

The Principles of Good Laboratory Practice: Application to *In Vitro* Toxicology Studies

The Report and Recommendations of ECVAM Workshop 37^{1,2}

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Preface

This is the report of the thirty-seventh of a series of workshops organised by the European Centre for the Validation of Alternative Methods (ECVAM). ECVAM's main goal, as defined in 1993 by its Scientific Advisory Committee, is to promote the scientific and regulatory acceptance of alternative methods which are of importance to the biosciences and which reduce, refine or replace the use of laboratory animals. One of the first priorities set by ECVAM was the implementation of procedures which would enable it to become well-informed about the state-of-the-art of non-animal test development and validation, and the potential for the possible incorporation of alternative tests into regulatory procedures. It was decided that this would be best achieved by the organization of ECVAM workshops on specific topics, at which small groups of invited experts would review the current status of *in vitro* tests and their potential uses and make recommendations about the best ways forward (1). In addition, other topics related to the Three Rs (reduction, refinement, replacement) concept of alternatives to animal experiments have been considered in several ECVAM workshops.

ECVAM brought together experts in the field of cell culture technology and Good Laboratory Practice (GLP) to stimulate the use and acceptance of *in vitro* toxicology data during the human risk assessment process, at both the European and world levels. The ECVAM workshop on The Principles of Good Laboratory Practice: Application to *In Vitro* Toxicology Studies was held in Angera, Italy, on 6-9 December 1998. The workshop was chaired by Robin Cooper-Hannan (Qualitas, Hurstpierpoint, UK) and John Harbell (Institute for *In Vitro* Science, Gaithersburg, MD, USA), and was attended by cell culture technologists, toxicologists and quality assurance personnel from industry, academia and government. The aim of the workshop was to discuss and make recommendations on the application of the OECD Principles of GLP to good quality cell and tissue culture practices. In addition to reviewing the application of GLP to single-site and multi-site studies, this document pays specific attention to multi-study *in vitro* toxicology trials, including ECVAM's prevalidation/validation studies which employ blind-coded chemicals. The consensus reached at the workshop was that validation efforts for *in vitro* toxicology studies should be carried out under GLP, to facilitate the regulatory acceptance of high quality validated *in vitro* tests.

Introduction

The Principles of GLP are intended to identify the GLP requirements for test facilities (laboratories) which perform studies for regulatory purposes. These principles define a quality system concerned with the organisational process and the conditions under which studies are planned, performed, monitored, recorded, reported and archived. GLP is concerned with the quality of test data and the management of quality studies. The generation of test data according to current scientific knowledge and good management practices has been seen as the best way of promoting the reliability, and hence the international acceptability, of data. GLP addresses an overall structure intended to promote and maintain quality data. Being a management practice, these principles do not interfere with the use of scientific knowledge or practices, but rather complement it.

The Principles of GLP were originally written to address animal-based toxicology. However, there has been a growing appreciation that certain additions/modifications are required to meet the current state-of-the-art for *in vitro* studies and to assure the quality of the data they provide. To this end, ECVAM and the Institute for *In Vitro* Sciences (IIVS) convened the workshop on GLP. It should be emphasised that this workshop was not an effort to diminish the Principles of GLP, but to enhance them. It drew on successful approaches used by industry, quality assurance professionals and regulatory agencies with *in vitro* bioassays. The primary goals were:

- a. to recommend additions/modifications to the OECD Principles of GLP needed to address the specific needs of *in vitro* bioassays (for example, test system characterization, facilities);
- b. to formalise standards of practice to ensure quality data from *in vitro* studies (for example, use of controls and performance standards);
- c. to provide assistance in the implementation of the Principles of GLP; and
- d. to address the specific needs of prevalidation and validation with respect to *in vitro* toxicology multi-study trials.

The current OECD Principles of GLP, which were adopted by the OECD in 1997 (2), were used as the primary GLP reference for this workshop report.

The report commences with a general account of GLP, including the history of GLP, and outlines the types of studies which this document addresses (single-site and multi-site studies and multi-study trials). The OECD Principles of GLP are presented, in tabular form, with additions and modifications applicable to *in vitro*. The OECD Principles of GLP primarily address the needs of single-site and multi-site studies (2-5). The application of GLP to prevalidation and validation in multi-study trials involving blind-coded chemicals is a special case, for which additional guidelines are necessary. Therefore, this report also discusses the organization of multi-study trials, including the terms "trial plan" and "trial report".

Definitions of terms used in the OECD Principles of GLP are presented in Appendix 1. Amendments and additional terms, as defined by the workshop participants, are presented as bold and underlined text.

Scope of the Principles of Good Laboratory Practice

The OECD Principles of GLP are intended to be applied to the non-clinical safety testing of test items contained in pharmaceuticals, pesticides, cosmetics and veterinary drugs, as well as medical devices, food additives, feed additives and industrial chemicals. These test items are frequently synthetic chemicals, but can be of natural or biological origin and, in some circumstances, can be living organisms. The purpose of testing these items is to obtain data on their properties and/or their safety with respect to human health and/or the environment.

The OECD has stated 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". Therefore, it is relevant to validate the increasing numbers of *in vitro* toxicology studies in accordance with GLP, in order to facilitate their acceptance by Member Countries (6, 7).

History of the Principles of Good Laboratory Practice

In 1975, the US Food and Drug Administration (FDA) raised concerns about the quality and integrity of some safety studies submitted to them. This inquiry resulted in the production by the FDA of proposals for GLP regulations in 1976, to provide guidance to test facilities for promoting the development of quality data. A task force of FDA investigators was set up to conduct a pilot programme of inspections. Between 1976 and 1978, the inspectors looked at 98 laboratories (mostly in the USA, but some in Europe) to determine conformity with the proposed GLP regulations. These investigations showed that the integrity of some studies was open to question, revealing problems so severe that studies could not be relied upon for regulatory decision-making. The conclusion of the FDA's review of laboratories was that there was an obvious need for improving standards across industry as a whole.

