World Health Organization

SECOND EDITION

HANDBOOK

GOOD LABORATORY PRACTICE (GLP)

Quality practices
for regulated non-clinical
research and development

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

WHO Library Cataloguing-in-Publication Data

Handbook: good laboratory practice (GLP): quality practices for regulated non-clinical research and development - 2nd ed.

1.Laboratories - organization and administration. 2.Laboratories - handbooks. 3.Laboratories techniques and procedures. 4.Manuals. I.UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

ISBN 978 92 4 154755 0 (NLM classification: QY 25)

Printed in Switzerland

Design: Lisa Schwarb
Layout: OnProd, Lausanne

HANDBOOK

GOOD LABORATORY PRACTICE (GLP)

Quality practices for regulated non-clinical research and development

World Health Organization

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

FOREWORD

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

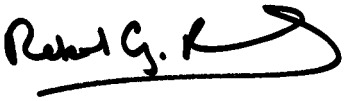
The demand for this series was so substantial that it became one of the most frequent "hits" on the TDR website, generating interest and demand for a second edition. This Second-edition GLP series is presented here in a revised and updated format. It supports continued technology transfer and capacity-building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

This Second-edition *GLP Handbook* contains all of the required support material for implementing GLP in a laboratory. The handbook comprises four parts, all updated, including: 1) explanation of the fundamentals of GLP; 2) support for GLP training; 3) methodology for GLP implementation in DEC research institutions; 4) GLP principles and guidance produced by the Organisation of Economic Co-operation and Development (OECD), and reproduced here with OECD permission.

Since publication of the initial GLP edition, TDR-fostered GLP training efforts throughout the world, and particularly in Asia, Latin America and Africa, have led to the formation of a network of GLP trainers. These trainers, acting as testers and critics, had a significant impact on the revision and expansion of this Second-edition GLP series, and particularly in the creation of a section on 'stepwise' implementation of GLP, identifying clear milestones for the process.

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

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



Dr R. Ridley
Director TDR

THE DEVELOPMENT OF THIS HANDBOOK

To enjoy the advantages of new or improved methods for the control of tropical diseases, disease endemic countries (DECs) will need to rely to a large extent on their own research activities. It is therefore necessary to strengthen the capacity of these countries to conduct research and drug product development studies at a level comparable to that in other parts of the world.

The pertinent regulations in the preclinical scenario are the Good Laboratory Practice (GLP) regulations. These regulations are the subject of this handbook, which is a reference and support document, to help in the implementation of GLP. The Principles of Good Laboratory Practice of the Organisation for Economic Cooperation and Development (OECD) form the basis of this series of guidance documents.

This is the second version of the WHO Handbook on GLP. It is the result of experience gained since the first version was published. It also refers to material related to GLP developments over the last seven years. Since the publication of the first GLP Handbook and training manuals, many training programmes have been conducted all over the world. The WHO-TDR Network of GLP Trainers was formed to continue propagating training and implementation of GLP in DECs. The network recommended the revision of this guidance document in order to reflect the progress in international GLP.

The modifications in this second version are as indicated below:

Chapter 1. Introduction to the WHO/TDR Handbook on GLP has been the subject of minor modifications to help understanding and facilitate reading.

Chapter 2. GLP Training: This has been reorganised and updated. The order of the five fundamental points now reads "resources – characterisation -– rules – results (instead of documentation) – quality assurance". Minor corrections have been made and extra explanations added to this part dealing with the fundamentals of GLP.

Notable changes include:

- New section on the role of the Study Director in the Multi-Site situation.
- Reference to the prescriptive and descriptive documents in GLP studies.
- Reference to Principal Investigators.
- Reference to the Validation of Computerised Systems.
- New section on the role of Quality Assurance in the Multi-Site situation.

Chapter 3. Stepwise implementation now identifies clearer milestones in the process of setting up GLP, as requested by the GLP Network of Trainers.

Chapter 4. OECD guidance documents has been expanded to include those published since the first edition of the handbook. These represent entirely new items compared with the first version. At the time of going to press, all the OECD guidance documents on GLP are included in the handbook. The guidance documents are:

- the application of the OECD Principles of GLP to the organisation and management of multi-site studies;
- the application of the principles of GLP to in vitro Studies;
- establishment and control of archives that perate in compliance with the principles of GLP.

Thus, this second edition of the GLP Handbook represents an up-to-date GLP reference document which we trust will be useful to support future deployment of GLP in research centres of DECs.

Contributors to the first edition:

Scientific Working Group on GLP issues:

Dr J. P. Seiler** (International Office for the Control of Medecines (IOCM), Switzerland), Chair
Mr D. Long** (GXP Consultant, France), Rapporteur
Dr D. Turnheim** (OECD, France)
Dr N. Gawadi** (H. Lundbeck, Denmark)
Dr N. K. Nair** (University of Sains malaysia, Malaysia)
Dr P. Palittaponkarnpim* (National Center for Genetic Engineering and Biotechnology, Thailand)
Dr Ch. O. N. Wambebe** (National Institute for Pharmaceutical Research and development, Nigeria)
Dr M. T. Ham** (Ministry of health, Welfare and Sports, The Netherlands
Dr A. Walubo* (University of the Orange Free state, South Africa)
Mr P. Withers* (Phoenix International, France)
Dr G. Murilla* (Kenya Medical Research Institute, Kenya)
Dr J.-M. Sapin* (Agence française de sécurité des aliments (AFSSA), France)

Dr Sansanee Chaiyaroj* (Mahidol University, Thailand)
Dr M. Arevalo* (Institute de Immunologia del Valle, Colombia)
Dr J. F. McCormack* (Food and Drug Administration (FDA), USA)
Dr Ch. K. Maitai** (University of Nairobi, Kenya)

WHO Secretariat:
Dr D. Kioy** (Preclinical Coordinator, TDR/CDS)
Dr B. Halpaap** (TDR/CDS)
Dr E. Griffiths** (HTP)
Dr H. Engers** (TDR/CDS)
Dr S. Kopp-Kubel* (HTP)
Dr C. Heuck* (HTP)
Dr T. Kanyok* (TDR/CDS)
Dr M. Demesmaeker* (HTP)

** Participation in both meetings
* Participation in one meeting
CDS: Communicable Diseases
HTP: Health Technology and Pharmaceuticals

Contributors to the second edition

WHO/TDR Network of GLP Trainers
Dr Deepak Kumar AGRAWAL (Industrial Toxicology Research Centre, Lucknow, INDIA)
Dr Myriam AREVALO (Instituto de Immunologia del Valle, COLOMBIA1061)
Dr Sarita BHALLA (Central Insecticide Laboratory, Faridad, INDIA)
Dr Daniel CHAI Chivatsi (Institute of Primate Research (IPR), Nairobi, KENYA)
Dr K.S. GAMANIEL (National Institute for Pharmaceutical Research and Development, Abuja, NIGERIA)
Dr Sandhya KULSHRESTHA (Central Insecticide Laboratory, New Delhi, INDIA)
M. David LONG, (Facilitator Consultant, Paris, FRANCE)
Dr Lazara MARTINEZ (Centro para el Control Estatal de la Calidad de los Medicamentos – CECMED, CUBA)
Dr Paul N. MBUGUA (University of Nairobi, KENYA)

Dr M.J. MOSHI (Muhimbili University, Dar-es-Salaam, TANZANIA)
Dr Grace MURILLA (Kenya Trypanosomiasis Research Institute (KETRI), KENYA)
Dr Maina NGOTHO (Kenya Trypanosomiasis Research Institute (KETRI), KENYA)
Dr Geetha RAJASHEKHER (Rallis Research Centre, Bangalore, INDIA)
Dr Geoffrey RUKUNGA (Kenya Medical Research Institute (KEMRI), KENYA)
Dr Rokia SANOGO (Département Médecine Traditionnelle, (DMT) B-P., MALI)
Dr Sudhir SRIVASTAVA (Central Drug Research Institute, Lucknow, INDIA)
Dr Vincent Pryde K. TITANJI (University of Buea, Buea, CAMEROON)
Dr A. WALUBO (University of the Orange Free State, SOUTH AFRICA)
Dr Dorcas YOLE (Institute of Primate Research (IPR), KENYA)
Dr Mariano ZALIS (Univ. Federal do Rio de Janeiro, Rio de Janeiro, BRASIL)

Editorial Group:

Dr Deborah Kioy (Preclinical Coordinator, WHO/TDR)
Mr David Long (Consultant, France)
Dr Sarita Bhalla (Deputy Director, Medical Toxicology, INDIA)
Dr Juerg Seiler (ToxiConseil, Switzerland)

ACKNOWLEDGEMENTS

This Good Laboratory Practice (GLP) Handbook is designed to aid those wishing to upgrade their laboratories to GLP status. It has been developed as part of a significant technology transfer and capacity building programme in the area of preclinical development in Disease Endemic Countries (DECs).

The first version of the GLP Handbook was produced as an initiative of the Scientific Working Group (SWG) on GLP issues, convened by the UNDP / World Bank / WHO special programme for Research and Training in Tropical Diseases (TDR), which comprised independent scientific specialists from around the world. This revised second edition was an initiative of the WHO/TDR Network of GLP Trainers.

The handbook is broadly based on the Organisation for Economic Cooperation and Development (OECD) Principles of GLP. The handbook will provide laboratories and trainers in DECs with the necessary technical aid for implementing GLP programmes.

TDR gratefully acknowledges the work and support of all those involved in the production of this handbook, the author David Lang, the editorial group, the WHO/TDR Network of GLP Trainers and the original SWG. Our special thanks to the OECD, which kindly allowed us to reprint the OECD Principles of GLP and the related guidance documents. The OECD documents are provided as an annexe to this handbook.

For all correspondence:

Dr Deborah Kioy
Pre-clinical Coordinator
TDR/WHO
Avenue Appia 20
Geneva 27 – Switzerland

Tel: + 41 22 791 3524
Fax: + 41 22 791 4854
E-mail: kioyd@who.int

TABLE OF CONTENTS

CHAPTER

1. INTRODUCTION TO THE WHO/TDR HANDBOOK ON GLP 1

GENERAL INTRODUCTION 1

INTRODUCTION TO GLP AND ITS APPLICATION 5
The history of GLP 5
What is GLP ? 7

2. GOOD LABORATORY PRACTICE TRAINING 9

INTRODUCTION 9

THE FUNDAMENTAL POINTS OF GLP 10
Resources. 11
Characterisation 12
Rules 12
Results 13
Quality Assurance 14

RESOURCES 14
Personnel. 14
Facilities: Buildings and Equipment 18

CHARACTERISATION 23
The Test Item. 23
Test System 31

RULES FOR PERFORMING STUDIES. 35
General Points. 35
The Study Plan or Protocol 35
Standard Operating Procedures (SOPs) 40

RESULTS - RAW DATA AND DATA COLLECTION 43
General Points 43
Records and Recording 43
The Study Report 46
Archives and Archiving 48

QUALITY ASSURANCE UNIT 50
Protocol (or Study Plan) Review 51
SOP Review 51
Planning (Master schedule; Inspection plan) 52
Audits and inspections 52
Quality Assurance Statement 55
QA Inspections of Suppliers and Contractors 56
Quality Assurance in the Multi-Site Situation 56
The Distribution and Archiving of QA Files and Reports 56

3. STEPWISE IMPLEMENTATION OF GLP 59

INTRODUCTION 59

IMPLEMENTATION AS A PROJECT 60

STEPWISE IMPLEMENTATION OF GLP REQUIREMENTS 63

ANNEXES

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE MONITORING

I. OECD PRINCIPLES ON GOOD LABORATORY PRACTICE 77

II. GUIDANCE FOR GLP MONITORING AUTHORITIES: REVISED GUIDELINES FOR COMPLIANCE MONITORING PROCEDURES 113

III. GUIDANCE FOR GLP MONITORING AUTHORITIES: REVISED GUIDANCE FOR THE CONDUCT OF LABORATORY INSPECTIONS AND STUDY AUDITS 133

IV. QUALITY ASSURANCE AND GLP 155

V. COMPLIANCE OF LABORATORY SUPPLIERS WITH GLP PRINCIPLES . . 167

VI. THE APPLICATION OF THE GLP PRINCIPLES TO FIELD STUDIES 175

VII. THE APPLICATION OF THE GLP PRINCIPLES TO SHORT TERM STUDIES 189

VIII. THE ROLE AND RESPONSIBILITIES OF THE STUDY DIRECTOR IN GLP STUDIES 203

IX. GUIDANCE FOR GLP MONITORING AUTHORITIES: GUIDANCE FOR THE PREPARATION OF GLP INSPECTION REPORTS 215

X. THE APPLICATION OF THE PRINCIPLES OF GLP TO COMPUTERISED SYSTEMS 221

XI. THE ROLE AND RESPONSIBILITIES OF THE SPONSOR IN THE APPLICATION OF THE PRINCIPLES OF GLP 235

XII. REQUESTING AND CARRYING OUT INSPECTIONS AND STUDY AUDITS IN ANOTHER COUNTRY 245

XIII. THE APPLICATION OF THE OECD PRINCIPLES OF GLP TO THE ORGANISATION AND MANAGEMENT OF MULTI-SITE STUDIES 253

XIV. THE APPLICATION OF THE PRINCIPLES OF GLP TO IN-VITRO STUDIES 271

XV. ESTABLISHMENT AND CONTROL OF ARCHIVES THAT OPERATE IN COMPLIANCE WITH THE PRINCIPLES OF GLP 289

1. INTRODUCTION TO THE WHO/TDR HANDBOOK ON GLP

GENERAL INTRODUCTION

The need to implement quality standards in drug research, development and testing; the situation in developing countries and the role of WHO/TDR

Tropical diseases are a major public health problem in developing countries (Disease Endemic Countries – DECs). For many of these diseases no new, effective and affordable medicines have been developed, while older therapeutic agents are increasingly compromised by the emergence of resistance. Because multinational pharmaceutical companies have not traditionally focused on tropical disease research and development (R&D), WHO has initiated R&D 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 geographical regions most affected by such diseases. If such R&D is to result in marketing approval of effective and safe new drug products, the component studies must comply with current research practice standards ensuring the quality, reliability and integrity of study data. Market authorisation regulations require that quality standards, i.e. Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Clinical Practice (GCP), are followed in the respective stages of the development and life-cycle of a drug product.

WHO published standards for Good Manufacturing Practice (GMP)[1] in 1999 (covering the manufacture of a drug product) and Good Clinical Practice (GCP)[2] in 1995 (covering clinical trials in man). However, until the publication of the first version of this handbook in 2001, WHO had not addressed quality standards for non-clinical testing for the safety of potential

[1] Quality assurance of pharmaceuticals: A compendium of guidelines and related materials. Volume 2 Good manufacturing practices and inspection, WHO Geneva 1999

[2] Guidelines for good clinical practices (GCP) for trials on pharmaceutical products. WHO Geneva 1995

products: Good Laboratory Practice (GLP). This handbook, and its associated training volumes, specifically address this gap in WHO recommendations.

The introduction of GLP quality standards in test facilities of developing countries was seen as an urgent issue and, accordingly, WHO convened a working party **(Scientific Working Group on GLP issues – SWG)** in 1999 and 2000 to address the WHO position on GLP.

During the SWG discussions it became evident that, for test facilities in developing countries, the introduction of GLP could be impeded by resource constraints (e.g. few trained personnel, inadequate facilities and equipment) or by the instability of the infrastructure (e.g. water or electricity supply), either within the testing laboratory itself or in the community as a whole. However, GLP could result in tangible returns through the number of studies placed with research organisations in DECs, resulting in an overall increase in funding. It is clear that as funding is scarce sponsors will not invest in studies if the reliability of results cannot be assured. Specifically, WHO/TDR will be reluctant to allocate their limited funding to non-clinical safety studies unless the results can be reliable on and thus support decisions concerning the progress of products to clinical stages and eventually to product registration.

The deliberations of the Scientific Working Group on GLP issues underlined the following points:

- In DECs, demonstrating compliance with GLP will become a prerequisite for non-clinical safety testing and for drug registration particularly where drug products are projected for markets other than the country of origin;
- It is essential to avoid the co-existence of two or more international GLP regulatory standards for non-clinical safety testing;
- Guidance is needed for the implementation of GLP.

With such considerations in mind the SWG recommended that WHO/TDR adopt the Revised OECD Principles of Good Laboratory Practice as its official guidance for non-clinical safety testing. The handbook sets forth the OECD Principles in their original text, supplemented by sections on training and the implementation of GLP.

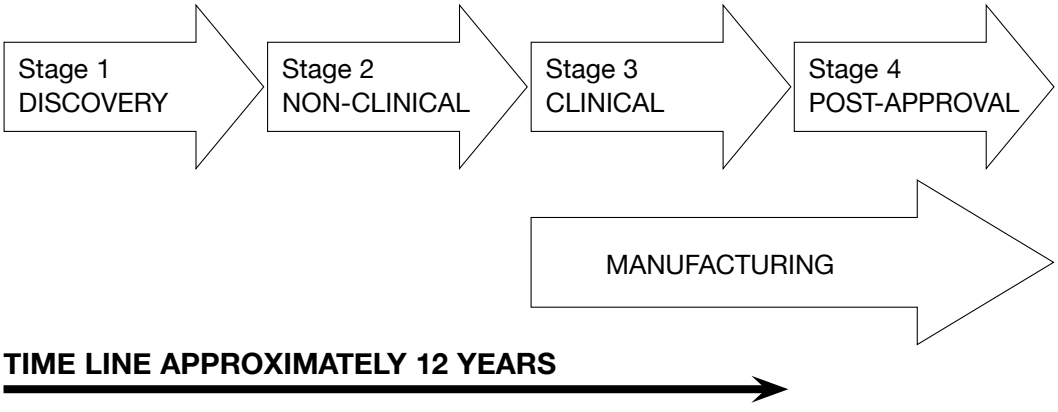
The drug discovery and development process: non-regulated vs. regulated research

The drug discovery and development process can be divided into a number of distinct stages which may overlap in time (e.g. clinical Phase I studies may be started before the completion of toxicology studies of longer duration; oncogenicity studies may not even have been started at this point).

Typically, the process starts with basic discovery activities, the results of which may then be used to define efficacy targets for the potential drug. The discovery phase often involves thousands or even tens of thousands of new molecular entities (NMEs) being screened for activity against a target disease. The ten or twenty successful NMEs are then checked for their potential toxic effects, again in screening-type tests, further reducing the number of potential drug substances taken forward to full development. In countries without an established pharmaceutical industry, the discovery process may be different; 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 plant remedy for certain indications. After observational studies to ascertain whether the practice is sound, one could set up chemical studies to find the active principles, and perhaps prepare a set of chemical analogues. In this case the number of starting compounds would be more modest, but this does not fundamentally alter the process. The need for rigorous testing further along in the development pathway will remain the same. Studies performed subsequent to this selection contribute to the overall assessment of safety and efficacy of the candidate compound. In the R&D stages downstream of discovery, the investigations are regulated by internationally accepted guidelines and quality requirements.

The different steps in classical drug development (drug life-cycle) are characterised by four well-defined stages, which are summarised in the diagram below.

DRUG DEVELOPMENT STAGES



STAGE 1

The first stage, the discovery of a potential NME, is not covered by a regulatory standard, nor are studies that demonstrate proof of concept. The WHO has recently published guidance on this early research phase : Quality Practices in Basic Biomedical Research – QPBR.

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 humans. Their primary purpose is safety testing. Toxicology and safety pharmacology studies, with a potential extension to pharmacokinetics and bioavailability, are those studies where compliance with GLP is required. From the diagram above, the somewhat restricted scope of GLP is evident.

STAGE 3

The third stage, following on from safety studies of stage 2, encompasses clinical studies in human subjects. Here, GCP is the basic requirement 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-centric, clinical efficacy trials in hundreds or thousands of subjects).

STAGE 4

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

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 Active Pharmaceutical Ingredients (API – drug substance) and formulated medicines (drug product).

The scope of this handbook is restricted to the GLP-regulated area (stage 2 of the above diagram) i.e. to the " ... 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 prop-

erties 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, regulatory, concept of "Good Laboratory Practice" (GLP) originated in the USA in the 1970s because of concerns about the validity of non-clinical 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 revealed instances of inadequate planning and incompetent execution of studies, insufficient documentation of methods and results, and even cases of fraud. For example, replacing animals which had died during a study with 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 gross necropsy observations because the histopathologist received no specimens of these lesions; and retrospectively changing raw data in order to "fit the result tables" in the final report. These deficiencies were made public in the Kennedy-Hearings of the US Congress, and the political outcome of these hearings led to the FDA's publication of Proposed Regulations on GLP in 1976, with establishment of the Final Rule in June 1979 (21 CFR 58). The GLP regulations provided the basis for assurance that reports on studies submitted to FDA would reflect faithfully and completely the experimental work carried out. In the chemical and pesticide field, the US Environmental Protection Agency (EPA) had also encountered similar problems with study quality. Accordingly, it 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 their different legal bases) in 1983.

On the international level, the Organisation for Economic Co-operation and Development (OECD) assembled an expert group to formulate the first OECD Principles of GLP. This was an attempt 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. The expert group's 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)]; 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 recognised that these GLP Principles needed explanation and interpretation, as well as further development, and in the following years a number of OECD workshops addressed these issues. The outcomes of these workshops were published by OECD in the form of consensus or guidance documents. After some 15 years of successful application, the OECD Principles were revised by an international group of experts and 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 consensus/guidance documents are reprinted as annexes of this handbook.

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

Internationally, compliance with GLP is a prerequisite for the mutual acceptance of data; different countries or regulatory authorities accept laboratory studies from other countries provided they comply with the OECD GLP Principles. This mutual acceptance of safety test data precludes unnecessary repetition of studies carried out in order to comply with individual regulations of different countries. In order to facilitate further the mutual acceptance of data and to extend this possibility to outside countries, the OECD Council adopted on 26th 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 after satisfactory implementation, are allowed to join the corresponding part of the OECD Chemicals Programme. Mutual acceptance of conformity of test facilities and studies with GLP 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 2nd 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 information on the compliance of test facilities inspected, and also

provide relevant information concerning the countries' procedures for monitoring compliance. Although devoid of such officially recognised National Compliance Monitoring Authorities, some developing countries do have an important pharmaceutical industry, where non-clinical safety data are already developed under GLP. In these cases, individual studies may be audited by foreign GLP inspectors.

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 the Principles of Good Laboratory Practice is to promote the development of quality test data and provide a tool to ensure a sound approach to the management of laboratory studies, including conduct, reporting and archiving. The Principles may be considered as a set of standards for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions and the traceability of data. The Principles require institutions to assign roles and responsibilities to staff in order to ensure good operational management of each study and to focus on those aspects of study execution (planning, monitoring, recording, reporting, archiving) that are of special importance for the reconstruction of the whole study. Since all these aspects are of equal importance for compliance with GLP Principles, it is not permissible to partially implement GLP requirements and still claim GLP compliance. No test facility may rightfully claim GLP compliance if it has not implemented, and does not comply with, the full array of the GLP rules.

As far as pharmaceutical development is concerned, the GLP Principles, in their regulatory sense, apply only to studies which:

- are non-clinical, i.e. mostly studies on animals or in vitro, including the analytical aspects of such studies;
- are designed to obtain data on the properties and/or the safety of items with respect to human health and/or the environment;
- are intended to be submitted to a national registration authority with the purpose of registering or licensing the tested substance or any product derived from it.

