme should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.
3. This individual(s) should not be involved in the conduct of the study being assured.

2.2 Responsibilities of the Quality Assurance Personnel

1. The responsibilities of the Quality Assurance personnel include, but are not limited to, the following functions. They should:
 - a) maintain copies of all approved study plans and Standard Operating Procedures in use in the test facility and have access to an up-to-date copy of the master schedule;
 - b) verify that the study plan contains the information required for compliance with these Principles of Good Laboratory Practice. This verification should be documented;
 - c) conduct inspections to determine if all studies are conducted in compliance with these Principles of Good Laboratory Practice. Inspections should also determine that study plans and Standard Operating Procedures have been made available to study personnel and are being followed.

Inspections can be of three types as specified by Quality Assurance Programme Standard Operating Procedures:

- Study-based inspections,
- Facility-based inspections,
- Process-based inspections.

Records of such inspections should be retained.

- d) inspect the final reports to confirm that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the studies;
- e) promptly report any inspection results in writing to management and to the Study Director, and to the Principal Investigator(s) and the respective management, when applicable;
- f) prepare and sign a statement, to be included with the final report, which specifies types of inspections and their dates, including the phase(s) of the study inspected, and the dates inspection results were reported to management and the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

In section II.7.4.5 the “operation of Quality Assurance personnel in planning, scheduling, performing, documenting and reporting inspections” is one of the categories of laboratory activities for which Standard Operating Procedures (SOPs) should be available.

In section II.9.2.4, a final study report is required to include “a Quality Assurance Programme statement listing the types of inspections made and their dates, including the phase(s) inspected, and the dates any inspection results were reported to management and to the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data”.

Finally, in section II.10.1(b) “records of all inspections performed by the Quality Assurance Programme, as well as master schedules” should be retained in the archives for the period specified by the appropriate authorities.

The QA-management link

Management of a test facility has the ultimate responsibility for ensuring that the facility as a whole operates in compliance with GLP Principles. Management may delegate designated control activities through the line management organisation, but always retains overall responsibility. An essential management responsibility is the appointment and effective organisation of an adequate number of appropriately qualified and experienced staff throughout the facility, including those specifically required to perform QA functions.

The manager ultimately responsible for GLP should be clearly identified. This person's responsibilities include the appointment of appropriately qualified personnel for both the experimental programme and for the conduct of an independent QA function. Delegation to QA of tasks which are attributed to management in the GLP Principles must not compromise the independence of the QA operation, and must not entail any involvement of QA personnel in the conduct of the study other than in a monitoring role. The person appointed to be responsible for QA must have direct access to the different levels of management, particularly to top level management of the test facility.

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Qualifications of QA personnel

QA personnel should have the training, expertise and experience necessary to fulfil their responsibilities. They must be familiar with the test procedures, standards and systems operated at or on behalf of the test facility.

Individuals appointed to QA functions should have the ability to understand the basic concepts underlying the activities being monitored. They should also have a thorough understanding of the Principles of GLP.

In case of lack of specialized knowledge, or the need for a second opinion, it is recommended that the QA operation ask for specialist support. Management should also ensure that there is a documented training programme encompassing all aspects of QA work. The training programme should, where possible, include on-the-job experience under the supervision of competent and trained staff. Attendance at in-house and external seminars and courses may also be relevant. For example, training in communication techniques and conflict handling is advisable. Training should be continuous and subject to periodic review.

The training of QA personnel must be documented and their competence evaluated. These records should be kept up-to-date and be retained.

QA involvement in developing SOPs and study plans

Management is responsible for ensuring that Standard Operating Procedures (SOPs) are produced, issued, distributed and retained. QA personnel are not normally involved in drafting SOPs; however it is desirable that they review SOPs before use in order to assess their clarity and compliance with GLP Principles.

Management should ensure that the study plan is available to QA before the experimental starting date of the study. This allows QA:

- to monitor compliance of the study plan with GLP;
- to assess the clarity and consistency of the study plan;
- to identify the critical phases of the study; and
- to plan a monitoring programme in relation to the study.

As and when amendments are made to the study plan, they should be copied to QA to facilitate effective study monitoring.

QA inspections

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QA programmes are frequently based upon the following types of inspections:

- Study-based inspections: These are scheduled according to the chronology of a given study, usually by first identifying the critical phases of the study.
- Facility-based inspections: These are not based upon specific studies, but cover the general facilities and activities within a laboratory (installations, support services, computer system, training, environmental monitoring, maintenance, calibration, etc.).
- Process-based inspections: Again these are performed independently of specific studies. They are conducted to monitor procedures or processes of a repetitive nature and are generally performed on a random basis. These inspections take place when a process is undertaken very frequently within a laboratory and it is therefore considered inefficient or impractical to undertake study-based inspections. It is recognised that performance of process-based inspections covering phases which occur with a very high frequency may result in some studies not being inspected on an individual basis during their experimental phases.

QA planning and justification of QA activities and methods.

QA should plan its work properly and its planning procedures as well as the operation of QA personnel in performing, documenting and reporting inspections should be described in SOPs. A list of studies planned and in progress should be kept. QA should have access to an up-to-date copy of the master schedule. Such a list is necessary for planning QA activities and assessing the QA workload in the laboratory.

As is the case for any other operative procedures covered by the GLP Principles, the QA programme of inspections and audits should be subject to management verification. Both the QA staff and management should be able to justify the methods chosen for the performance of their tasks.

QA inspection reports

National GLP monitoring authorities may request information relating to the types of inspections and their dates, including the phase(s) of the study inspected. However, QA inspection reports should not normally be examined for their contents by national monitoring authorities as this may inhibit QA when preparing inspection reports. Nevertheless, national monitoring authorities may occasionally require access to the contents of inspection reports in order to verify the adequate functioning of QA. They should not inspect such reports merely as an easy way to identify inadequacies in the studies carried out.

Audits of data and final reports

The review of a study's raw data¹ by QA can be carried out in a number of ways. For example, the records may be examined by QA during experimental phases of the study, during process inspections or during audits of final reports. Management should ensure that all final reports for which GLP compliance is claimed are audited by QA. This audit should be conducted at the final draft stage, when all raw data have been gathered and no more major changes are intended.

The aims of the audit of the final report should be to determine whether:

- the study was carried out in accordance with the study plan and SOPs;
- the study has been accurately and completely reported;
- the report contains all the elements required by GLP;
- the report is internally consistent; and
- the raw data are complete and in compliance with GLP.

QA may find it helpful to record the audit of the final report in a form that is sufficiently detailed to enable the audit to be reconstructed. Procedures must be established so that QA is made aware of all additions or changes made to the study data and report during the audit phase.

Before signing the QA statement, QA should ensure that all issues raised in the QA audit have been appropriately addressed in the final report, that all agreed actions have been completed, and that no changes to the report have been made which would require a further audit.

Any correction of or addition to a completed final report must be audited by QA. A revised or additional QA statement would then need to be provided.

¹ In the GLP Principles, raw data are defined as “all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study”. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium, that has been recognised as capable of providing secure storage of information for a time period as stated in section 10 below [Section I.2.3(7)].

The QA statement

The Principles of GLP require that a signed quality assurance statement be included in the final report, which specifies types of inspections and their dates, including the phase(s) of study inspected, and the dates inspections results were reported to management and the Study Director and the Principal Investigator(s), if applicable [Sections II.2.2(1f) and II.9.2(4)]. Procedures to ensure that this statement reflects QA's acceptance of the Study Director's GLP compliance statement and is relevant to the final study report as issued are the responsibility of management.

The format of the QA statement will be specific to the nature of the report. It is required that the statement include full study identification and the dates and phases of relevant QA monitoring activities. Where individual study-based inspections have not been part of the scheduled QA programme, a statement detailing the monitoring inspections that did take place must be included, for example, in the case of short-term studies where repeated inspections for each study are inefficient or impractical.

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 would also serve to confirm that the final report reflects raw 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.

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QA and non-regulatory studies

Compliance with GLP is a regulatory requirement for the acceptance of certain studies. However, some test facilities conduct in the same area studies which are and which are not intended for submission to regulatory authorities. If the non-regulatory studies are not conducted in accordance with standards comparable to GLP, this will usually have a negative impact on the GLP compliance of regulatory studies.

Lists of studies kept by QA should identify both regulatory and non-regulatory studies to allow a proper assessment of work load, availability of facilities and possible interferences. QA should have access to an up-to-date copy of the master schedule to assist them in this task. It is not acceptable to claim GLP compliance for a non-GLP study after it has started. If a GLP-designated study is continued as a non-GLP study, this must be clearly documented.

QA at small test facilities

At small test facilities it may not be practicable for management to maintain personnel dedicated solely to QA. However, management must give at least one individual permanent, even if part-time, responsibility for co-ordination of the QA function. Some continuity in the QA staff is desirable to allow the accumulation of expertise and to ensure consistent interpretation. It is acceptable for individuals involved in studies that comply with GLP to perform the QA function for GLP studies conducted in other departments within the test facility. It is also acceptable for personnel from outside the test facility to undertake QA functions if the necessary effectiveness required to comply the GLP principles can be ensured.

This concept may be additionally applied to multi-site studies, for example field studies, on the condition that overall responsibility for co-ordination is clearly established.



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Compliance of laboratory suppliers with GLP principles

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FOREWORD

In the framework of the OECD Consensus Workshop on Good Laboratory Practice, held 16th-18th October 1990 in Bad Dürkheim, Germany, a Working Group met to discuss and arrive at consensus on the compliance of laboratory suppliers with Principles of GLP. The Working Group was chaired by Dr. David Moore (Head, GLP Compliance Monitoring Authority, United Kingdom). Participants in the Working Group represented GLP compliance monitoring units and test facilities in Austria, Finland, France, Germany, Japan, Sweden and the United Kingdom.

The Working Group established the context of this consensus document, and made recommendations related to the role of suppliers vis-à-vis GLP Principles including the role of accreditation as a complementary tool to GLP compliance. It reached consensus and provided guidance on issues related to several specific categories of supplies. These issues are set out in the document.

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The draft consensus document developed by the Working Group was circulated to Member countries and revised, based on the comments received. It was subsequently endorsed by the OECD Panel on GLP and the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals. The Environment Committee then recommended that this document be derestricted under the authority of the Secretary-General.

In light of the adoption of the Revised OECD Principles of GLP in 1997, this Consensus Document was reviewed by the Working Group on GLP and revised to make it consistent with modifications made to the Principles. It was endorsed by the Working Group in April 1999 and, subsequently by the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in August 1999. It too is declassified under the authority of the Secretary-General.

GLP CONSENSUS DOCUMENT

COMPLIANCE OF LABORATORY SUPPLIERS WITH GLP PRINCIPLES

Background

The responsibilities of the management of test facilities are defined in the OECD Principles of Good Laboratory Practice¹ under the heading of Test Facility Organisation and Personnel (Section II.1). Test facility management should ensure that the GLP Principles are complied with at the test facility and that a sufficient number of qualified personnel, appropriate facilities, equipment and materials are available for the timely and proper conduct of the study. They also should ensure that test facility suppliers meet requirements appropriate to their use in a study. On the basis of these requirements, suppliers of materials used in studies submitted to regulatory authorities need not be included in national GLP compliance programmes but they do play a definite role relating to the responsibilities of the management of test facilities.

As by definition in the GLP Principles, the responsibility for the quality and fitness for use of equipment and materials rests entirely with the management of the test facility. The acceptability of equipment and materials in GLP-compliant laboratories should therefore be guaranteed to any regulatory authority to whom studies are submitted. The main purpose of this document is to offer advice to both test facility management and suppliers as to how they might meet GLP requirements through national accreditation schemes and/or working to formal national or international standards, or by adopting other measures which may be appropriate to a particular product. National or international standards, which may be set by an accreditation organisation, may be applied whenever they are acceptable to the test facility's management. The management of facilities, individually or in co-operation with each other, should thus maintain close contacts with suppliers and with their accreditation organisations.

Standards and accreditation schemes

Laboratories use various supplied materials in studies conducted in compliance with the GLP Principles. Suppliers have attempted to produce products which satisfy users' obligations as set out in the GLP Principles. Many suppliers have adopted manufacturing practices which comply with formal national or international standards, or have become accredited within various national schemes. These initiatives have been taken in the anticipation that supplied products will therefore be acceptable to regulatory authorities who require studies to be conducted in compliance with GLP Principles.

Suppliers are recommended to implement International Standard ISO 9001, and particularly Part 1 – Specification for Design/Development, Production, Installation and Servicing. This International Standard can be supported with European Standard EN 45001; the importance of Paragraph 5.4.7 of the latter, which refers to subcontracting, is emphasized.

¹ See *The OECD Principles of Good Laboratory Practice* (as revised in 1997), No. 1 in this OECD series on Principles of GLP and Compliance Monitoring.

Where appropriate, accreditation can be especially useful to suppliers. Accreditation schemes frequently monitor members' implementation of national and international standards; thus a supplier or manufacturer's accreditation certificate may signify to the customer the satisfactory implementation of a standard in addition to other aspects of accreditation. It is recommended that suppliers seek membership, where feasible and/or appropriate, in national accreditation schemes.

Although accreditation is a useful complementary tool to support compliance with the GLP Principles, it is not an acceptable alternative to GLP compliance nor will it lead to international recognition in the context of meeting the requirements for the mutual acceptance of data as set out in the OECD Council Acts².