In 1978, the FDA issued the regulations specifying the principles of GLP for adequate safety testing. These regulations became law in the USA in 1979. This established the FDA as the first government agency to assess laboratory compliance with GLP regulations. In 1987, the FDA regulations on GLP were revised. The FDA's action stimulated much interest in the US Environmental Protection Agency (EPA), in other countries and in international organizations such as the OECD.

The FDA Principles of GLP provided the basis for the OECD Principles of GLP published in 1981. These OECD Principles of GLP were set out as an integral part of the OECD Decision on Mutual Acceptance of Data in the Assessment of Chemicals. The OECD identified three essential elements on which the mutual acceptance of data can be based, namely: the application of the OECD Principles of GLP; the establishment of harmonized national GLP compliance programme and guidance for national inspectors in the performance of inspections and audits; and the use of the OECD Test Guidelines.

Since the OECD Principles of GLP were adopted by Member Countries, including the European Economic Community (notably via *Directives 87/18/EEC, 88/1320/EEC and 90/18/EEC*), the interpretation of GLP is essentially the same among OECD Member Countries (8, 9). After a decade and a half of use, the OECD 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 area of safety testing. This led to the revised OECD Principles of 1997 (2).

Claiming Good Laboratory Practice Compliance

The requirements of national GLP compliance programme can vary among countries. It can be the case that a test facility might only be able to claim formal GLP compliance if it is within a compliance programme run by the relevant national GLP Monitoring Authority. It is recommended that a test facility should clarify this, as appropriate, with the applicable national GLP Monitoring Authority. Test facilities within a national GLP compliance programme are periodically visited by government inspectors who undertake a comprehensive assessment and determine the status of GLP compliance (10).

The quality assurance (QA) monitoring of a participating test site in a study, which is not within a national GLP compliance programme, might not confer formal GLP compliance. If work is conducted in a non-GLP compliant facility, in support of a GLP study consideration should be given to informing the relevant national GLP Monitoring Authority. Study reports and trial reports must clearly identify facilities which do not adhere to formal GLP, and must address any impact that non-compliance could have had on integrity of the study.

Regulatory and Non-Regulatory Studies

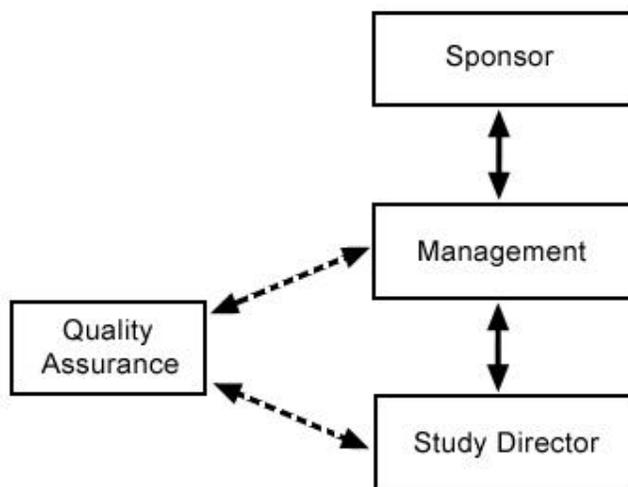
A test facility can conduct both "regulatory studies", intended for review by the regulatory authorities, and "non-regulatory studies" (including test development and fundamental research) which are not intended for submission to the regulatory authorities. Where this is the practice in the same GLP area, it will be necessary for the non-regulatory work to also be conducted in compliance with GLP. Essentially, the main differences between such regulatory and non-regulatory studies is that the latter can be subject to reduced QA monitoring and can have fewer specific GLP documentation requirements.

Study Organisation

Single-Site Studies

The original OECD Principles of GLP, issued in 1981, were primarily considered for single-site studies (Figure 1). A single-site study is one in which the test facility, the Study Director and all study procedures are based in one location. The Study Director is the individual responsible for the overall conduct of a study. The role of Study Director is of central importance in GLP (see section on Study responsibilities). Each single-site study, conducted in accordance with GLP, has one Study Director, one study plan and one study report.

Figure 1: Organisation of a Single-Site Study

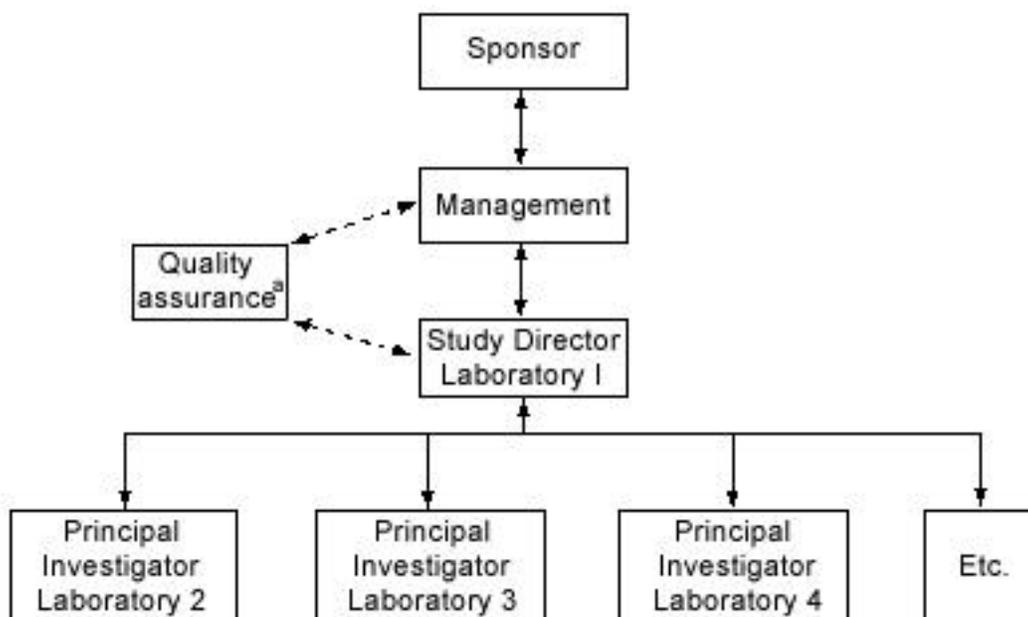


Dashed lines indicate quality assurance staff involvement.