Depending on national legal situations, the GLP requirements for non-clinical laboratory studies conducted to evaluate drug safety 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 sensitisation studies, or testing for suspected addictive and/or withdrawal effects of drugs.

GLP Principles are independent of the site where studies are performed. They apply to studies planned and conducted in a manufacturer's laboratory, at a contract or subcontract facility, or in a university or public sector laboratory.

GLP is not directly concerned with the scientific design of studies. The scientific design may be based on test guidelines and its scientific value is judged by the (Drug) Regulatory Authority that provides marketing authorisation. However, adherence to GLP will remove many sources of error and uncertainty, adding to the overall credibility of the study. Through the application of technically valid and approved Standard Operating Procedures many sources of systematic error and artefacts may be avoided. The requirement to formulate a study plan with a defined scientific purpose for the study will prevent false starts and diminish the incidence of incomplete or inconclusive studies. Respecting the GLP Principles will thus indirectly optimise the scientific yield of studies.

When implementing GLP in a test facility, and particularly during training, it is important to clearly differentiate between the formal, regulatory use of the term Good Laboratory Practice and the general application of "good practices" in scientific investigations. Since the term "Good Laboratory Practice" is not a trade-mark protected term, any laboratory may consider that it is following good practices in its daily work. This does not comprise GLP compliance.

It must be clearly understood that only adherence to, and compliance with, all the requirements of the OECD GLP Principles constitutes real compliance with GLP. Therefore, the use of similar terminology to describe quality practices outside the scope of GLP proper should be strongly discouraged.

2. GOOD LABORATORY PRACTICE TRAINING

INTRODUCTION

The history and scope of GLP are discussed in chapter 1 of this WHO/TDR Handbook on GLP. This present part (chapter 2) of the Handbook is intended to supplement the WHO/TDR training manuals and should be used in conjunction with them.

Regulatory GLP started when the Food and Drug Administration (FDA) issued mandatory GLP requirements. These came into force on 20th June 1979. They were a reaction to cases of malpractice and fraud in the non-clinical testing of drugs performed by some pharmaceutical companies and contract research organisations. Subsequently the FDA revised these regulations a number of times but their scope remains the same: the regulations still apply to non-clinical studies used to evaluate safety. Preliminary pharmacological studies and pharmacokinetic studies not designed to test safety are thus exempt from GLP requirements. A little later, in 1981, the Organisation for Economic Co-operation & Development (OECD) issued Principles for GLP concerning the safety testing of any chemical substance. These Principles were revised in 1997 to reflect more recent developments. Each of the thirty OECD member states has agreed to accept the data from safety studies performed by any other member state provided that they have been conducted in compliance with the OECD GLP Principles. The OECD GLP Principles have, therefore, gradually 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. The fact that the OECD GLP Principles have acquired wide international acceptance is the reason why they are used as the reference guide for the WHO/TDR GLP training programme. WHO/TDR wishes to thank the OECD Directorate for Environment for allowing the publication *in extenso* of the OECD GLP documents in this Handbook (Annexes).

The WHO/TDR effort to promote the development of therapeutic substances against tropical diseases and the conduct of studies in DECs is a matter of high priority. For studies to be readily accepted by regulatory authorities world-wide GLP implementation in laboratories conducting non-clinical safety studies is of major importance. Part of

achieving this goal in regions where there is limited knowledge of and experience with formal quality concepts like GLP is to promote "technology" or "knowledge transfer", through the training of scientists, thus enabling them to work in compliance with these standards. Therefore, WHO/TDR is actively promoting training courses designed to provide an understanding of the concepts of GLP and to facilitate the practical implementation and application of these principles.

The WHO/TDR GLP training course in GLP is seen as an enabler aiming to assist institutes in Disease Endemic Countries (DECs) to reach GLP compliance thus allowing them to increase the international credibility of their data and results. Therefore, this GLP training contributes pertinently to capacity building in DECs which is one of the specific aims of WHO/TDR.

THE FUNDAMENTAL POINTS OF GLP

The GLP Principles set out the requirements for the appropriate management of non-clinical safety studies. This helps the researcher to perform his/her work in compliance with his/her own pre-established scientific design. GLP Principles help to define and standardise the planning, performance, recording, reporting, monitoring and archiving processes within research institutions. The regulations are not concerned with the scientific or technical content of the studies *per se*. The regulations do not aim to evaluate the scientific value of the studies: this task is reserved first for senior scientists working on the research programme, then for the Registration Authorities, and eventually for the international scientific community as a whole. The GLP requirements for proper planning, for controlled performance of techniques, for faithful recording of all observations, for appropriate monitoring of activities and for complete archiving of all raw data obtained, serve to eliminate many sources of error.

Whatever the industry targeted, GLP stresses the importance of the following main points:

1. Resources: Organisation, personnel, facilities and equipment;
2. Characterisation: Test items and test systems;
3. Rules: Protocols, standard operating procedures (SOPs);
4. Results: Raw data, final report and archives;
5. Quality Assurance: Independent monitoring of research processes.

The WHO/TDR training programme takes each of these 5 fundamental points in turn and explains the requirements of GLP in each case. The major points addressed are summarised below and then dealt with in detail in the sections which follow.

Resources

ORGANISATION AND PERSONNEL

GLP regulations require clear definitions of the structure of the research organisation and the responsibilities of the research personnel. This means that the organisational chart should reflect the reality of the institution and should be kept up to date. Organisational charts and job descriptions give an immediate idea of the way in which the laboratory functions and the relationships between the different departments and posts.

GLP also stresses that the number of personnel available 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 education and training records. To maintain adequate levels of competence, GLP attaches considerable importance to the qualifications of staff, and to both internal and external training given to personnel.

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 person is appointed by the test facility management and will assume full responsibility for the GLP compliance of all activities within the study. He/she is responsible for the adequacy of the study protocol and for the GLP compliant conduct of the study. He/she will assert this at the end of the study in his/her dated and signed GLP Compliance Statement which is included in the study report. The Study Director must therefore be aware of all events that may influence the quality and integrity of the study, evaluate their impact and institute corrective actions as necessary. Even when certain phases or parts of the study are delegated to other test sites (as in the case of multi-site studies), the Study Director retains overall responsibility for the entire study, including the parts delegated, and for the global interpretation of the study data.

(The OECD has produced a guidance document on the roles and responsibilities of the Study Director which is in the annexe to this Handbook. A specific training module on the Study Director is included in the WHO/TDR GLP Training Manuals.)

FACILITIES AND EQUIPMENT

The GLP Principles emphasise that facilities and equipment must be sufficient and adequate to perform the studies. The facilities should be spacious enough to avoid problems

such as overcrowding, cross contamination or confusion between projects. Utilities (water, electricity etc.) must be adequate and stable.

All equipment must be in working order; a 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 status of the equipment and its history.

Characterisation

In order to perform a study correctly, it is essential to know as much as possible about the materials used during the study. For non-clinical studies intended to evaluate the safety-related properties of pharmaceutical compounds, it is a prerequisite to have detailed knowledge about the properties of the test item, and of the test system (often an animal or isolated part thereof) to which it is administered.

Characteristics such as identity, potency, composition, stability, impurity profile, etc. 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, normal biological values, etc.

Rules

PROTOCOL OR STUDY PLAN

The study plan or protocol outlines the design and conduct of the study and provides evidence that the study has been properly thought through and planned: the principal steps of studies conducted in compliance with GLP are thus described in the study protocol. The protocol must be approved by the Study Director, by dated signature, before the study starts. Alterations to the study design can only be made through formal amendment procedures. All this will ensure that the study can be reconstructed at a later point in time. The GLP Principles list the essential elements to be included in a study protocol.

WRITTEN PROCEDURES

It is not reasonable to include all the technical details of study conduct in the protocol. The details of all routine procedures are described in Standard Operating Procedures (SOPs) which are part of the documentation system of the institution. SOPs contribute to reducing bias in studies by standardising frequently performed techniques. Laboratories also need to standardise certain techniques to facilitate comparison of results between studies; here again written SOPs are an invaluable tool. To be able to exactly reconstruct

a study is *a sine qua non* for the mutual acceptance of data; another reason why routine procedures are described in written SOPs, used throughout the institution.

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

Results

RAW DATA

All studies generate raw data, sometimes called source data. Raw data are the original data collected during the conduct of a procedure. But, raw data also document the procedures and circumstances under which the study was conducted. They are, therefore, essential for the reconstruction of studies and contribute to the traceability of the events of a study. Raw data are the results of the experiment upon which the conclusions of the study will be based. Some of the raw data will be treated statistically, while others may be used directly. Whatever the case, the results and their interpretations provided by the scientist in the study report must be a true and accurate reflection of the raw data.

STUDY REPORT

The study report, like all the other scientific aspects of the study, is the responsibility of the Study Director. He/she must ensure that it describes the study accurately. The Study Director is responsible for the scientific interpretation included in the study report and is also responsible for declaring to what extent the study was conducted in compliance with the GLP Principles. The GLP Principles list the essential elements to be included in a final study report.

ARCHIVES

A study may have to be reconstructed many years after it has ended. Thus the storage of records must enable their safekeeping for long periods of time without loss or deterioration and, preferably, in a way which allows quick retrieval. In order to promote safe storage of precious data, it is usual practice to restrict access to archive facilities to a limited number of staff and to record the documents logged in and out. Even if the access is restricted to certain staff, records are also kept of the people entering and leaving the archives.

Quality Assurance

Quality Assurance (QA) – sometimes also known as the Quality Assurance Unit (QAU) - as defined by GLP is a team of persons charged with assuring management that GLP compliance has been attained in the test facility as a whole and in each individual study. QA must be independent of the operational conduct of the studies, and functions as a "witness" to the whole preclinical research process.

(The OECD has produced a guidance document on the Quality Assurance and GLP which is in the annexe to this Handbook.)

RESOURCES

Personnel

The managerial and organisational requirements of GLP account for about 15% of GLP regulations but, unfortunately, are still seen by regulators and QA as one of the principal sources of non-compliance. Without full management commitment and formal involvement of all personnel, GLP systems lack credibility and will not function as they should. Personnel are, therefore, a critical element when implementing GLP and maintaining compliance in a laboratory.

It is clear that the manager of a test facility has overall responsibility for the implementation of both **good science** and **good organisation**, including compliance with GLP.

GOOD SCIENCE

- Careful definition of experimental design and parameters.
- Performance of experiments based on valid scientific procedures.
- Control and documentation of experimental and environmental variables.
- Careful, complete evaluation and reporting of results.
- Assuring that results become part of accepted scientific knowledge.

GOOD ORGANISATION:

- 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 organised archives.
- Implementation of a process for the verification of results.
- Compliance with GLP.

In the matrix of good science and good organisation, GLP concentrates largely on organisational and managerial aspects of studies, many of which are directly dependent upon the competence of personnel running the studies.

PERSONNEL AND MANAGEMENT

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

- Planning / Resource allocation
- Personnel management traced through documents
- Training
- The special position of the Study Director in the multi-site situation also requires comment

Planning/Resource allocation (Master schedule)

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

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

The planning/resource allocation system required by GLP is captured on a document called the **master schedule**. This document provides key information on all studies within the institution and their status: planned, on-going or finished. The master schedule 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 incorporated.
- The system is the "official" one (i.e. don't have two or more competing systems for the same purpose).
- The system is described in an approved SOP.
- Responsibility for its maintenance and updating are defined.
- The various versions of the master schedule are approved and maintained in the archive as raw data.
- Distribution is adequate and key responsibilities are identified.

By the time the protocol has been signed and distributed, the study has also been entered onto the master schedule. Often the responsibility for drawing up the schedule and for its maintenance is a project management function and is computerised 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. QA will largely base their audit/inspection programme on the events listed in the master schedule. The QA responsibilities are described later.

Personnel Management

Management has the responsibility for the overall organisation of the test facility. With respect to personnel, this organisation is usually reflected in the Organisation Chart. This is often the first document requested by National Monitoring Authorities during the course of their inspections: it should provide a clear idea of how the facility functions.

GLP requires that personnel have the necessary competence (education, experience and training) to perform their functions. Personnel competence is reflected in job descriptions, CVs and training records.

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

Definition of tasks and responsibilities / Job descriptions

All quality systems are based on making people responsible for their actions. This responsibility is illustrated by the two aphorisms below:

- "Don't perform a procedure if you don't understand the reason, the context and the consequences of it".
- "Signing your work means you take full responsibility for the correct completion of your task".

There must be clear definitions of tasks and responsibilities: these are delineated in job descriptions.

The contents of job descriptions should correspond to the qualifications as described in the CV. In addition, these documents are:

- Updated regularly, typically at a set interval of a year (fixed by an SOP).
- Usually 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 reorganisation, helps the facility management to ensure that their organisation is coherent.

Curriculum vitae - CV

A procedure should ensure that CVs:

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

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 the following in a CV:

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

Training

Finally, training records complement CVs and job descriptions. Job competence depends largely on internal and external specialised training. GLP explicitly requires that all personnel understand the importance of GLP 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 personnel using it. Some organisations have training schemes linking training to motivation, professional advancement and reward.

The training system should have elements common to all GLP management systems, i.e. it is:

- Formal.
- Approved.
- Documented to a standard format.
- Described in a Standard Operating Procedure.
- Possible to perform an historical reconstruction of training through the archived documents.

Study Director and the Multi-Site Situation

Special mention must be made of the important role of the Study Director. This person is the single point of study control. He/she has the overall responsibility for the planning and conduct of the study, the interpretation of the results and the authorship of the final study report. This responsibility is expressed through the signature of the study plan or protocol, the supervision of the study in progress and the signature of the final report. The Study Director must include in the final report a GLP compliance statement indicating the extent to which his/her study complies with the Principles of GLP.

When studies are performed on several sites, i.e. at the test facility (main site where the Study Director is normally located) and at one or more test sites (where only certain phases of the study are performed), the Study Director retains overall responsibility for the study, including the phases delegated to test sites. The Study Director is responsible for the protocol covering the whole of the study, including the delegated phases. On the test sites the delegated phases are under the supervision and responsibility of a Principal Investigator (PI). The PI reports to the Study Director and follows the protocol provided by the Study Director. Any problems relating to the study phase under the control of the PI must be communicated to the Study Director who will decide whether or not the problem encountered requires his/her input, perhaps in the form of a protocol amendment.

At the end of a multi-site study, it is the Study Director who has the responsibility of writing the final report even if it includes contributions provided by the PI. The Study Director includes a GLP statement covering the entire study, including the phases that were delegated to the PI.

(The OECD has produced a guidance document on the roles and responsibilities of the Study Director and another on the special situation of multi-site studies. Both are in the annexe to this Handbook. Specific training modules on the Study Director and the multi-site situation are included in the WHO/TDR GLP Training Manuals.)

Facilities: Buildings and Equipment

BUILDINGS: GENERAL PRINCIPLES

Test facilities should be of suitable size, construction and location to meet the requirements of the study and to minimise disturbances that could interfere with the study. They should be designed to provide an adequate degree of separation of the diverse elements of the study.

The purpose of these requirements is to ensure that the study is not compromised because of inadequate facilities. It is important to remember that fulfilling the requirements of the study does not necessarily mean providing “state of the art” constructions,

but carefully considering whether the objectives of the study can be achieved using the facilities available.

Separation ensures that disturbances are minimised and that different activities do not interfere with one another or adversely affect the study. This can be achieved by:

- Physical Separation; e.g. walls, doors, filters or separate cabinets or isolators. In new buildings, or those recently renovated, separation will be part of the design.
- Organisational Separation; e.g. carrying out different activities in the same area but at different times, allowing for cleaning and preparation between operations, maintaining separation of staff, or by establishing defined work areas within a laboratory.

  As an illustration of the principles involved we shall consider:
- Pharmacy and Dose Mixing 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 zone dealing with test item work flow: receipt, storage, dispensing, weighing, mixing, dispatch to the animal house and waste disposal.

Size

The area 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 one another'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. To reduce the chance of mix-up of materials or of cross-contamination, there should also be a degree of physical separation between the workstations

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

Construction

The zone must be built of materials that allow easy cleaning and that are not likely to allow test materials to accumulate and contaminate one another. 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 mix 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 dose formulations.
- Cleaning equipment.
- Offices and refreshment rooms.
- Changing rooms.

ANIMAL FACILITY

The facility should be designed and operated in order to minimise the effects of environmental variables on the animal. Consideration should also be given to measures which prevent the animal from 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. 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 well designed animal house would maintain separation by providing areas for:

- Different species.
- Different 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 enough space for animals and studies to be separated and to allow the operators to work efficiently.

The environment and control system should maintain the temperature, humidity and airflow at the defined levels depending on the species concerned.

The surfaces of walls, doors, floors and ceilings should be constructed to allow for easy and complete cleaning, and there should be no gaps or ledges where dirt and dust can build up, or where water will collect, for instance on uneven floors.

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

- Minimising the number of staff allowed to enter the building.
- Restricting entry into animal rooms.
- Organising work flow so that clean and dirty material are moved around the facility at different times of day (if the construction of the facility does not permit other solutions) and so that corridors are cleaned between these times.
- Requiring staff to put on different clothing in different zones within the facility.
- Ensuring that rooms are cleaned and sanitised regularly, particularly between studies.

EQUIPMENT

For the proper conduct of the study, appropriate equipment of adequate capacity must be available. All equipment should be suitable for its intended use, and it should be properly calibrated and maintained to ensure reliable and accurate performance. Records of repairs and routine maintenance and of any non-routine work should be retained. Remember that the purpose of these GLP requirements is to ensure the reliability of data generated and to ensure that data are not invalidated or lost as a result of inaccurate, inadequate or faulty equipment.

Suitability

Suitability can only be assessed by considering the tasks that the equipment is expected to perform: there is no need to have a balance capable of weighing to decimals of a milligram to obtain the weekly weight of a rat, but a balance of this precision may well be required in the analytical laboratory. Deciding on the suitability of equipment is a scientific responsibility and is usually defined in SOPs.

Calibration

All equipment, 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 work to fixed specifications. Proof that specifications are being met 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 analytical equipment a sample of known concentration will be used to ensure that the equipment is functioning as expected, as well as providing a basis for the calculation of the final result. Other equipment, such as air conditioning systems for animal facilities or constant temperature storage rooms, will be checked periodically by the use of calibrated instruments (probes, thermometers…). Verifications should be performed at a frequency that allows action to be taken in time to prevent any adverse effect on the study should it be discovered that the equipment is not operating within specifications.

Maintenance

The requirement that equipment be properly maintained is based on the assertion that this ensures the constant performance of equipment to specifications and that it reduces the likelihood of an unexpected breakdown and consequent loss of data.

Maintenance may be carried out in two quite distinct ways:

- Preventive maintenance; when parts are changed regularly based upon the expected life of the part concerned. Planned maintenance of this type may be a useful precaution for large items of equipment or items that do not possess suitable backup or alternatives. Regular preventive maintenance therefore reduces the risk of breakdown.
- Curative maintenance; when repairs are made in the case of a fault being detected. This approach particularly applies to equipment such as modern computer driven analysers or electronic balances that do not easily lend themselves to preventive maintenance. It is good practice to adopt contingency plans in case of failure; these may include having equipment duplicated or assuring that there is immediate access to a maintenance technician or 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. For example, a laboratory carrying out animal studies may, as a minimum, need a stand-by generator capable of maintaining the animal room environment, even if it does not allow the laboratory to function completely as normal; for example test item analysis could wait until power is restored.

Early warning that equipment is malfunctioning is important; hence the checking interval should be assigned to assure this. Alarms are very valuable, particularly if a problem occurs at a time when staff are not present in the laboratory.

DOCUMENTATION

Routine maintenance should be documented in such a way that users of equipment can be assured that it is reliable and not outside its service interval. A label attached to equipment or the 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 equipment used was adequate for the task and 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, for example when parameters exceeded acceptable limits staff were aware of this and took appropriate remedial action.

CHARACTERISATION

The Test Item

The identity, activity, stability and bioavailability of the test item are central to the validity of the study. To validate the study you must be able to show that the test system (often an animal) has received the correct amount of test item (often a chemical formulation). This is assured by proper control of the test item at all stages of its use, and by the accompanying records and documents.

TEST ITEM CONTROL BEFORE FORMULATION

Receipt

The test item is supplied by the manufacturer/study sponsor. The supplier may be a department within the same test facility or a separate organisation 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 test item receipt, storage and control. Staff must be designated to be responsible for receipt and handling of the test item. In a large laboratory the designated staff comprise a central group who record the receipt, identity, issue, retention and final disposal of the test item, but in small facilities the designated person may be an authorised technician or the Study Director. The assignment of responsibility should be documented in an SOP or other document.

The responsible person should be informed in advance about the arrival of test item to ensure correct handling and storage conditions. In the case of a study conducted by a Contract Research Organisation (CRO), the sponsor should provide test item information

to enable safe handling and storage as well as other details which may help in the preparation of the dose formulation. A standard form for the sponsor to record this information is helpful.

The sponsor will either supply, or indicate that he has obtained or will obtain, the necessary data on chemical characterisation 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. Packaging of the test item is very important. The sponsor should keep in mind the method of transport and the duration of the journey. This is particularly true when the material is packed in fragile containers, such as glass bottles, or needs to be transported long distances using public transport under special conditions, e.g. kept frozen. Consideration should always be given to the unexpected such as airport delays, strikes or bad weather.

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

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

Each container should be clearly labelled with sufficient information for identification, enabling the test 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.

The testing facility should have a procedure for handling and recording receipt of test item. It is most important that the substance is logged in immediately to ensure complete traceability and to demonstrate that it has not been held under conditions which might

compromise its chemical activity. The receipt procedure should include handling instructions if the designated person is absent or if the container is damaged upon receipt. The Study Director should be informed of the arrival of the test item.

Test facility's documentation about the arrival of test item normally includes the following information:

- Test item name.
- Batch number(s).
- Description of the test item on arrival at the laboratory; which should be compared to 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 environmental conditions. Only designated staff should have access to the material. The stores should be kept locked when not in use. Separate areas should be available for storage at different temperatures such as at ambient temperature, at +4°C and at -20° C.

The storage of test items is arranged to minimise the risk of any cross contamination between items and containers. Where possible, the primary containers are housed within an outer container (secondary packaging) 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 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 sample will be retained by the test facility in the test item archive for at least the same duration as the study raw data and specimens. Normally this sample will not be used unless required for confirmatory analysis.

Test Item Use

Recording each use of the test item allows a running check to be established. Not only does this provide complete traceability of the quantity of 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 weighing these are also recorded).
- Gross weight after use. The container and contents are weighed after use.
- Weight of test item 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; an explanation of any differences in expected values, e.g. spillage.
- Stock remaining; a running total of the quantity of material remaining in the container which provides a warning to order additional material when needed.

Disposal

At the end of a study, surplus amounts of test item should be disposed of in an environmentally acceptable way. This final event must also be documented so that it is possible to account for the totality of test item consumed.

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, therefore, necessary.

Initial preparation and planning

Before the study begins, a number of factors must be taken into consideration so that instructions can be communicated to staff by the Study Director.