Test systems

The Revised Principles of GLP [Section II.8.2(5b)] require that the characterisation of test systems (animals, plants and other organisms) should be given in the study plan. This is the requirement that can be directly fulfilled by information from the supplier. In some countries where GLP has been implemented, suppliers belong to national regulatory or voluntary accreditation schemes (for example, for laboratory animals) which can provide users with additional documentary evidence that they are using a test system of a defined quality.

Animal feed, bedding and water

Although not specifically indicated in the Revised GLP Principles, animal feed should be analysed at regular intervals to establish its composition in order to avoid any potential interference with the test system. Water and bedding should also be analysed to ensure that contaminants are not present at levels capable of influencing the results of a study. Certificates of analysis are routinely provided by suppliers, including water authorities. Suppliers should provide appropriate documentary evidence to ensure the reliability of the analyses carried out.

Radio-labeled chemicals

Commercial pressure has forced suppliers of radio-labeled chemicals to seek formal GLP compliance by inclusion in national GLP compliance programmes. In many instances these suppliers produce labeled test items which are required to be fully characterised by procedures which comply with the GLP Principles. Suppliers of radio-labeled chemicals may need to be covered through national GLP compliance monitoring programmes.

² Decision of the Council concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)], adopted 12th May 1981, and Council Decision-Recommendation on Compliance with the Principles of Good Laboratory Practice [C(89)87(Final)], adopted 2nd October 1989. For the texts of both Council Acts, see The OECD Principles of Good Laboratory Practice (as revised in 1997), No. 1 in this OECD series on Principles of GLP and Compliance Monitoring.

Computer systems, applications software

All computer software, including that obtained from an external supplier, should normally be acceptance-tested before being put into service by a laboratory. From this requirement it can be inferred that it is acceptable for formal validation of applications software to be carried out by the supplier on behalf of the user, provided that the user undertakes the formal acceptance tests.

The user should ensure that all software obtained externally has been provided by a recognised supplier. Many suppliers have endeavoured to meet users' requirements by implementing ISO 9001. This is considered to be useful.

The Revised Principles of GLP (Section II.1.2.2g) place the responsibility to ensure that software programmes have been validated with the Study Director. The validation may be undertaken by the user or the supplier, but full documentation of the process must be available and should be retained in the archives. In cases where the validation is performed by the user, Standard Operating Procedures should be available [Section II.7.4(2b)].

It is the responsibility of the user to undertake an acceptance test before use of the software programme. The acceptance test should be fully documented.

[See OECD Consensus Document No. 10, The Application of the Principles of GLP to Computerised Systems, 1995.]

Reference items

It is the responsibility of test facility management to ensure that all manufactured reference items meet the GLP requirements for identity, composition, purity and stability for each batch of material (Sections II.6.2.2 and II.6.2.4 of the Revised Principles of GLP).

Certificates provided by suppliers should cover data on identity, purity and stability (under specified conditions if needed) and any other characteristics to define each batch appropriately. In special cases the supplier may need to provide further information on, for example, methods of analysis, and should be prepared to demonstrate national/international measures of quality control, for example by reference to Good Manufacturing Practice or a national/international pharmacopoeia.

Apparatus

It is the responsibility of test facility management to ensure that instruments are adequate and functioning according to their intended use. Test facility management should also ensure that instruments are inspected and calibrated at prescribed intervals. Calibration should be traceable to national or international standards of measurement as appropriate. If reference standards are kept by the user they should be calibrated by a competent body at prescribed intervals.

Sterilised materials

It is the responsibility of test facility management to ensure that materials which should be free from sources of infection have been properly sterilised with appropriate control procedures. Suppliers should be able to provide proper evidence, for example through certificates or reference to national standards, that materials sterilised by irradiation or other means or agents are free from sources of infection or undesirable residues from sterilisation agents.

General reagents

The user should be responsible for ensuring, by arrangement with the supplier, that all reagents are labeled with sufficient detail to comply with the specific requirements of GLP.

Detergents and disinfectants

The user should be aware of all active constituents to enable a suitable choice for use and to remove the potential for any contamination or interference which could be said to affect the integrity of a study.

Products required for microbiological testing

The supplier should ensure that documentation is available giving evidence of any accreditation status. Where there is no national accreditation scheme the supplier should provide the user with a validation document which gives evidence of the fact that the product is as described by its label.



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Number 6 (Revised)

CONSENSUS DOCUMENT

The Application of the GLP principles to field studies

814457

Document complet disponible sur OLIS dans son format d'origine
Complete document available on OLIS in its original format

FOREWORD

In the framework of the Second OECD Consensus Workshop on Good Laboratory Practice, held 21st-23rd May 1991, in Vail, Colorado, experts discussed and reached consensus on the application of the GLP Principles to field studies. The Workshop was chaired by Dr. David Dull (Director, EPA Laboratory Data Integrity Program, United States). Experts from the following countries took part in the Consensus Workshop: Belgium, Canada, Denmark, Finland, Germany, the Netherlands, Switzerland, the United Kingdom and the United States.

The issues to be dealt with by the Workshop were defined at the First Consensus Workshop on GLP held in October 1990 in Bad Dürkheim, Germany. The Second Consensus Workshop was able to reach agreement on the management of field studies in relation to compliance with the GLP Principles, interpreting such concepts as study, test site, study director, management responsibilities, quality assurance, etc. for application in this specific context. The Consensus Document gives guidance for the interpretation of the relevant GLP Principles in relation to field studies.

The draft Consensus Document developed by the Second Consensus Workshop was circulated to Member countries, and revised based on the comments received. It was subsequently endorsed by the OECD Panel on GLP and the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals. The Environment Committee then recommended that this document be derestricted under the authority of the Secretary-General.

In light of the adoption of the Revised OECD Principles of GLP in 1997, this Consensus Document was reviewed by the Working Group on GLP and revised to make it consistent with modifications made to the Principles. It was endorsed by the Working Group in June 1999 and, subsequently by the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in August 1999. It too is declassified under the authority of the Secretary-General.

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GLP Consensus Document

THE APPLICATION OF THE GLP PRINCIPLES TO FIELD STUDIES

Background

The Principles of Good Laboratory Practice (GLP), as adopted by the OECD in 1981 and revised in 1997, provide recommended test management standards for a wide variety of studies done for regulatory purposes or other assessment-related purposes. The report of the Expert Group¹ which developed the GLP Principles in 1981 expressly lists the following types of tests as covered by the GLP Principles:

- physico-chemical properties;
- toxicological studies designed to evaluate human health effects (short- and long-term);
- ecotoxicological studies designed to evaluate environmental effects (short- and long-term); and
- ecological studies designed to evaluate environmental chemical fate (transport, biodegradation, and bioaccumulation).

Testing intended to determine the identity and magnitude of pesticide residues, metabolites, and related compounds for tolerance and other dietary exposure purposes is also included in the overall classification of ecological studies. The GLP Principles are intended to cover a broad range of commercial chemical products including pesticides, pharmaceuticals, cosmetics, veterinary drugs as well as food additives, feed additives and industrial chemicals.

Most experience in GLP compliance monitoring by the national monitoring authorities in OECD Member countries has been gained in areas related to (non-clinical) toxicological testing. This is because these studies were traditionally deemed of greatest importance from a human health standpoint, and early identified laboratory problems primarily involved toxicological testing. Many established compliance monitoring procedures of the OECD Member countries were thus developed from experience gained in the inspection of toxicology laboratories. Compliance monitoring procedures for laboratories performing ecotoxicological studies are also relatively well developed.

The area of field studies with pesticides or veterinary drugs, such as residue, metabolism, and ecological studies, presents a substantial challenge to GLP monitoring authorities and experimental testing facilities in that study plans, conditions, methods, techniques, and findings differ significantly from those traditionally associated with toxicological testing, as well as most laboratory-based ecotoxicological testing.

In the following the special issues associated with field studies are identified and addressed in order to provide meaningful guidance and interpretation with respect to the Revised Principles of GLP. Many of the points in the original Consensus Document were integrated into the Revised Principles. The following deals only with those issues which might still be considered to need further interpretation.

¹ *Good Laboratory Practice in the Testing of Chemicals*, OECD, 1982, out of print.

Interpretations Related to Definitions of Terms

The expression “non-clinical health and environmental safety study” in the definition of Good Laboratory Practice is understood to include field studies. A field study is a study which includes experimental activities carried out outside the usual laboratory situation, such as on land plots, in outdoor ponds or in greenhouses, often in combination or in sequence with activities carried out in a laboratory.

Field studies include, but are not limited to, studies for determining:

- magnitude of residue;
- photodegradation;
- plant metabolism;
- soil metabolism;
- rotational crop uptake;
- soil dissipation;
- effects on mesocosms;
- bioaccumulation; and
- effects on non-target organisms.

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The term “test facility”, when applied to field studies, may include several “test sites”, at one or more geographical locations, where phases or components of a single overall study are conducted. The different test sites may include, but are not limited to:

- Research laboratory(ies) where test/reference item characterisation (including determination of identity, purity/strength, stability, and other related activities) is conducted;
- One or more agricultural or other in- or outdoor sites (like greenhouses) where the test or control item is applied to the test system;
- In some cases, a processing facility where harvested commodities are treated to prepare other items, e.g. the conversion of tomatoes into juice, puree, paste, or sauce;
- One or more laboratories where collected specimens (including specimens from processing) are analysed for chemical or biological residues, or are otherwise evaluated.

“Study Director” and “Principle Investigator”: In field studies which could involve work at more than one test site, some of the Study Director’s responsibilities may be delegated. At each test site when the Study Director cannot exercise immediate supervision, study procedures may be controlled by a member of the staff, called the Principal Investigator. The Principal Investigator means an individual responsible for the conduct of certain defined phases of the study, acting on behalf of the Study Director.

The responsibilities of the Principal Investigator are described in the Revised GLP Principles in Section II.1. and in the section on “Principal Investigator’s Responsibilities” below.

A “non-clinical health and environmental safety study” in the field, at one or more test sites, could include both the field and laboratory phases defined in a single “study plan”.

“Test system” could also include complex ecological systems.

“Test item” could include but need not be limited to: a chemical substance or mixture, a radio-labelled compound, a substance of biological origin, or a process waste. In the context of field residue or environmental studies, the test item is generally *an active ingredient* or a mixture (formulation) comprising active ingredient(s) and one or more inert components such as emulsifiers. Other field studies on plant and soil metabolism are designed to study the *fate* of the test item and use radio-labelled forms of the chemical; the test item can be *analytical grade* or *technical grade* material which may be formulated at the field site immediately prior to application.

In the context of field studies, “reference items” are also understood to include analytical standards. They should be adequately characterised for the type of study being conducted, and this characterisation should be addressed in the study plan.

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In field studies the term “vehicle” generally refers to the diluent, if any, used to dilute the test item (usually a formulation or a tank mix of a pesticide). The term also includes any additional solvents, surface active agents or other chemicals used to enhance the solubility or application characteristics.

Interpretations Related to Test Facility Organisation and Personnel

Test Facility Management’s Responsibilities

Management, from the perspective of the GLP Principles, has several connotations and may involve several persons in several locations. The management level to which the Study Director reports has the *ultimate* responsibility for ensuring that the facilities operate in compliance with GLP Principles. In the context of field studies, there may also be several “test site management” entities that are primarily responsible for personnel, facilities, apparatus and materials at each test site and for formally assuring the Study Director (in writing) that these requirements can be met for the appropriate phase of each study.

Test site management must also assure the Study Director that the provisions of the GLP Principles will be followed. Test site management must assure the Study Director and his/her management that there is an appropriately qualified individual (Principal Investigator) at the test site who can effectively carry out his/her phase of the study in conformance with the study plan, applicable SOPs, the GLP Principles and the specific technical requirements. The overall management must have a firm understanding and working agreement with the test site management as to how and by whom the Quality Assurance Programme (QAP) will be carried out.

With multiple levels of management, study personnel and QAP staff, it is critical that there are clear lines of authority and communication, and assigned responsibilities, so that the Study Director can effectively carry out his/her GLP responsibilities. This should be documented in writing. It is the responsibility of the overall management to ensure that clear lines of communication exist.

There are likely to be some test sites where aspects of study conduct are indirectly (or directly) carried out by non-permanently employed personnel. Where these persons have generated or entered raw data, or have performed unsupervised activities relevant to the conduct of the study, records of their qualifica-

tions, training and experience should be maintained. Where these individuals have carried out routine maintenance operations such as crop thinning, weeding, fertilisation, etc. subject to supervision by more highly qualified staff, no such personnel records need be maintained.

Study Director's Responsibilities

The designation of the Study Director is a key decision in assuring that a study will be properly conducted according to the GLP Principles. The terminology “responsibility for the overall conduct of the study and for its final report” may be interpreted in a broad sense for most field studies, as the Study Director may be geographically remote from parts of the actual experimental work. The Study Director thus will have to rely heavily on his/her designated Principal Investigator(s) and associated technical personnel at each test site to assure technical reliability and GLP compliance. The responsibilities of such personnel should be explicitly fixed in writing.

Effective communications have to be established and maintained between the Study Director and all associated personnel to ensure that the study plan and SOPs are being followed, and that all other GLP requirements are being met. Communications with participating QAP personnel are also critical to ensure that they are properly notified of critical phase activity, that QAP inspection reports are transmitted in a timely manner, and that corrective actions are implemented in a meaningful fashion.