Multi-Site Studies

Safety studies in a variety of disciplines, most notably in studies examining the fate of chemical substances in the environment (field studies) are often undertaken as multi-site studies. A multi-site study is one study with one Study Director, but involving several test sites, which can be geographically remote and or in separate institutions (Figure 2). Each multi-site study, conducted in accordance with GLP, has one Study Director, one study plan and one study report (3, 4).

Figure 2: Organisation of a Multi-Site Study



^aQuality assurance staff will also have communication links with each laboratory.

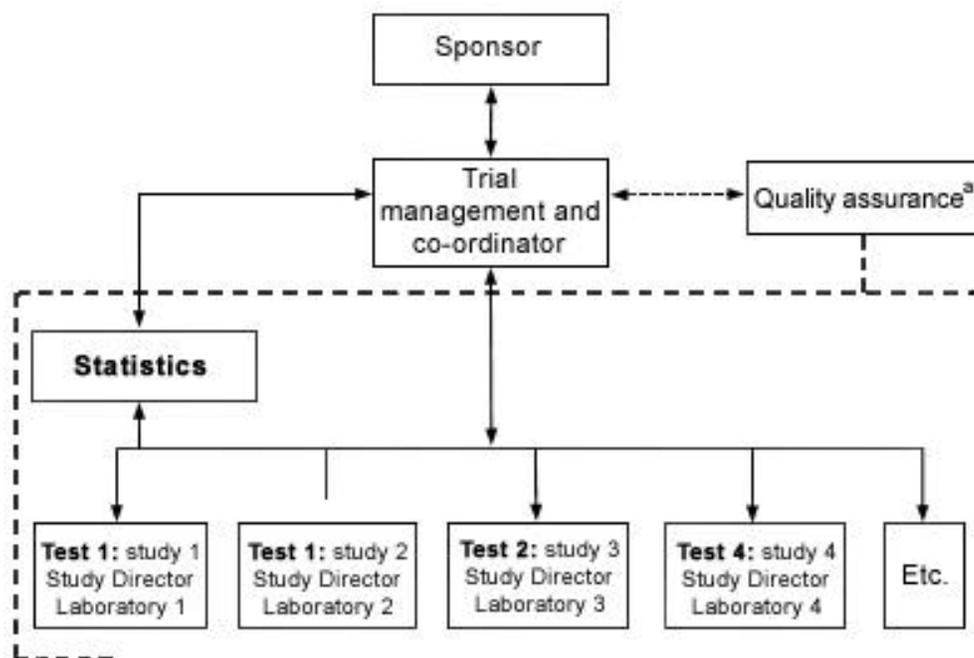
Dashed lines indicate quality assurance staff involvement.

A multi-site study can present a challenge with respect to the need for the Study Director to maintain responsibility for the overall conduct of the study. The OECD recognised this and introduced the role of Principal Investigator into the revised OECD Principles of GLP of 1997 (2). In a multi-site study, the Principal Investigator is an individual who acts on behalf of the Study Director and who has defined responsibilities for delegated phases of the study. Principal Investigators prepare contributory reports on their work for the Study Director. The role and responsibilities of the Principal Investigator are discussed in section 3.1.4.

Multi-Study Trials

A multi-study trial, such as interlaboratory prevalidation/validation blind trials (11-13), will consist of two or more related studies in relation to each test undergoing prevalidation/validation, with each study being independent and separate from the other studies. Therefore, each study will have its own Study Director, study plan and study report, and each study might be conducted as either a single-site or a multi-site study (Figure 3). The blind nature of these trials means that the Study Director and study personnel are not fully aware of details about the test items during the conduct of the study, or during the preparation and finalisation of the study report.

Figure 3: Good Laboratory Practice Organisation for a Multi-Study Trial (Including Prevalidation and Validation Studies)



^aSeveral quality assurance units might be involved in a multi-study trial.

Dashed lines indicate quality assurance staff involvement.

The study reports are forwarded to an independent facility for data and statistical analyses and for preparation of the trial report. Through necessity, the participating laboratories will be reporting results on coded test items and so cannot address the analytical requirements of GLP compliance. The management and reporting of multi-study trials are further discussed later.

The Principles of Good Laboratory Practice and *In Vitro* Studies

This section discusses the Principles of GLP and their application to *in vitro* studies. The text should be read together with the tables and [Appendix 1](#).

The OECD Principles of GLP have been presented by the OECD in ten GLP topics. The OECD text for these topics is presented in Tables 1-10 (the first topic is covered by Tables 1A-1C). The additions and modifications recommended by the workshop participants are shown as bold and underlined text, and the topics not considered relevant to *in vitro* studies are shown as italicised and underlined text.

Test Facility Organisation and Personnel

The Principles of GLP relevant to the test facility are presented in Table 1A-1C.

Test Facility Management's responsibilities

The Principles of GLP related to Test Facility Management's responsibilities are shown in Table 1A.