- Dose levels, number of animals and dose volume. This information in the protocol enables the Study Director to calculate how much test item is required for the whole study. As part of this consideration he/she also checks on the purity of the test item. In most studies the test item is assumed to be 100% active ingredient, but if significantly less than this it will be necessary to adjust the amounts to be weighed out (and to investigate the impact of impurities on the validity of the study).
- Concentration of the dose, amount or volume required. The volume required will vary throughout the study with the animals' weights; the Study Director will keep this under review.
- SOPs must exist for each procedure in the preparation of the formulation, its analysis, the operation of all equipment and the way in which data will be collected.
- The method of preparation of the dose form should be tested prior to study start. This entails a trial preparation, usually of at least the highest dose level, to confirm that the various procedures detailed in the SOPs produce an acceptable formulation 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 in the vehicle used must also be assessed.
  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. In this situation the importance of recording clearly what is planned and what is actually done cannot be overemphasised. But even when the Study Director carries out the whole process, the formulation recipe and the records relating to the preparations are important elements of the study records.

Before the container of test item is opened the persons carrying out the procedure should ensured that:

- There is a dedicated workstation of adequate size for the formulation procedure.
- The preparation bench 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 minimises the possibility of mix-ups or cross-contamination.

The identity of the test item obtained from the store is checked against the protocol instructions and/or requisition form, and the correct amount is weighed out as per instructions.

The control or vehicle mixes are usually made up first. Then the test item is mixed with the vehicle exactly following, without deviation, the method determined during the trial preparation. 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 some of this stock concentration to obtain the lower dose levels.

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

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

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 / sex (if relevant).
- Weight of container and contents.
- Date formulated.
- Storage conditions.

It may be useful to colour-code the label for each dose using the same colours as for 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 the concentration, stability and homogeneity of the test item/vehicle mixtures are 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 avoid waste of

time and resources and useless dosing of test systems if a dose form is subsequently shown to be unsuitable for the experiment.

As indicated above, the measurement of stability and homogeneity of the test item/vehicle formulation is best 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 to stand 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 (or periods of it), 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 formulations are made up fresh each time. It is good practice if 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 not only provides information on the concentration dosed to the animals but also gives further confirmation of homogeneity and stability of the test article in real time 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 the dosing procedure is to deliver the required amount of test formulation to the required animal accurately and consistently. Therefore, the procedure adopted must be very conscientiously carried out and the records should be capable of confirming that all the animals were dosed with the correct volume and concentration.

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

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

On arrival in the animal area the identity of the dose formulations should be checked. Checks should also be made to ensure that the amount delivered is the same as the amount issued from the formulation department and the same as the amount requested by the Study Director. 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.

Dosing should proceed in a fixed order to minimise 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:

- Animals are dosed group by group, usually working in order of ascending dose levels.
- Only one dose container is open at any time and for each dose level there is a separate, dedicated catheter and syringe.
- All cages from one group should be identified before the group is dosed, using the group number and label colour code as a confirmatory check.
- The container, catheter and syringe used for one group are removed from the dosing station before a new group is dosed.
- The outside of the catheter is wiped off with a clean tissue before each animal is dosed. This reduces the possibility of test material being drawn into the lungs.
- Only one cage of animals is open at a time. If the study animals are individually housed, each is immediately returned to its cage following dosing before proceeding to open the next cage and dose the next animal. If group-housed, animals should be placed in a second container until all animals from the cage have been dosed and then returned to their original cage.
- At the time of dosing, each animal is positively identified (e.g. from its tattoo), not merely by the cage number.

The dose volume is calculated relative to body weight. It is good practice to prepare a list giving the required volume for each weight to avoid the risk of calculation error during the dosing operation.

Records should identify:

- The staff involved in dosing.
- The dose given to each animal.

- The date and time of dosing.
- The weight of each dose level container before and after dosing. This allows you to compare, approximately, the amount actually used with the amount theoretically needed. This verification is a means of detecting gross dosing errors.

Test System

INTRODUCTION

Often test systems are animals, but they can also be plants, bacteria, organs, cells or even analytical equipment. The GLP definition of a test system is therefore very broad. In general, a test system is any system exposed to a test item during a safety study. This section of the Handbook describes the situation when the test systems are animals.

Housing conditions and the way animals are treated must satisfy the scientific needs of the study and accommodate national animal welfare legislation. The WHO/TDR training course has not been designed to cover these issues specifically, but reference is made to husbandry since this impacts upon the laboratory and its procedures.

FACILITIES

For each study, the Study Director and/or the animal care manager must ensure that personnel, procedures, facilities and equipment are in place to fulfil the needs of the study. In particular, it is important to purchase 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; intended therapeutic use in man.
- Study and project objectives.
- Availability of historical background data and past experience.

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

SUPPLIERS, ORDERING, TRANSPORT AND RECEIPT

In comparison with the total cost of non-clinical testing, the amount spent on test system purchase is negligible. We should, therefore, always insist on the best quality available. No

amount or effort spent on facilities, environmental control and equipment can compensate for the impact of poor quality animals on a study.

The quality of the animal, feed and bedding is of paramount importance for studies. It is good practice to assess these factors by auditing the processes of the suppliers. Usually the QA group and the person responsible for animal care will undertake this. Purchasers should make sure that they get what they pay for and that no variables (e.g. pesticide contamination, colony renewal, sickness, veterinary treatments, transport problems, etc.) are compromising quality. Ideally, the test facility and the suppliers should consider each other as "partners in research". The suppliers should be experts in their field. They usually appreciate constructive comment, will volunteer useful information, and can make valuable suggestions to improve study quality in relation to their product. A documented dialogue should be established and maintained with principal suppliers. The different suppliers should provide certificates of animal health, freedom from parasites, nutritional food quality, contaminants in bedding etc.

Animal order forms, transport certificates and suppliers' invoices are part of the raw data. On arrival the animals will be inspected per SOP, i.e. they are counted, sexed, and evaluated for general health and transport-induced stress. Paperwork (including a check to verify that animals comply with age and weight specifications as defined in the protocol) should then be completed and placed in the study 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.

ACCLIMATISATION

For most studies the SOPs and the protocol require the animals to undergo a period of acclimatisation during which their health status is evaluated and unsuitable individuals are eliminated. The length of this acclimatisation period depends upon the species, the supplier and the type of study.

Records of room preparation, animal receipt, husbandry, environmental conditions and 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 and may attain permanent status afterwards; this should be done as described in the protocol or SOP. The Animal Management Department should use the consecutive temporary numbers to

ensure animal accountability. Permanent cage-cards will often use a standard internal colour code (the same as for dose formulations etc.). Animal numbers should be unique within the study; they should appear on all data and specimens pertaining to the animal throughout all phases of the study. When animals are assigned to groups, each individual must be identified to prevent mix-ups. Subsequently, each time an animal is removed from its cage SOPs should require an identity check of the animal. In many laboratories the individual animal identification (for example the tattooed tail) is even included in the wet tissue jar at the end of the study (after histological processing) and is archived with the wet tissues. This is done to foster complete traceability.

ASSIGNMENT TO GROUPS

Animals must be assigned to groups before the dosing period starts. If animals are randomised, a copy of the statistical or random tables should be included in the raw data as should the table listing the temporary and permanent animal numbers. Rack and cage locations should be recorded from this point onwards. Special attention must be given to full recording any disqualification of animals during the acclimatisation period. These data may indicate systematic problems with the supplier or the animal type. Alarming or unexpected findings concerning the animal should be brought to the supplier's notice. 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 recorded in the animal room logbook, or other appropriate system. Any relevant observations made at this time (e.g. empty feeder, blood in litter, etc.) should be documented and the Study Director notified as necessary.

Control and monitoring of environmental variables

Fundamental to our concern over animal care and the scientific impact of variables is the requirement in the GLP Principles that the study report must 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 processes defined in SOPs and, of course, the training of scientific, technical and quality assurance staff. The diversity of factors that may interfere with a study is so vast that only major variables can be covered here. There is, however, substantial and helpful literature available on this subject.

Once SOPs are defined and approved for each experimental situation (length and type of study, species…), data are collected and evaluated regularly by the professional staff. Excursions from the defined norm or unexpected events are documented and evaluated for corrective action, for any possible effect on the study and subsequent consideration in the final report.

In general, each variable is evaluated regarding:

Source

Examples: Variations in temperature or humidity are often related to the Heating ventilation and Air Condition (HVAC) systems 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

Examples: Barrier procedures against incoming microbiological contamination are more important for lifetime studies than for acute studies. Bedding/litter characteristics and noise can be critical for teratology or blood pressure studies less so for other types. Light-timer failure can be more critical for albino strains than for others. Water quality concerns can be much greater with automatic watering systems than with bottles.

We can see that much of our risk evaluation is study, species or project specific; for example, feed characteristics (particle size) can affect diet-admix quality, basal dietary Vitamin A level may be critical in retinoid testing but not for other families of test molecules. Likewise, bedding variations can affect studies in many different ways because of the physical and chemical characteristics of litter.

Monitoring

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

Control

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

Both systematic and fortuitous detection of abnormal situations are recorded in the data and their impact on the experimental results is evaluated by the Study Director. 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 deviations from the norm would then trigger review of animal care and environmental control data and procedures.

RULES FOR PERFORMING STUDIES

General Points

The laboratory should have prescriptive documents to direct the conduct of the scientific studies. The purpose of these is to:

- State general policies, decisions and principles applied at the institution.
- Instruct staff about how to carry out operations within the study.
- Provide retrospective documentation of what was planned.

The document types fall into three main categories: Policy statements, Standard Operating Procedures describing routine laboratory activities, and Study Plans or Protocols, which detail how the work will be organised for each study. GLP attaches particular importance to study plans and SOPs; these are discussed below.

The Study Plan or Protocol

The Protocol is a pivotal document used by the Study Director to communicate his/her planned study organisation to study staff and also to third parties such as the QAU or the sponsor. If the study is conducted by a Contract Research Organisation (CRO), the protocol may also function as the basis for the contract between the sponsor and CRO. The protocol describes the design of the study, contains an overall time schedule of the study and its various stages, and indicates the methods and materials that will be employed during the study.

It is most important to remember that the protocol is the principal means of instruction to study staff about how the study should be performed; the contents, style and layout must suit that purpose.

CONTENT OF THE PROTOCOL

The content of the protocol must be coherent with the scientific requirements of the study and must also comply with GLP.

Identification

Identification by a study number provides a means of uniquely identifying all laboratory records which are connected to the study and of confirming the identity of all data generated during the conduct of the study. There are no set rules for the numbering system used.

Title and statement of purpose

The title of the study should be both informative and short. It should include, as a minimum, the name of the test item, the type of study, its duration and the test system. It is particularly important to define why a study is being done. The purpose of the study must be determined in advance. Stating this purpose in the protocol ensures that the results of the study cannot unknowingly be utilised for an unsuitable end. The purpose of the study may be based on both scientific and regulatory considerations.

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 characterisation 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 providing information on the vehicle.

Names and addresses of the sponsor, the test facility and test site(s)

The sponsor and the test facility may or may not be the same organisation. The protocol should indicate the location where the study is to be carried out and also the address of any contract organisations or consultants you plan to use. In the case of multi-site studies, all sites where work is to be performed must be identified in the study plan.

Name of study director and other responsible personnel

The name of the Study Director must appear in the protocol. It is also a requirement to identify any other responsible scientists who are going to contribute significantly to the study. As a rule of thumb, most laboratories include the names of scientists who will be responsible for the interpretation of the data generated under their responsibility (e.g. pathologists, clinical pathologists). For contracted studies it is usual to include the name of the monitor or sponsor contact person. If the study is a multi-site study, the protocol

must cite the name of the Principal Investigator at the test site; this is the person responsible for the conduct of the phase of the study at that test site.

Proposed dates

The proposed dates for the study are the expected start and finish dates (corresponding to the date when the protocol is signed and the date when the report will be signed by the Study Director). In addition it is a requirement to provide the experimental dates corresponding to the dates when the first and last experimental data will be collected.

To help study personnel to perform their work, the protocol may include a more detailed schedule, but this may be produced in a separate document.

Planned 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 management.

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 scientific test guidelines. However, it is still important that the protocol contains a reason why the test system has been chosen for the study. 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 experiments using animals, the test system description will usually 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 (e.g. temperature and humidity limits), type of cage, diet and its source, etc.

Experimental design

Design will cover the following points:

- Dosing details:
- Dose levels.
- Dosing route.
- Frequency of dosing.
- Vehicles used.
- Method of preparation of the dose concentrations.
- Storage conditions of the formulation.

- Quality control.
- Animal assignment to groups or randomisation.
- Parameters to be examined and measured:

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

N.B. Analytical methods are not usually included in detail in most protocols but will be available as SOPs or Methods documents which are held in the analytical laboratory together with the study data.

- Statistical methods.
- Data to be retained after the study.
- Quality Assurance: Frequently the protocol outlines the proposed QA programme but this is not mandatory.

PROTOCOL APPROVAL

A GLP study must not be started before the protocol is approved. This is done by dated signature of the Study Director. It is good practice to review the draft protocol before the study starts in order to assess its compliance with the GLP requirements; this review is done by the QAU. It is also good practice (and incidentally mandatory in some countries) that the Sponsor agrees 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. QA should receive a copy of the final, approved, study plan in order to allow them to plan their audit/inspections.

If you do not allow sufficient time between finalising the protocol and starting the study serious problems may well occur later in the study.

Allow sufficient time 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.
- Programme a study initiation meeting.

Only then should any study work start.

Many laboratories refuse to proceed with certain critical steps of the study, such as ordering animals, until a signed, approved protocol is available.

ISSUING THE PROTOCOL

All staff involved in the study should have easy access to a copy of the protocol. In order to ensure that everybody who should have a copy actually gets one, a distribution list is usually drawn up. It is often worthwhile asking each recipient to sign a document when they get their copy. It is good practice to hold a meeting with staff before the study starts to ensure that everybody is cognisant 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 – "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 and any modifications made using an agreed process, usually referred to as a Change Control Procedure.

A protocol amendment must be issued to document a prospective change in the study design or conduct. If a change in a procedure needs to be urgently instituted before a formal protocol amendment can be generated, this must be recorded and a protocol amendment is issued as soon as possible afterwards.

It is not acceptable practice to use the amendment to retrospectively authorise omissions or errors that had occurred during the study. Such unplanned, one off, occurrences should be documented in a file note as "deviations" and should reference the relevant raw data.

The important elements of a protocol amendment are that:

- The study being amended is clearly identified.
- The amendment is uniquely numbered.
- The reason for the amendment is clear and complete.
- The section of the original protocol being amended is clearly identified.
- The new instruction is clear.
- The amendment is issued to the same people as the original protocol.

In practice, there are many adequate ways of amending a protocol. For example the modified section of the protocol may be included in full in the protocol amendment. Alternatively, the amendment may only comprise a description of how the protocol section has been changed. As with the original protocol, the most important factor is that the staff who will carry out the amended procedure are instructed in the clearest way. Once again, they must have adequate notice of all modifications. It is, therefore, vital that they

all receive the amendment and are made aware of its contents; otherwise the instructions in the original protocol will still be followed.

As with the original protocol, the Study Director is the person who approves the amendment and is responsible for issuing it. He/she is also responsible for ensuring that the new instruction is rigorously respected. It is as essential to review an amendment for GLP compliance as it is to review the protocol: this is a QA function. However, because amendments are by their very nature extremely urgently required by Study staff, this review is sometimes performed retrospectively.

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

Standard Operating Procedures (SOPs)

A full set of good Standard Operating Procedures (SOPs) is a prerequisite for successful GLP compliance. Setting up the SOP system is often seen as the most important and most time-consuming compliance task.

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

Remember the following quote based on an idea from Deming & Juran:

"Use standards (here: SOPs) as the liberator that relegates the problems that have already been solved to the field of routine, and leaves the creative faculties free for the problems that are still unsolved".

The successful implementation of SOPs requires:

- Sustained and enthusiastic support from all levels of management, with commitment to establishing SOPs as an essential element in the organisation and culture of the laboratory.
- SOP-based education and training of personnel, so that the procedures are performed in the same way by everyone.
- A sound SOP management system to ensure that current SOPs are available in the right place.

SOP SYSTEM OVERVIEW

The SOP 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, monitoring and reporting,
- "scientific" administrative policies 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. The procedures should be written (or translated) into the local language of the operational personnel and expressed with an appropriate vocabulary. All personnel should be encouraged to contribute to improving SOPs. It is good practice to encourage the people who perform the procedures to write the instructions, thus promoting their sense of responsibility for the work they do.

Usability and traceability. For reasons of traceability and easy use, a two-tier system of SOPs is often the preferred approach. For example, one tier reflects general policies and procedures (e.g. protocol writing, review, approval, distribution and modification, general rules for equipment use and maintenance, archives, etc.), the second represents technical methods (e.g. methods of staining in histology, analytical methods, specific procedures for use and maintenance of equipment, etc.). It is advisable to present the SOPs in binders (SOP manuals) with an up to date table of contents, logical chapter divisions. Be selective when distributing SOPs, to avoid forming mushrooming packets 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 hand-written margin comments are not admissible. As we have seen for the protocol, you should have a change control procedure for modifying SOPs (see below).

Understanding. Staff must fully understand the SOPs they use and follow them rigorously. If deviations occur, communication with the Study Director and management should ensure respect of GLP requirements and the credibility of the system.

Responsibility. Someone 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 (often fixed at 2 years).

Change control. A formal system should be in place which enables 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 approval rapid, not involving too many signatories.

Centralised organisation. A centralised organisation is preferable for formatting, numbering, issuing, modifying and withdrawal of SOPs. This helps avoid duplication of effort, inconsistency between SOPs, delays, lack of traceability and incomplete distribution.

Availability. SOPs should be 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 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:

- Standardised, consistent procedures minimises person to person and test to test variability.
- An opportunity to optimise processes.
- Capture of technical and administrative improvements.
- Demonstration of management commitment to quality as part of the SOP approval process.
- Ease of documenting complicated techniques 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, even after a lapse of several years.
- A means of communication in case of audit, visits, technology transfer, etc.

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

- A two tier system.
- A defined format.
- Thorough review, including QAU review.
- Formal approval by at least two people:
  - a designated author,
  - an appropriate member of test facility management.
- A formal change control system, co-ordinated by a designated person/group.
- A standardised and traceable procedure for issuing/archiving/retirement of SOPs.

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

RESULTS - RAW DATA AND DATA COLLECTION

General Points

The laboratory should have descriptive documents which are records describing what actually happened during the course of the experimentation. The records are the qualitative and quantitative results of the study.

The Study Director uses the records as the basis for the scientific interpretation of the study. This interpretation, as well as an accurate representation of the data, will be incorporated into the final report of the study. The authorship of the final report is the responsibility of the Study Director.

Finally, at study completion, all the documents, both prescriptive and descriptive, are archived so that when necessary full study reconstruction will be possible through examining the archived material.

Carrying out Procedures and Recording Observations

Before any procedure is conducted in a study, 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 where the procedures will be performed.
- SOPs 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 that the equipment is in working order. The operator should ensure that such checks have been done by reference to the appropriate logbook or equipment label.

Records and Recording

Making a record is essential for complete reconstruction of the study. It is the only way of showing what actually went on at the time. Records must not only contain the data generated, but also prove that all the required procedures were correctly carried out at the correct time. If data are lost, or a complete record has not been made, the study validity may be seriously compromised.

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

The data should therefore indicate:

WHAT was done

A description of the conduct of the technique, including the results of the observation or measurement, and demonstrating that the actions required by the protocol were carried out.

HOW it was done

The data should indicate that they were collected and recorded in accordance with the methods set out in the SOPs and Protocol, or indicate where there were deviations from these instructions.

WHEN the work was performed

A demonstration of compliance with the schedule defined in the protocol. This is done by recording the date and, if necessary, the time that the procedure was conducted. For certain procedures (for example sampling in a toxicokinetic study) very exact timing is necessary and the data must demonstrate that the schedule was strictly followed.

WHO performed the work

The data should clearly identify who was responsible for carrying out the procedure and recording the data. If more than one person is involved in a procedure this should be recorded in the data, along with an identification of the responsibilities of each.

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

Identified: The study number, animal number, etc. must be recorded with the data in order to ensure that data mix-ups do not occur. The parameter evaluated 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 acquired directly by computer the raw data are considered to be the electronic medium. For data derived from equipment, the raw data may be a direct print out (or trace) or in an electronic form.
Promptly: Data must be recorded as the operation is done. It is not acceptable to make the record some time after the task has been completed.
Accurately: This is most important as the accuracy underpins the scientific interpretation and integrity of the study.
Legibly: Data that cannot be read are useless and records that are difficult to decipher raise doubts 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-print outs. Some print disappears quickly (or become totally black) as is the case with light-sensitive print-outs from thermo-printers. In this case, take an authorised (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 showing why a change was carried out, when and by whom.

Data should be recorded and organised in a way that facilitates both the making of the record and the performance of 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 required, without forgetting any. A clear structure for the study file, defined up-front, helps you to organise and archive the documents as they are produced in real-time, preventing loss and facilitating reference between records.

The Use of Computerised Systems

Most laboratories rely heavily on computerised systems for the performance of their studies. Computers are used not only for the collection of data but also for planning and

other organisational purposes. The use of computerised systems has undoubtedly increased the efficiency of study performance and the reliability of data. However, under GLP it is important to demonstrate that such systems are performing correctly, precluding, for instance, the risk of data loss or corruption. This demonstration is called validation and the OECD has recognised the importance of this work by the publication of a specific guideline on this subject (The Application of The Principles of GLP to Computerised Systems) appended to this Handbook and discussed in the training manuals.

The Study Report

The report of the study, approved by the Study Director, contains an account of the practical conduct of the study, any deviations from the intended course of action, tabulated results, a presentation of the significant features and results of the experiment, a critical discussion and a conclusion.

When the report relates a multi-site study, the Principal Investigator's contribution about the phase concerned may be appended to the report or incorporated into the body of the report. In either case, the Study Director takes responsibility for the entire report, including the scientific interpretation and the GLP compliance of the work.

There are also specific elements required by GLP which must be in the study report:

- Name and address of test facility.
- Dates of start and finish of experimental work.
- Name of Study Director.
- Study objectives.
- Details of test item(s) and vehicle(s).
- Description of test system.
- Details of dosing, route and duration.
- Results.
- Statistics.
- Discussion.
- References.
- GLP Compliance Statement from Study Director.
- QA statement of Inspections/Audits
- Signed/dated reports from responsible scientists.

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

results. Finally, the Study Director must indicate in a GLP compliance statement whether or not the study was conducted in compliance with GLP.

"The report should fully and accurately reflect the raw data..."

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

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

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

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

After the report has been drafted it will pass through a review stage and a QA audit. During this, modifications may be made to the report, but it is important to remember that any alterations made must be agreed and accepted by the Study Director. The process of review and approval is designed to ensure that the report, when finalised, is unlikely to require modification: after finalisation this can only be achieved by writing a formal amendment, approved and signed by the Study Director, which identifies the changes made with a reason for each.

Archives and Archiving

During the study, the Study Director must ensure safe storage of data as they are derived. At the end of every study, all data pertaining to the study should be collected together with the study plan and final report and combined into a single package of information – the study file. The study file should then be formally archived in order to guarantee the integrity of the data and the study.

The archiving process is considered to be of such importance that GLP requires the test facility management to formally designate an archivist; this named person should be included in the organisational chart and have appropriate qualifications and training.