As part of his/her duties, the Study Director has responsibility in ensuring that: 1) adequately characterised test and reference items are available at the test sites, as necessary; 2) there is adequate coordination between field (or processing) sites and analytical laboratories for specimen analyses; and 3) data from field, processing and laboratory sites are properly collated and archived.

Principal Investigator's Responsibilities

Where a Study Director cannot exercise on-site supervisory control over any given phase of the study, a Principal Investigator will be identified/nominated to act on the Study Director's behalf for the defined phase.

The Principal Investigator will be named in the study plan or amendment, which will also delineate the phase(s) of the study covered by his responsibilities. The Principal Investigator will be an appropriately qualified and experienced individual suitably positioned to be able to immediately supervise the applicable phase.

The Principal Investigator, acting on behalf of the Study Director, will ensure that the relevant phase(s) of the study are conducted in accordance with the study plan, relevant SOPs, and with GLP. These responsibilities will include, but are not necessarily limited to:

- a) Collaborate as appropriate with the Study Director and other study scientists in the drafting of the study plan;
- b) Ensure that the study personnel are properly briefed, that such briefings are documented, and that copies of the study plan and relevant SOPs are freely accessible to personnel as necessary;

- c) Ensure that all experimental data, including unanticipated responses of the test system, are accurately recorded;
- d) Ensure that all deviations from SOPs and the study plan (unforeseen occurrences or inadvertent errors) are noted when they occur and that, where necessary, corrective action is immediately taken; these are recorded in the raw data. As soon as practicable, inform the Study Director of such deviations. Amendments to the study plan (permanent changes, modifications or revisions), however, must be approved in writing by the Study Director;
- e) Ensure that all relevant raw data and records are adequately maintained to assure data integrity and that they are transferred in a timely way to the Study Director or as directed in the study plan;
- f) Ensure that all samples and specimens taken during the relevant study phase(s) are adequately protected against confusion and deterioration during handling and storage. Ensure that these samples and specimens are dispatched in an appropriate manner;
- g) Sign and date a report of the relevant phase(s), certifying that the report accurately presents all the work done, and all the results obtained, and that the work was conducted in compliance with GLP. Include in this report sufficient commentary to enable the Study Director to write a valid Final Report covering the whole study, and send the report to the Study Director. The Principal Investigator may present the original raw data as his report, where applicable, including a statement of compliance with GLP.

Interpretations Related to the Quality Assurance Programme

Usually a single individual will not be able to perform the quality assurance function for field studies, but rather there will be a need for a number of persons. In some cases, these persons may all be in the employment of a single unit (for example, that of the study sponsor); in other cases they may be employed by different units (for example, part by the study sponsor and part by contractors). There must be a full, frank flow of information from the different quality assurance persons to the responsible test site management, to the responsible Principal Investigator(s), to the Study Director as the person responsible for the overall conduct of the study, to the Study Director's management, and to the latter's Quality Assurance Programme. Likewise, it will be necessary to assure effective communications from the Study Director and/or Principal Investigators to the quality assurance personnel for notification of critical activities.

Because of the complex nature of field studies, which may involve similar activities at separate locations, and the fact that the exact time of certain activities will depend upon local weather or other conditions, flexible quality assurance procedures may be required. [See "Quality Assurance and GLP", No. 4 in this OECD Series on the Principles of Good Laboratory Practice and Compliance Monitoring.]

The geographical spread of test sites may mean that quality assurance personnel will also need to manage language differences in order to communicate with local study personnel, the Study Director, Principal Investigators and test site management.

Irrespective of where the test sites are located, the written reports of quality assurance personnel must reach both management and the Study Director. The actual receipt of such reports by management and the Study Director should be documented in the raw data.

Interpretations Related to Facilities

General

Facilities for a field study will typically consist wholly or partially of agricultural or farming units, forested areas, mesocosms or other outdoor study areas where there is customarily much less, or even no, control over the environmental conditions than that achievable in an enclosed laboratory or a greenhouse. Also, security and oversight of operations and facilities are not as manageable as for a laboratory-based study.

An issue of concern in pesticide field studies is the potential for contamination of the study plots from drift or overspray of pesticides being used on neighbouring property. This can particularly be a problem for test plots located in the midst of, or adjacent to, other land used for commercial agricultural activities. Study plot locations should be chosen so as to ensure minimal possibility of off-site interferences. Preferably, the plots should be located in areas free of interfering chemicals or where the historical pesticide use (both study and normal use applications) has been documented.

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It is recognised that laboratories conducting pesticide residue analysis must be especially cognisant of the potential for contaminating specimens, as well as of reference standards. Receipt and storage areas for specimens must be separate from storage areas for pesticide formulations and other test or reference items. Areas used for specimen and sample preparation, instrumentation, calibration of sprays, reference standard preparation, and for washing glassware should be adequately isolated from each other and from other functions of the laboratory which might introduce contamination.

Facilities for Handling Test and Reference Items

Storage areas for test and reference items at all test sites should be environmentally monitored, if required, to assure conformance with established stability limits for these materials. Test and reference items should not be placed in the same storage containers with collected test system specimens and other materials of low concentrations which are being stored for shipment to the analytical laboratory or to off-site archives. There should be adequate storage and disposal facilities available for pesticide and related wastes such that there is no potential for cross-contamination of test systems, of test or reference items or of collected specimens.

Waste Disposal

Of particular concern at field sites is the storage and disposal of excess pesticide dilutions (or tank mixes). The minimum volume of such dilutions should be prepared. In addition to assuring that these potentially hazardous wastes are not endangering human health or the environment, these materials also need to be controlled in such a way that there is no impact on test systems, specimens or other materials or equipment used in studies. It should also be assured that unused test and reference items are returned to the sponsors or suppliers, or are disposed of in a legal and responsible manner.

Interpretations Related to Apparatus, Material and Reagents

In the field phase, the frequency of operations such as inspection, cleaning, maintenance and calibration may need to reflect possible transport of the equipment (for example when balances are moved from site to site). These operations should be described by Standard Operating Procedures.

Apparatus which is used only for one specific study (e.g. leased or rented equipment, or equipment such as sprayers which have been specifically configured for use in one study) may not have records of periodic inspection, cleaning, maintenance and calibration. In such cases, this information may be recorded in the study-specific raw data. If it is not feasible to document the relevant procedures as SOPs, they can be documented in study plans, with references to handbooks.

Materials and reagents should be verified as being non-interfering by the analysis of an adequate number of “reagent blanks”.

Interpretations Related to Test Systems

Some test systems utilised in field studies may consist of complex ecosystems that will be difficult to characterise, identify or otherwise document to the extent that can be accomplished for more traditional test systems. However, these more complex test systems should be described by location and characteristics, to the degree possible, in the study plan, and the actual study plot areas identified by signs, markers or other means. Plants, seeds, soils and other materials being used as test systems should be described and documented as to their source, date(s) of acquisition, variety, strain, cultivar or other identifying characteristics, as appropriate. Soil should be characterised to the degree necessary and documented to verify suitability for its use in field studies.

As noted under “Facilities”, test systems for pesticide studies should be free from interferences from outside sources, particularly drift or overspray from neighbouring plots. If relevant, the study plan should discuss the need for analysis of preliminary or pre-treatment control samples. Control plots and buffer zones are to be used to the degree necessary to account for or minimise potential interferences or other forms of study bias.

Interpretations Related to Test and Reference Items and Reference Items

Receipt, Handling, Sampling and Storage

The following documentation should be present at the test site:

- Source, e.g. commercial formulation, special formulation, etc.;

- Mode of transfer, with retention of shipping documents;

- Date of receipt;

- Condition of substance on receipt;

- Storage location and conditions;

- Complete log documenting distribution, accounting for the total amount of the test item and final disposal.

Characterisation

It is not necessary to have all characterisation records and data available at each test site. However, sufficient information needs to be present to assure that the test and reference items have been adequately characterised. This generally will comprise: name of the chemical (e.g. CAS number, code name, etc.); lot or batch number; amount of active ingredient; site where the analyses were conducted, and where the relevant raw data are archived; stability with regard to storage and transfer conditions (i.e. expiry date, temperature range); and safety precautions.

Product chemistry data based on separate laboratory experiments will frequently have defined the stability of test item mixtures in the vehicle over a range of pH, temperature and hardness values. If relevant restrictions are known, then the study plan may specify appropriate ranges for the application, and the actual values should be recorded in the raw data as well as the time of mixing and the termination of the application.

Similar data for homogeneity are also often available from producers that show non-separation of mixture phases over various periods of time under specified conditions.

If tank mix samples are to be analysed, this requirement should be specified in the study plan, along with sampling and analytical methodology.

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Interpretations Related to Standard Operating Procedures

Special emphasis should be placed on key procedures for field studies, such as test item storage, data collection in the field, application equipment calibration, test item application, and specimen collection and transportation.

The study plan will also require inclusion of all methodologies intended to be used for specimen analyses. This may require an approved study plan amendment if the method has not been fully developed or validated at the time the original study plan is signed. The study plan should also provide for all speciality analysis, e.g. confirmation procedures.

Interpretations Related to Performance of the Study

Study Plan

Study plans intended for most field studies will need to reflect more flexibility than traditional laboratory studies due to the unpredictable nature of the weather, the possibility of the need to employ borrowed or rented equipment, special arrangements for the preservation, storage and transport of specimen samples, or other special circumstances. Rather than citing specific dates in the study plan for key phases such as test item application, culturing operations and specimen sampling, a more realistic approach would be to specify commodity growth stages for these activities to the degree possible and giving only approximate time frames.

In order to approve study plan amendments in a timely and effective fashion, special communication procedures will need to be established between the personnel at the test sites and the Study Director if the two entities are not at the same location.

Conduct of the Study

In view of the importance of quality control measures in residue and environmental analyses, these should be addressed in SOPs and/or in the study plan. Procedures to evaluate reproducibility, freedom from interferences, and confirmation of analytidentity would typically be included.

Raw data includes any worksheets, records, memoranda, notes, or exact copies thereof that are the result of original observations and activities of a study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g. tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. Examples of raw data include photographs, microfilm, or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

It is recommended that all entries be made with indelible ink. Under some circumstances use of pencil in the field may be unavoidable. When this is necessary, “verified” copies should be prepared as soon as practicable. Any entries in pencil or in different colours should be appropriately identified on the verified copies. In addition, study records should clearly state the reason for using pencil.

Interpretations Related to Reporting of Study Results

The report(s) of the Principal Investigator(s) can be attached to the overall study report by the Study Director as appendices as described in paragraph g in the note under Principal Investigator’s Responsibilities, above.

Interpretations Related to Storage and Retention of Records and Materials

One potential problem area associated with remote test sites is the temporary storage of materials from ongoing studies until they can be transferred to archives at the end of the study. Temporary storage facilities at all test sites should be adequate to ensure the integrity of the study materials.



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OECD SERIES ON PRINCIPLES OF GLP AND COMPLIANCE MONITORING
Number 7 (Revised)

CONSENSUS DOCUMENT

The application of the GLP principles to short-term studies

814449

Document complet disponible sur OLIS dans son format d'origine
Complete document available on OLIS in its original format

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FOREWORD

In the framework of the third OECD Consensus Workshop on Good Laboratory Practice held 5th to 8th October 1992 in Interlaken, Switzerland, a working group of experts discussed the interpretation of the GLP Principles as applied to short-term studies. This working group was chaired by Ms Francisca E. Liem (United States Environmental Protection Agency); the rapporteur was Dr. Hans-Wilhelm Hembeck (German GLP Federal Office). Participants in the Working Group were from both national GLP compliance monitoring authorities and from testing laboratories in the following countries: Australia, Austria, Czech Republic, Finland, France, Germany, Ireland, Netherlands, Poland, Sweden, Switzerland, United Kingdom and United States. Two sub-working groups were formed and chaired by Ms Liem (short-term biological studies) and Dr. Hembeck (physical-chemical studies); the respective rapporteurs were Mr. David Long (France) and Dr. Stephen Harston (Germany). The document developed by the working group cites the appropriate OECD Principles of GLP and gives guidance on their interpretation in relation to short-term studies in a series of notes.

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The draft document developed by the Working Group was circulated to Member countries for comments. The text was revised, based on comments received, and reviewed by the OECD Panel on Good Laboratory Practice at its fifth meeting in March 1993, which amended the text and forwarded it to the Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals. At its 20th Session, the Joint Meeting endorsed the document with minor editorial changes and recommended that it be derestricted under the authority of the Secretary-General.

In light of the adoption of the Revised OECD Principles of GLP in 1997, this Consensus Document was reviewed by the Working Group on GLP and revised to make it consistent with modifications made to the Principles. It was endorsed by the Working Group in April 1999 and subsequently by the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in August 1999. It too is declassified under the authority of the Secretary-General.

**Note by the OECD Working Group on GLP
to the revised Consensus Document on the Application of the Principles
of GLP to Short-Term Studies**

**(endorsed by the Joint Meeting of the Chemicals Committee and Working Party
on Chemicals in August 1999)**

The Principles of GLP are general guidance which were originally drafted primarily to define the way in which chronic toxicity studies should be planned, conducted and reported. The expansion of the scope of application of GLP to other study types which may differ significantly from chronic toxicity studies has made it necessary to interpret the application of the GLP Principles to such special areas.