The primary GLP responsibility of Test Facility Management is to ensure that a sufficient number of qualified personnel, and appropriate facilities, equipment and materials, are available for the timely and proper conduct of studies. The test facility includes the persons, premises and operational units necessary for the conduct of a study. The test site is the location(s) at which a phase(s) of a study is conducted in a multi-site study. It is important to document the name of the person who acts as Test Facility Management, in terms of GLP. In general, it will be the level of management which has overall responsibility for ensuring GLP compliance. The roles of Test Facility Management, Study Director and QA manager should each be performed by different persons, so that there are checks and balances in the overall programme. Test Facility Management is not the same as the Trial Management Team, which has responsibilities for the overall conduct of a multi-study trial and is discussed later in this document.

Study Director

The Study Director is appointed by Test Facility Management. When appointing a Study Director to a study, management should be aware of that individual's current or anticipated workload. The Master Schedule, as described below, lists the studies planned, in progress and completed, and should be used as a reference when appointing a Study Director.

In the event that a Study Director has to be replaced during a study (for example, because of a career change), it will be necessary for Test Facility Management to issue a statement detailing the change and the reason, and naming the replacement Study Director. The date on which the change is to take effect should also be noted. A study plan amendment should be prepared to record this change, and should be signed by the replacement Study Director, Test Facility Management and, if applicable, the sponsor.

At the time of replacement, it is the responsibility of the replacement Study Director to determine whether the study has been conducted in compliance with GLP. If any GLP deficiencies are noted during this review, it is the responsibility of the replacement Study Director to fully document them.

Principal Investigator

Test Facility Management should ensure in a multi-site study, that, if needed, a Principal Investigator is designated who is appropriately trained, qualified and experienced, and whose understanding of GLP is sufficient for supervision of the delegated phase(s) of the study. The replacement of a Principal Investigator should be done according to procedures established by Test Site Management and be similar to those for the replacement of a Study Director.

Organisation chart

An organization chart for the test facility should be available, which should include the identity of the most senior manager who has overall responsibility for GLP compliance and should include the lines of reporting and communication in the test facility. The chart should identify the main job areas associated with GLP, and should identify the individuals who have designated responsibilities with respect to GLP organization. Includes the maintenance of lists of individuals who can be appointed as a Study Director and, where appropriate, a list of those individuals who can be appointed as Principal Investigators. Other positions appropriate for the organisation chart are laboratory manager, test substance controller, Standard Operating Procedure (SOP) administrator, archivist and QA personnel. Superseded organization charts and superseded lists of designated Study Directors and Principal Investigators should be retained in the archives.

Master schedule

Reference to the Master Schedule is a useful means for Test Facility Management to identify the allocation of resources. The Master Schedule is used to assess the volume of work being performed and by which individuals. It also permits an awareness of studies planned, in progress and completed.

The Master Schedule should normally provide the following study information: unique study identification, test system, test item, nature of study, name of Study Director/Principal Investigator and start and completion study dates. The inclusion of further information, such as the date of the issue of the study report and the date of archiving, is considered appropriate.

The Master Schedule at the test facility must show overall dates and the identity of the Study Director, whereas a Master Schedule at a test site need only show local dates and local activities, and the identity of the relevant Principal Investigator.

In some test facilities, there is the conduct of both regulatory studies, intended for submission to the regulatory authorities, and non-regulatory studies, for example, test development and fundamental research studies. Non-regulatory studies can be conducted under GLP, but can have a reduced amount of QA monitoring and reduced specific GLP documentation requirements. Where a laboratory has these two types of studies, it is appropriate to identify in the Master Schedule which are the regulatory studies and which are the non-regulatory studies.

Site plans

Site plans are relevant documents for Test Facility Management, since they can be used to demonstrate that laboratories are well organised and that there is adequate and appropriate separation of activities and functions. Site plans need not be detailed, such as in engineering site plans, but they should be dated and should indicate the main functional areas, such as test item store, formulation area and archives. Superseded site plans should be archived.

Personnel records

Test Facility Management must ensure the maintenance of a record of the qualifications, training, experience and job description of each professional individual with GLP responsibilities. Also, there must be assurance that personnel clearly understand the functions they are to perform and, where necessary, are provided with training for these functions.

It is usual for the qualifications, together with a brief account of education, employment history and experience, to be recorded in the form of a curriculum vitae.

Job descriptions will be presented in a GLP-compliant manner, if they include job title, qualifications and experience necessary for the position, reporting relationships and an outline of the key objectives of the job position, especially those objectives affecting GLP. Job descriptions should be signed by both employee and manager.

Training is usually documented in the form of an on-going training record listing specific tasks which need to be signed off before an individual can undertake such tasks without direct supervision. Training records are considered to be key GLP documents, since they demonstrate those procedures which an individual can undertake. One method that can be used by Test Facility Management, or the Study Director or QA personnel, to determine whether an individual has been trained in a given procedure, is to check the training record.

The need for restraining, for example, after a period of absence or when there have been procedural and technical revisions, should always be considered.

Training records should be described in a Standard Operating Procedure (SOP), which should address who should have training records and who can authorise training records. Training records should be considered for all grades of professional staff with GLP duties, to at least the level of Study Director. The SOP should describe where the training records are to be located, and should identify that a training record should be forwarded to the archives when an individual no longer has GLP responsibilities. The SOP should also outline the documentation for attendance at courses and conferences.

In certain cases, especially for personnel with advanced training, self-education and self-certification may be possible. Test Facility Management should judge whether and when this is appropriate.

Standard Operating Procedures

It is appropriate for Test Facility Management to ensure an individual has been assigned responsibility for the administration of the SOP system. Such a role serves to ensure that SOPs are reviewed at

appropriate time intervals, that new and revised SOPs are authorised and issued in a timely manner, that SOPs are appropriately distributed, and that a historical file of superseded SOPs is maintained. In multi-site studies it might be decided to assign an individual with SOP responsibilities for ensuring the administration and control of certain SOPs across test sites. SOP administration of this nature would need to be clarified in the study plan.