When multi-site studies are performed, a decision has to be taken concerning the location(s) where data from the geographically separate test sites will be archived. There are no set rules about this, though most facilities like to centralise the data at a single site. However, the place(s) where the archives are located must be given in the final study report and it should also be defined ahead of time in the study plan.

Function

Modern Archives have functions hat go beyond simple storage; they provide:

- A centralised, secure repository for the storage and retrieval of original scientific data, master documents and reports.
- A means of controlling and documenting distribution and modifications of holdings for reasons of both accuracy and confidentiality.
- An efficient organisational tool for preparing project summary documentation (DMF, IND, CTC, NDA, investigator brochures, etc.) made possible by a formal filing system and cross-indexation.
- A unique repository for all project related work facilitating the quick and complete retrieval needed for historical reconstruction in case of scientific or product related reasons or internal or external audit.

"WHAT" is archived?

- All study data, both raw data and derived data.
- Supporting data (e.g. records of environmental conditions, maintenance records, training records…).
- Study plan and amendments.
- Study report and amendments.
- Specimens and samples.
- QA files.

For most studies, the core "study file" is described in the protocol. It is important that study files be pre-collated before submission in envelopes, boxes or in loose leaf or bound form. Specimens and samples are inventoried, labelled and packaged according to standard operating procedures. Supporting data (personnel files, animal transport and arrival, Heating ventilation and Air Condition (HVAC) maintenance) and associated Quality assurance material are submitted periodically and are filed separately from the study file. Notebooks usually have mandatory tables of contents which are used for cross-indexation. The location of any required study related item not present (i.e. not yet ready or lost) at the time of submission is documented. Scientific departments must also respect defined security rules (no raw data allowed out of lab, all study material together in a secure place…) for the period during the study and before archiving.

"WHEN" are archives submitted and by "WHOM" ?

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

Term of storage

The retention period is stated in national GLP regulations. Often, however, because reports are submitted to several authorities at different times or may be needed for other purposes, the period of retention may exceed these. Each event of archive destruction must, therefore, be treated on a case by case basis.

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

Therefore, laboratories impose strict destruction policies. When a space problem arises, very old holdings and abandoned projects belonging to chemical families holding no current interest may be destroyed upon justification and written authorisation of upper management. If a company goes out of business, product licence holders should be notified and archival responsibility transferred.

"HOW" are holdings submitted?

All records and material transferred to the Archives should be personally transported by designated persons. The originals of all documents should be submitted. All material submitted should be accompanied by a document submission form.

"HOW" are holdings stored?

Securely:

- Only authorised personnel permitted.
- Fire, pest and vandalism protection.

Under conditions which minimise deterioration:

- Air conditioned general environment.
- Copies of heat sensitive papers made.
- Refrigeration used where necessary.
- General warehousing procedures defined.
- Blocks sealed, tissues wrapped in preservative soaked gauze on heat sealed bags, slides cover slipped, etc.
- Computer backups maintained in security cabinet.

Indexing

As rapid retrieval may be necessary, it is good practice to impose a rigorous system of indexing archived material. This is often computerised and provides complete and quick retrieval starting from any one of the indexed parameters. For example, all study or lot specific materials are given a unique holding number which corresponds to a specific location. Facility specific material is filed using common-sense (i.e. chronologically, alphabetically).

Retrieval from Archives

Once an item has become an official Central Archives holding, the original should be subject to restricted access. It can be examined in situ with formal authorisation but only within the Central Archives area, and in the presence of the archivist. Photocopies may be provided upon request.

Removal of original holdings from the Central Archive will be allowed only under exceptional circumstances when justified and authorised in writing by upper management. The history of each holding must be documented.

QUALITY ASSURANCE UNIT

GLP defines the minimum quality assurance requirements necessary to ensure the integrity of the study and thus the validity of experimental results. The Quality Assurance Unit (referred to as the QAU, or, more often, simply as Quality Assurance QA) is part of this quality assurance process. QA's mandated role is that of an independent witness to the whole preclinical research process and its organisation. In particular, QA assures management that studies are performed in compliance with GLP.

The role of QA as facilitator and consultant during the establishment of quality systems is understood, at least implicitly, in most laboratories. However, with respect to the GLP regulations the role of the QAU is that of an independent control service.

In this capacity, QA must review all phases of non-clinical studies. This means that QA will audit/inspect the planning activities of the laboratory, the activities while studies are on-going, and the reporting and archiving activities when the live phases of the study have been completed.

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

Protocol (or Study Plan) Review

QA reviews the protocol for compliance, completeness and clarity.

At some laboratories QA signs the protocol, but this signature is not mandatory. If QA signs the study plan it should be absolutely clear, possibly by a definition in an SOP, that the signature does not constitute approval of the technical/scientific content of the protocol, but rather an indication that it has passed through a GLP review.

Often the original protocol is archived immediately after being signed by the Study Director. This ensures against loss, controls distribution of any subsequent amendments and opens the archive file. QA receives and maintains a copy of all protocols with any subsequent amendments.

QA needs the study plans, which must be provided by the Study Directors, to plan its own study monitoring and inspection activities.

SOP Review

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

Usually QA has the responsibility of reviewing SOPs; it is a recommendation of the OECD, but not mandatory in the OECD consensus document on QA and GLP. In those laboratories where QA signs the SOPs it is to indicate that the SOP is GLP compliant, complete, clear and not in conflict with other SOPs that exist at the research site: signing the SOP is not a mandatory duty of QA, indeed some authorities are opposed to this.

Planning (Master schedule; Inspection plan)

Once the protocol is signed and distributed, the study is confirmed as starting and updated on the master schedule sheet (MSS), a list of all studies at the facility. The maintenance of the MSS may be under the responsibility of QA although more frequently this is a project management role. However QA must be aware of all planned studies and must have a copy of, or direct access to, the MSS.

The inspections and audits performed by QA constitute the QA audit programme which should be described in an SOP. QA plans the inspections and audits needed to support the study, with input from the Study Director if needed. Audits and inspections are performed in compliance with the QA programme. QA maintains its own inspection and audit schedule for all the activities of the facility. The inspections/audits are entered onto a planning system in the QA department and updated when completed. There are arguments for and against performing unannounced QA inspections; usually inspections and audits are scheduled in advance with the Study Director or his/her representative.

Audits and inspections

An audit or an inspection is a methodical evaluation of a process, an activity, a set of data etc. An audit is not an inquisition or a punitive exercise. Audits provide best information when performed in co-operation with the people audited.

The OECD GLP Principles recommend that QA performs three types of audits/inspections:

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

Typically, management also requests QA to inspect contractors and suppliers.

Inspections/audits

Some general points:

- The auditor should be well prepared for the audit. Usually this means reviewing the protocol, applicable SOPs and past inspections beforehand.

- The inspector/auditor must follow all rules (such as safety, hygiene and access) which are applicable to other personnel. They must not disrupt the work in progress.
- The inspector/auditor must allow sufficient time for the inspection.
- Checklists may be used if considered necessary. Adherence to a checklist is no guarantee of completeness but it is useful for training and as a memory aide. Checklists may also enable management to approve QA methods and coverage, and provide technical staff with a means of self verification. Checklists are usually established formally and are updated as needed. However strict adherence to a checklist during an audit may engender the risk of missing unexpected findings.
- Logically, and out of consideration for study staff, at the close of the audit, or at least before a report is generated, the auditor should discuss all problems with the persons audited. Any major error (e.g. dosing error, animal ID) should, obviously, be pointed out immediately without waiting for the end of the audit.
- The findings of each audit should be written up in an audit report. This is issued to the Study Director and any other manager concerned.
- Audit comments in reports should be clear and specific. They should be constructive. It is good practice for experienced auditors to suggest solutions to problems seen during audits where this is possible.
- The audit report is also issued to facility management, usually after responses from the Study Director have been obtained.
- Rules for the writing, approval, distribution, and archiving of inspection/audit reports as well as arbitration procedures should be included in the SOPs.
- As a general rule, internal QA inspections and audits target events and organisation, not people. The more problems uncovered and resolved the better the level of quality.
- Inspections are performed as planned with additional or follow-up inspections if necessary. There are numerous useful guides available on inspection and audit techniques.

Study-based inspections/audits

Study based inspections target specific "critical" phases of the study. Determining what is critical to a study is an important part of QA work. It can seldom be done alone because it usually requires input from scientific specialists, the Study Director for example. Many QA groups use Risk Analysis techniques to assist them in identifying what the critical phases are. All the techniques used by QA should be explained in their SOPs.

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

Facility or system-based inspections/audits

These are performed independently of studies. Frequency should be justifiable in terms of efficiency vs. use of resources. The results of a facility or system-based audit are reported to the appropriate manager at 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.

facility or system-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. The frequency of process-based inspections is justified by efficiency and use of resources. 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, recognises "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-organisational processes – for example, the transfer of test samples from the animal facilities to the bio-analysis laboratory.

Final Report/Raw Data Audit

QA should audit all reports from GLP studies with reference to the protocol and its amendments, 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. QA is also looking for evidence for authenticity and GLP compliance in the data, i.e. signatures, dates, handling of corrections and deviations, consistency, etc.

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

- Contents.
- Data completeness.
- Protocol compliance.
- Animal Environment Records.
- Test item QC/Accountability.
- Dose preparation/Dosing/QC records.
- Individual tables versus Raw Data (usually on a sample basis).
- Summary tables.
  - Appendices.
  - Conclusions.

Whatever the plan used to conduct the audit, it should exist in writing and be kept as part of the audit file.

Quality Assurance Statement

The QA statement that is placed in the report provides the dates on which the study was audited/inspected and the dates the findings were reported to the Study Director and Management. As recommended by the OECD, the QA statement also includes the study phases inspected.

The QA statement is not a GLP compliance statement. The Study Director provides the statement that the study has been conducted in compliance with the applicable principles of GLP.

However, the recommendations of the OECD with regard to the QA 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 QA statement becomes a sort of "release" document and assures that:

- The study report is complete and accurately reflects the conduct and data of the study.
- The study was performed to GLP.
- That all audit findings have been satisfactorily resolved.
- That the Study Director's claim to GLP compliance is correct.

QA Inspections of Suppliers and Contractors

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

QA may also inspect contract facilities before contracting out work. This applies whether the work concerned is a whole study, or a part of a study (e.g. analytical work). QA may also be involved in the selection of GLP compliant test sites when a study is a multi-site study.

For pivotal studies, QA 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.

Quality Assurance in the Multi-Site Situation

When studies are performed at several sites, i.e. at the test facility (main site where the Study Director is normally located) and at one or more test sites (where only certain phases of the study are performed) the QA roles are organised to ensure complete coverage of the study. To perform the QA duties, a Lead QA is appointed by the Test Facility Manager (Lead QA is usually at the site where the Study Director is found). At the other site(s) a QAU will undertake the QA responsibilities for those phases of the study being conducted at the Test Site concerned.

It is important to make certain that the Study Director is well informed of all the findings relating to his/her study whether they concern the parts of the study at the Test Facility or the phases at the Test Site. It is indispensable to set up communication channels between the Study Director (at the test Facility), the Principal Investigator (at the Test Site), Lead QA and Test Site QA so that no findings go unreported and so that all phases of the study are adequately monitored. Such communication channels should be operative before the start of the study and each actor should be well aware of his/her role within the overall organisation of the study.

The Distribution and Archiving of QA Files and Reports

QA inspection reports are internal working documents and are issued to the Study Director and to management. They are particularly valuable if important findings are picked up during the study so that corrective actions may be taken.

QA audit reports are not normally made available to national monitoring authorities; under normal circumstances the inspectors will not request these during a monitoring inspection. This encourages QA to report findings honestly, without fears that the facility could be damaged by findings getting into the public arena.

It follows that QA reports are not for general distribution and should be handled with discretion. It is best to archive reports separately from the study files so that national monitoring authorities or other 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) represents a significant challenge to novice organisations. This part of the WHO/TDR Handbook has been written as 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 GLP 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, enthusiastically supported by top management and involving personnel from a variety of disciplines including research, quality assurance, maintenance, metrology, human resources, document management and archiving etc. Implementation is best organised in the form of a project, with a team of persons deriving their authority directly from upper management.

Management should set the scope of GLP implementation by giving the Project Team a clear mandate and timeframe. 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; they need to retain a measure of impartiality to facilitate conflict resolution. The Project Team members must have the explicit support of their immediate superiors, since they will need relief from some of their usual duties during the lifetime of the project. Finally, the Project Team Leader must have immediate access to all levels of management in all departments concerned.

IMPLEMENTATION AS A PROJECT

Once management has appointed a Project Team, the team should draw up a list of steps to be achieved within an agreed timeframe. It is unwise to be too ambitious when setting the overall time allotted to implement GLP as thimay disrupt the regular work of the organisation. Experience shows that allowing 24 months for implementation is reasonable. However, it is possible to do some tasks in parallel, and overlapping some of these could reduce the implementation time to 18 months. A 24-month schedule will allow staff to continue their other work, albeit at a slightly reduced pace, and yet will require that momentum be maintained.

The momentum may be maintained by setting up the main, high-level steps, for the project and identifying individual tasks within each step. Each task should be assigned to a designated responsible person and given a deadline for completion. 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 throughout the life of the project assures timely completion of each task, helps encourage harmonisation, and co-ordinate implementation.

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

Table I describes the stages and milestones for completing GLP implementation

TABLE I Project stages and milestones

No	Stage	Description
1	**Appoint GLP Implementation Project Team**	• Upper management appoints a Project Team Leader. • The Project Team Leader appoints a multidisciplinary project team, with management buy-in. • Project team leader draws up a formal document to inform personnel of the missions, objectives and dates of the project. - Project objectives include an overall time plan for completion of the project. - Calendar dates are set for the Project Team meetings.
	MILESTONE 1	Upper management holds a Project Launch meeting to explain the importance of the project and circulates a formal document to all staff.
2	**Establish Project Tasks to be achieved during the life of the project**	• Perform a Gap Analysis to evaluate the organisation's shortfall in meeting GLP compliance. An expert (internal or external to the organisation) performs this analysis based on an audit of the organisation over a 4-5 day period. - The essential steps for GLP implementation are suggested in Table 2. • The Project Team members jointly agree on the priorities and details of the tasks necessary to achieve GLP compliance. - Table 3, below, is a model of this type of table. • Based on the gap analysis, the project team draws up a detailed plan of action (The Project Task Table) to achieve implementation. - To achieve this table, the project team meetings are held more frequently than during the rest of the project life span.
	MILESTONE 2	Establishment of detailed Project Task Table. Presentation of Project Task Table to top management.
3	**Project Review meetings**	• The team reviews Project progress monthly. • The Project Task Table is updated at each meeting. • The team investigates tasks not completed on time and finds solutions.

No	Stage	Description
4	**Project progress**	• Communicate progress to all staff at regular intervals. • Communication is organised in the form of attractive wall charts, short meetings that describe progress, or articles in the institution's broadsheet or intranet pages.
	MILESTONE 3	Six monthly or annual meetings with top management of all Project Team, with management communication to all staff of the institution. This milestone would occur at one or two carefully selected strategic points in the project, for example when major activities or key documents have been implemented (protocols, final reports, change control SOP, established archives, validation of major computer systems etc.). These milestones would be agreed with management when establishing the Project Task Table.
5	**Task implementation**	• As the various tasks are completed, they are progressively implemented and become part of the routine processes of the organisation. • At some stage of the project implementation, a Quality Assurance Unit (QAU) will be appointed. When this QAU has been implemented it will be responsible for the verification of the good functioning of the processes.
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 (can be the same auditor that 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 may add this to the Study Director's Statement in the final reports.
	MILESTONE 4	Management meets all staff (equivalent to kick-off meeting) to appropriately 'celebrate' successful completion of GLP implementation

STEPWISE IMPLEMENTATION OF GLP REQUIREMENTS

Table II shows a typical GLP implementation roll-out over a 24-month period. The assumption is that the laboratory in question has no GLP systems or documentation in place at the start, as shown by gap analysis. The stepwise process is designed to tackle the implementation in a structured way so that progress is evident and steps build upon one another. The early successes in implementation of relatively simple systems (such as 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 (model shown in table III) on the basis of the steps shown below.

TABLE II Part 1 (3 months)

Step	Content	Comments
1.1	Arrange General GLP training for all staff.	Training of 1-2 days underlines the fundamental points of GLP and the importance of GLP for the organisation. Emphasis is placed on the way in which data are collected and handled.
1.2	Construct an organisational chart for the organisation.	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: • Study Directors. • Quality Assurance personnel. • Archivist.	Management drafts formal memos 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 standard formats for personnel documents. • Curricula vitae. • Job descriptions. • Training records.	Obtain management agreement for the formats.

Step	Content	Comments
1.5	Compile the personnel documents for all staff using the formats agreed upon in 1.4 above.	Ensure that the persons concerned sign their 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 organisational charts and personnel documents.	
1.7	Decide who will be responsible for the management of the organisation's SOP system Define the system in an SOP. All the new SOPs will be managed through the defined system.	In small organisations the management of SOPs may be the responsibility of the QA group. It is a not a trivial task; it demands time, resources, careful planning and follow-up. The definition should cover the way in which SOPs are identified, written, approved by signature, reviewed, revised, archived, issued and withdrawn.
1.8	Establish archives. Write an SOP for the archiving process.	Ensure that access to archives is restricted to as few people as 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 an SOP for content, layout and format of protocols. Prepare template protocols.	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 organisation.

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 the type concerned. Review problems revealed by the use of the template. 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 of reports, or prepare template reports for the types of studies performed by the organisation.	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 organisation.
2.6	Write an SOP on the workflow (writing, review, approval, amendment, distribution and archiving) of reports.	Do not forget to include QA review in the circuit of report production.

TABLE II Part 3 (6 months)

Step	Content	Comments
3.1	Agrees on a system between all interested parties regarding the identification of the equipment and instruments. • Write an SOP explaining the system used for the identification of equipment and instruments.	The identification numbers will be used later when acquiring raw data and to ensure traceability to operations such as calibration and maintenance.
3.2	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. • Etc.	The list should include balances, pH meters, HPLC system components, and all measuring instruments that will require maintenance and/or calibration. Ensure that each piece of equipment is uniquely identified It is not sensible to list consumable items such as glassware, or basic equipment such as cages, desks
3.3	Physically identify (label) all listed equipment/instruments according to the system.	
3.4	Write an SOP on the equipment logbook (life-cycle approach), its importance and use.	
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, anomalies and corrective actions etc. Once each logbook is established, management must insist on its use.

Step	Content	Comments
3.6	Decide the method of maintenance and metrology for each piece of equipment (creation of maintenance and metrology unit or maintenance responsibilities stay with operational units etc.) Define in SOPs the maintenance schedule for all listed equipment.	The way in which you organise maintenance for the laboratory's equipment will depend upon the amount of the GLP activity and the size of the equipment park. Only large organisations will need to establish separate maintenance units. However, even if maintenance is managed by each local unit, it is a good idea to appoint a person responsible for maintenance.
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 non-clinical studies, it is usual to qualify the Heating Ventilation Air Condition (HVAC) systems in animal rooms. Equally, in microbiology laboratories, the laminar flow systems may also need qualifying. Other installations may require qualification.
3.8	Qualify the systems chosen for qualification.	Specialised contractors can be used to qualify systems, but in small units it is practical and cost effective to do this oneself.
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.	Qualification work needs a formal qualification protocol and a formal report after completion. It is time and resource consuming If there are many systems requiring qualification, or if the systems are complex, it is not reasonable to expect the qualification to be completed in the 6-month period of this stage; it will take much longer.

TABLE II Part 4 (2 months)

Step	Content	Comments
4.1	Establish a Quality Assurance Unit	In small organisations this unit may only consist of one person. Upper management should issue a formal memo to define the roles and responsibilities of QA and the reporting line. This is well explained in the OECD Principles of GLP and in the OECD Consensus document on QA &GLP.
4.2	Train the QAU personnel audit/ inspection techniques.	External training programmes exist in these techniques. 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 3 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 characterised. 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 shelf life of reagents and reference items. Write SOPs for the labelling of all test items, solutions and 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.
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 the way in which the preparation is documented, the tests necessary (e.g. homogeneity tests, stability tests or others) 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 characterisation 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. Define the rules for the acquisition, modification and approval of raw data.	Some raw data will be hand written. Define the way to record these data; for example in laboratory notebooks or on pre-established forms. Some will be printed from equipment (e.g. balance printouts). Some raw data will be directly acquired through computerised systems. Such systems will require validation. The method for signing and storing such data must be established. The organisation should have a single rule on how corrections to data are made (signed, dated etc.) justified and authorised. 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. Define the QC steps conducted on data and reports prior to requesting QA audit. Write SOPs on this verification and QC work.	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% data audits of all data supplied to them. 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 organisation.	
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 computerised systems to help you.

Step	Content	Comments
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 worth seeking external help in the validation process. It is helpful to appoint a Validation Team to be responsible for the validation for each system selected. QA and IT personnel may assist in writing the protocol, but the responsibility lies with the system owner. 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 (e.g. by password) is adequate.
7.4	Conduct the validation testing following the validation protocols.	Remember that final responsibility lies with the user who should ensure that systems that he/she uses are validated. Hence, the user should perform the bulk of the validation protocol.
7.5	Write formal validation reports for the validated systems.	These should be signed off by the person(s) responsible for the systems 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	Write SOPs for the use and maintenance of the computerised systems.	
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.	Specialised contractors can be used to qualify systems, but in small units it is practical and cost effective to do this oneself.

Step	Content	Comments
7.9	Define the organisational rules for access rights and passwords and write SOP for this process.	It is usual to have a centrally organised unit (normally within the IT department) responsible for establishing and issuing 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 SOPs.	The newly established QA group will be able to assist in establishing the list of SOPs that 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 organisation. Decide who should manage this schedule, and complete an SOP regarding its management and maintenance.	
8.4	Perform a second gap analysis to determine any remaining shortfall in GLP compliance. Draw up an action plan to address these issues.	The gap analysis 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 (such as those above) to bring the organisation to the level of GLP compliance. It is subsequently used as the basis for follow-up during project team meetings. The extract below is an illustrative (and obviously very incomplete) 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				
– Analytical laboratory	Mr B	Mr E	02	C
– Clinical Pathology laboratory	Mr C	Mr F	02	C
– Histology laboratory	Mr L	Ms G	03	
Set up Calibration records / logbooks	Ms T	Ms Z	03	C
Production of standard logbook format	Ms U	Mr G	03	C
– Resistivity meter	Ms V	Ms Y	03	C
– Balances	Ms W	Mr B	07	A
– pH meters	Ms X	Mr F	08	A
– Manometers	Ms Y	Ms U	03	C
– Thermometers	Mr L	Ms G	04	C
– Micropipettes	Ms F	Mr H	04	A
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 the tasks are completed the status is revised. A spreadsheet is an appropriate medium to use for this table.

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 is responsible for maintaining the table. The table is always presented at the regular project team meetings.

For a laboratory that has never implemented a quality management system, the project task table is likely to run to 20-25 pages.

ANNEXES

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE MONITORING

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

OLIS : 21-Jan- 1998
Dist.: 26-Jan- 1998

Or. Eng.

ENVIRONMENT DIRECTORATE
CHEMICALS GROUP AND MANAGEMENT COMMITTEE

ENV/MC/CHEM(98)17
Unclassified

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

OECD Principles on Good Laboratory Practice (as revised in 1997)

61011

Or. Eng.