One such area where the application of the GLP Principles may require further interpretation is that of so-called “short-term studies”. The revised OECD Principles and this revised Consensus Document provides further guidance in this area. However, the expression “short-term studies” encompasses such a wide variety of study types that it has proven to be impossible to arrive at a meaningful, all-embracing and clear-cut, but nevertheless concise definition. Consensus could not be reached in OECD on a precise definition nor even on a comprehensive list of short-term tests.

The revised OECD Principles of GLP could go no further than to define short-term studies as “studies of short duration with widely used, routine methods” – a definition which still leaves the expression “short duration” open to interpretation. Due to the wide diversity of the studies concerned, it has not been possible to link the expression “short” to any definite length of study duration which would define exactly and comprehensively a short-term study. This is because what might be considered “short” in the context of biological studies may not be regarded as “short” in a physical-chemical study. This makes it advisable to treat biological studies differently from physical-chemical ones with regard to the application of the provisions for short-term studies.

For the reasons above the OECD Working Group on GLP found it more useful to consider those characteristics of the conduct of a study which may qualify it to be classified as a “short term study”. These include the duration of critical phases, the frequency with which such studies are conducted and the complexity of the test system as well as the routine of the personnel involved, which will increase with growing frequency of study conduct. It is recognised that common sense must be exercised in defining what is considered to be a “short term study” as discussed above.

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GLP CONSENSUS DOCUMENT

THE APPLICATION OF THE PRINCIPLES OF GOOD LABORATORY PRACTICE TO SHORT-TERM STUDIES

Background

The OECD Principles of GLP are general and not specific to any particular type of test or testing discipline. The initial experience in OECD Member countries in compliance monitoring has been primarily in long-term toxicity studies. Although subject to the OECD Principles of GLP, short-term studies present special concerns to management and compliance monitoring authorities based upon the existence of particular procedures and techniques.

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The Revised Principles of GLP define a short-term study as “a study of short duration with widely used, routine techniques” [I.2.3.2]. Short-term biological studies include acute toxicity studies, some mutagenicity studies, and acute ecotoxicological studies.

Physical-chemical studies are those studies, tests or measurements which are of a short duration (typically not more than one working week), employ widely-used techniques (e.g. OECD Test Guidelines) and yield easily repeatable results, often expressed by simple numerical values or verbal expressions.

Typical physical-chemical studies include but are not limited to chemical characterisation studies, melting point, vapour pressure, partition coefficient, explosive properties and other similar studies for which test guidelines exist. However, the regulatory agencies/receiving authorities in Member countries will specify which of these tests should be submitted to them and which should be conducted under the Principles of GLP.

NOTES TO THE GLP PRINCIPLES

The following paragraphs of the Revised OECD Principles of GLP need interpretation for their application to short-term studies. Paragraphs of the Revised OECD Principles which do not require interpretation are not repeated here. Notes are given for further guidance and interpretation.

II.1. TEST FACILITY ORGANISATION AND PERSONNEL

II.1.2. *Test Facility Management's Responsibilities*

- II.1.2.g) (Test facility management should) ensure that for each study an individual with the appropriate qualifications, training, and experience is designated by the management as the Study Director before the study is initiated....

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

II.2. QUALITY ASSURANCE PROGRAMME

II.2.1. *General*

- II.2.1.1. The test facility should have a documented Quality Assurance Programme to assure that studies performed are in compliance with these Principles of Good Laboratory Practice.

[NOTE 1]: All references to “quality assurance programme” in this document should be interpreted with reference to the OECD Principles of GLP and the OECD Consensus Document on *Quality Assurance and GLP**. In respect of physical-chemical studies it is recognised that other published standards (e.g. ISO 9000 series) use the term “quality assurance” in a different way.

[NOTE 2]: The documentation of the quality assurance programme should include a description of the use made of “study-based”, “facility-based” or “process-based” inspections as defined in the OECD Consensus Document No. 4 “Quality Assurance and GLP”. These definitions are reproduced below:

“Study-based inspections: These are scheduled according to the chronology of a given study, usually by first identifying the critical phases of the study.

Facility-based inspections: These are not based upon specific studies, but cover the general facilities and activities within a laboratory (installations, support services, computer system, training, environmental monitoring, maintenance, calibration, etc.).

* OECD Series on Principles of Good Laboratory Practice and Compliance No. 4, *Quality Assurance and GLP*, Paris, 1992 (as revised in 1999).

Process-based inspections: Again these are performed independently of specific studies. They are conducted to monitor procedures or processes of a repetitive nature and are generally performed on a random basis. These inspections take place when a process is undertaken very frequently within a laboratory and it is therefore considered inefficient or impractical to undertake study-based inspections. It is recognised that performance of process-based inspections covering phases which occur with a very high frequency may result in some studies not being inspected on an individual basis during their experimental phases”.

II.2.2. *Responsibilities of the Quality Assurance Personnel*

II.2.2.1. The responsibilities of the Quality Assurance personnel include, but are not limited to, the following functions. They should:

- a) maintain copies of all approved study plans and Standard Operating Procedures in use in the test facility and have access to an up-to-date copy of the master schedule;
- b) verify that the study plan contains the information required for compliance with these Principles of Good Laboratory Practice. This verification should be documented;
- c) conduct inspections to determine if all studies are conducted in accordance with these Principles of Good Laboratory Practice. Inspections should also determine that study plans and Standard Operating Procedures have been made available to study personnel and are being followed.

[NOTE]: Because of the high frequency and routine nature of some standard short-term studies, it is recognised in the OECD Consensus Document on *Quality Assurance and GLP* that each study need not be inspected individually by Quality Assurance during the experimental phase of the study. In these circumstances, a process-based inspection programme may cover each study type. The frequency of such inspections should be specified in approved Quality Assurance Standard Operating Procedures, taking into account the numbers, frequency and/or complexity of the studies being conducted in the facility. The frequency of inspections should be specified in the relevant QA Standard Operating Procedures, and there should be SOPs to ensure that all such processes are inspected on regular basis.

- f) prepare and sign a statement, to be included with the final report, which specifies types of inspections and their dates, including the phase(s) of the study inspected, and the dates inspection results were reported to management and the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

[NOTE]: Where individual study-based inspections did not take place, the QA-statement must clearly describe which types of inspections (e.g. process-based) were performed and when. The QA-statement must indicate that the final report was audited.

II.3. FACILITIES

II.3.1. *General*

- II.3.1.1. The test facility should be of suitable size, construction and location to meet the requirements of the study and to minimise disturbances that would interfere with the validity of the study.
- II.3.1.2. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study.

[NOTE]: The issue of concern, primarily for biological *in vitro* studies is the possibility of contamination of the test system. Laboratories should establish facilities and procedures which demonstrably prevent and/or control such potential contamination.

II.4. APPARATUS, MATERIAL AND REAGENTS

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- II.4.2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement.

[NOTE]: Calibration should, where appropriate, provide for traceability of measurements to fundamental physical quantities maintained by appropriate national authorities. Apparatus should be checked periodically for continuing accuracy of measurement. Calibration substances should be treated as reference items, but need not be retained.

II.5 TEST SYSTEMS

II.5.1. *Physical/Chemical*

[NOTE]: There is overlap between the requirements for “Physical/chemical test systems” in section II.5.1.1 of the Revised OECD GLP Principles and those for “apparatus” in section II.4.1. This overlap seems to have no practical implications for studies of this type. Apparatus used in a physical/chemical test system should be periodically inspected, cleaned, maintained, and calibrated according to SOPs, as specified above (Section II.4 of the Revised GLP Principles).

II.5.2. *Biological*

- II.5.2.1. Proper conditions should be established and maintained for the storage, housing, handling and care of biological test systems, in order to ensure the quality of the data.
- II.5.2.2. Newly received animal and plant test systems should be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, this lot should not be used in studies and, when appropriate, should be humanely destroyed. At the experimental starting date of a study, test systems should be free of any disease or condition that might interfere with the purpose or conduct of the study. Test systems that become diseased or injured during

the course of a study should be isolated and treated, if necessary to maintain the integrity of the study. Any diagnosis and treatment of any disease before or during a study should be recorded.

- II.5.2.3. Records of source, date of arrival, and arrival condition of test systems should be maintained.
- II.5.2.4. Biological test systems should be acclimatised to the test environment for an adequate period before the first administration/application of the test or reference item.
- II.5.2.5. All information needed to properly identify the test systems should appear on their housing or containers. Individual test systems that are to be removed from their housing or containers during the conduct of the study should bear appropriate identification, wherever possible.
- II.5.2.6. During use, housing or containers for test systems should be cleaned and sanitised at appropriate intervals. Any material that comes into contact with the test system should be free of contaminants at levels that would interfere with the study. Bedding for animals should be changed as required by sound husbandry practice. Use of pest control agents should be documented.

[NOTE 1]: Test system information: Record keeping is required to document the growth, vitality and absence of contamination of batches of *in vitro* test systems. It is important that the origin, sub-strain and maintenance of the test system be identified and recorded for *in vitro* studies.

[NOTE 2]: Characterisation of the test system, primarily for *in vitro* studies: It is essential that there is assurance that the test system as described in the study plan is being used, and is free of contamination. This can be accomplished, for example, by periodically testing for genetic markers, karyotypes, or testing for mycoplasma.

[NOTE 3]: Isolation of test systems: In the case of short-term biological studies, isolation of animal and plant test systems may not be required. The test facility SOPs should define the system for health status evaluation (e.g. historical colony and supplier information, observations, serological evaluation) and subsequent actions.

[NOTE 4]: Control of interfering materials in *in vitro* studies: There should be assurance that water, glassware and other laboratory equipment are free of substances which could interfere with the conduct of the test. Control groups should be included in the study plan to meet this objective. Periodic systems tests may also be performed to complement this goal.

[NOTE 5]: Characterisation of culture media: The types of media, ingredients and lot numbers of the media (e.g. antibiotics, serum, etc.) should be documented. Standard Operating Procedures should address the preparation and acceptance of such media.

[NOTE 6]: Test system use: Under certain circumstances, some Member countries will accept the reuse of an animal or the simultaneous testing of multiple test items on one animal. The GLP issue of concern is that in all cases, complete historical documentation on the former use of the animal must be maintained and be referenced in the final report. It must also be documented that these practices do not interfere with the evaluation of the test item(s).

II.6 TEST AND REFERENCE ITEMS

II.6.2. *Characterisation*

- II.6.2.1. Each test and reference item should be appropriately identified (e.g., code, Chemical Abstracts Service Registry Number [CAS number], name, biological parameters).
- II.6.2.2. For each study, the identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test or reference items should be known.
- II.6.2.3. In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation between the sponsor and the test facility, to verify the identity of the test item subject to the study.
- II.6.2.4. The stability of test and reference items under storage and test conditions should be known for all studies.
- II.6.2.5. If the test item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined. For test items used in field studies (e.g., tank mixes), these may be determined through separate laboratory experiments.
- II.6.2.6. A sample for analytical purposes from each batch of test item should be retained for all studies except short-term studies.

[NOTE 1]: Adequate characterisation information should be available for each batch of the test and reference items. To promote acceptability in all Member countries, it is recommended that this information is generated in compliance with the Revised Principles of GLP when needed. Where the test item is in an early stage of development it is acceptable for the analytical characterisation to be performed after the conduct of the biological study. However, there should be some information on the chemical structure of the test item before the study initiation date.

[NOTE 2]: To promote acceptability in all Member countries, it is recommended that the stability of the test and reference items under conditions of storage should be determined in compliance with Principles of GLP when needed.

[NOTE 3]: There are considerable differences between the requirements of Member countries concerning the evaluation of the concentration, stability and homogeneity of the test item in a vehicle. In addition, for certain short-term biological tests, it is not always possible to conduct such analyses concomitantly. For certain of these tests, if the time interval between preparation and application of a usually stable substance is only a few minutes, it might not be relevant to determine the stability of the test item. For these reasons it is essential that analytical requirements are specified and approved in the study plan and clearly addressed in the final report.

[NOTE4]: The data related to points II.6.2.4 and II.6.2.5 under “Characterisation” of test and reference items in the GLP Principles (above) may not be known in the case of physical-chemical studies being conducted to determine such data.

II.7 STANDARD OPERATING PROCEDURES

[NOTE]: The illustrative examples given in the section II.7.4.4. of the Revised Principles of GLP (Test system) refer mainly to biological test systems and may thus not be relevant in the context of physical-chemical studies. It is the responsibility of test facility management to ensure that appropriate Standard Operating Procedures are produced for the studies performed in the facilities.

II.8. PERFORMANCE OF THE STUDY

II.8.1. *Study Plan*

II.8.1.1. For each study, a written plan should exist prior to the initiation of the study. The study plan should be approved by dated signature of the Study Director and verified for GLP compliance by Quality Assurance personnel as specified in Section II.2.2.1.b, above. The study plan should also be approved by the test facility management and the sponsor, if required by national regulation or legislation in the country where the study is being performed.

II.8.1.3. For short-term studies, a general study plan accompanied by a study specific supplement may be used.

[NOTE]: Where a particular short-term study or a series of such studies is performed frequently within a laboratory, it may be appropriate to prepare a single general study plan containing the majority of general information required in such a plan and approved in advance by the testing facility management and by the Study Director(s) responsible for the conduct of such studies and by QA.

Study-specific supplements to such plans (e.g. with details on test item, experimental starting date) should then be issued as a supplementary document requiring only the dated signature of the designated Study Director. The combined document – the general study plan and the study-specific supplement – is the study plan. It is important that such supplements are provided promptly to test facility management and to QA assurance personnel.