Test Site Management

In a multi-site study, Test Site Management will have the responsibilities defined in Table 1A, with the following exceptions:

- a. the appointment of the Study Director, and the replacement of the Study Director, if applicable;
- b. ensuring documented approval of the study plan by the Study Director;
- c. ensuring that the Study Director has made the approved study plan available to the QA personnel; and
- d. ensuring that clear lines of communication exist between the Study Director, Principal Investigator(s), study personnel and QA personnel.

Table 1A: Test Facility Organisation and Personnel

1.1 Test Facility Management's Responsibility
<p>1. Each Test Facility Management should ensure that the Principles of Good Laboratory Practice complied with in its test facility.</p>
<p>2. At a minimum it should:</p> <ul style="list-style-type: none"> a. ensure that a statement exists which identifies the individual(s) within a test facility who fulfils 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; 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 a historical file of all Standard Operating Procedures; l. ensure that an individual is identified as responsible for the management of the

<p>archive(s);</p> <p>m. ensure the maintenance of a master schedule;</p> <p>n. ensure that test facility supplies meet requirements appropriate to their use in a study;</p> <p>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> <p>p. ensure that test, reference and control items are appropriately characterised;</p> <p>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.</p>
<p>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: 2g, 2i, 2j and 2o.</p>

Recommended additions to the test are in bold and underlined.

Study Director's responsibilities

The Principles of GLP relevant to the Study Director's responsibilities are shown in Table 1B.

Table 1B: Test Facility Organisation and Personnel

<p>1.2 Study Director's Responsibilities</p>
<p>1. The Study Director is the single point of study control and has responsibility for the overall conduct of the study and for its <u>study</u> report.</p>
<p>2. These responsibilities should include, but not be limited to, the following functions. The Study Director should:</p> <ul style="list-style-type: none"> 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 <u>study</u> 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 active 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 <u>study</u> 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 <u>study</u> report, raw data and supporting materials are archived.

Recommended additions to the text are in bold and underlined.

The role of Study Director is of fundamental importance, and it is the Study Director who is accountable for ensuring the GLP compliance in the conduct of the study and in the study report. The Study Director is the single critical point of study control and must ensure clear lines of communication between the Study Director and study personnel.

Before any work on a study is undertaken, the Study Director should ensure that Test Facility Management have committed adequate resources, that study personnel are adequately trained, and that the equipment to be used in the study has been appropriately calibrated and maintained. The Study Director should also ensure that appropriate arrangements have been made for the supply of the test systems, and test, control and reference items, which meet the requirements of the study, and that there are appropriate SOPs for the study.

It is the responsibility of the Study Director to approve the study plan, and any amendments to the study plan, by dated signature. It is also the Study Director's responsibility to ensure that copies of the study plan, any amendments, and relevant SOPs are readily available to personnel, that personnel are properly briefed, and that any deviations from the study plan or SOPs are documented and acted upon. The Study Director should ensure that QA personnel have a copy of the study plan, and any amendments, in a timely manner and communicate effectively with them, as required during the conduct of the study.

Study Director involvement during the course of a study should include reviewing procedures and data, in order to ensure compliance with the study plan and the SOPs. To demonstrate the monitoring activities of the Study Director, the type and frequency of the reviews should be documented in the study records. The impact of any deviations from the study plan on the quality and integrity of the study should be assessed and appropriate corrective action should be taken, if necessary. The Study Director should acknowledge all deviations from SOPs during the conduct of the study.

The Study Director must sign and date the study report to indicate acceptance of responsibility for the validity of the data and that the study report accurately reflects the work conducted and all the results obtained.

The Study Director should ensure that all relevant raw data and records are properly maintained, to ensure data integrity, and that upon completion, or termination, of the study, these records are transferred in a timely manner to the archives.

Principal Investigator and Study Personnel

Principal Investigator

The Principles of GLP related to the Principal Investigator are shown in Table 1C.

Table 1C: Principle Investigator's Responsibilities

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).

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| 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. |

In a multi-site study, it is unreasonable to expect a Study Director to maintain direct supervision over all test sites. Therefore, it is appropriate to have a Principal Investigator appointed at test sites which are remote from the Study Director. The Principal Investigator must be an appropriately qualified individual at the test site, who can effectively carry out the technical phase of the study in conformance with the study plan, applicable SOPs, the Principles of GLP and the specific technical requirements. It must be noted that, although a Study Director can delegate duties to a Principal Investigator, the Study Director's responsibilities cannot be delegated.

There should not be a need to appoint a Principal Investigator to work on the study at the Study Director's geographical and managerial location. The Principal Investigator should indicate acceptance of the study plan, and any amendments to the study plan, by dated signature. Management and sponsor dated signatures should be provided, as appropriate. In a situation where a Principal Investigator undertakes a specialist activity, the Principal Investigator can prepare, if necessary, an amendment to the study plan, in consultation with the Study Director. However, the Study Director must be responsible for the numbering, approval and issue of all study plan amendments. All study plan amendments should be issued to all recipients of the original study plan.

The Principal Investigator is responsible for ensuring that QA personnel are kept informed about study activities for which the Principal Investigator is responsible, so that QA personnel can plan the inspection schedule. It is also necessary for the Principal Investigator to respond, in a timely manner, to QA reports.

On completion of a Principal Investigator's study activity, the Principal Investigator should sign and date the contributory report, to confirm that it accurately reflects the work conducted and all the results obtained. Sufficient commentary should be included to enable the Study Director to write the study report. The Principal Investigator should include a signed GLP compliance statement confirming compliance with GLP, or indicating clearly where there were any deviations from GLP.