OECD Environmental Health and Safety Publications

Series on Principles of Good Laboratory Practice
and Compliance Monitoring

No. 1

OECD Principles of Good Laboratory Practice

(as revised in 1997)

Environment Directorate

Organisation for Economic Co-operation and Development

Paris 1998

Also published in the Series on Principles of Good Laboratory Practice and Compliance Monitoring

No. 2, Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice (1995)

No. 3, Revised Guidance for the Conduct of Laboratory Inspections and Study Audits (1995)

No. 4, Quality Assurance and GLP (1992)

No. 5, Compliance of Laboratory Suppliers with GLP Principles (1992)

No. 6, The Application of the GLP Principles to Field Studies (1992)

No. 7, The Application of the GLP Principles to Short-term Studies (1993)

No. 8, The Role and Responsibilities of the Study Director in GLP Studies (1993)

No. 9, Guidance for the Preparation of GLP Inspection Reports (1995)

No. 10, The Application of the Principles of GLP to Computerised Systems (1995)

No. 11, The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP

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 co¬ordination 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/)

or contact:

OECD Environment Directorate,
Environmental Health and Safety Division

2 rue André-Pascal
75775 Paris Cedex 16
France

Fax: (33-1) 45 24 16 75

E-mail: ehscont@oecd.org

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

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

in 1996, was led by Germany and comprised experts from Australia, Austria, Belgium, Canada, the Czech 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

CONTENTS

PART ONE: THE OECD PRINCIPLES OF GLP

SECTION I INTRODUCTION 87

Preface 87

1. Scope 87

2. Definitions of Terms 88

2.1 *Good Laboratory Practice* 88
2.2 *Terms Concerning the Organisation of a Test Facility* 88
2.3 *Terms Concerning the Non-Clinical Health and Environmental Safety Study* 89
2.4 *Terms Concerning the Test Item* 90

SECTION II GOOD LABORATORY PRACTICE PRINCIPLES 91

1. Test Facility Organisation and Personnel 91

1.1 *Test Facility Management's Responsibilities* 91
1.2 *Study Director's Responsibilities* 92
1.3 *Principal Investigator's Responsibilities* 93
1.4 *Study Personnel's Responsibilities* 93

2. Quality Assurance Programme 94

2.1 *General* 94
2.2 *Responsibilities of the Quality Assurance Personnel* 94

3. Facilities 95

3.1 *General* 95
3.2 *Test System Facilities* 95
3.3 *Facilities for Handling Test and Reference Items* 95
3.4 *Archive Facilities* 96
3.5 *Waste Disposal* 96

4. Apparatus, Material, and Reagents 96

5. Test Systems 96

5.1 *Physical/Chemical* 96
5.2 *Biological* 96

6. Test and Reference Items 97

6.1 *Receipt, Handling, Sampling and Storage* 97
6.2 *Characterisation* 97

7. Standard Operating Procedures 98

8. Performance of the Study 99

8.1 *Study Plan* 99
8.2 *Content of the Study Plan* 100
8.3 *Conduct of the Study* 101

9. Reporting of Study Results 102

9.1 *General* 102
9.2 *Content of the Final Report* 102

10. Storage and Retention of Records and Materials 103

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]** 105

Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practice **[C(89)87(Final)]** 107

Council Decision on 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]** 110

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

* 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].

well as food additives, feed additives, and industrial chemicals. These test items are frequently synthetic 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

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 non¬clinical 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 mix¬up 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 Retrieva*l

   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 an 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

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

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 non¬tariff 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 non-members, 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.

OCDE/GD(95)66

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

GENERAL DISTRIBUTION

OCDE/GD(95)66

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

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 Practice[1] 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 Group.[2] 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 Facilites 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.

TABLE OF CONTENTS

PART ONE:

Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice 118

PART TWO:

Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practice [C(89)87(Final)] 124

ANNEX III:

Revised Guidance for the Exchange of Information concerning National Procedures for Monitoring Compliance 130

PART ONE:

REVISED GUIDES FOR COMPLIANCE MONITORING PROCEDURES FOR GOOD LABORATORY PRACTICE[3]

(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.

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.

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.

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;

i. the frequency with which the GLP Compliance Status of the test facilities is to be assessed;

i. the number and complexity of the studies undertaken by those test facilities

i. 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;

i. encourage consultations, including joint training activities where necessary, with the staff of (National) GLP Monitoring Authorities in other Member countries in order to promote international 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.

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;

i. 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 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 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;

   i. designate an authority or authorities to discharge the functions required by the procedures for monitoring compliance; and

   i. 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.[5]

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 III[6] which is an integral part of this Decision-Recommendation; and

i. 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

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[7] 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 125.

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

REVISED GUIDES FOR COMPLIANCE MONITORING PROCEDURES FOR GOOD LABORATORY PRACTICE

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. 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 non¬compliance, 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.

OCDE/GD(95)67

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

GENERAL DISTRIBUTION

OCDE/GD(95)67

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE
AND COMPLIANCE MONITORING
Number 3 (Revised)

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 Practice[1] 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 1982.[2] The current Guidance was first published in 1988 in the Final Report of the Working Group.[3] 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.

TABLE OF CONTENTS

PART ONE:

Revised Guidance for the Conduct of Laboratory Inspections and Study Audits 138

PART TWO:

Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practice [C(89)87(Final)] 151

PART ONE:

REVISED GUIDANCE FOR THE CONDUCT OF TEST FACILITY INSPECTIONS AND STUDY AUDITS[4]

(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.

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 cross-contamination.

Standard Operating Procedures

PURPOSE: To determine whether the test facility has written SOPs relating to all the important aspects of the 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;

ix. use of pest control and cleaning agents;

x. Quality Assurance programme operations.

Performance of the Study

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.

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.

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 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 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-Recommendation.[7]

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;

ii. exchange with other Member countries relevant information concerning their procedures for

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.

monitoring compliance, in accordance with the guidance set out in Annex III[8] 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

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[9] 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 152.

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

OLIS : 22-Oct-1999
Dist. : 26-Oct-1999

Or. Eng.

ENV/JM/MONO(99)20
Unclassified

ENVIRONMENT DIRECTORATE

JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS

Cancels & replaces the same document :
distributed 13-Sep-1999

OECD SERIES ON PRINCIPLES OF GLP AND COMPLIANCE MONITORING
Number 4 (Revised)

CONSENSUS DOCUMENT

Quality assurance and GLP

833306

Or. Eng.

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.

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.

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

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 data[1] 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

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)].

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.

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.

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.

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

OLIS : 27-Sep-2000
Dist. : 28-Sep-2000

Or. Eng.

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(99)21
Unclassified

Cancels & replaces the same document:
distributed 26-Oct-1999

OECD SERIES ON PRINCIPLES OF GLP AND COMPLIANCE MONITORING
Number 5 (Revised)

CONSENSUS DOCUMENT

Compliance of laboratory suppliers with GLP principles

958824

Or. Eng.

FOREWORD

In the framework of the OECD Consensus Workshop on Good Laboratory Practice, held 16th-18th October 1990 in Bad DŸrkheim, 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.

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 Practice[1] 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 Acts.[2]

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.

Suppliers are expected to provide all information necessary for the correct performance of the instruments. For certain types of instruments, for example balances and reference thermometers, calibration certificats should also be provided.

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 ensure that reagents are obtained only from an accredited supplier. The supplier should provide documentary evidence of any accreditation status. Whre there is no national accreditation scheme the user should ensure receipt of a certificate of analysis from the supplier which guarantees that the reagent is a described by the label.

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 user should be responsible for ensuring by arrangement with the supplier that all such products are labeled with at least the following inform ation: source, identity, date of production, shelf life, storage conditions.

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.

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

OLIS : 14-Sep-1999
Dist. : 15-Sep-1999

Or. Eng.

ENVIRONMENT DIRECTORATE

JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS

ENV/JM/MONO(99)22
Unclassified

OECD SERIES ON PRINCIPLES OF GLP AND COMPLIANCE MONITORING
Number 6 (Revised)

CONSENSUS DOCUMENT

The Application of the GLP principles to field studies

814457

Or. Eng.

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 DŸrkheim, 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.

CONTENTS

BACKGROUND 179
INTERPRETATIONS RELATED TO DEFINITIONS OF TERMS 180
INTERPRETATIONS RELATED TO TEST FACILITY ORGANISATION AND PERSONNEL 181
Test Facility Management's Responsibilities 181
Study Director's Responsibilities 182
Principal Investigator's Responsibilities 182
INTERPRETATIONS RELATED TO THE QUALITY ASSURANCE PROGRAMME 183
INTERPRETATIONS RELATED TO FACILITIES 184
General 184
Facilities for Handling Test and Reference Items 184
Waste Disposal 184
INTERPRETATIONS RELATED TO APPARATUS, MATERIAL AND REAGENTS 185
INTERPRETATIONS RELATED TO TEST SYSTEMS 185
INTERPRETATIONS RELATED TO TEST AND REFERENCE ITEMS 185
Receipt, Handling, Sampling and Storage 185
Characterisation 186
INTERPRETATIONS RELATED TO STANDARD OPERATING PROCEDURES 186
INTERPRETATIONS RELATED TO PERFORMANCE OF THE STUDY 187
Study Plan 187
Conduct of the Study 187
INTERPRETATIONS RELATED TO REPORTING OF STUDY RESULTS 187
INTERPRETATIONS RELATED TO STORAGE AND RETENTION OF RECORDS AND MATERIALS 187

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[1] which developed the GLP Principles in 1981expressly 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.

---

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

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.

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.

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 responsi-

bilities 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.

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 qualifications, 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.

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.

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 analyticdentity 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.

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

OLIS : 14-Sep-1999
Dist. : 15-Sep-1999

Or. Eng.

ENVIRONMENT DIRECTORATE

JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS

ENV/JM/MONO(99)23
Unclassified

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

Or. Eng.

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.

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.

CONTENTS

BACKGROUND 194

NOTES TO THE GLP PRINCIPLES 195

TEST FACILITY ORGANISATION AND PERSONNE 195

QUALITY ASSURANCE PROGRAMME 195

FACILITIES 8 APPARATUS, MATERIAL AND REAGENTS 197

TEST SYSTEMS 197

TEST AND REFERENCE ITEMS 198

STANDARD OPERATING PROCEDURES 199

PERFORMANCE OF THE STUDY 199

REPORTING OF STUDY RESULTS 201

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.

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.

d) 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

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, substrain 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 re¬use 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.

[NOTE 4]: 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.8.1.2. 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.8.2.2. 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.)

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

OLIS : 14-Sep-1999
Dist. : 15-Sep-1999

Or. Eng.

ENVIRONMENT DIRECTORATE

JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS

ENV/JM/MONO(99)24
Unclassified

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

814453

Or. Eng.

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.

CONTENTS

THE ROLE OF THE STUDY DIRECTOR 207

MANAGEMENT RESPONSIBILITIES 207

Appointment of Study Directors *208*

Training of Study Directors *208*

RESPONSIBILITIES OF THE STUDY DIRECTOR 208

Study initiation *208*

Study conduct *209*

Final Repor *209*

Archives *210*

Sub-contracting *210*

STUDY PLAN AMENDMENTS AND DEVIATIONS 210

Study Plan Amendment *210*

Study Deviations *210*

QUALIFICATIONS OF THE STUDY DIRECTOR 211

INTERFACE WITH THE STUDY 211

REPLACEMENT OF THE STUDY DIRECTOR 211

LEGAL STATUS OF THE STUDY DIRECTOR 212

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.

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 computer¬generated 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.

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.

OCDE/GD(95)114

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

GENERAL DISTRIBUTION

OCDE/GD(95)114

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE
AND COMPLIANCE MONITORING
Number 9

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 responsibilities.

OCDE/GD(95)115

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

GENERAL DISTRIBUTION

OCDE/GD(95)115

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE
AND COMPLIANCE MONITORING
Number 10

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 predetermined 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 com-

puter 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 terms[1]

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.

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

OLIS : 21-Jan-1998
Dist. : 22-Jan-1998

Or. Eng.

ENVIRONMENT DIRECTORATE
CHEMICALS GROUP AND MANAGEMENT COMMITTEE

ENV/MC/CHEM(98)16
Unclassified

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE MONITORING
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

Or. Eng.

Also published in the Series on Principles of Good Laboratory Practice and Compliance Monitoring

No. 1, *OECD Principles of Good Laboratory Practice* (as revised in 1997)

No. 2, *Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice* (1995)

No. 3, *Revised Guidance for the Conduct of Laboratory Inspections and Study Audits* (1995)

No. 4, *Quality Assurance and GLP* (1992)

No. 5, *Compliance of Laboratory Suppliers with GLP Principles* (1992)

No. 6, *The Application of the GLP Principles to Field Studies* (1992)

No. 7, *The Application of the GLP Principles to Short-term Studies* (1993)

No. 8, *The Role and Responsibilities of the Study Director in GLP Studies* (1993)

No. 9, *Guidance for the Preparation of GLP Inspection Reports* (1995)

No. 10, *The Application of the Principles of GLP to Computerised Systems* (1995)

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 of 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 co¬ordination 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/)

or contact:

**OECD Environment Directorate,
Environmental Health and Safety Division**

**2 rue André-Pascal
75775 Paris Cedex 16
France**

Fax: (33-1) 45 24 16 75

E-mail: ehscont@oecd.org

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 entity[1*] 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.

---

* "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.

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 nos. 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.

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

25-Jun-2002

English - Or. Eng.

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2000)3
Unclassified

Cancels & replaces the same document of 25 September 2000

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

JT00128864

English - Or. English

Also published in the Series on Principles of Good Laboratory Practice and Compliance Monitoring

No. 1, OECD Principles of Good Laboratory Practice (as revised in 1997)

No. 2, Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice (1995)

No. 3, Revised Guidance for the Conduct of Laboratory Inspections and Study Audits (1995)

No. 4, Quality Assurance and GLP (as revised in 1999)

No. 5, Compliance of Laboratory Suppliers with GLP Principles (as revised in 1999)

No. 6, The Application of the GLP Principles to Field Studies (as revised in 1999)

No. 7, The Application of the GLP Principles to Short-term Studies (as revised in 1999)

No. 8, The Role and Responsibilities of the Study Director in GLP Studies (as revised in 1999)

No. 9, Guidance for the Preparation of GLP Inspection Reports (1995)

No. 10, The Application of the Principles of GLP to Computerised Systems (1995)

No. 11, The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP (1998)

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 co¬ordination 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/)

or contact:

**OECD Environment Directorate,
Environmental Health and Safety Division**

**2 rue André-Pascal
75775 Paris Cedex 16
France**

Fax: (33-1) 45 24 16 75

E-mail: ehscont@oecd.org

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.

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

25-Jun-2002

English - Or. Eng.

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2002)9
Unclassified

Cancels & replaces the same document of 11 March 2002

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE
AND COMPLIANCE MONITORING
Number 13

Consensus Document of the Working Group on Good Laboratory Practice

The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies

JT00128856

English - Or. English

Also published in the Series on Principles of Good Laboratory Practice and Compliance Monitoring

No. 1, OECD Principles of Good Laboratory Practice (as revised in 1997)

No. 2, Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice (1995)

No. 3, Revised Guidance for the Conduct of Laboratory Inspections and Study Audits (1995)

No. 4, Quality Assurance and GLP (as revised in 1999)

No. 5, Compliance of Laboratory Suppliers with GLP Principles (as revised in 1999)

No. 6, The Application of the GLP Principles to Field Studies (as revised in 1999)

No. 7, The Application of the GLP Principles to Short-term Studies (as revised in 1999)

No. 8, The Role and Responsibilities of the Study Director in GLP Studies (as revised in 1999)

No. 9, Guidance for the Preparation of GLP Inspection Reports (1995)

No. 10, The Application of the Principles of GLP to Computerised Systems (1995)

No. 11, The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP (1998)

No. 12, Requesting and Carrying Out Inspections and Study Audits in Another Country (2000)

ABOUT THE OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 30 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 Environment, Health and Safety Division. The Environment, Health and Safety Division publishes free-of¬charge documents in eight different series: **Testing and Assessment; Principles on Good Laboratory Practice and Compliance Monitoring; Pesticides; PRTRs; Risk Management; Chemical Accidents; Emission Scenario and Harmonisation of Regulatory Oversight in Biotechnology**. More information about the Environment, 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 co¬ordination 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/)

or contact:

**OECD Environment Directorate,
Environmental Health and Safety Division**

**2 rue André-Pascal
75775 Paris Cedex 16
France**

Fax: (33-1) 45 24 16 75

E-mail: ehscont@oecd.org

FOREWORD

It is becoming increasingly common for non-clinical health and environmental safety studies to be conducted at more than one site. For example, companies may use facilities which specialise in different activities located at sites in various countries; or field trials on agrochemicals may have to be conducted on different crops or soil types located in different regions or countries. Toxicology studies may also have phases of the study conducted by different departments of the same organisation or different companies.

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. An OECD Consensus Document on "The Application of the GLP Principles to Field Studies" was subsequently published in 1992 and revised in 1999 [ENV/JM/MONO(99)23]. Among other aspects, this document introduced the concept of a "Principal Investigator" who could assume delegated responsibility for a phase of a field study being conducted at a test site that was remote from the Study Director. Although the concept of a Principal Investigator had originally been developed to assist in the conduct of field studies that included trials being conducted at several different locations, the concept is equally applicable to any other type of multi-site study.

The revised OECD Principles of Good Laboratory Practice published in 1997 now refer to the role of the Principal Investigator in the conduct of any multi-site study.

A study can be a "multi-site" study for a variety of reasons. A single site that undertakes a study may not have the technical expertise or capability to perform a particular task that is needed, so this work is performed at another site. A sponsor who has placed a study at a contract research organisation may request that certain study activities, such as bioanalysis, be contracted out to a specified laboratory or the sponsor may request that specimens be returned to them for analysis

The purpose of this document is to provide guidance on the issues that are involved in the planning, performance, monitoring, recording, reporting and archiving of multi-site studies. It was developed by the Fourth OECD Consensus Workshop in Horley, United Kingdom in June 2001. It was endorsed by the Working Group on GLP in December 2001 and, subsequently, by the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in February 2002. It was declassified under the authority of the Secretary-General.

This guidance is complementary to that given in other documents in the OECD Series on GLP and Compliance Monitoring.

CONTENTS

INTRODUCTION 260

MANAGEMENT AND CONTROL OF MULTI-SITE STUDIES 260

QUALITY ASSURANCE 264

MASTER SCHEDULES 265

STUDY PLAN 265

PERFORMANCE OF THE STUDY 265

REPORTING OF STUDY RESULTS 266

STANDARD OPERATING PROCEDURES 267

STORAGE AND RETENTION OF RECORDS AND MATERIALS 268

INTRODUCTION

The planning, performance, monitoring, recording, reporting and archiving of a multi-site study present a number of potential problems that should be addressed to ensure that the GLP compliance of the study is not compromised. The fact that different study activities are being conducted at different sites means that the planning, communication and control of the study are of vital importance.

Although a multi-site study will consist of work being conducted at more than one site (which includes the test facility and all test sites), it is still a single study that should be conducted in accordance with the OECD Principles of GLP. This means that there should be a single study plan, a single Study Director, and ultimately, a single final report. It is therefore essential that, when the study is first planned, personnel and management at the contributing sites are made aware that the work they will perform is part of a study under the control of the Study Director and is not to be carried out as a separate study.

It is imperative that the work to be carried out by the various sites is clearly identified at an early stage of planning, so that the necessary control measures can be agreed upon by the parties concerned before the study plan is finalised.

Many of the problems associated with the conduct of multi-site studies can be prevented by clear allocation of responsibilities and effective communication among all parties involved in the conduct of the study. This will include the sponsor, the Study Director, and the management, the Principal Investigator(s), Quality Assurance and study personnel at each site.

All of these parties should be aware that when a multi-site study is conducted in more than one country there might be additional issues due to differences in national culture, language and GLP compliance monitoring programmes. In these situations it may be necessary to seek the advice of the national GLP compliance monitoring authority where the site is located.

The guidance contained within this document should be considered during the planning, performance, monitoring, recording, reporting and archiving of any study that will be conducted at more than one site. The guidance applies to all types of non-clinical health and environmental safety studies.

MANAGEMENT AND CONTROL OF MULTI-SITE STUDIES

A multi-site study means any study that has phases conducted at more than one site. Multi-site studies become necessary if there is a need to use sites that are geographically remote, organisationally distinct or otherwise separated. This could include a department of an organisation acting as a test site when another department of the same organisation acts as the test facility.

A phase is a defined activity or set of activities in the conduct of a study.

The decision to conduct a multi-site study should be carefully considered by the sponsor in consultation with test facility management assigned by the sponsor before study initiation. The use of multiple test sites increases the complexity of study design and management tasks, resulting in additional risks to study integrity. It is therefore

important that all of the potential threats to study integrity presented by a multi-site configuration are evaluated, that responsibilities are clear and that risks are minimised. Full consideration should be given to the technical/scientific expertise, GLP compliance status, resources and commercial viability of all of the test sites that may be used.

Communication

For a multi-site study to be conducted successfully it is imperative that all parties involved are aware of their responsibilities. In order to discharge these responsibilities, and to deal with any events that may need to be addressed during the conduct of the study, the flow of information and effective communication among the sponsor, management at sites, the Study Director, Principal Investigator(s), Quality Assurance and study personnel is of paramount importance.

The mechanism for communication of study-related information among these parties should be agreed in advance and documented.

The Study Director should be kept informed of the progress of the study at all sites.

Study management

The sponsor will assign a study to a test facility. Test facility management will appoint the Study Director who need not necessarily be located at the site where the majority of the experimental work is done. The decision to conduct study activities at other sites will usually be made by test facility management in consultation with the Study Director and the sponsor, where necessary.

When the Study Director is unable to perform his/her duties at a test site because of geographical or organisational separation, the need to appoint a Principal Investigator(s) at a test site(s) arises. The performance of duties may be impracticable, for example, because of travel time, time zones, or delays in language interpretation. Geographical separation may relate to distance or to the need for simultaneous attention at more than one location.

Test facility management should facilitate good working relationships with test site management to ensure study integrity. The preferences of the different groups involved, or commercial and confidentiality agreements, should not preclude the exchange of information necessary to ensure proper study conduct.

Roles and Responsibilities

Sponsor

The decision to conduct a multi-site study should be carefully considered by the sponsor in consultation with test facility management before study initiation. The sponsor should specify whether compliance with the OECD Principles of GLP and applicable national legislation is required. The sponsor should understand that a multi-site study must result in one final report.

The sponsor should be aware that, if its site acts as a test site undertaking a phase(s) of a multi¬site study, its operations and staff involved in the study are subject to control of the Study Director. According to the specific situation, this may include visits from test facility management, the Study Director and/or inspections by the lead Quality Assurance. The Study Director has to indicate the extent to which the study complies with GLP, including any work conducted by the sponsor.

Test Facility Management

Test facility management should approve the selection of test sites. Issues to consider will include, but are not limited to, practicality of communication, adequacy of Quality Assurance arrangements, and the availability of appropriate equipment and expertise. Test facility management should designate a lead Quality Assurance that has the overall responsibility for quality assurance of the entire study. Test facility management should inform all test site quality assurance units of the location of the lead Quality Assurance. If it is necessary to use a test site that is not included in a national GLP compliance monitoring programme, the rationale for selection of this test site should be documented. Test facility management should make test site management aware that it may be subject to inspection by the national GLP compliance monitoring authority of the country in which the test site is located. If there is no national GLP compliance monitoring authority in that country, the test site may be subject to inspection by the GLP compliance monitoring authority from the country to which the study has been submitted.