II.8.2. *Content of the Study Plan*

[NOTE]: The contents of the complete study plan (that is, of the general study plan and the study-specific supplement) should be as described in the Revised OECD Principles of GLP, with the possible exceptions noted below.

The study plan should contain, but not be limited to the following information:

II.8.2.1. *Identification of the Study, the Test Item and Reference Item*

- a) A descriptive title;
- b) A statement which reveals the nature and purpose of the study;

[NOTE]: This may not be needed if this information is provided by the descriptive title.

- c) Identification of the test item by code or name (IUPAC; CAS number, biological parameters etc);
- d) The reference item to be used.

II.8.2.5. *Issues (where applicable)*

- a) The justification for selection of the test system;
- b) Characterisation of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age, and other pertinent information;
- c) The method of administration and the reason for its choice;
- d) The dose levels and/or concentration(s), frequency, and duration of administration/application.

[NOTE]: Issues a – d, above, may not be needed for physical-chemical studies.

- e) Detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed, and statistical methods to be used (if any).

[NOTE]: This may generally be given in a brief, summary form, or with reference to appropriate SOPs or Test Guidelines.

II.9 **REPORTING OF STUDY RESULTS**

II.9.1. *General*

- II.9.1.1.** A final report should be prepared for each study. In the case of short term studies, a standardised final report accompanied by a study specific extension may be prepared.

[NOTE]: Where short-term studies are performed using general study plans, it may also be appropriate to issue “standardised final reports” containing the majority of general information required in such reports and authorised in advance by the testing facility management, and by the Study Director(s) responsible for the conduct of such studies. Study-specific extensions to such reports (e.g. with details of the test item and the numerical results obtained) may then be issued as a supplementary document requiring only the dated signature of the Study Director. It is not acceptable to utilise a “standardised final report” when the study plan is revised or amended prior to or during the conduct of the study unless the “standardised final report” is amended correspondingly.

II.9.2. *Content of the Final Report*

[NOTE]: The contents of the complete final report (that is, of the “standardised final report” and the study-specific supplement) should be as described in the Revised OECD Principles of GLP, with the possible exceptions noted below:

The final report should include, but not be limited to, the following information.

II.9.2.1. *Identification of the Study, the Test and Reference Item*

- a) A descriptive title;
- b) Identification of the test item by code or name (IUPAC; CAS number, biological parameters, etc.);
- c) Identification of the reference item by chemical name;
- d) Characterisation of the test item including purity, stability and homogeneity.

[NOTE]: This may not be relevant when the study is carried out to determine such data.

II.9.2.4. *Statement*

A Quality Assurance Programme statement listing the types of inspections made and their dates, including the phase(s) inspected, and the dates any inspection results were reported to management and to the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

[NOTE]: This may need to reflect the use of process-based inspection. The QA Statement must clearly indicate that the final report was audited. (See also the note under “Responsibilities of the Quality Assurance Personnel, II.2.2.1.f”, above).



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ON CHEMICALS

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OECD SERIES ON PRINCIPLES OF GLP AND COMPLIANCE MONITORING
Number 8 (Revised)

CONSENSUS DOCUMENT

The role and responsibilities of the Study Director in GLP studies

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FOREWORD

In the framework of the third OECD Consensus Workshop on Good Laboratory Practice held 5th to 8th October 1992 in Interlaken, Switzerland, a working group of experts discussed the interpretation of the GLP Principles as applied to the role and responsibilities of the Study Director. This working group was chaired by Dr. David F. Moore of the United Kingdom GLP Compliance Monitoring Authority; the Rapporteur was Dr. Heinz Reust (Swiss Federal Office of Public Health). Participants in the Working Group were from both national GLP compliance monitoring authorities and from testing laboratories in the following countries: Austria, Canada, Federation of Russia, Finland, Germany, Japan, Netherlands, Switzerland, United Kingdom and United States.

The draft document developed by the working group was circulated to Member countries for comments. The text was revised, based on comments received, and reviewed by the OECD Panel on Good Laboratory Practice at its fifth meeting in March 1993, which amended the text and forwarded it to the Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals. At its 20th Session, the Joint Meeting endorsed the document with minor editorial changes and recommended that it be derestricted under the authority of the Secretary-General.

In light of the adoption of the Revised OECD Principles of GLP in 1997, this Consensus Document was reviewed by the Working Group on GLP and revised to make it consistent with modifications made to the Principles. It was endorsed by the Working Group in April 1999 and, subsequently by the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in August 1999. It too is declassified under the authority of the Secretary-General.

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GLP CONSENSUS DOCUMENT

THE ROLE AND RESPONSIBILITIES OF THE STUDY DIRECTOR IN GLP STUDIES

The Role of the Study Director

The Study Director represents the single point of study control with ultimate responsibility for the overall scientific conduct of the study. This is the prime role of the Study Director, and all duties and responsibilities as outlined in the GLP Principles stem from it. Experience has shown that unless responsibility for the proper conduct of a study is assigned to one person, there is a potential for personnel to receive conflicting instructions, which can result in poor implementation of the study plan. There can be only one Study Director for a study at any given time. Although some of the duties of the Study Director can be delegated, as in the case of a subcontracted study, the ultimate responsibility of the Study Director as the single central point of control cannot.

In this regard, the Study Director serves to assure that the scientific, administrative and regulatory aspects of the study are controlled. The Study Director accomplishes this by coordinating the inputs of management, scientific/technical staff and the Quality Assurance programme.

In multi-site studies which involve work at more than one test site and the Study Director cannot exercise immediate supervision, study procedures may be controlled by an appropriately trained, qualified and experienced member of the staff, called the Principal Investigator. He is responsible for the conduct of certain defined phases of the study in accordance with the applicable Principles of Good Laboratory Practice, acting on behalf of the Study Director.

Scientifically, the Study Director is usually the scientist responsible for study plan design and approval, as well as overseeing data collection, analysis and reporting. The Study Director is responsible for drawing the final overall conclusions from the study. As the lead scientist, the Study Director must coordinate with other study scientists, and/or Principal Investigator(s) keeping informed of their findings during the study and receiving and evaluating their respective individual reports for inclusion in the final study report.

Administratively, the Study Director must request and coordinate resources provided by management, such as personnel, equipment and facilities, to ensure they are adequate and available as scheduled for the proper conduct of the study.

Compliance with regulations is also the responsibility of the Study Director. In this role the Study Director is responsible for ensuring that the study is carried out in accordance with the Principles of GLP, which require the Study Director's signature on the final study report to confirm compliance with the GLP Principles.

Management Responsibilities

Management of a testing facility is responsible for ensuring that the facility operates in compliance with GLP Principles. This responsibility includes the appointment and effective organisation of an adequate

number of appropriately qualified and experienced staff throughout the facility, including Study Directors, and, in the event of multi-site studies, Principal Investigator(s), if needed.

Appointment of Study Directors

Management should maintain a policy document defining the procedures adopted for selection and appointment of Study Directors, their deputies, and Principal Investigator(s) if required by national programmes.

When appointing a Study Director to a study, management should be aware of that person's current or anticipated workloads. The master schedule, which includes information on the type and timing of studies allocated to each Study Director, can be used to assess the volume of work being performed by individuals within the testing facility and is a useful management tool when allocating studies.

Replacement of a Study Director and/or Principal Investigator should be done according to established procedures and should be documented.

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Training of Study Directors

Management should ensure that there is documentation of training in all aspects of the Study Director's work. A training programme should ensure that Study Directors have a thorough understanding of GLP Principles and an appropriate knowledge of testing facility procedures. This may include an awareness and working knowledge of other guidelines and regulations pertinent to the testing facility and the particular study type, for example, the OECD Test Guidelines. Training may include work experience under the supervision of competent staff. Observation periods or work experience within each discipline involved in a study can provide a useful basic understanding of relevant practical aspects and scientific principles, and assist in the formation of communication links. Attendance at in-house and external seminars and courses, membership in professional societies and access to appropriate literature may allow Study Directors to maintain current awareness of developments within their scientific field. Professional development should be continuous and subject to periodic review. All training should be documented and records should be retained for the period specified by the appropriate authorities.

Documented records of such a programme should reflect the progression of training and provide a clear indication of the type of study that an individual is considered competent to direct. Further training or retraining may be necessary from time to time, for example, following the introduction of new technology, procedures or regulatory requirements.

Responsibilities of the Study Director

The Study Director is the individual who has overall responsibility for the scientific conduct of a study and can confirm the compliance of the study with the OECD Principles of Good Laboratory Practice.

Study Initiation

The Study Director has to approve the study plan which is prepared before study initiation by dated signature. This document should clearly define the objectives and the whole conduct of the study and how

they are to be achieved. Any amendments to the study plan have to be approved as mentioned above. For a multi-site study the study plan should identify and define the role of any Principal Investigator(s) and any test facilities and test sites involved in the conduct of the study.

The Study Director should take responsibility for the study by dated signature of the study plan, at which stage the study plan becomes the official working document for that study (study initiation date). If appropriate, the Study Director should also ensure that the study plan has been signed by the sponsor and the management, if required by national programmes.

Before the study initiation date the Study Director should make the study plan available to Quality Assurance (QA) staff for verifying that it contains all information required for compliance with the GLP Principles.

Before the experimental starting date of the study, the Study Director should assure that copies of the study plan are supplied to all personnel involved in the study; this should include Quality Assurance (QA) staff.

Before any work on the study is undertaken, the Study Director should ascertain that management have committed adequate resources to perform the study, and that adequate test materials and test systems are available.

Study Conduct

The Study Director has responsibility for the overall conduct of the study and should ensure that the procedures laid down in the study plan including amendments are followed and all data generated during the study are fully documented. Specific technical responsibilities may be delegated to competent staff, and need to be documented.

The Study Director's involvement during the course of the study should include overviewing the study procedures and data to ensure that the procedures laid down in the study plan are being followed and that there is compliance with the relevant Standard Operating Procedures, and should include computergenerated data. In order to demonstrate this, the type and frequency of the reviews should be documented in the study records.

As all decisions that may affect the integrity of the study should ultimately be approved by the Study Director, it is important that he remains aware of the progress of the study. This is of particular importance following temporary absence from the study and can only be achieved by maintaining effective communication with all the scientific, technical and administrative personnel involved, and for a multi-site study with Principal Investigator(s). Of necessity, lines of communication should ensure that deviations from the study plan can be rapidly transmitted and that issues arising are documented.

If data are recorded on paper, the Study Director should ensure that the data generated are fully and accurately documented and that they have been generated in compliance with GLP Principles. For data recorded electronically onto a computerised system, the Study Director's responsibilities are the same as for paper systems. In addition, the Study Director should also ensure that computerised systems are suitable for their intended purpose, have been validated, and are fit for use in the study.

Final Report

The final report of a study should be produced as a detailed scientific document outlining the purpose of the study, describing the methods and materials used, summarising and analysing data generated, and stating the conclusions drawn.

If the Study Director is satisfied that the report is a complete, true and accurate representation of the study and its results, then and only then, should the Study Director sign and date the final report to indicate acceptance of responsibility for the validity of the data. The extent of compliance with the GLP Principles should be indicated. He should also assure himself that there is a QA statement and that any deviations from the study plan have been noted.

Archives

On completion (including termination) of a study the Study Director is responsible for ensuring that the study plan, final report, raw data and related material are archived in a timely manner. The final report should include a statement indicating where all the samples of test and reference items, specimens, raw data, study plan, final report and other related documentation are to be stored. Once data are transferred to the archives, the responsibility for it lies with management.

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Sub-contracting

Where parts of any study are contracted out, the Study Director (and QA staff) should have knowledge of the GLP compliance status of that facility. If a contract facility is not GLP compliant, the Study Director must indicate this in the final report.

Study Plan Amendments and Deviations

Study Plan Amendment

A study plan amendment should be issued to document an intended change in study design after the study initiation date and before the event occurs. An amendment may also be issued as a result of unexpected occurrences during the study that will require significant action. Amendments should indicate the reason for the change and be sequentially numbered, dated, signed and distributed to all recipients of the original study plan by the Study Director.

Study Deviations

Whereas an amendment is an intended change to the study plan, a deviation is an unintended change which occurs during the execution of the study. Study information such as a deviation from the study plan should be noted in the study documentation. Such notes may be initiated by other personnel involved in the study, but should be acknowledged, described, explained and dated in a timely fashion by the Study

Director and/or Principal Investigator(s) and maintained with the study raw data. The Study Director should approve any corrective action taken. The Study Director should consider whether to consult with other scientists to determine the impact of any such information on the study, and should report (and discuss where necessary) these deviations in the final report.

Qualifications of the Study Director

Qualifications for a Study Director will be dictated by the requirements of each individual study. Setting the criteria is the responsibility of the management. Furthermore, management has the responsibility for selection, monitoring and support of the Study Director to ensure that studies are carried out in compliance with the GLP Principles. Any minimal qualifications established by management for the position of Study Director should be documented in the appropriate personnel records. In addition to a strong technical background, the coordinating role of the Study Director requires an individual with strengths in communication and problem solving and managerial skills.

Interface with the Study

The Study Director has the overall responsibility for the conduct of a study. The term “responsibility for the overall conduct of the study and for its final report” may be interpreted in a broad sense for those studies where the Study Director may be geographically remote from parts of the actual experimental work. With multiple levels of management, study personnel and QA staff, it is critical that there are clear lines of authority and communication, and assigned responsibilities, so that the Study Director can effectively carry out his GLP responsibilities. This should be documented in writing. Test facility management should ensure that for multi-site studies clear lines of communication exist between the Study Director, Principal Investigator(s), the Quality Assurance Programme(s) and the study personnel.