If study documents and/or materials are to be archived locally, the archiving arrangements should be confirmed in the contributory report.

Study personnel

All study personnel involved in the conduct of the study must be knowledgeable in the aspects of the Principles of GLP which are applicable to their involvement in the study, and should be sure they are undertaking only duties in which they have been adequately trained (Table 1C).

Study personnel should have ready access to the study plan and relevant SOPs. It is their responsibility to comply with the instructions given in these documents. Any deviations from these instructions should be documented and communicated directly to the Study Director and/or, if appropriate, to the Principal Investigator.

All study personnel are responsible for recording raw data promptly and accurately and in compliance with GLP, and are responsible for the quality of their data.

Study personnel should take the necessary personal and health precautions to avoid any contamination of test systems and test items, and should take adequate safety precautions when handling materials of known, or unknown, hazard.

Quality Assurance

The Principles of GLP specific to QA are presented in Table 2. The establishment and effective operation of a QA programme is a requirement of GLP and is one of the principal means by which study personnel, Management, sponsors and ultimately the regulatory authorities are assured of the GLP compliance status of studies. The QA function is based on organizational, rather than scientific, procedures. Therefore, QA does not interfere with the technical and scientific conduct of studies.

Table 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, who are familiar with the test procedures.
3. Such individuals should not be involved in the conduct of the study being assured.
2.2 Responsibilities of the Quality Assurance Personnel
<p>1. The responsibilities of the Quality Assurance personnel include, but are not limited to, the following functions. They should:</p> <ul style="list-style-type: none"> 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 whether 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: d. <ul style="list-style-type: none"> i. study-based inspections; ii. facility-based inspections; and iii. process-based inspections. <p>Records of such inspections should be retained;</p> e. inspect the <u>study</u> 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; f. 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; g. prepare and sign a statement, to be included with the <u>study</u> 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 <u>study</u> report reflects the raw data.

Recommended additions to the text are in bold and underlined.

Test Facility Management has ultimate responsibility for compliance with the Principles of GLP. This includes the appointment and effective organization of a QA function. Persons undertaking QA activities must be independent of the studies inspected, and should report to a level of management where the overall responsibility for GLP resides. In small facilities, it might not be feasible to maintain full-time QA personnel. However, Management must appoint at least one individual to have permanent, albeit part-time, coordination of QA. Management can contract out the QA function, so the QA function need not be in-house.

QA inspections include reviews of procedures to assure compliance with the study plan, SOPs and the Principles of GLP. They pay attention to the flow of information and the chain of custody of samples and data across interfaces. This is particularly relevant to multi-site studies, where it is necessary to coordinate QA activities across sites, to ensure that all critical phases and interfaces are subject to QA monitoring. In the case of a laboratory that is not within a national GLP compliance programme, but which is participating in a GLP study, increased QA monitoring of that laboratory should be considered.

Inspections of facilities, procedures and study reports result in QA reports, which are forwarded to relevant study personnel including the Study Director and Test Facility Management. QA reports should be seen as a way of promoting awareness of GLP issues. There should be an agreed time-frame for recipients to respond to QA reports, for example, within 2 weeks. Significant findings should be reported, and responses should be made, as quickly as possible.

QA personnel should prepare and sign a QA statement for inclusion in the study report. The QA statement specifies the inspections undertaken, their dates, and the dates when the QA findings were reported. This statement also serves to confirm that the study report reflects the raw data. The QA statement is usually presented as a stand-alone document, within the study report, to confirm the independence of QA.

Facilities

The Principles of GLP specific to facilities are presented in Table 3. The basic requirements for facilities will be dictated by the types of test systems employed and the types of studies to be performed. Facilities include all of the buildings, individual room(s) and equipment provided to maintain the specified, controlled environment for the test system(s). Initial quarantine, diagnosis/ treatment of disease, maintenance before and after treatment with the test item, and isolation from external disturbances, must be provided. External disturbances might come in the form of contamination from other studies/test systems (across species), dust from the preparation of test or control items for dosing (for example, dose feed preparation, treatment or harvest of individual test subjects, environmental sources such as noise, light and bioburden). A test facility appropriate for one type of test system might be wholly insufficient for another.

GLP was originally developed for facilities in terms of rooms or areas (portion of a room), since those units are appropriate for most *in vivo* studies where test systems are exposed to room air, so environmental conditions for maintenance and isolation need to be directed at that level. In contrast, most *in vitro* (especially cell and organ culture) systems are manipulated in vertical laminar flow biological safety cabinets to protect both the test system and the operator. The test system is maintained within an incubator, which provides the required environmental conditions. It is further isolated from other cultures by the flasks, tubes or plates in which it is grown or treated. Therefore, modifications are necessary to the wording of the OECD Principles of GLP for facilities conducting *in vitro* studies. The addition of the term "or equipment" in the facilities' requirements is intended to remedy this situation (Table 3).

Table 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, areas <u>or appropriate equipment (for example, biological safety cabinets)</u> 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, areas, <u>or equipment (for example, biological safety cabinets)</u> should be available for the <u>treatment and cultivation of the <i>in vitro</i> test systems, in order to ensure that there is no contamination of the test system(s).</u>
3. There should be storage rooms or areas as needed for supplies and equipment. Storage rooms, areas <u>or equipment</u> should be separated from rooms, areas <u>or equipment</u> housing the test systems and should provide adequate protection against infestation, contamination, and/or deterioration.
4. <u>The facilities should provide adequate equipment (for example, biohazard hoods, ventilated cabinets), for the protection of the study personnel, environment and test system.</u>
3.3 Facilities for the Handling Test, Reference, <u>and Control</u> Items
1. To prevent contamination or mix-ups, there should be separate rooms, areas <u>or storage cabinets</u> for receipt and storage of the test, reference and <u>control</u> items. <u>Mixing of the test, reference and control items with a vehicle should be performed so as to preclude contamination and mix-up.</u>
2. Storage rooms, areas <u>or storage cabinets</u> for the test, <u>reference and control</u> items should be separate from rooms, areas, <u>or storage equipment</u> 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, <u>study</u> 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.