Test Site Management

Test site management is responsible for the provision of adequate site resources and for selection of appropriately skilled Principal Investigator(s). If it becomes necessary to replace a Principal Investigator, test site management will appoint a replacement Principal Investigator in consultation with the sponsor, the Study Director and test facility management where necessary. Details should be provided to the Study Director in a timely manner so that a study plan amendment can be issued. The replacement Principal Investigator should assess the GLP compliance status of the work conducted up to the time of replacement.

Study Director

The Study Director should ensure that the test sites selected are acceptable. This may involve visits to test sites and meetings with test site personnel.

If the Study Director considers that the work to be done at one of the test sites can be adequately controlled directly by him(her)self without the need for a Principal Investigator to be appointed, he/she should advise test facility management of this possibility. Test facility management should ensure that appropriate quality assurance monitoring of that site is arranged. This could be by the test site's own Quality Assurance or by the lead Quality Assurance.

The Study Director is responsible for the approval of the study plan, including the incorporation of contributions from Principal Investigators. The Study Director will approve and issue amendments to and acknowledge deviations from the study plan, including those relating to work undertaken at sites. The Study Director is responsible for ensuring that all staff are clearly aware of the requirements of the study and should ensure that the study plan and amendments are available to all relevant personnel.

The Study Director should set up, test and maintain appropriate communication systems between him(her)self and each Principal Investigator. For example, it is prudent to verify telephone numbers and electronic mail addresses by test transmissions, to consider signal strength at rural field stations, etc. Differences in time zones may need to be taken into account. The Study Director should liase directly with each Principal Investigator and not via an intermediary except where this is unavoidable (e.g., the need for language interpreters).

Throughout the conduct of the study, the Study Director should be readily available to the Principal Investigators. The Study Director should facilitate the co-ordination and timing of events and movement of samples, specimens or data between sites, and ensure that Principal Investigators understand chain of custody procedures.

The Study Director should liase with Principal Investigators about test site quality assurance findings as necessary. All communication between the Study Director and Principal Investigators or test site quality assurance in relation to these findings should be documented.

The Study Director should ensure that the final report is prepared, incorporating any contributions from Principal Investigators. The Study Director should ensure that the final report is submitted to the lead Quality Assurance for inspection. The Study Director will sign and date the final report to indicate the acceptance of responsibility for the validity of the data and to indicate the extent to which the study complies with the OECD Principles of Good Laboratory Practice. This may be based partly on written assurances provided by the Principal Investigator(s).

At sites where no Principal Investigator has been appointed, the Study Director should liase directly with the personnel conducting the work at those sites. These personnel should be identified in the study plan.

Principal Investigator

The Principal Investigator acts on behalf of the Study Director for the delegated phase and is responsible for ensuring compliance with the Principles of GLP for that phase. A fully co-operative, open working relationship between the Principal Investigator and the Study Director is essential.

There should be documented agreement that the Principal Investigator will conduct the delegated phase in accordance with the study plan and the Principles of GLP. Signature of the study plan by the Principal Investigator would constitute acceptable documentation.

Deviations from the study plan or Standard Operating Procedures (SOPs) related to the study should be documented at the test site, be acknowledged by the Principal Investigator and reported to and acknowledged by the Study Director in a timely manner.

The Principal Investigator should provide the Study Director with contributions which enable the preparation of the final report. These contributions should include written assurance from the Principal Investigator confirming the GLP compliance of the work for which he/she is responsible.

The Principal Investigator should ensure that all data and specimens for which he/she is responsible are transferred to the Study Director or archived as described in the study plan. If these are not transferred to the Study Director, the Principal Investigator should notify the Study Director when and where they have been archived. During the study, the Principal Investigator should not dispose of any specimens without the prior written permission of the Study Director.

Study Personnel

The GLP Principles require that all professional and technical personnel involved in the conduct of a study have a job description and a record of the training, qualifications and experience which support their ability to undertake the tasks assigned to them. Where study personnel are required to follow approved SOPs from another test site, any additional training required should be documented.

There may be some sites where temporarily employed personnel carry out aspects of study conduct. Where these persons have generated or entered raw data, or have performed activities relevant to the conduct of the study, records of their qualifications, training and experience should be maintained. Where these individuals have carried out routine operations such as livestock handling subject to supervision by more highly qualified staff, no such personnel records need be maintained.

QUALITY ASSURANCE

The quality assurance of multi-site studies needs to be carefully planned and organised to ensure that the overall GLP compliance of the study is assured. Because there is more than one site, issues may arise with multiple management organisations and Quality Assurance programmes.

Responsibilities of Lead Quality Assurance

The lead Quality Assurance should liase with test site quality assurance to ensure adequate quality assurance inspection coverage throughout the study.

Particular attention should be paid to the operation and documentation relating to communication among sites. Responsibilities for quality assurance activities at the various sites should be established before experimental work commences at those sites.

The lead Quality Assurance will ensure that the study plan is verified and that the final report is inspected for compliance with the Principles of GLP. Quality assurance inspections of the final report should include verification that the Principal Investigator contributions (including evidence of quality assurance at the test site) have been properly incorporated. The lead Quality Assurance will ensure that a Quality Assurance Statement is prepared relating to the work undertaken by the test facility including or referencing quality assurance statements from all test sites.

Responsibilities of Test Site Quality Assurance

Each test site management is usually responsible for ensuring that there is appropriate quality assurance for the part of the study conducted at their site. Quality assurance at each test site should review sections of the study plan relating to operations to be conducted at their site. They should maintain a copy of the approved study plan and study plan amendments.

Quality assurance at the test site should inspect study-related work at their site according to their own SOPs, unless required to do otherwise by the lead Quality Assurance, reporting any inspection results promptly in writing to the Principal Investigator, test site management, Study Director, test facility management and lead Quality Assurance.

Quality assurance at the test site should inspect the Principal Investigator's contribution to the study according to their own test site SOPs and provide a statement relating to the quality assurance activities at the test site.

MASTER SCHEDULES

A multi-site study in which one or more Principal Investigators have been appointed should feature on the master schedule of all sites concerned. It is the responsibility of test facility management and test site management to ensure that this is done.

The unique identification of the study must appear on the master schedule in each site, cross¬referenced as necessary to test site identifiers. The Study Director should be identified on the master schedule(s), and the relevant Principal Investigator shown on each site master schedule.

At all sites, the start and completion dates of the study phase(s) for which they are responsible should appear on their master schedule.

STUDY PLAN

For each multi-site study, a single study plan should be issued. The study plan should clearly identify the names and addresses of all sites involved.

The study plan should include the name and address of any Principal Investigators and the phase of the study delegated to them. It is recommended that sufficient information is included to permit direct contact by the Study Director, e.g. telephone number.

The study plan should identify how data generated at sites will be provided to the Study Director for inclusion in the final report.

It is useful, if known, to describe in the study plan the location(s) at which the data, samples of test and reference items and specimens generated at the different sites are to be retained.

It is recommended that the draft study plan should be made available to Principal Investigators for consideration and acknowledgement of their capability to undertake the work assigned to them, and to enable them to make any specialised technical contribution to the study plan if required.

The study plan is normally written in a single language, usually that of the Study Director. For multi-national studies it may be necessary for the study plan to be issued in more than one language; this intention should be indicated in the original study plan, the translated study plan(s) and the original language should be identified in all versions. There will need to be a mechanism to verify the accuracy and completeness of the translated study plan. The responsibility for the accuracy of the translation can be delegated by the Study Director to a language expert and should be documented.

PERFORMANCE OF THE STUDY

This section repeats the most important requirements from the Principles of GLP and recommendations from the Consensus Document on the Application of the GLP Principles to Field Studies in order to provide useful guidance for organisation of multi-site studies. These documents should be consulted for further details.

Facilities

Sites may not have a full time staff presence during the working day. In this situation it may be necessary to take additional measures to maintain the physical security of the test item, specimens and data.

When it is necessary to transfer data or any materials among sites, mechanisms to maintain their integrity need to be established. Special care needs to be taken when transferring data electronically (e¬mail, internet, etc.).

Equipment

Equipment being used in a study should be fit for its intended purpose. This is also applicable to large mechanical vehicles or highly specialised equipment that may be used at some sites.

There should be maintenance and calibration records for such equipment that serve to indicate their "fitness for intended purpose" at the time of use. Some apparatus (e.g., leased or rented equipment such as large animal scales and analytical equipment) may not have records of periodic inspection, cleaning, maintenance and calibration. In such cases, information should be recorded in the study-specific raw data to demonstrate "fitness for intended purpose" of the equipment.

Control and accountability of study materials

Procedures should be in place that will ensure timely delivery of study related materials to sites. Maintaining integrity/stability during transport is essential, so the use of reliable means of transportation and chain of custody documentation is critical. Clearly defined procedures for transportation, and responsibilities for who does what, are essential.

Adequate documentation should accompany each shipment of study material to satisfy any applicable legal requirements, e.g., customs, health and safety legislation. This documentation should also provide relevant information sufficient to ensure that it is suitable for its intended purpose on arrival at any site. These aspects should be resolved prior to shipment.

When study materials are transported between sites in the same consignment it is essential that there is adequate separation and identification to avoid mix-ups or cross contamination. This is of particular importance if materials from more than one study are transported together.

If the materials being transported might be adversely affected by environmental conditions encountered during transportation, procedures should be established to preserve their integrity. It may be appropriate for monitoring to be carried out to confirm that required conditions were maintained.

Attention should be given to the storage, return or disposal of excess test and reference items being used at sites.

REPORTING OF STUDY RESULTS

A single final report should be issued for each multi-site study. The final report should include data from all phases of the study. It may be useful for the Principal Investigators to produce a signed and dated report of the phase delegated to them, for incorporation into the final report. If prepared, such reports should include evidence that appropriate quality assurance monitoring was performed at that test site and contain sufficient commentary to enable the Study Director to write a valid final report covering the whole study. Alternatively, raw data may be transferred from the Principal Investigator to the Study Director, who should ensure that the data are presented in the final report. The final report produced in this way should identify the Principal Investigator(s) and the phase(s) for which they were responsible.

The Principal Investigators should indicate the extent to which the work for which they were responsible complies with the GLP Principles, and provide evidence of the quality assurance inspections performed at that test site. This may be incorporated directly into the final report, or the required details may

be extracted and included in the Study Director's compliance claim and Quality Assurance statement in the final report. When details have been extracted the source should be referenced and retained.

The Study Director must sign and date the final report to indicate acceptance of responsibility for the validity of all the data. The extent of compliance with the GLP Principles should be indicated with specific reference to the OECD Principles of GLP and Regulations with which compliance is being claimed. This claim of compliance will cover all phases of the study and should be consistent with the information presented in the Principal Investigator claims. Any sites not compliant with the OECD Principles of GLP should be indicated in the final report.

The final report should identify the storage location(s) of the study plan, samples of test and reference items, specimens, raw data and the final report. Reports produced by Principal Investigators should provide information concerning the retention of materials for which they were responsible.

Amendments to the final report may only be produced by the Study Director. Where the necessary amendment relates to a phase conducted at any test site the Study Director should contact the Principal Investigator to agree appropriate corrective actions. These corrective actions must be fully documented.

If a Principal Investigator prepares a report, that report should where appropriate comply with the same requirements that apply to the final report.

STANDARD OPERATING PROCEDURES (SOPs)

The GLP Principles require that appropriate and technically valid SOPs are established and followed. The following examples are procedures specific to multi-site studies:

- Selection and monitoring of test sites;
- Appointment and replacement of Principal Investigators;
- Transfer of data, specimens and samples between sites;
- Verification or approval of foreign language translations of study plans or SOPs; and
- Storage, return or disposal of test and reference items being used at remote test sites.

The Principles of GLP require that SOPs should be immediately available to study personnel when they are conducting activities, regardless of where they are carrying out the work.

It is recommended that test site personnel should follow test site SOPs. When they are required to follow other procedures specified by the Study Director, for example SOPs provided by the test facility management, this requirement should be identified in the study plan. The Principal Investigator is responsible for ensuring that test site personnel are aware of the procedures to be followed and have access to the appropriate documentation.

If personnel at a test site are required to follow SOPs provided by the test facility management, it is necessary for test site management to give written acceptance.

When SOPs from a test facility have been issued for use at a test site, test facility management should ensure that any subsequent SOP revisions produced during the course of the study are also sent to the test site and the superseded versions are removed from use. The Principal Investigator should ensure that all test site personnel are aware of the revision and only have access to the current version.

When SOPs from a test facility are to be followed at test sites, it may be necessary for the SOPs to be translated into other languages. In this situation it is essential that any translations be thoroughly checked to ensure that the instructions and meaning of the different language versions remain identical. The original language should be defined in the translated SOPs.

STORAGE AND RETENTION OF RECORDS AND MATERIALS

During the conduct of multi-site studies attention should be given to the temporary storage of materials. Such storage facilities should be secure and protect the integrity of their contents. When data are stored away from the test facility, assurance will be needed of the site's ability to readily retrieve data which may be needed for review.

Records and materials need to be stored in a manner that complies with GLP Principles. When test site storage facilities are not adequate to satisfy GLP requirements, records and materials should be transferred to a GLP compliant archive.

Test site management should ensure that adequate records are available to demonstrate test site involvement in the study.

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

30-Nov-2004

English - Or. Eng.

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2004)26
Unclassified

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE
AND COMPLIANCE MONITORING
Number 14

Advisory Document of the Working Group on Good Laboratory Practice

The Application of the Principles of GLP to in vitro Studies

JT00174939

English - Or. English

Also published in the Series on Principles of Good Laboratory Practice and Compliance Monitoring

No. 1, OECD Principles of Good Laboratory Practice (as revised in 1997)

No. 2, Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice (1995)

No. 3, Revised Guidance for the Conduct of Laboratory Inspections and Study Audits (1995)

No. 4, Quality Assurance and GLP (as revised in 1999)

No. 5, Compliance of Laboratory Suppliers with GLP Principles (as revised in 1999)

No. 6, The Application of the GLP Principles to Field Studies (as revised in 1999)

No. 7, The Application of the GLP Principles to Short-term Studies (as revised in 1999)

No. 8, The Role and Responsibilities of the Study Director in GLP Studies (as revised in 1999)

No. 9, Guidance for the Preparation of GLP Inspection Reports (1995)

No. 10, The Application of the Principles of GLP to Computerised Systems (1995)

No. 11, The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP (1998)

No. 12, Requesting and Carrying Out Inspections and Study Audits in Another Country (2000)

No. 13, The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies (2002)

ABOUT THE OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 30 industrialised countries in North America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise 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 working 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 working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in nine different series: **Testing and Assessment; Good Laboratory Practice and Compliance Monitoring; Pesticides and Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; and Emission Scenario Documents.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (http://www.oecd.org/ehs/).

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

or contact:

OECD Environment Directorate,
Environmental Health and Safety Division

2 rue André-Pascal
75775 Paris Cedex 16
France

Fax: (33-1) 45 24 16 75

E-mail: ehscont@oecd.org

FOREWORD

As efforts to decrease the use of animals in safety testing are intensifying, *in vitro* methods are gaining a more prominent role as alternatives or supplements to in vivo safety testing. Anticipated developments in the fields of toxicogenomics, toxicoproteomics, toxicometabonomics and in various high through-put screening techniques are expected to enhance the importance of *in vitro* methodologies for safety testing, beyond their traditional use as test systems in the area of genetic toxicity testing. The OECD Working Group on Good Laboratory Practice considered it therefore worthwhile to develop further guidance specifically of relevance to the application and interpretation of the OECD Principles of GLP[1] to *in vitro* studies.

The Working Group established a Task Force under the leadership of Switzerland, which met in Bern on 12 to 13 February 2004. The Task Force comprised members of the Working Group or experts in *in vitro* testing nominated by them representing Belgium, France, Germany, Japan, the Netherlands, Switzerland, the United States and the European Commission.

The draft Advisory Document developed by the Task Force was examined by the Working Group at its 18th Meeting in May 2004, where it was amended and endorsed. The Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology at its 37th Joint Meeting in turn endorsed the document and recommended that it be declassified under the authority of the Secretary-General.

1 See No. 1 of the Series on Good Laboratory Practice and Compliance Monitoring

Advisory Document of the Working Group on GLP

THE APPLICATION OF THE PRINCIPLES OF GLP TO *IN VITRO* STUDIES

Introduction

Studies involving *in vitro* test systems have long been used to obtain data on the safety of chemicals with respect to human health and the environment. National legislation usually requires that these studies be conducted in accordance with Good Laboratory Practice (GLP) requirements.[2]

Traditionally *in vitro* methods have been mainly used in the area of genetic toxicity testing, where the hazard assessment is based to a large extent on data derived from studies using *in vitro* test systems. As efforts to decrease the use of animals in safety testing are intensifying, *in vitro* methods are gaining a more prominent role as alternatives or supplements to *in vivo* safety testing. Furthermore, developments in the area of toxicogenomics, toxicoproteomics, toxicometabonomics and various (e.g., micro-array) high through-put screening techniques will also enhance the importance of *in vitro* methodologies for safety testing.

The requirement that safety studies be planned, conducted, recorded, reported and archived in accordance with the *OECD Principles of Good Laboratory Practice* (hereafter the GLP Principles) does not differ for different study types. Therefore, the GLP Principles and the associated Advisory Documents[3] describe requirements for and provide general guidance on the conduct of all nonclinical health and environmental safety studies, including *in vitro* studies. In order to facilitate the application and interpretation of the GLP Principles in relation to the specific *in vitro* testing situation, further clarification and guidance was considered useful.

Purpose of this Document

The purpose of this document is to facilitate the proper application and interpretation of the GLP Principles for the organisation and management of *in vitro* studies, and to provide guidance for the appropriate application of the GLP Principles to *in vitro* studies, both for test facilities (management, QA, study director and personnel), and for national GLP compliance monitoring authorities.

This Advisory Document intends to provide such additional interpretation of the Principles and guidance for their application to *in vitro* studies carried out for regulatory purposes. It is organised in such a way as to provide easy reference to the GLP Principles by following the sequence of the different parts of these GLP Principles.

---

2 Revised OECD Principles of Good Laboratory Practice [C(97)186 (Final)]

3 See OECD series on Good Laboratory Practice and Compliance Monitoring

Scope

This document is specific to the application of the Principles of GLP to *in vitro* studies conducted in the framework of 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 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.

Unless specifically exempted by national legislation, the 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.

Definitions

a) In vitro Studies

in vitro studies are studies which do not use multicellular whole organisms, but rather microorganisms or material isolated from whole organisms, or simulations thereof as test systems.

Many *in vitro* studies will qualify as short-term studies under the definition provided by the GLP Principles. For these studies, the *OECD Advisory Document on The Application of the GLP Principles to Short-Term Studies* should be consulted and used as appropriate, in order to allow for the application of the provisions facilitating the work of Study Director and QA.

b) Reference Item

Test guidelines for *in vitro* studies mandate in many cases the use of appropriate positive, negative and/or vehicle control items which may not serve, however, as the GLP definition of "reference items" implies, to grade the response of the test system to the test item, but rather to control the proper performance of the test system. Since the purpose of these positive, negative and/or vehicle control items may be considered as analogous to the purpose of a reference item, the definition of the latter may be regarded as covering the terms "positive, negative, and/or vehicle control items" as well. The extent to which they should be analytically characterized may, however, be different from the requirements of reference items.

Responsibilities

a) Test Facility Management

Most of the responsibilities of test facility management are of a general nature and are equally applicable to *in vivo* and *in vitro* studies, such as the requirements that test facility management has to ensure the availability of qualified personnel, and of appropriate facilities and equipment for the timely and proper conduct of the study. However, test facility management should be aware that *in vitro* testing may influence

the execution of some of their responsibilities For example, test facility management must ensure that personnel clearly understand the functions they are to perform. For *in vitro* studies this may entail ensuring that specific training is provided in aseptic procedures and in the handling of biohazardous materials. *in vitro* testing may also necessitate the availability of specialized areas and the implementation of procedures to avoid contamination of test systems. Another example is provided by the requirement that test facility management should ensure that test facility supplies meet requirements appropriate to their use in a study. Certain *in vitro* studies may necessitate the use of proprietary materials or test kits. Although the *OECD Advisory Document on Compliance of Laboratory Suppliers with GLP Principles* states that materials to be used in a GLP compliant study should be produced and tested for suitability using an adequate quality system, thus placing the primary responsibility for their suitability on the manufacturer or supplier, it is the responsibility of the test facility management to confirm that these conditions are adequately fulfilled through assessment of the suppliers practices, procedures and policies.

b) Study Director

The general responsibilities of the Study Director are independent of the type of study and the responsibilities listed in the Principles apply to *in vitro* studies as well. The study director continues to be the single point of study control and has the responsibility for the overall conduct and reporting of the study.

In *in vitro* studies the Study Director should pay particular attention to documenting the justification and characterization of the test system, an activity which may be more difficult to accomplish for *in vitro* studies. See the section on Test Systems, below, regarding the documentation required to justify and characterize the test system. In *in vivo* studies these activities have been rather straightforward. For example, the use of a particular species may be justified by documenting the characteristics of that species that make it an appropriate model for assessing the effect of interest. Characterization of a particular animal may be accomplished by simply documenting the animal species, strain, substrain, source of supply, number, body weight range, sex, and age.

These required activities may be more difficult to accomplish for *in vitro* studies:

Justification of the test system may require that the Study Director document that the test method has been validated or is structurally, functionally, and/or mechanistically similar to a validated reference test method. Prior to the use of new test methods that are structurally, functionally and/or mechanistically similar to a validated reference test method, the Study Director should therefore provide documented evidence that the new test method has comparable performance when evaluated with appropriate reference items.

Characteristics of *in vitro* systems may also be difficult to document. Although the Study Director may be able, with the assistance of the supplier, to document some characteristics of the test system (e.g., cell line, age/passage, origin) he/she should also characterize the test system by documenting that the test system provides the required performance when evaluated with appropriate reference items, including positive, negative, and untreated and/or vehicle controls, where necessary. A special case may be seen in the use of proprietary materials or test kits in the conduct of *in vitro* studies. While the performance of such materials or test kits should be assured by the supplier, producer or patent holder, and while the test facility management is responsible for ensuring that the supplier meets the quality criteria as mentioned above, e.g., by reviewing vendor practices, procedures and policies, it is the responsibility of the Study Director to ensure that the performance of these

materials or kits indeed meets the requirements of the study, and to ensure that test kits have been adequately validated and are suitable for their intended purpose. Since the quality and reliability of study results will be influenced directly by the quality and performance of these materials or test kits, it is especially important that the completeness and acceptability of the quality control documentation provided by the supplier should be thoroughly examined and critically evaluated by the Study Director. At a minimum, the Study Director should be able to judge the appropriateness of the quality system used by the manufacturer, and have available all documentation needed to assess the fitness for use of the test system, e.g., results of performance studies.

c) Study Personnel

Personnel should meticulously observe, where applicable, the requirements for aseptic conditions and follow the respective procedures in the conduct of *in vitro* studies to avoid pathogen contamination of the test system. Similarly, personnel should employ adequate practices (see "Sources for Further Information", ref 1) to avoid cross-contamination between test systems and to ensure the integrity of the study. Study personnel should be aware of, and strictly adhere to, the requirements to isolate test systems and studies involving biohazardous materials. Appropriate precautions to minimize risks originating from the use of hazardous chemicals should be applied during *in vitro* studies as well.