For studies that have delegated responsibilities to a Principal Investigator(s), the Study Director will rely on that individual to assure that relevant phase(s) of the study are conducted in accordance with the study plan, relevant SOPs and with GLP Principles. The Principal Investigator should contact the Study Director when event(s) occur that may affect the objectives defined in the study plan. All communications should be documented.

Communication between the Study Director and QA is required at all stages of the study.

This communication may involve:

- an active involvement with QA, for example, review of study plans in a timely manner, involvement in the review of new and revised Standard Operating Procedures, attendance of QA personnel at study initiation meetings and in resolving potential problems related to GLP.
- responding to inspection and audit reports promptly, indicating corrective action and, if necessary, liaising with QA staff and scientific and technical personnel to facilitate responses to inspection/audit findings.

Replacement of the Study Director

The Study Director has the responsibility for the overall conduct of a study according to the GLP Principles and he has to ascertain that in every phase of a study these principles are fully complied with, that the study plan is followed faithfully and that all observations are fully documented. Theoretically, this responsibility can only be fulfilled if the Study Director is present all the time during the whole study. This is not always feasible in practice and there will be periods of absence which might make replacement necessary. While the circumstances under which a Study Director would be replaced are not defined in the GLP Principles, they should be addressed to the degree feasible by the facility's SOPs. These SOPs should also address the procedures and documentation necessary to replace a Study Director.

The decision for replacement or temporary delegation is the responsibility of management. All such decisions should be documented in writing. There are two circumstances where replacement might be considered, both of which are of importance only in longer-term studies, since the continuing presence of a Study Director during a short study may be assumed. In the event of termination of employment of a Study Director, the need for replacing this key person is obvious. In this case, one of the responsibilities of the replacement Study Director is, with the assistance of Quality Assurance personnel, to assure himself as soon as practicable of the GLP compliance in the study as conducted to date. The replacement of a Study Director and the reasons for it must be documented and authorised by management. It is also recommended that the results of any interim GLP review should be documented in case deficiencies or deviations have been found.

The second circumstance is when a Study Director is temporarily absent because of holidays, scientific meeting, illness or accident. An absence of short duration might not necessitate the formal replacement of the Study Director if it is possible to communicate with him if problems or emergencies arise. If critical study phases are expected to fall into the period of absence, they may either be moved to a more suitable time (with study plan amendment, if necessary), or a replacement of the Study Director may be considered, either by formally nominating a replacement Study Director or by temporary delegation of responsibilities to competent staff for this specific phase of the study. Should the unavailability of the Study Director be of longer duration, a replacement should be named rather than delegation to competent staff.

The returning Study Director must ascertain as soon as practicable whether or not deviations from GLP Principles have occurred, irrespective of whether or not he was formally replaced during his absence. Deviations from GLP Principles during his absence should be documented by the returning Study Director.

Legal Status of the Study Director

The Study Director, by virtue of his signature in the final report confirming compliance with the GLP Principles, assumes responsibility for the performance of the study in compliance with GLP Principles and for the accurate representation of the raw data in the final report. However, the legal liability of the Study Director is established by national legislation and legal processes, and not by the OECD Principles of GLP.



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Number 9

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GUIDANCE FOR GLP MONITORING AUTHORITIES

Guidance for the preparation of GLP inspection reports

Environment Monograph No. 115

Paris 1995

FOREWORD

Under the auspices of the OECD Panel on Good Laboratory Practice, a working group met in Rockville, Maryland, from 21st through 23rd September 1994, to develop harmonised guidance for the preparation of GLP inspection reports. The working group was chaired by Mr. Paul Lepore of the United States Food and Drug Administration. Participants were from national GLP compliance monitoring authorities in the following countries: Canada, France, Germany, Norway, Sweden, Switzerland and the USA. The working group reached consensus on a draft document aimed at providing guidance for GLP monitoring authorities on the information on specific test facility inspections to be exchanged with their colleagues in other GLP monitoring authorities.

The Panel on GLP reviewed and amended the draft document prepared by the working group and subsequently forwarded the document to the Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals, which, in turn, slightly amended the draft and recommended that it be considered by the Environment Policy Committee. The Environment Policy Committee subsequently recommended that this document be derestricted under the authority of the Secretary-General.

GUIDANCE FOR THE PREPARATION OF GLP INSPECTION REPORTS

One of the goals of the work of the OECD Panel on Good Laboratory Practice is to facilitate the sharing of information from GLP compliance monitoring programmes conducted by Member countries. This goal requires more than the promulgation of enforceable principles of GLP and the conduct of an inspection programme by the national monitoring authority. It is also necessary to have the reports of the inspections prepared in a useful and consistent manner. The Guidance for the Preparation of GLP Inspection Reports developed by the Panel on GLP set forth below suggests elements and/or concepts that can contribute to a useful report of a GLP inspection and study audit. It may be used by Member countries as a component of their compliance monitoring programme.

Report Headings

There are many acceptable ways to organise an inspection report, but the key is to make sure that it contains the required information and meets the requirements of the regulatory authority. Generally, report headings include a Summary, an Introduction, a Narrative, a Summary of the Exit Discussion, and Annexes. All of the information presented under these headings should portray an accurate picture of the adherence of the testing facility to the Principles of GLP and the quality of any study report that may have been audited.

The narrative headings may contain information as follows:

1. Summary

The summary section of the report should be presented first and should provide background information on the test facility, the type of inspection that was conducted, the deviations from the GLP Principles that were noted, and the responses of the test facility to the presented deviations. In accord with national practice, the report may include the compliance designation of the laboratory that was assigned by the inspectors.

2. Introduction

The introductory section should include some or all of the following elements:

- 2.1 The purpose and general description of the inspection, including the legal authority of the inspectors and the quality standards serving as the basis for the inspection.
- 2.2 An identification of the inspectors and the dates of inspection.
- 2.3 A description of the type of inspection (facility, study audit, etc.).
- 2.4 An identification of the test facility, including corporate identity, postal address, and contact person(s) [with telephone and telefax number(s)].

- 2.5 A description of the test facility identifying the categories of test substances and testing that is done and presenting information on the physical layout and the personnel.
- 2.6 The date of the previous GLP inspection, resulting GLP compliance status, and any relevant changes made by the test facility since that inspection.

3. Narrative

The Narrative portion of the report should contain a complete and factual description of the observations made and activities undertaken during the course of the inspection. Generally, the information recorded in this section should be reflected under the headings in the GLP Principles, as listed below:

- 3.1 Organisation and Personnel.
- 3.2 Quality Assurance Programme.
- 3.3 Facilities.
- 3.4 Apparatus, Materials, Reagents and Specimens.
- 3.5 Test Systems.
- 3.6 Test and Reference Substances.
- 3.7 Standard Operating Procedures.
- 3.8 Performance of the Study.
- 3.9 Reporting of Study Results.
- 3.10 Storage and Retention of Records.

Deviations from the GLP Principles should be supported by documentation (i.e., photocopies, photographs, test samples, etc.). All such documentation should be referenced and discussed in the Narrative and attached in the Annexes.

When a study has been selected for audit, the inspection report should describe the procedure for conducting the audit, including a description of the portion of the data or study that was actually examined. Any findings during the audit should be described in the Narrative and documented in the Annexes.

4. Exit Discussion

At the end of an inspection/study audit, an Exit Conference should be held between the inspection team and the responsible management of the test facility, at which GLP deviations found during the inspection/study audit may be discussed. During this Exit Conference, if allowed by national policy, a written list of observations should be presented describing the GLP deviations if any have been observed. The exit discussion should be summarized in this section.

The report should note the date and time of the Exit Conference; the names of attendees (inspection team, facility and others), with their affiliations. It should also give a brief summary of GLP deviations noted by the inspection team during the facility inspection and/or study audits. Responses of facility representatives to the inspection team's remarks should also be described.

In the case where a written list of observations has been made available, the test facility should acknowledge the inspectors' findings and make a commitment to take corrective action.

If a receipt of documents taken by the inspection team was prepared and signed by facility management, the person to whom the receipt for documents was provided should be identified. A copy of the receipt should be included in the Annexes.

5. Annexes

The Annexes should contain copies of documents that have been referenced in the report. Such documents may include:

- organisational charts of the facility;
- the agenda for the inspection;
- a listing of SOPs that have been demonstrated during the inspection;
- a listing of deviations that have been observed;
- photocopies that document observed deviations.

Other Information

In addition to the information described above, reports may contain other headings and information as appropriate or as required by a Member country's compliance monitoring programme. For example, the inspection report may address correction of deficiencies noted during previous inspections or any corrective action taken during the current inspection. Others may include a cover page which contains descriptive

information that briefly identifies the inspection. Others find it useful to use a table of contents, especially when the inspection is of a large, complex facility to categorize, index, and identify information in the report. Some reports include a "conclusion" section which notifies the testing facility of the compliance status classification as judged by the inspection. Any, or all of these, are acceptable.

Approval

Reports should be signed and dated by the lead inspector and by other inspectors in accordance with their



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Number 10

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GLP CONSENSUS DOCUMENT

The application of the principles of GLP to computerised systems

Environment Monograph No. 116

Paris 1995

FOREWORD

Within the framework of the third OECD Consensus Workshop on Good Laboratory Practice held 5th to 8th October 1992, in Interlaken, Switzerland, a working group of experts discussed the interpretation of the GLP Principles as applied to computerised systems. The working group was chaired by Dr. Theo Helder of the Dutch GLP Compliance Monitoring Authority. The Rapporteur was Mr. Bryan Doherty (Chairman of the Computing Committee of the British Association for Research Quality Assurance). Participants in the Working Group were from both national GLP compliance monitoring authorities and from testing laboratories in the following countries: Austria, Belgium, Denmark, Finland, France, Germany, Japan, the Netherlands, Switzerland, United Kingdom, United States. That Working Group was unable to reach consensus on a detailed guidance document in the time available to it. It did, however, develop a document entitled “Concepts relating to Computerised Systems in a GLP Environment”, which set out the general principles and described the issues involved for each. That document was circulated to comments to Member countries.

In light of the comments received, the Panel on Good Laboratory Practice at its fifth meeting in March 1993, agreed that further work needed to be done and called for a second working group meeting to be held. Under the chairmanship of Dr. Helder, and with Mr. Doherty as rapporteur, that group met in Paris from 14th to 16th December 1994. Participants representing government and industry from Canada, Denmark, France, Germany, Japan, the Netherlands, Sweden, the United Kingdom and the United States took part.

The draft Consensus Document developed by the working group was based on the document emanating from the Interlaken workshop, comments from Member countries thereto and a document developed by a United Kingdom joint government-industry working party. It was subsequently reviewed, modified and endorsed by the Panel and the Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals. The Environment Policy Committee thus recommended that this document be derestricted under the authority of the Secretary-General.

GLP CONSENSUS DOCUMENT:

THE APPLICATION OF GLP PRINCIPLES TO COMPUTERISED SYSTEMS

Throughout recent years there has been an increase in the use of computerised systems by test facilities undertaking health and environmental safety testing. These computerised systems may be involved with the direct or indirect capture of data, processing, reporting and storage of data, and increasingly as an integral part of automated equipment. Where these computerised systems are associated with the conduct of studies intended for regulatory purposes, it is essential that they are developed, validated, operated and maintained in accordance with the OECD Principles of Good Laboratory Practice (GLP).

Scope

All computerised systems used for the generation, measurement or assessment of data intended for regulatory submission should be developed, validated, operated and maintained in ways which are compliant with the GLP Principles.

During the planning, conduct and reporting of studies there may be several computerised systems in use for a variety of purposes. Such purposes might include the direct or indirect capture of data from automated instruments, operation/control of automated equipment and the processing, reporting and storage of data. For these different activities, computerised systems can vary from a programmable analytical instrument, or a personal computer to a laboratory information management system (LIMS) – with multiple functions. Whatever the scale of computer involvement, the GLP Principles should be applied.

Approach

Computerised systems associated with the conduct of studies destined for regulatory submission should be of appropriate design, adequate capacity and suitable for their intended purposes. There should be appropriate procedures to control and maintain these systems, and the systems should be developed, validated and operated in a way which is in compliance with the GLP Principles.

The demonstration that a computerised system is suitable for its intended purpose is of fundamental importance and is referred to as computer validation.

The validation process provides a high degree of assurance that a computerised system meets its pre-determined specifications. Validation should be undertaken by means of a formal validation plan and performed prior to operational use.

The Application of the GLP Principles to Computerised Systems

The following considerations will assist in the application of the GLP Principles to computerised systems outlined above:

1. Responsibilities

- a) *Management* of a test facility has the overall responsibility for compliance with the GLP Principles. This responsibility includes the appointment and effective organisation of an adequate number of appropriately qualified and experienced staff, as well as the obligation to ensure that the facilities, equipment and data handling procedures are of an adequate standard.

Management is responsible for ensuring that computerised systems are suitable for their intended purposes. It should establish computing policies and procedures to ensure that systems are developed, validated, operated and maintained in accordance with the GLP Principles. Management should also ensure that these policies and procedures are understood and followed, and ensure that effective monitoring of such requirements occurs.

Management should also designate personnel with specific responsibility for the development, validation, operation and maintenance of computerised systems. Such personnel should be suitably qualified, with relevant experience and appropriate training to perform their duties in accordance with the GLP Principles.