Recommended additions to the text are in bold and underlined.

The handling of test, reference and control items (7) for an *in vitro* study is generally performed in containment equipment to protect the items and the operator. The volumes of sample being prepared are quite small compared to those used in many *in vivo* studies. Changes to Table 3 focus on the need for the absence of contamination and mix-up, and reflect the facilities used for *in vitro* studies and the volumes of material to be manipulated.

There should be adequate storage facilities for supplies and equipment (for example, refrigerators, freezers, cryopreservators, ventilated cabinets, storage rooms). Storage facilities should be adequately

separated from the test system and should provide adequate protection against infestation, contamination, and/or deterioration.

Some facilities work with dedicated GLP and non-GLP areas, while others will conduct both regulatory and non-regulatory studies within a single GLP-compliant area. If a test facility carries out both regulatory and non-regulatory studies, it is essential that the GLP compliance of the regulatory studies is not compromised by the non-regulatory studies.

Management must clearly establish policies and procedures which preclude compromising the GLP compliance of regulatory studies by non-regulatory studies. If a test facility does have dedicated GLP and non-GLP areas, a base level of GLP compliance for the complete facility could be established, in order to introduce a general GLP working practice among all laboratory personnel (for example, for weighing, labelling and calibration).

Personnel should not undertake activities within a GLP area unless they have been trained in the appropriate GLP requirements. The presence of both GLP and non-GLP activities within the same facility requires constant vigilance on the part of Test Facility Management, Study Directors, supervisors and QA personnel, to ensure continual GLP compliance.

The GLP practices in the non-regulatory studies must not run counter to those for the regulatory studies. For example, cell cultures associated with a non-regulatory study placed in a GLP-compliant incubator must have the same labelling and freedom from adventitious agents as those used for the GLP studies.

Apparatus, Material and Reagents

The Principles of GLP specific to this area are presented in Table 4. Procedures on how apparatus is inspected, cleaned, maintained and calibrated must conform to the needs of the study plan and SOPs. This conformity must be documented as raw data.

Table 4: Apparatus, Materials 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, <u>monitored for its performance</u> 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 measurements.
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.

Recommended additions to the text are in bold and underlined.

The apparatus used to maintain test system isolation and environment is particularly critical for *in vitro* studies. For example, a study plan should specify an acceptable temperature range for the incubator. The incubator must be able to conform to that range, and a record of the monitoring must be maintained. There will usually be several parameters that should be maintained and documented daily (temperature,

humidity, CO₂ concentrations), and others which can be assessed and documented periodically (cleaning and bioburden).

Clearly, the quality of the apparatus must meet the expected and established levels of accuracy and precision. The specific requirements for a certain piece of apparatus (for example, frequency of cleaning or calibration) might not be the same in all laboratories or for all assay systems. Management and the Study Director should establish appropriate requirements. As a minimum requirement, the manufacturer's specifications should be met. The implementation of a monitoring/calibration programme is recommended.

The acceptance testing of new, or changed, computer systems for data capture, manipulation and storage is complex, involving both hardware and software components, and should be conducted and documented in a GLP-compliant manner. Before a computer system is used for GLP studies, it must be demonstrated that it is suitable for its intended use and that there are procedures for maintaining and controlling the system. The raw data for each computer system should be defined, and the system design should always provide for the retention of audit trails, to show all changes to data, without obscuring the original data. Responsibilities for computer systems must be clearly defined before a study begins.

The focus of the acceptance testing effort should be on the application(s) being used, rather than on the computer system itself. That is, do the hardware and software together produce the desired result when challenged by rigorous testing with known data sets? For example, a spreadsheet might be prepared to manipulate data in a study. The performance of that spreadsheet, for its intended purpose, would be tested and documented, rather than an attempt to evaluate an entire commercial spreadsheet program. Any data transfer steps between platforms and any direct data capture functions from instrumentation would be included in the evaluation. In such cases, it will be essential to define precisely the form of the raw data. If the raw data are in the form of an electronic file, electronic signatures and date stamps must meet GLP standards, as defined by the appropriate regulatory authorities.

The requirement that the apparatus and materials used in a study do not interfere with a test system is also critical for *in vitro* studies. As study plans, and equipment maintenance, cleaning and decontamination procedures (i.e. SOPs) are developed, consideration must be given to avoidance of the introduction of chemical residues, temperature fluctuations or other environmental factors which will affect the test system. For example, consideration must be given to the effects of bright sunlight on culture media, or of incubator vibration on cell culture uniformity.

The labelling of chemicals, reagents and solutions, including commercially prepared media and reagent solutions, should be conducted in such a way as to ensure compliance with GLP requirements. Revised labelling should be prepared when appropriate; for example, supplementation of a medium with a labile component could change the expiry date.

Test Systems

The Principles of GLP in relation to test systems are presented in Table 5. Several additions to this table have been made, which are directed toward cell/tissue culture systems. These address the needs to authenticate the origin of the test system, its freedom from adventitious agents and its condition upon arrival. Also, within the facility, the test system must be propagated and maintained in order to preserve its biological integrity for its intended application.