Quality Assurance

In general, Quality Assurance (QA) activities will not be greatly different between *in vitro* and *in vivo* studies. *in vitro* studies may qualify in certain cases for treatment under the conditions of short-term studies; in these cases, the *OECD Advisory Document on The Application of the GLP Principles to Short-Term Studies* will be applicable. Thus, such studies may be inspected, if applicable and permitted by national regulations, by QA on a process-based inspection programme. Since the GLP Principles require QA to inspect especially the critical phases of a study, it is important that, in the case of *in vitro* studies, QA is well aware of what constitutes critical phases (and critical aspects) of such studies. Corresponding guidance for QA inspections should be developed in co-operation with Study Directors, Principal Investigators and study personnel in the relevant areas. Since the QA programme should, wherever indicated, explicitly cover specific aspects of *in vitro* testing, education and training of QA personnel should also be explicitly directed towards the ability to recognise potential problems in specific areas of *in vitro* testing.

Specific areas to be inspected may include, but not be limited to, the procedures and measures for:

- monitoring of batches of components of cell and tissue culture media that are critical to the performance of the test system (e.g. foetal calf serum, etc.) and other materials with respect to their influence on test system performance;
- assessing and ensuring functional and/or morphological status (and integrity) of cells, tissues and other indicator materials;
- monitoring for potential contamination by foreign cells, mycoplasma and other pathogens, or other adventitious agents, as appropriate;
- cleaning and decontamination of facilities and equipment and minimizing sources of contamination of test items and test systems;

- ensuring that specialised equipment is properly used and maintained;
- ensuring proper cryopreservation and reconstitution of cells and tissues;
- ensuring proper conditions for retrieval of materials from frozen storage;
- ensuring sterility of materials and supplies used for cell and tissue cultures;
- maintaining adequate separation between different studies and test systems.

Facilities

a) General

The GLP Principles mandate that test facilities should be suitable to meet the requirements of the studies performed therein, and that an adequate degree of separation should be maintained between different activities to ensure the proper and undisturbed conduct of each study. Due to the fact that *in vitro* studies generally occupy only limited workspace and do not normally require dedicated facilities that exclude the performance of other studies, measures should be taken to ensure the appropriate separation of *in vitro* studies co-existing in the same physical environment.

b) Test System Facilities

The GLP Principles require that a sufficient number of rooms or areas should be available to ensure the isolation of test systems, and that such areas should be suitable to ensure that the probability of contamination of test systems is minimized. The term "areas", however, is not specifically defined and its interpretation is therefore adaptable to various *in vitro* situations. The important aspect here is that the integrity of each test system and study should not be jeopardised by the possibility of potential contamination or cross-contamination or mix-up.

In this way it may be possible to incubate cells or tissues belonging to different studies within the same incubator, provided that an adequate degree of separation exists (e.g., appropriate identifiers, labelling or separate placement to distinguish between studies, etc.), and that no test item is sufficiently volatile so as to contaminate other studies that are co-incubated.

Separation of critical study phases may be possible not only on a spatial, but also on a temporal basis. Manipulation of cell and tissue cultures, e.g., subcultivation procedures, addition of test item, etc., is normally performed in vertical laminar flow cabinets to assure sterility and to protect the test system as well as study personnel and the environment. Under these circumstances, adequate separation to prevent cross-contamination between different studies will be achieved by sequential manipulation of the test systems used in the individual studies, with careful cleaning and decontamination/sterilization of the working surfaces of the cabinet and of related laboratory equipment performed between the different activities, as necessary.

Another important aspect is the availability of devoted rooms or areas with special equipment for the long¬term storage of test systems. The equipment, including storage containers, should provide adequate conditions for maintenance of long-term integrity of test systems.

c) Facilities for Handling Test and Reference Items

While the requirements of the GLP Principles for handling test and reference items apply equally to *in vitro* tests as far as the prevention of cross-contamination by test and reference items is concerned, another aspect needs to be taken into account: Since sterility is an important consideration in *in vitro* studies it should be ensured that rooms or areas used for preparation and mixing of test and reference items with vehicles be equipped so as to allow working under aseptic conditions, and thus protecting the test system and the study by minimizing the probability of their contamination by test and reference item preparations.

Apparatus, Material, and Reagents

While the commonly observed, routine requirements for apparatus used in a GLP compliant environment apply equally to apparatus used for *in vitro* studies, there are some specific points and issues of particular importance. As an example, it may be of importance for the integrity and reliability of some *in vitro* studies to ensure that the proper conditions of certain equipment, like microbalances, micropipettes, laminar air flow cabinets or incubators are regularly maintained, and monitored and calibrated where applicable. For specific equipment, critical parameters should be identified requiring continuous monitoring or the setting of limit values together with installation of alarms.

The requirements in the GLP Principles for reagents with respect to labelling and expiry dates apply equally to those used for *in vitro* studies.

Test Systems

in vitro test systems are mainly biological systems, although some of the more recent developments in alternatives to conventional in vivo testing (e.g., gene arrays for toxicogenomics) may also exhibit some attributes of physical-chemical test systems, and still others, e.g., toxicometabonomics, may mainly rely on analytical methodology. Test kits, including proprietary test kits, should also be considered as test systems.

a) Conditions for Test Systems

As for any other biological test systems, adequate conditions should be defined, maintained and monitored to ensure the quality and integrity of the test system. during storage and within the study itself. This includes the documented definition, maintenance and monitoring of the viability and responsiveness of the test system, including recording of cell passage number and population doubling times. Records should also be kept for environmental conditions (e.g., liquid nitrogen level in a liquid nitrogen cryostorage system, temperature, humidity and CO2 concentration in incubators, etc.) as well as for any manipulation of the test system required for the maintenance of its quality and integrity (e.g., treatment with antibiotics or antifungals, subcultivation, selective cultivation for reducing the frequency of spontaneous events). Since maintenance of the proper environmental conditions during the storage of test systems may influence data quality to a greater degree than for other biological systems, these records may be of special importance in the maintenance of data quality and reliability.

b) Newly Received Test Systems

Documentation obtained from the supplier of *in vitro* test systems (e.g., origin, age/passage number, cell doubling time and other relevant characteristics that help identify the test system) should be reviewed and retained in the study records. Predefined criteria should be used to assess the viability, suitability (e.g. functional and/or morphological status of cells and tissues, testing for known or suspected microbial or viral contaminants) and responsiveness of the test system. Results of such evaluations should be documented and retained in the study records. If no such assessment is possible, as, e.g., with primary cell cultures or "reconstituted organs", a mechanism should exist between the supplier and the user to ascertain and document the suitability of the test system. Monitoring and recording performance against negative and positive control items may constitute sufficient proof for the responsiveness of a given test system. Any problems with the test system that may affect the quality, validity and reliability of the study should be documented and discussed in the final report. Problems with vendor-supplied test systems should be brought to the attention of the vendor and corrective measures sought.

c) Test System Records

The GLP Principles require that records be maintained of source, date of arrival and arrival condition of test systems; for cells and tissues these records should include not only the immediate source (e.g., commercial supplier), but also the original source from where the cells or tissues have been derived (e.g., primary cells or tissues with donor characteristics; established cell lines from recognized sources, etc.). Other information to be maintained should include, but not be limited to, the method by which cells or tissues were originally obtained (e.g., derived from tissue explants, biopsies of normal or cancer tissues, gene transfer by plasmid transfection or virus transduction, etc.), chronology of custody, passage number of cell lines, culture conditions and subcultivation intervals, freezing/thawing conditions, etc. For transgenic test systems, it is necessary, in addition, to ascertain the nature of the transgene and to monitor maintenance of expression with appropriate controls.

Special attention should be paid to the proper labelling of test systems during storage and use, which includes measures to ensure the durability of labelling. Especially where the size of containers and the conditions of storage (e.g., cryovials in liquid nitrogen, multiple test systems stored in one container) may be critical factors for labelling, measures should be in place to ensure the correct identification of test systems at all times.

The requirements in the OECD Principles of GLP for test items and reagents with respect to labelling and expiry dates apply equally to test kits used as *in vitro* test systems. Test kits, whether used as test systems or in any other way, e.g., for analytical purposes, should have an expiry date. Extending this expiry date can be only acceptable on the basis of documented evaluation (or analysis). For test kits used as test systems, such documented evaluation may, e.g., consist of the historical record of observed responses obtained with the respective batch of the test kit to positive, negative and/or vehicle control items, and proof that, even after the expiry date, the response did not deviate from the historical control values. A documented decision of the Study Director as to the extension of the expiry date should provide evidence for this evaluation process.
In order to avoid possible confusion, the nomenclature for the test systems should be clearly defined, and test system labels as well as all records obtained from individual studies should bear the formally accepted designation of the test system.

Test and Reference Items (including Negative and Positive Control Items)

In general, there are no specific requirements for receipt, handling, sampling, storage and characterisation for test and reference items that are used in studies utilising *in vitro* test systems besides those listed in the GLP Principles. Aseptic conditions may, however, be required in their handling to avoid microbial contamination of test systems.

For negative, vehicle and positive control items, it may or may not be necessary to determine concentration and homogeneity, since it may be sufficient to provide evidence for the correct, expected response of the test system to them.

The expiry date of such control items may also be extended by documented evaluation or analysis. Such evaluation may consist of documented evidence that the response of the respective test systems to these positive, negative and/or vehicle control items does not deviate from the historical control values recorded in the test facility, which should furthermore be comparable to published reference values.

Standard Operating Procedures (SOPs)

In addition to the examples cited in the GLP Principles (see section 7.4.1 – 7.4.5) there are activities and processes specific to *in vitro* testing that should be described in Standard Operating Procedures. Such SOPs should therefore be additionally available for, but not be limited to, the following illustrative examples for test facility activities related to *in vitro* testing.

a) Facilities

Environmental monitoring with respect to pathogens in the air and on surfaces, cleaning and disinfection, actions to take in the case of infection or contamination in the test facility or area.

b) Apparatus

Use, maintenance, performance monitoring, cleaning, and decontamination of cell and tissue culture equipment and instruments, such as laminar-flow cabinets and incubators; monitoring of liquid nitrogen levels in storage containers; calibration and monitoring of temperature, humidity and CO2-levels in incubators.

c) Materials, Reagents and Solutions

Evaluation of suitability, extension of expiry dates, assessment and maintenance of sterility, screening for common pathogen contaminants; description of procedures for choice and use of vehicles; verification procedures for compatibility of vehicles with the test system.

d) Test Systems

Conditions for storage and procedures for freezing and thawing of cells and tissues, testing for common pathogens; visual inspection for contaminations; verification procedures (e.g., use of acceptance criteria)

for ensuring properties and responsiveness on arrival and during use, whether immediately after arrival or following storage; morphological evaluation, control of phenotype or karyotype stability, control of transgene stability; mode of culture initiation, culture conditions with subcultivation intervals; handling of biohazardous materials and test systems, procedures for disposal of test systems.

e) Performance of the Study

Aseptic techniques, acceptance criteria for study validity, criteria for assay repetitions.

f) Quality Assurance

Definition of critical phases, inspection frequencies.

Performance of the Study and Reporting of Study Results

The GLP requirements for the performance of *in vitro* studies are identical to those provided for the more conventional safety studies. In many cases, the *OECD Advisory Document on The Application of the GLP Principles to Short-Term Studies* may be consulted in combination with the OECD GLP Principles in order that *in vitro* studies may be conducted in a GLP compliant way.

There are a number of issues specific to *in vitro* testing that should be addressed in the study plan as well as in the final study report. These issues, however, are mainly of a scientific, technical nature, such as the (scientific) requirement that any internal controls (appropriate positive, negative, and untreated and/or vehicle controls), carried out in order to control bias and to evaluate the performance of the test system, should be conducted concurrently with the test item in all *in vitro* studies. More specific guidance as to what topics should be addressed in the study plan and the final report will be found in the respective OECD test guidelines or other appropriate references.

Storage and Retention of Records and Materials

The general retention requirements of the GLP Principles apply to *in vitro* studies as well. Additionally, it should be considered to retain samples of long-term preservable test systems, especially test systems of limited availability (e.g., special subclones of cell lines, transgenic cells, etc.), in order to enable confirmation of test system identity, and/or for study reconstructability.

Retention of samples of test item should be considered also for such *in vitro* studies which can be categorised as short-term studies, especially in cases where *in vitro* studies constitute the bulk of safety studies.

Records of historical positive, negative, and untreated and/or vehicle control results used to establish the acceptable response range of the test system should also be retained.

Glossary of Terms

Within the context of this document the following definitions are used:

Aseptic conditions: Conditions provided for, and existing in, the working environment under which the potential for microbial and/or viral contamination is minimized.

Cell lines: Cells that have undergone a genetic change to immortalization and that, in consequence, are able to multiply for extended periods *in vitro*, and can be expanded and cryopreserved as cell bank deposits. A continuous cell line is generally more homogeneous, more stable, and thus more reproducible than a heterogeneous population of primary cells.

Control, negative: Separate part of a test system treated with an item for which it is known that the test system should not respond; the negative control provides evidence that the test system is not responsive under the actual conditions of the assay.

Control, positive: Separate part of the test system treated with an item the response to which is known for the test system; the positive control provides evidence that the test system is responsive under the actual conditions of the assay.

Control, untreated: Separate untreated part of a test system that is kept under the original culture conditions; the untreated control provides baseline data of the test system under the conditions of the assay.

Control, vehicle: Separate part of a test system to which the vehicle for the test item is added; the vehicle control provides evidence for a lack of influence of the chosen vehicle on the test system under the actual conditions of the assay.

Critical phases: Individual, defined procedures or activities within a study, on the correct execution of which the study quality, validity and reliability is critically dependent.

Cross-contamination: Contamination of a test item by another test item or of a test system by another test item or by another test system that is introduced inadvertently. and taints the test item or impairs the test system.

Cryopreservation: Storage of cells and tissues by keeping them frozen under conditions where their viability is preserved.

Cryovial: Special vial used for cryopreservation. A cryovial has to satisfy special conditions such as tightness of closure even at extremely low temperatures and extreme temperature changes encountered during freezing and thawing.

Ex vivo: Cells, tissues, or organs removed for further analysis from intact animals.

Gene transfection: The introduction of foreign, supplemental DNA (single or multiple genes) into a host cell.

High through-put screening: The use of miniaturized, robotics-based technology to screen large compound libraries against an isolated target gene, protein, cell, tissue, etc. to select compounds on the basis of specific activities for further development.

Micro-arrays: Sets of miniaturized chemical reaction areas arranged in an orderly fashion and spotted onto a solid matrix such as a microscope slide. A DNA microarray provides a medium for matching known and

unknown DNA samples based on base-pairing rules and allows for the automation of the process of identifying unknown DNA samples for use in probing a biological sample to determine gene expression, marker pattern or nucleotide sequence of DNA/RNA.

Primary cells: Cells that are freshly isolated from animal or plant sources. Freshly isolated primary cells may rapidly dedifferentiate in culture, and they often have a limited lifespan. Primary cultures isolated from animals or humans may represent heterogeneous populations with respect, for example, to differences in cell types and states of differentiation depending on purification techniques used. Each isolate will be unique and impossible to reproduce exactly. Primary cell cultures commonly require complex nutrient media, supplemented with serum and other components. Consequently, primary cell culture systems are extremely difficult to standardise.

Proprietary material: Material protected by (patent, copyright, or trademark) laws from illicit use.

Test kit: Ready-to-use compilation of all components necessary for the performance of an assay, test or study.

Tissues: Multicellular aggregates of differentiated cells with specific function as constituents of organisms.

Toxicogenomics: The study of how genomes respond to environmental stressors or toxicants. The goal of toxicogenomics is to find correlations between toxic responses to toxicants and changes in the genetic profiles of the objects exposed to such toxicants. Toxicogenomics combines the emerging technologies of genomics and bioinformatics to identify and characterize mechanisms of action of known and suspected toxicants. Currently, the premier toxicogenomic tools are the DNA microarray and the DNA chip, which are used for the simultaneous monitoring of expression levels of hundreds to thousands of genes.

Toxicometabonomics: The quantitative measurement of the time-related multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification by the systematic exploration of biofluid composition using NMR/pattern recognition technology in order to associate target organ toxicity with NMR spectral patterns and identify novel surrogate markers of toxicity.

Toxicoproteomics: The study of how the global protein expression in a cell or tissue responds to environmental stressors or toxicants. The goal of toxicoproteomics is to find correlations between toxic responses to toxicants and changes in the complete complements of proteins profiles of the objects exposed to such toxicants.

Transgenic cells: Cells transfected with one or more foreign gene(s) which consequently express characteristics and functions that are normally not present, or at low expression levels only, in the parental cell.

Sources for Further Information on *in vitro* Testing

Webpages of:

1. Good Cell Culture Practices
   http://ecvam.jrc.it/publication/index5007.html

2. MIAME Guideline
   http://www.mged.org/Workgroups/MIAME/miame.html

3. ECVAM
   http://ecvam.jrc.it/index.htm

4. ICCVAM
   http://iccvam.niehs.nih.gov/

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

11-Jun-2007

English - Or. Eng.

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2007)10
Unclassified

Cancels & replaces the same document of 04 June 2007

OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE MONITORING
Number 15

Advisory Document of the Working Group on Good Laboratory Pratice

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

English - Or. English

JT03228850

Also published in the Series on Principles of Good Laboratory Practice and Compliance Monitoring

No. 1, OECD Principles of Good Laboratory Practice (as revised in 1997)

No. 2, Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice (1995)

No. 3, Revised Guidance for the Conduct of Laboratory Inspections and Study Audits (1995)

No. 4, Quality Assurance and GLP (as revised in 1999)

No. 5, Compliance of Laboratory Suppliers with GLP Principles (as revised in 1999)

No. 6, The Application of the GLP Principles to Field Studies (as revised in 1999)

No. 7, The Application of the GLP Principles to Short-term Studies (as revised in 1999)

No. 8, The Role and Responsibilities of the Study Director in GLP Studies (as revised in 1999)

No. 9, Guidance for the Preparation of GLP Inspection Reports (1995)

No. 10, The Application of the Principles of GLP to Computerised Systems (1995)

No. 11, The Role and Responsibilities of the Sponsor in the Application of the principles of GLP (1998)

No. 12, Requesting and Carrying Out Inspections and Study Audits in Another Country (2000)

No. 13, The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies (2002)

No. 14, The Application of the Principles of GLP to in vitro studies (2004)

ABOUT THE OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 30 industrialised countries in North America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise 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 working 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 working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in nine different series: **Testing and Assessment; Good Laboratory Practice and Compliance Monitoring; Pesticides and Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; and Emission Scenario Documents.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (http://www.oecd.org/ehs/).

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

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co¬ordination in the field of chemical safety. The participating organisations are FAO, ILO, OECD, UNEP, UNIDO, UNITAR and WHO. The World Bank and UNDP are observers. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, 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 this and many other Environmental Health and Safety publications, consult the OECD's World Wide Web site (http://www.oecd.org/ehs/)

or contact:

**OECD Environment Directorate,
Environmental Health and Safety Division**

**2 rue André-Pascal
75775 Paris Cedex 16
France**

Fax: (33-1) 44 30 61 80

E-mail: ehscont@oecd.org

FOREWORD

The OECD Working Group on Good Laboratory Practice, at its 17th meeting in 2003, established a drafting group under the leadership of the Netherlands (Mr. Theo Helder), with participation by Germany, Italy, Sweden, Switzerland the United Kingdom and the United States. After reviewing existing material on archiving in a GLP environment, the group develop a first draft document, which was reviewed by the Working Group at its 20th meeting in 2006.

The Working Group agreed that it would circulate the draft for comment to stakeholders in industry and receiving authorities and that Members would prepared consolidated national comments. Comments were received from Australia, Belgium, Denmark, Finland, Germany, Ireland, Israel, Italy, Japan, Korea, Netherlands, Slovenia, Spain, Sweden, Switzerland, and United States. The Working Group then reviewed, amended and endorsed a revised version of the document at its 21st Meeting in 2007.

The Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology endorsed the document on 25 May 2007and agreed that it be declassified and published in the OECD series on GLP and Compliance Monitoring as an Advisory Document of the Working Group on GLP.

TABLE OF CONTENTS

1. INTRODUCTION 296

2. SCOPE 296

3. DEFINITION OF TERMS 285

4. ROLES & RESPONSIBILITIES 298

4.1 Sponsor 298
4.2 Test Facility Management 298
4.3 Archive Contracting Facility 298
4.4 Test Site Management 298
4.5 Study Director 299
4.6 Principal Investigator 299
4.7 Archivist 299
4.8 Information Technology (IT) Personnel 299
4.9 Quality Assurance (QA) Personnel 299

5. ARCHIVE FACILITIES 300

5.1 Archive Conditions 300
5.2 Disaster Recovery 301

6. SECURITY 301

6.1 Physical and Operational Security 301
6.2 Access to the Archive 301

7. ARCHIVING PROCEDURES 302

7.1 Standard Operating Procedures 302
7.2 Records and Materials to be retained 302
7.3 Indexing 303
7.4 Placement of Records and Materials into the Archives 303
7.5 Transfers 303
7.6 Retention Period 304
7.7 Retrieval 304
7.8 Disposal of Records and Materials 305

8. ARCHIVING ELECTRONIC RECORDS 306

8.1 Decision to Retain Records Electronically 306
8.2 Storage Media 306
8.3 Defined Archive Area on a Computerised System 306
8.4 Dedicated Electronic Archive System 306
8.5 Maintenance and Preservation of Electronic Records 307

9. QUALITY ASSURANCE 307

10. CONTRACT ARCHIVE SERVICES 307
10.1 Contracts and/or Service Level Agreements 307
10.2 Access Arrangements 307
10.3 Conditions of Storage 307
10.4 Inspections 307

11. CLOSURE OF AN ARCHIVE 308
11.1 Principle 308
11.2 Measures to be Taken 308
11.3 Inspections by Monitoring Authorities 308

12. REFERENCES 309

Advisory Document of the Working Group on GLP

ESTABLISHMENT AND CONTROL OF ARCHIVES THAT OPERATE IN COMPLIANCE WITH THE PRINCIPLES OF GLP

1. INTRODUCTION

The archiving of records and materials generated during the course of a non-clinical health or environmental safety study is an important aspect of compliance with the Principles of Good Laboratory Practice (GLP). The maintenance of the raw data associated with a specific study and the specimens generated from that study are the only means that can be used to reconstruct the study, enabling the information produced in the final report to be verified and the compliance with GLP of a specific study to be confirmed.

The purpose of the guidance contained in this document is to assist in conforming to the requirements of the OECD Principles of Good Laboratory Practice as they relate to archiving.

This guidance does not supersede any requirement set out in national regulations and/or legislation, e.g. pertaining to the timeliness of archiving or retention periods.

2. SCOPE

This document is intended for use by test facilities that are required to operate in compliance with the Principles of GLP, for organisations that supply support, e.g. contract archives, contract quality assurance units or IT services and for sponsors, GLP compliance monitoring authorities and receiving authorities.