- b) *Study Directors* are responsible under the GLP Principles for the overall conduct of their studies. Since many such studies will utilise computerised systems, it is essential that Study Directors are fully aware of the involvement of any computerised systems used in studies under their direction.

The Study Director's responsibility for data recorded electronically is the same as that for data recorded on paper and thus only systems that have been validated should be used in GLP studies.

- c) *Personnel*. All personnel using computerised systems have a responsibility for operating these systems in compliance with the GLP Principles. Personnel who develop, validate, operate and maintain computerised systems are responsible for performing such activities in accordance with the GLP Principles and recognized technical standards.
- d) *Quality Assurance (QA)* responsibilities for computerised systems must be defined by management and described in written policies and procedures. The quality assurance programme should include procedures and practices that will assure that established standards are met for all phases of the validation, operation and maintenance of computerised systems. It should also include procedures and practices for the introduction of purchased systems and for the process of in-house development of computerised systems.

Quality Assurance personnel are required to monitor the GLP compliance of computerised systems and should be given training in any specialist techniques necessary. They should be

sufficiently familiar with such systems so as to permit objective comment; in some cases the appointment of specialist auditors may be necessary.

QA personnel should have, for review, direct read-only access to the data stored within a computerised system.

2. Training

The GLP Principles require that a test facility has appropriately qualified and experienced personnel and that there are documented training programmes including both on-the-job training and, where appropriate, attendance at external training courses. Records of all such training should be maintained.

The above provisions should also apply for all personnel involved with computerised systems.

3. Facilities and Equipment

Adequate facilities and equipment should be available for the proper conduct of studies in compliance with GLP. For computerised systems there will be a number of specific considerations:

a) *Facilities*

Due consideration should be given to the physical location of computer hardware, peripheral components, communications equipment and electronic storage media. Extremes of temperature and humidity, dust, electromagnetic interference and proximity to high voltage cables should be avoided unless the equipment is specifically designed to operate under such conditions.

Consideration must also be given to the electrical supply for computer equipment and, where appropriate, back-up or uninterruptable supplies for computerised systems, whose sudden failure would affect the results of a study.

Adequate facilities should be provided for the secure retention of electronic storage media.

b) *Equipment*

i) *Hardware and Software*

A computerised system is defined as a group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

Hardware is the physical components of the computerised system; it will include the computer unit itself and its peripheral components.

Software is the programme or programmes that control the operation of the computerised system.

All GLP Principles which apply to equipment therefore apply to both hardware and software.

ii) *Communications*

Communications related to computerised systems broadly fall into two categories: between computers or between computers and peripheral components.

All communication links are potential sources of error and may result in the loss or corruption of data. Appropriate controls for security and system integrity must be adequately addressed during the development, validation, operation and maintenance of any computerised system.

4. Maintenance and Disaster Recovery

All computerised systems should be installed and maintained in a manner to ensure the continuity of accurate performance.

a) *Maintenance*

There should be documented procedures covering both routine preventative maintenance and fault repair. These procedures should clearly detail the roles and responsibilities of personnel involved. Where such maintenance activities have necessitated changes to hardware and/or software it may be necessary to validate the system again. During the daily operation of the system, records should be maintained of any problems or inconsistencies detected and any remedial action taken.

b) *Disaster Recovery*

Procedures should be in place describing the measures to be taken in the event of partial or total failure of a computerised system. Measures may range from planned hardware redundancy to transition back to a paper-based system. All contingency plans need to be well documented, validated and should ensure continued data integrity and should not compromise the study in any way. Personnel involved in the conduct of studies according to the GLP Principles should be aware of such contingency plans.

Procedures for the recovery of a computerised system will depend on the criticality of the system, but it is essential that back-up copies of all software are maintained. If recovery procedures entail changes to hardware or software, it may be necessary to validate the system again.

5. Data

The GLP Principles define raw data as being all original laboratory records and documentation, including data directly entered into a computer through an instrument interface, which are the results of original observations and activities in a study and which are necessary for the reconstruction and evaluation of the report of that study.

Computerised systems operating in compliance with GLP Principles may be associated with raw data in a variety of forms, for example, electronic storage media, computer or instrument printouts and microfilm/fiche copies. It is necessary that raw data are defined for each computerised system.

Where computerised systems are used to capture, process, report or store raw data electronically, system design should always provide for the retention of full audit trails to show all changes to the data without obscuring the original data. It should be possible to associate all changes to data with the persons making those changes by use of timed and dated (electronic) signatures. Reasons for change should be given.

When raw data are held electronically it is necessary to provide for long term retention requirements for the type of data held and the expected life of computerised systems. Hardware and software system changes must provide for continued access to and retention of the raw data without integrity risks.

Supporting information such as maintenance logs and calibration records that are necessary to verify the validity of raw data or to permit reconstruction of a process or a study should be retained in the archives.

Procedures for the operation of a computerised system should also describe the alternative data capture procedures to be followed in the event of system failure. In such circumstances any manually recorded raw data subsequently entered into the computer should be clearly identified as such, and should be retained as the original record. Manual back-up procedures should serve to minimise the risk of any data loss and ensure that these alternative records are retained.

Where system obsolescence forces a need to transfer electronic raw data from one system to another then the process must be well documented and its integrity verified. Where such migration is not practicable then the raw data must be transferred to another medium and this verified as an exact copy prior to any destruction of the original electronic records.

6. Security

Documented security procedures should be in place for the protection of hardware, software and data from corruption or unauthorised modification, or loss. In this context security includes the prevention of unauthorised access or changes to the computerised system as well as to the data held within the system. The potential for corruption of data by viruses or other agents should also be addressed. Security measures should also be taken to ensure data integrity in the event of both short term and long term system failure.

a) *Physical Security*

Physical security measures should be in place to restrict access to computer hardware, communications equipment, peripheral components and electronic storage media to authorised personnel only. For equipment not held within specific 'computer rooms' (e.g., personal computers and terminals), standard test facility access controls are necessary as a minimum. However, where such equipment is located remotely (e.g., portable components and modem links), additional measures need to be taken.

b) *Logical Security*

For each computerised system or application, logical security measures must be in place to prevent unauthorised access to the computerised system, applications and data. It is essential to ensure that only approved versions and validated software are in use. Logical security may include the need to enter a unique user identity with an associated password. Any introduction of data or software from external sources should be controlled. These controls may be provided by the computer operating system software, by specific security routines, routines embedded into the applications or combinations of the above.

c) *Data Integrity*

Since maintaining data integrity is a primary objective of the GLP Principles, it is important that everyone associated with a computerised system is aware of the necessity for the above security considerations. Management should ensure that personnel are aware of the importance of data security, the procedures and system features that are available to provide appropriate security and the consequences of security breaches. Such system features could include routine surveillance of system access, the implementation of file verification routines and exception and/or trend reporting.

d) *Back-up*

It is standard practice with computerised systems to make back-up copies of all software and data to allow for recovery of the system following any failure which compromises the integrity of the system e.g., disk corruption. The implication, therefore, is that the back-up copy may become raw data and must be treated as such.

7. Validation of Computerised Systems

Computerised systems must be suitable for their intended purpose. The following aspects should be addressed:

a) *Acceptance*

Computerised systems should be designed to satisfy GLP Principles and introduced in a pre-planned manner. There should be adequate documentation that each system was developed in a controlled manner and preferably according to recognised quality and technical standards (e.g. ISO/9001). Furthermore, there should be evidence that the system was adequately tested for conformance with the acceptance criteria by the test facility prior to being put into routine use. Formal acceptance testing requires the conduct of tests following a pre-defined plan and retention of documented evidence of all testing procedures, test data, test results, a formal summary of testing and a record of formal acceptance.

For vendor-supplied systems it is likely that much of the documentation created during the development is retained at the vendor's site. In this case, evidence of formal assessment and/or vendor audits should be available at the test facility.

b) *Retrospective Evaluation*

There will be systems where the need for compliance with GLP Principles was not foreseen or not specified. Where this occurs there should be documented justification for use of the systems; this should involve a retrospective evaluation to assess suitability.

Retrospective evaluation begins by gathering all historical records related to the computerised system. These records are then reviewed and a written summary is produced. This retrospective evaluation summary should specify what validation evidence is available and what needs to be done in the future to ensure validation of the computerised system.

c) *Change Control*

Change control is the formal approval and documentation of any change to the computerised system during the operational life of the system. Change control is needed when a change may affect the computerised system's validation status. Change control procedures must be effective once the computerised system is operational.

The procedure should describe the method of evaluation to determine the extent of retesting necessary to maintain the validated state of the system. The change control procedure should identify the persons responsible for determining the necessity for change control and its approval.

Irrespective of the origin of the change (supplier or in-house developed system), appropriate information needs to be provided as part of the change control process. Change control procedures should ensure data integrity.

d) *Support Mechanism*

In order to ensure that a computerised system remains suitable for its intended purpose, support mechanisms should be in place to ensure the system is functioning and being used correctly. This may involve system management, training, maintenance, technical support, auditing and/or performance assessment. Performance assessment is the formal review of a system at periodic intervals to ensure that it continues to meet stated performance criteria, e.g., reliability, responsiveness, capacity.

8. Documentation

The items listed below are a guide to the minimum documentation for the development, validation, operation and maintenance of computerised systems.

a) *Policies*

There should be written management policies covering, *inter alia*, the acquisition, requirements, design, validation, testing, installation, operation, maintenance, staffing, control, auditing, monitoring and retirement of computerised systems.

b) *Application Description*

For each application there should be documentation fully describing:

- The name of the application software or identification code and a detailed and clear description of the purpose of the application;
- The hardware (with model numbers) on which the application software operates;
- The operating system and other system software (e.g., tools) used in conjunction with the application;
- The application programming language(s) and/or data base tools used;
- The major functions performed by the application;
- An overview of the type and flow of data/data base design associated with the application;
- File structures, error and alarm messages, and algorithms associated with the application;
- The application software components with version numbers;
- Configuration and communication links among application modules and to equipment and other systems.

c) *Source Code*

Some OECD Member countries require that the source code for application software should be available at, or retrievable to, the test facility.

d) *Standard Operating Procedures (SOPs)*

Much of the documentation covering the use of computerised systems will be in the form of SOPs. These should cover but not be limited to the following:

- Procedures for the operation of computerised systems (hardware/software), and the responsibilities of personnel involved;
- Procedures for security measures used to detect and prevent unauthorised access and programme changes;
- Procedures and authorisation for programme changes and the recording of changes;
- Procedures and authorisation for changes to equipment (hardware/software) including testing before use if appropriate;
- Procedures for the periodic testing for correct functioning of the complete system or its component parts and the recording of these tests;
- Procedures for the maintenance of computerised systems and any associated equipment;
- Procedures for software development and acceptance testing, and the recording of all acceptance testing;
- Back-up procedures for all stored data and contingency plans in the event of a breakdown;
- Procedures for the archiving and retrieval of all documents, software and computer data;
- Procedures for the monitoring and auditing of computerised systems.

9. Archives

The GLP Principles for archiving data must be applied consistently to all data types. It is therefore important that electronic data are stored with the same levels of access control, indexing and expedient retrieval as other types of data.

Where electronic data from more than one study are stored on a single storage medium (e.g., disk or tape), a detailed index will be required.

It may be necessary to provide facilities with specific environmental controls appropriate to ensure the integrity of the stored electronic data. If this necessitates additional archive facilities then management should ensure that the personnel responsible for managing the archives are identified and that access is limited to authorised personnel. It will also be necessary to implement procedures to ensure that the long-term integrity of data stored electronically is not compromised. Where problems with long-term access to data are envisaged or when computerised systems have to be retired, procedures for ensuring that continued readability of the data should be established. This may, for example, include producing hard copy printouts or transferring the data to another system.

No electronically stored data should be destroyed without management authorization and relevant documentation. Other data held in support of computerised systems, such as source code and development, validation, operation, maintenance and monitoring records, should be held for at least as long as study records associated with these systems.

Definition of terms¹

Acceptance Criteria: The documented criteria that should be met to successfully complete a test phase or to meet delivery requirements.

Acceptance Testing: Formal testing of a computerised system in its anticipated operating environment to determine whether all acceptance criteria of the test facility have been met and whether the system is acceptable for operational use.

Back-up: Provisions made for the recovery of data files or software, for the restart of processing, or for the use of alternative computer equipment after a system failure or disaster.

Change Control: Ongoing evaluation and documentation of system operations and changes to determine whether a validation process is necessary following any changes to the computerised system.

Computerised System: A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

Electronic Signature: The entry in the form of magnetic impulses or computer data compilation of any symbol or series of symbols, executed, adapted or authorized by a person to be equivalent to the person's handwritten signature.

Hardware: The physical components of a computerised system, including the computer unit itself and its peripheral components.

Peripheral Components: Any interfaced instrumentation, or auxiliary or remote components such as printers, modems and terminals, etc.

Recognised Technical Standards: Standards as promulgated by national or international standard setting bodies (ISO, IEEE, ANSI, etc.)

Security: The protection of computer hardware and software from accidental or malicious access, use, modification, destruction or disclosure. Security also pertains to personnel, data, communications and the physical and logical protection of computer installations.

¹ Further definitions of terms can be found in the "OECD Principles of Good Laboratory Practice".

Software (Application): A programme acquired for or developed, adapted or tailored to the test facility requirements for the purpose of controlling processes, data collection, data manipulation, data reporting and/or archiving.