Organisations should ensure that they evaluate applicable regulatory requirements against their business needs. Certain aspects of archive construction and operation may have implications for compliance with building regulations or legislation regarding public health and safety. Guidance on these aspects is outside the scope of this document.

Test facilities and other organisations, engaged in archiving GLP records and material, might benefit from the use of recognised archiving management standards including those concerning metadata.

3. DEFINITION OF TERMS

Archive: A designated area or facility (e.g. cabinet, room, building or computerised system) for the secure storage and retention of records and materials.

Archive Staff: Individuals who work under the supervision of the archivist and who are responsible for the routine archive operations.

Archivist: An individual designated by test facility or test site management to be responsible for the management of the archive, i.e. for the operations and procedures for archiving.

Electronic archives: Facilities and systems provided to maintain electronic records as required by the Principles of GLP.

Electronic record: 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.

Metadata: Data that describe the attributes of other data. Most commonly these are data that describe the structure, data elements, inter-relationships and other characteristics of electronic records.

Migration: The transfer of electronic records from one format, media or computerised system to another.

System Owner: The manager, or designee, of the department that is most impacted by, or is the primary user of, the system.

4. ROLES & RESPONSIBILITIES

4.1 Sponsor

The sponsor is assumed to play an active role in confirming that all non-clinical health and environmental safety studies are conducted in compliance with GLP.

The sponsor therefore should ensure that materials and records in support of regulatory studies are retained and maintained under conditions that ensure their integrity and continued access. Also if records and materials are transferred into the sponsor‘s possession, storage should be in archives that meet the requirements of the Principles of GLP. The sponsor should also ensure that such material and records are retained for as long as required by relevant authorities. The archive and retained materials and records should be available for inspection during normal office hours. If electronic records are kept, it should be possible to make them available in human readable form.

4.2 Test Facility Management

Test facility management is responsible for the provision of archive facilities. Test facility management is also responsible for the appointment of an individual and, if necessary, additional archive staff for the operation of the archives. A back-up archivist should also be appointed to perform the duties of the archivist in the event that the archivist is unable or unavailable to perform the archivist‘s duties. These appointments should be documented. When appointing the archivist and the back-up archivist, test facility management should avoid possible conflicts of interest through incompatibilities of functions.

Test facility management should ensure that the records and materials generated in the test facility that are necessary to reconstruct studies, and the documentation required to demonstrate the GLP compliance of the test facility, are archived.

Test facility management should ensure that appropriate archiving procedures are established.

Test facility management should ensure that only selected authorised personnel shall have access to the archive(s). Access should be controlled and the accessing procedure should be documented. Security and technical personnel should be granted access only when necessary (e.g. in case of emergencies) also in a controlled and documented manner.

Test facility management might be expected to inform sponsors on GLP requirements and the responsibilities of the sponsor regarding archiving where necessary.

4.3 Archive Contracting Facility

If a sponsor or test facility management uses a contract archive for the storage of records and/or materials for a GLP study, the contracting parties should ensure compliance with the relevant sections of the Principles of GLP.

4.4 Test Site Management

Test site management has the same responsibilities as test facility management with regards to archive facilities and procedures at their own site.

4.5 Study Director

The Study Director is responsible for ensuring that during or immediately after completion (including termination) of a study, all study related records and materials are transferred to the archive(s). The Study Director is responsible for the completeness of the study records and materials and for assuring that all materials are archived before or at the close of the study.

4.6 Principal Investigator

A Principal Investigator should ensure that records and materials for which he/she is responsible are sent to the Study Director, or transferred to an agreed archive location latest upon completion of the study or phase of the study. The Principle Investigator should inform the Study Director about the date of transfer or archiving.

4.7 Archivist

The archivist is responsible for the management, operations and procedures for archiving in accordance with established Standard Operating Procedures, and the Principles of GLP.

The archivist should therefore, inter alia,

– ensure that access to the archive is controlled;

– ensure that the orderly storage and retrieval of records and materials is facilitated by a system of indexing; and

– ensure that movement of records and materials in and out of the archives is properly controlled and documented

Where there is a need for several staff to perform archiving duties, staff should work under the direction and supervision of the designated archivist. It is recognized that in certain circumstances it may be necessary for the archivist to delegate specific archiving tasks, for example management of electronic record. Respective tasks, duties and responsibilities have to be specified and detailed in SOPs.

4.8 Information Technology (IT) Personnel

IT personnel involved in archiving operations (such as ensuring integrity of electronic records) should be adequately trained and their activities should conform to GLP requirements. Since activities pertaining to archiving are the primary responsibility of the archivist, these IT personnel ideally should work under the direction and supervision of the archivist. Because it is recognised that such organisational structures are not feasible in modern companies, the co-operation between the archivist and IT personnel should be ensured in other ways, for instance in SOPs or written service level agreements.

4.9 Quality Assurance (QA) Personnel

QA personnel are responsible for inspecting all aspects of archiving for compliance with the Principles of GLP. This includes the inspection of archiving operations and procedures, including procedures for electronic records, facilities, stored records and materials.

5. ARCHIVE FACILITIES

The archive facility should be suitably designed and constructed to accommodate the archived records and materials. This may be one or more buildings, rooms, safes or lockable cabinets or other locations that provide suitable security. The archive facility should be physically secure to prevent unauthorised access to the retained records and materials. The use of locks or electronic entry systems is required. The components that provide storage of unique electronic records should also be physically secure. The computerised archive facility should have processes to prevent unauthorised access and virus protection.

The building(s) or room(s) that house the archive should be constructed to withstand the elements of local weather, etc. Consideration may need to be given to specific local conditions such as a risk of flooding. The archive design should protect the contents from untimely deterioration for example by leakage of running water pipes in the archive areas. The risk of fire and explosion should be minimised. In most circumstances it will be necessary that an automated fire and/or smoke detection system be installed. Management may also consider an automated fire suppression system that minimises the risk of damage. If there is a risk of flooding, a water detector and/or water drain should be considered.

The archive facility should be designed to prevent the entry of rodent and insect pests. Where appropriate, pest control procedures should be in place.

Where necessary, back-up electrical power should be provided for all temperature-critical equipment (e.g., refrigerators and freezers).

5.1 Archive Conditions

Storage conditions should be designed to preserve and not adversely affect the quality and integrity of retained records and materials. Special storage conditions may be required to maintain the integrity of some retained record(s) and material(s) for the specified retention period(s). For example, it might be appropriate to store wet tissues, blocks and reserve samples of test items separate from paper and histology slides.

Special storage conditions may be required for particular materials. Examples are materials required to be stored frozen, refrigerated, desiccated, etc., or free from dust or magnetic interference in the case of electronic media. The need for special storage conditions should be defined in relevant test facility Standard Operating Procedures.

If special storage conditions have been defined, environmental monitoring procedures should be implemented within archive storage areas to confirm that specified conditions of storage are being achieved.

Where continuous (automated) monitoring systems are used (which may also act as alarms that are activated in the event that defined conditions are outside specified limits), these systems should be regularly maintained, tested, and verified, and records thereof retained, as required by the Principles of GLP.

5.2 Disaster Recovery

Test facilities and contract archives should have procedures in place to minimise damage to archived records and materials caused by adverse events. Some of the more common adverse events to be considered include fire, electrical failure, extreme weather-related damage, flooding, theft, and sabotage.

The procedures may cover protective measures that may be implemented, as well as the recovery and/or restoration of lost or damaged records and materials and re-establishment of security. The plan should include useful and emergency contacts, the location of necessary equipment, and the records that should be made (e.g., documentation of the event and the steps taken to resolve and/or restore).

6. SECURITY

6.1 Physical and Operational Security

The archive facility should be both physically and operationally secure to prevent unauthorised access and changes to or loss of retained records and materials. Test facility management should ensure security by implementing appropriate measures that should be described in the test facility‘s SOPs.

The security controls necessary to restrict access to electronic records will usually be different from those applied to other record types. Since many electronic storage media can be re-used (e.g. overwritten), measures should be implemented to ensure that records cannot be altered or deleted.

6.2 Access to the Archive

With normal archive operations, access to the archive should be controlled by and restricted to the archivist and archive staff. For emergency access (especially during off-hours or for safety reasons), emergency personnel may enter and/or operate the archive unaccompanied. Otherwise visitors should be accompanied by the archivist or a member of the archive staff. The procedures for access to archive storage areas should be documented. The record of such visits should be retained. For electronic archives the above mentioned restrictions might not be applicable, but as a minimum deletion or alteration of electronic records in electronic archives should be avoided. Management might authorise read-only access on electronic records to a broader community.

7. ARCHIVING PROCEDURES

7.1 Standard Operating Procedures

The following issues should be addressed in the Archive Standard Operating Procedures, where applicable:

- Access to the archives.
- Definition and description of the archive.
- Indexing procedures, including electronic records.
- Conditions under which records and materials should be stored.
- Procedures for the receipt of records and materials to be archived.
- Procedures for accessing, removal and return of records and materials.
- Responsibilities of the archivist and archiving staff.
- Security of the archive facility and the records and materials retained.
- Climate control.
- Retention period.
- Disposal of archived records and materials.
- Contract archiving services, if applicable.
- Transfer to sponsors or third parties, if applicable.
- Disaster recovery.
- Training requirements for the archivist and archiving staff.
- Frequency of archiving non-study specific records.
- Periodic refreshing of electronic records.

7.2 Records and Materials to be retained

Records to be retained include paper records, photographs, microfilms or microfiches, computer media, dictated observations, recorded data from automated instruments, or any other storage medium containing the data generated in the conduct of a non-clinical health or environmental safety study.

Materials to be retained include wet tissues, paraffin blocks, specimens, slides, smears, test materials/ retention samples, etc. Records and materials may be study-specific, or relate to more than one study.

7.2.1 Study-specific records and materials

These are the records and materials generated during the conduct of a single study in accordance with the study plan. The Study Director is responsible for ensuring these records and materials are transferred to the archives latest after study completion. These records may be inspected for verification of the results reported from a specific study and for the general assessment of the compliance of the study with Principles of GLP. The following are examples of study-specific records and materials that should be retained in the archives.

- Study plan, raw data, and the final report of each study.
- Other study related documents and communication such as e.g. delivery receipts, phone notes, faxes etc.
- Samples of test and reference items.
- Specimens.
- Certificates of Analysis.

7.2.2 Facility records and materials

These are records and materials that are generated by a test facility/site, and may be specific to one or more studies performed at the facility/site. Such records and materials may be inspected for the reconstruction of a study and for the general assessment of the continuing compliance of a test facility with Principles of GLP. Management should address in an SOP how and by whom the archiving of these records and materials should be carried out.

The following are examples of facility records and materials that should be retained:

- Records of all inspections performed by the Quality Assurance.
- Master Schedules.
- Organisational charts.
- Floor/site plans.
- Records of qualifications, training, experience and job descriptions of personnel.
- Records and reports of the maintenance and calibration of apparatus.
- Validation documentation for computerised systems.
- Historical files of all Standard Operating Procedures.
- Environmental monitoring records.
- Samples of test and reference items, if used for more than one study.
- Certificates of Analysis, if used for more than one study.

7.3 Indexing

The Principles of GLP require that records and materials retained in the archives be indexed so as to facilitate orderly storage and rapid retrieval. The system of indexing employed should facilitate the retrieval of all information required to reconstruct a study from both the study and the facility records.

7.4 Placement of Records and Materials into the Archives

On completion (including termination) of a study the Study Director is responsible for ensuring that all study documentation, data and related records and materials are archived in a timely manner. The Study Director retains responsibility for the integrity of study documentation, data and related records and materials until they are accepted into the archive. Test facility management is responsible for maintaining the integrity of the records and materials once they are transferred to the archives. Test facility management should ensure that a time period for the transfer of material from the Study Director to the archivist is defined that is in compliance with national regulatory requirements, where existent.

Prior to transferring records and materials to the archive, the Study Director is responsible for establishing an inventory to be archived, confirming completeness of records and materials, and ensuring that these records and materials are transferred in their entirety to the archive. The archivist or archive personnel should check the completeness of records and materials upon their arrival by comparison with the inventory list and acknowledge receipt.

Test Facility Management should ensure that non study specific (facility) records such as maintenance records, staff training records, organisational charts, etc. are archived on a regular basis defined by test facility SOP. Procedures for archiving these records and materials should be similar to those employed for study records and materials.

In multi-site studies, procedures for archiving records and materials generated at individual test sites should be agreed upon and documented prior to/ or at the initiation of the study.

The Principal Investigator should notify the Study Director of the transfer of study materials to the archive.

7.5 Transfers

On occasion it may be necessary to transfer archived records and materials from one archive to another at a different physical location. The archivist transferring the records and materials, including electronic records, should ensure that there is a documented agreement and transfer plan between test facility management, management at the receiving facility and the sponsor before any transfer occurs. The documentation should include details of the records and materials to be transferred, the contact details/address of the receiving facility, and the means of transfer between locations.

Records and materials to be transferred should be clearly described in appropriate chain of custody documentation prepared by the archivist. The transportation of the material, and associated paperwork, between the two locations should be undertaken in such a way as to minimise the risk of loss or damage of the records and materials.

The recipient of the transferred records and materials should check that they correspond with the associated chain of custody documentation, and once accepted, the recipient becomes responsible for ensuring that anything is maintained and preserved appropriately. All parties involved in the transfer should retain copies of the chain-of-custody documentation. Transfer of archived materials between computerised archive systems should be documented and conducted according to a migration plan.

7.6 Retention Period

Retention periods should be, and in some countries are, defined by regulatory (receiving) authorities. The retention period defines the minimal period of time that data must be retained and must be available for review if the safety studies that support the registration of new products or marketed products need to be verified. It is strongly recommended that records and other sustaining material associated with such safety studies be retained for as long as regulatory authorities might request GLP audits of the respective studies.

When performing routine test facility inspections that include the carrying out of study audits, monitoring authorities and/or their inspectors will normally select studies completed or performed since the previous inspection or, in some countries, the two previous inspections. If the retention periods have not been defined by an applicable regulatory authority, it is highly recommended that records and materials should be retained for at least three inspection cycles so that inspectors can evaluate the compliance of the test facility with the Principles of GLP. For those studies that will not be submitted to regulatory authorities it may be acceptable (if justified) to dispose of the study specific records and materials after this period.

The Principles of GLP state: *"a sample for analytical purposes from each batch of test item should be retained for all studies except short-term studies"*. Samples of test and reference items may however be discarded when the quality of the material no longer permits evaluation. Obviously the storage conditions should be optimal for these samples. When samples of test and reference items or specimens are disposed of before the end of the required retention period, the reason for disposal should be justified and documented.

Perishable specimens, such as blood smears, freeze-dried preparations and wet tissues, may also be discarded when they can no longer be read or evaluated. For non-perishable specimens the general guidance will apply.

Electronic media may be discarded when the media itself no longer permits evaluation (due to hardware or software issues) provided the disposal is authorized, documented, and electronic records are migrated and any record losses documented.

7.7 Retrieval

Appropriate procedures should be established for retrieval of archived records and materials. These procedures should define the circumstances under which they may be removed from the archive (e.g. for inspection/ regulatory purposes, by sponsor, etc.). The procedures should also describe in detail who is permitted to withdraw records and materials, who can authorise removal of records and materials and the timeframe within which records and materials should be returned to the archives.

Viewing electronic records without the possibility of alteration or deletion of the archived electronic record or replicating within another computerized system does not constitute "retrieval" of a record.

The Principles of GLP require that movement of records and materials in and out of the archives should be properly recorded. There should be mechanisms in place to enable the archivist to track the movement of records and materials from and back to the archive and to identify any records and materials not returned within the specified timeframe. On return to the archive, the records and materials should be verified by the archivist or a designed member of the archive staff to be complete and unaltered. Management should be informed of any discrepancies.

7.8 Disposal of Records and Materials

Test facility management's and, if applicable, the sponsor's authorisation should be obtained before the disposal of any archived records and materials. The reasons for disposal should be recorded. It may be appropriate to inform QA. The disposal of archived records and materials should be documented.

8. ARCHIVING ELECTRONIC RECORDS

Requirements for the archiving of electronic records are the same as those for other record types, but there are additional features, which are addressed below. It is therefore important that management ensure that appropriate Standard Operating Procedures are established for the archiving of electronic media in a secure GLP environment.

8.1 Decision to Retain Records Electronically

The decision to retain records in electronic form has important implications. The long-term retention of electronic records may influence the choice of storage medium since deterioration of storage media can lead to permanent loss of records. Computer technology is developing rapidly and devices capable of reading storage media in common use today may not be available in the future. Electronic records should be stored in a format that is readable for the duration of the applicable record retention period.

8.2 Storage Media

Records may be migrated from a computerised system onto a storage medium, e.g. magnetic tape, diskette, CD or optical disk that can be placed in a physical archive. Archive procedures should include the consideration of additional controls for the migration of electronic records from old to new media of these records. Consideration should be given to future access to the data or records stored on these media. There may be a need for special storage conditions, e.g. protection from magnetic fields.

8.3 Defined Archive Area on a Computerised System

Electronic records may be moved from the production part of a computerised system to a discrete, secure archive area on the same computer system (physically separated, e.g. file record systems), or explicitly marked as archived (logically separated, e.g., database record systems). Records should be "locked"

such that they can no longer be altered or deleted without detection. Records archived in this way must be under the control of a designated archivist and be subject to equivalent controls to those applied to other record types.

8.4 Dedicated Electronic Archive System

Records may be migrated from the computer system that captured or manipulated them into a separate dedicated electronic archive system. All data associated with the reconstruction of the study needs to be migrated. This includes, but is not limited to raw data, metadata, audit trails, e-signatures and associated hardware and software that allow availability of all records in the future.

Where ideally the archivist should be the system-owner for the electronic archive system, it is recognised that the electronic archive system is likely to be managed by information technology (IT) personnel. The archivist, being ultimately responsible for managing the archive, has an important role in helping to ensure that regulatory requirements are met. Test facility management should, therefore, take care that the co-operation and co-ordination between the archivist and information technology personnel is ensured.

These IT staff should follow procedures agreed with the archivist and/or test facility management.

8.5 Maintenance and Preservation of Electronic Records

Electronic records are at risk without a preservation process to ensure that these records are available in the future. Procedures should be in place to ensure that essential information remains complete and retrievable throughout the specified retention period. If the record medium requires processing in order to render the retained records into a readable format, then the continued availability of appropriate equipment should be ensured. If availability cannot be guaranteed, the possibility of migrating data from one medium to another should be considered.

If electronic record migration is necessary, the process of migration should be fully documented, and validated to ensure complete and accurate migration of the original records before they are lost or destroyed. If it is impossible to migrate the records to new electronic media it may be necessary to migrate to paper records. Duplication of electronic archives should be considered as part of an archive preservation plan.

9. QUALITY ASSURANCE

Archive facilities and processes constitute an important component of a GLP compliant test facility. These aspects should, therefore, be subject to routine quality assurance (QA) inspections and audits. When archived records and materials are transferred, the transfer process should be monitored by the conduct of directed QA inspections.

10. CONTRACT ARCHIVE SERVICES

The Principles of GLP require that a test facility has an archive to provide secure storage of records and materials. This will usually consist of archive facilities within the test facility itself, but the use of contract archive facilities is not precluded. In this situation, the guidance contained within this document should equally apply to the contract archive facilities. Contract archive facilities are involved in processes dealing with GLP studies and thus should be subject to inspections by Quality Assurance Programs, and by Monitoring Authorities, to assess the compliance with the GLP Principles.

The following factors need to be considered when using contract archive facilities:

10.1 Contracts and/or Service Level Agreements

There should be a formal agreement that details the level and conditions of service to be provided by the contract archive facility. This agreement should cover the description of the records and materials to be archived, the transportation of records and materials to the archive, chain of custody, access to stored records and materials by the contract archive, services provided (e.g. regular check of containers for wet tissues), safety, storage conditions, duration of storage, method of retrieval/access and method of return/disposal, QA activities and responsibilities, and other considerations as addressed in this document. The contract archive organisation should follow relevant SOPs, either their own, or, in their absence, those provided by test facility management. This should be specified in the agreement.

10.2 Access Arrangements

Procedures should define how, and when, stored records and/or materials can be accessed by the depositor of the records and/or materials. Any such access should be approved and documented.

10.3 Conditions of Storage

The conditions of storage and the procedures followed by the contract archive facility should be the same standard as those expected of a test facility archive which is operated in compliance with the Principles of GLP. This will include the appointment of a suitably qualified archivist, written and approved SOPs describing archiving related activities and the provision of suitable storage areas to prevent deterioration or loss of stored records and materials.

10.4 Inspections

Periodically the contract archive facility should be inspected by Quality Assurance from or on behalf of the test facility or the sponsor, where applicable, to ensure that the conditions of the service level agreement are being met and that the systems and procedures operated by the contract archive facility comply with their SOPs and the Principles of GLP.

11. CLOSURE OF AN ARCHIVE

11.1 Principle

The OECD Principles of Good Laboratory Practice (in Section 10.4) state: 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)".

11.2 Measures to be Taken

If a test facility or test site no longer intends to operate the archive in compliance with the Principles of GLP or goes out of business, the following measures have to be taken:

- The applicable national GLP compliance monitoring authority should be informed in a timely manner by the test facility.
- Test facility management should ensure that sponsors are informed as soon as possible once a decision is made to close the archive or if the facility goes out of business. Sponsors should ensure that all study-related records and materials are transferred to an alternate GLP compliant archive and retained for the period specified by the appropriate authorities.
- For non study specific (facility) records or records which relate to studies of more than one sponsor and that should be retained according to the Principles of GLP, test facility management should agree with the sponsors on how to ensure that these records and materials are archived in a GLP compliant archive after the closure of the test facility or archive for the period specified by the appropriate authorities. Access of the sponsors to these study- related records and materials should be agreed upon and documented.

11.3 Inspections by Monitoring Authorities

After the transfer to a new archive facility has taken place the GLP monitoring authority will normally inspect the new archive. In case records or materials are transferred to facilities located in another country, the GLP monitoring authority in that country should also be informed.

12. REFERENCES

OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17, OECD, Paris, 1998. (No.1 in OECD Series on Good Laboratory Practice and Compliance Monitoring)

Revised Guidance for the Conduct of Laboratory Inspections an Study Audits, Environment Monograph No. 111, ENV/GD/(95)67, OECD, Paris, 1995 (No.3 in OECD Series on Good Laboratory Practice and Compliance Monitoring)

The Application of The Principles of GLP to Computerised Systems, Environment Monograph No. 116, OECD/GD(95)115, OECD, Paris, 1995. (No. 10 in OECD Series on Good Laboratory Practice and Compliance Monitoring)

DOI 10.2471/TDR.09. 978-924-1547550

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

TDR/World Health Organization
20, Avenue Appia
1211 Geneva 27
Switzerland

Fax: (+41) 22 791-4854
tdr@who.int
www.who.int/tdr

The Special Programme for Research and Training in Tropical Diseases (TDR) is a global programme of scientific collaboration established in 1975. Its focus is research into neglected diseases of the poor, with the goal of improving existing approaches and developing new ways to prevent, diagnose, treat and control these diseases. TDR is sponsored by the following organizations:

ISBN 978 92 4 154755 0

unicef UNDP World Bank World Health Organization