Software (Operating System): A programme or collection of programmes, routines and sub-routines that controls the operation of a computer. An operating system may provide services such as resource allocation, scheduling, input/output control, and data management.

Source Code: An original computer programme expressed in human-readable form (programming language) which must be translated into machine-readable form before it can be executed by the computer.

Validation of a Computerised System: The demonstration that a computerised system is suitable for its intended purpose.



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OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE
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Number 11

Advisory Document of the Panel on Good Laboratory Practice

**The role and responsibilities of the sponsor in the application
of the principles of GLP**

60994

Document complet disponible sur OLIS dans son format d'origine
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ABOUT THE OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 29 industrialised countries in North America, Europe and the Pacific, as well as the European Commission, meet to co-ordinate and harmonize policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised Committees and subsidiary groups composed of Member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's Workshops and other meetings. Committees and subsidiary groups are served by the OECD Secretariat, located in Paris, France, which is organised into Directorates and Divisions.

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This publication was produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC).

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FOREWORD

In the framework of the Revision of the OECD Principles on Good Laboratory Practice, the Expert Group was not able to reach consensus on whether and how to deal with the role and responsibilities of the sponsor of chemical safety studies in the Principles. The revised Principles of GLP* contain several explicit references to the sponsor, and the issue is implicit in several other principles. However, there was no agreement on the need for and content of a separate section in the Principles on this matter.

On the recommendation of the Chairman of the Expert Group, the Panel on GLP therefore agreed to develop a document which could advise the testing industry as far as possible on current practice in Member countries and the interpretation of Panel of the GLP Principles related to this issue. At its ninth meeting in March 1997, the panel endorsed a document drafted by a Task Group on the role and responsibilities of the sponsor. The Task Group had met in Lisbon on 8th and 9th January 1997, was chaired by Theo Helder (Netherlands), and comprised Panel Members or their representatives from Canada, Finland, France, Germany, Portugal, Sweden, and Switzerland.

The Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals at its 26th Meeting endorsed the document and recommended that it be derestricted under the authority of the Secretary-General. The Joint Meeting recommended that it be published alongside the Guidance Documents for GLP Monitoring Authorities and the Consensus Documents in the OECD Series on GLP and Compliance Monitoring as the first “Advisory Document”.

* See No. 1 of the Series in GLP and Compliance Monitoring, OECD, Paris, 1998.

Advisory Document of the Panel on GLP

THE ROLE AND RESPONSIBILITIES OF THE SPONSOR IN THE APPLICATION OF THE PRINCIPLES OF GLP

Introduction

1. Although the revised Principles of Good Laboratory Practice only explicitly assign a few responsibilities to the sponsor of a study, the sponsor has other implicit responsibilities. These arise from the fact that the sponsor is often the party who initiates one or more studies and directly submits the results thereof to regulatory authorities. The sponsor must therefore assume an active role in confirming that all non-clinical health and environmental safety studies were conducted in compliance with GLP. Sponsors cannot rely solely on the assurances of test facilities they may have contracted to arrange or perform such studies. The guidance given below attempts to outline both the explicit and implicit responsibilities of a sponsor necessary to fulfil his obligations.

Definition

2. “Sponsor means an entity which commissions, supports and/or submits a non-clinical health and environmental safety study.” (See revised OECD Principles of GLP, para. 2.2, point No. 5.)

Note: Sponsor can include:

- an entity¹ who initiates and support, by provision of financial or other resources, non-clinical health and environmental safety studies;
- an entity who submits non-clinical health and environmental safety studies to regulatory authorities in support of a product registration or other application for which GLP compliance is required.

Responsibilities of the Sponsor

3. The sponsor should understand the requirements of the Principles of Good Laboratory Practice, in particular those related to the responsibilities of the test facility management and the Study Director/Principal Investigator.

Note: If parts of the study are contracted out to subcontractors by the sponsor, the sponsor should be aware that the responsibility for the whole study remains with the Study Director, including the validity of the raw data and the report.

¹ “Entity” may include an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organisational unit thereof, or any other legally identifiable body.

4. When commissioning a non-clinical health and environmental safety study, the sponsor should ensure that the test facility is able to conduct the study in compliance with GLP and that it is aware that the study is to be performed under GLP.

Note: There are various tools for assessing the ability of a test facility to conduct a study in compliance with GLP. It can be useful for the sponsor to monitor contracted laboratories prior to the initiation of as well as during the study in accordance with its nature, length and complexity to ensure that its facilities, equipment, SOPs and personnel are according to GLP. If the test facility is in the national GLP compliance monitoring programme, the national monitoring authority² may also be contacted to determine the current GLP compliance status of the test facility.

5. Where several studies are presented to a regulatory authority in a single package, the responsibility for the integrity of the assembled package of unaltered final reports lies with the sponsor. It is necessary that the sponsor ensures that adequate communication links exist between his representatives and all parties conducting a study, such as the Study Director, Quality Assurance unit and test facility management.

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6. The sponsor is explicitly mentioned in several of the requirements of the revised OECD Principles of GLP:

Characterisation of Test Item: “In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation between the sponsor and the test facility, to verify the identity of the test item subject to the study.” (See revised Principles, para. 6.2, point No. 3.)

Note: This requirement has been added to the revised GLP Principles in order to ensure that there is no mix-up of test items.

Study Plan: “The study plan should also be approved by the test facility management and the sponsor if required by national regulation or legislation in the country where the study is being performed.” (See revised Principles, para. 8.1, point No. 1.)

Note: Some Member countries require approval of study plans by sponsors due to legal considerations related to responsibility for validity of test data.

Content of the Study Plan: “The Study Plan should contain ... information concerning the sponsor and the test facility ... the name and address of the sponsor” (See revised Principles, para. 8.2, point No. 2 a.)

“The Study Plan should contain... (the) date of approval of the study plan by signature of the test facility management and sponsor if required by national regulation or legislation in the country where the study is being performed.” (See revised Principles, para. 8.2, point No. 3a.)

² Sponsors should be aware that, notwithstanding any contractual requirements for confidentiality, national GLP monitoring authorities have access to all data produced by a GLP compliance facility.

Content of the Final Report: “The final report should include...information concerning the sponsor and the test facility ... name and address of the sponsor.” (See revised Principles, para. 9.2, point No. 2 a.)

Storage and Retention of Records and Materials: “If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archives of the sponsor(s) of the study(s).” (See revised Principles, para. 10.4.)

Note: In this case, the sponsor is expected to arrange for an archive for the appropriate storage and retrieval of study plans, raw data, specimens, samples of test and reference items and final reports in accordance with the Principles of GLP.

Other Issues

Provision of chemical safety information:

7. The sponsor should inform the test facility of any known potential risks of the test item to human health or the environment as well as any protective measures which should be taken by test facility staff.

Characterisation of the test item:

8. The revised OECD Principles of GLP include several requirements related to the characterisation of the test item (e.g. para. 6.2, point N^{os} 1 and 2; para. 9.2, point No. 1 d). These requirements call for careful identification of the test item and description of its characteristics. This characterisation is carried out either by the contracted test facility or by the sponsor. If the characterisation is indeed conducted by the sponsor, this fact should be explicitly mentioned in the final report. Sponsors should be aware that failure to conduct characterisation in accordance with GLP case could lead to rejection of a study by a regulatory authority in some Member countries.

9. If characterisation data are not disclosed by the sponsor to the contracted test facility, this fact should also be explicitly mentioned in the final report.

Submission of data to regulatory authorities:

10. The ultimate responsibility for the scientific validity of a study lies with the Study Director, and not with the sponsor, whose responsibility is to make the decision, based on the outcome of the studies, whether or not to submit a chemical for registration to a regulatory authority.



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OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE
AND COMPLIANCE MONITORING
Number 12

Advisory Document of the Working Group on Good Laboratory Practice

**Requesting and carrying out inspections and study
audits in another country**

956654

Document complet disponible sur OLIS dans son format d'origine
Complete document available on OLIS in its original format

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ABOUT THE OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 29 industrialised countries in North America, Europe and the Pacific, as well as the European Commission, meet to coordinate and harmonize policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised Committees and subsidiary groups composed of Member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's Workshops and other meetings. Committees and subsidiary groups are served by the OECD Secretariat, located in Paris, France, which is organised into Directorates and Divisions.

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FOREWORD

Environmental health and safety studies for the assessment of chemicals and chemical products are increasingly being carried out in multiple sites. This holds not only for field studies, but also for various phases of toxicology studies. The Revised Principles of Good Laboratory Practice*, adopted by OECD in 1997, cover the various aspects of the organisation of such studies. Nevertheless, the Working Group on Good Laboratory Practice felt that further guidance was needed about requesting and carrying out inspections and study audits of multi-site studies when the study site(s) are located in another country than that of the main test facility, as accorded by the 1989 Council Decision-Recommendation on Compliance with Principles of GLP [C(89)87(Final), Part II, 2.iii].

The Working Group therefore established a Steering Group on Multi-site Studies under the leadership of Germany. The Group met in Berlin on 2nd and 3rd September 1999 and included participants from the following countries: Denmark, France, Germany, the Netherlands, Sweden, Switzerland, the United Kingdom and the United States. It was chaired by Hans-Wilhelm Hembeck (Germany). The document prepared by the Steering Group was examined by the Working Group at its 12th Meeting in January 2000, where it was amended and endorsed.

The Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology at its 30th Meeting in turn endorsed the document and recommended that it be declassified under the authority of the Secretary-General. The Joint Meeting recommended that it be published as an Advisory Document of the Working Party on GLP in the OECD series on GLP and Compliance Monitoring.

* See No. 1 of the Series on GLP and Compliance Monitoring, OECD, Paris, 1998.

Advisory Document of the Working Group on GLP

RECOMMENDATIONS FOR REQUESTING AND CARRYING OUT INSPECTIONS AND STUDY AUDITS IN ANOTHER COUNTRY

Introduction

In the 1989 Council Decision-Recommendation on Compliance with the Principles of Good Laboratory Practice (C(89)87/Final), Member countries decided that, for purposes of the recognition of the assurance by another Member country that test data have been generated in accordance with GLP Principles countries “shall implement procedures whereby, where good reason exists, information concerning GLP compliance of a test facility (including information focusing on a particular study) within their jurisdiction can be sought by another Member country”. It is understood that such procedures should only be applied in exceptional circumstances.

The Working Group on Good Laboratory Practices proposed clarification of this decision based on the Revised OECD Principles of GLP and recommended the procedures set out below. This clarification was considered necessary, since it was recognised that some test facilities have test sites located under the jurisdiction of another country. These facilities or sites may not necessarily be part of the GLP compliance monitoring programme of the country of location, although many Member countries consider this desirable and useful.

The Working Group agreed, that the use of the term “test facility” in the 1989 Council Act encompassed both “test facility” and “test site” as defined in the Revised OECD Principles of GLP. Therefore any Member country can request an inspection/study audit from both test facilities and test sites located in another country. This request could concern any organisation associated with regulated GLP studies, whether these be main test facilities or test sites (dependent or independent of the test facility) which carry out phases of a study such as chemical analysis, histopathology or field studies.

Requests can also be made to inspect associated organisations such as independent Quality Assurance or archiving facilities if national legislation allows. However, this information exchange could be of a more informal nature and such operations need not necessarily appear in the Annual Overviews of Inspected Facilities exchanged among Members of the Working Group on GLP. These Annual Overviews should, however, include test facilities and test sites which were inspected or in which study audits were carried out.

In order to “implement procedures” to allow for this information exchange to take place smoothly and efficiently among monitoring authorities, to avoid duplication and wasting of resources and to assure that there is adequate compliance monitoring, the Working Group agreed that a process needed to be established for requesting inspections or study audits in another country.

The Working Group agreed that if justifiable requests to confirm compliance with GLP are made, every effort should be made to accommodate requests for inspections or study audits of test facilities or sites in other countries. If the country where the facility or site is located cannot accommodate the request in the framework of its current GLP monitoring programme and/or schedule, an alternative could be to allow the requesting country to undertake the inspection and/or audit itself (at its own expense as mutually agreed by both parties). Refusal to accommodate such requests may result in rejection of studies from the facility or site concerned. It was agreed that all Members of the Working Group on GLP should be informed of such refusals and that the circumstances should be discussed in the Working Group.

**Recommended Procedures to be followed in requesting and carrying out inspections
and study audits in another country**

1. The request for an inspection and/or study audit in another country should be made in writing and justified. The two countries should work out the arrangements to accommodate the request and for provision appropriate materials in a timely manner.
2. The liaison and lines of communication should be between the two national GLP Monitoring Authorities concerned.
3. The inspection/study audit will normally be led by the monitoring authority where the facility and/or site is located. An inspector or inspectors from the requesting country can be present at the inspection/study audit. Receiving authorities may participate if appropriate. The requesting country shall cover any costs involved for its own personnel.
4. The inspection/study audit report should be submitted to the requesting country (in an appropriate language as agreed between the two countries), with the appropriate measures taken to cover concerns about protection of commercial and industrial secrecy as required by national legislation.
5. Any major findings during such inspections/study audits should be followed up by the appropriate monitoring authority(ies).
6. Financial arrangements for inspections and study audits undertaken in this context will be made by the country in which they take place. The requesting country cannot be charged for this work.
7. Inspections and study audits undertaken in this context should appear in the Annual Overview of the country that led the inspection/study audit.