Table 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.	<u>The absence of contamination or defects in test systems should be demonstrated. If any damage or defect occurs (for example, contamination), this lot should not be used in studies and should be appropriately 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 contaminated or damaged during the course of a study should be appropriately destroyed, if necessary, to maintain the integrity of the study.</u>
3.	<u>The origin (for example, species and tissues), source, arrival condition and maintenance requirements of the <i>in vitro</i> test system should be documented.</u>
4.	Biological test systems should be acclimatised to the test environment for an adequate period before the first administration/application of the test, reference <u>or control</u> 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 container 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. <u>Bedding for animals should be changed as required by sound husbandry practice. Use of pest control agents should be documented.</u>
7.	<u>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.</u>

Recommended additions to the text are in bold and underlined. Recommended deletions are in italics and underlined

Many *in vitro* test systems are not directly isolated by the facility from the original species and tissue of origin, but are cell lines obtained from other sources. In some cases, the primary isolation might have occurred several decades earlier. In other cases, particularly with human cells and tissues, the donor records are not available to the end-user of the test system. Thus, the agency (cell repository or commercial source) providing the test system might be the primary source of data on the species and tissue of origin. It might also provide data on any tests performed to demonstrate the absence of adventitious agents and the purity (species and tissue type) of the test system. It is essential that the test facility is able to trace the lineage of the test system to its immediate source and to document the handling of that system within the test facility. This requirement is similar to documentation of the origin and basic health of an *in vivo* test system.

In vitro test systems are often propagated within test facilities. Both prokaryotic and eukaryotic systems can be expanded and banked to provide a continuous source of material. Since the study plan will have been prepared with certain expectations of the test system and specific performance criteria for the assay (see section *Performance of the Study*), the test system must be maintained in such a way as to promote stability over time. Test system maintenance and propagation should be addressed in the planning of a study (or study type) and documented in sufficient detail for the critical elements required to maintain stability to be included. Records of test system maintenance should also include all critical elements.

Characterisation of the *in vitro* test system is of the utmost importance. The handling of *in vitro* systems is perhaps more critical than that of *in vivo* systems. The following points should be considered.

1. Proper conditions should be established and maintained for the storage, handling and care of test systems, in order to ensure the quality of the data. High quality cell and tissue culture practices and good aseptic techniques, which are an essential part of *in vitro* work, should be enforced.

2. Characterisation of the test system is necessary, to ensure that it is what it claims to be, and any significant changes in the test system should be evaluated.
3. Newly received test systems should be controlled for their purity, lack of contamination, suitability and identity. Until the test system has met these pre-defined criteria, it should not be used in GLP-compliant studies and should be appropriately treated or destroyed. Any future contamination or defects which could affect the quality of the data should be investigated, and the test system returned to quarantine until it is "cleared". When beginning the experimental work in a study, the test system should be free of any contamination or defects, or any conditions which might interfere with the purpose or conduct of the study. Test systems that do not conform (for example, those with contamination, defects) during the course of a study should be appropriately treated, if possible, or destroyed, if necessary, to maintain the integrity of the study. Any diagnosis and treatment of non-conformity before, or during, a study should be recorded.
4. Records of origin (for example, species, tissue), maintenance requirements, identity, source, date of arrival, and arrival condition of *in vitro* systems should be maintained.
5. Test systems should be acclimatized (if necessary) to the test environment for an adequate period before the first administration or application of the test, control or reference item. The propagation of the *in vitro* test system after receipt by the test facility should be consistent with the study plan and/or SOPs.
6. All information needed to properly identify the *in vitro* test system should be adequately recorded throughout the course of the study. Individual test materials (for example, flasks, plates) that are prepared and used during the course of the study, should bear appropriate identification, wherever possible. Individual test system containers (i.e. transwells) too small to be individually labelled, should be contained in a properly labelled outer container.
7. Any material that comes into contact with the test system should be free of contaminants. Sterile equipment and good culture techniques should be used where appropriate (14).

Test, Reference and Control Items

The Principles of GLP specific to these matters are presented in Table 6. The category of control items has been added to the table, since control items do not meet the definition of reference items. Control items serve in monitoring the performance of the test system(s), but might not necessarily be compared with the test item(s) in the same way as a reference item (bench mark material). In many situations, only the positive control items are classed as separate item(s), since the negative control items might just be the diluent/medium used to prepare the test items, the positive controls and/or the reference items.

Table 6: Test, Reference and Control Items

6.1 Receipt, Handling, Sampling and Storage
1. Records including test, reference and control item characterisation, date of receipt, expiry date, and 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 that possible contamination or mix-ups are precluded.
3. Storage container(s) should carry identification information, expiry date and specific storage instructions.
6.2 Characterisation
1. Each test, reference and control item should be appropriately identified (for example, 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, reference or control items should be known.
3. In cases where the test, reference or control item is supplied by the sponsor, there should be a mechanism, developed in cooperation between the sponsor and the test facility, to verify the identity of the test item subject to the study, as appropriate .

4. The stability of test, reference and control items under storage and test conditions should be known for all studies.
5. If the test, reference or control item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined, as appropriate . <i>For test items used in field studies (for example, tank mixes), these may be determined through separate laboratory experiments.</i>
6. A sample from each batch should be retained for analytical purposes for all studies except short-term studies.

Recommended additions to the text are in bold and underlined. Recommended deletions are in italics and underlined.

Procedures must be established that are designed to prevent errors in the identification and cross-contamination of test, control, and reference items and their preparations. These procedures might include, for example, the separation of storage and handling areas for control and reference items from storage and handling areas for test items. There might also be separation of storage and handling areas for negative control items and for test and positive control substances. In addition, other procedures might be used to limit the risk of contamination or degradation; for example, limitations on the number of materials which might be manipulated at any one time and the strict colour coding of samples and receiving vessels.

Test, reference and control item accountability and supervision begin with receipt of the materials and continue throughout the life of the study until the final disposition (archiving, return and/or disposal) of the material. Test, reference and control item accounting encompasses the systems for receipt, storage, issue and use (by date and study), and final disposition. Once the study is completed, these records are archived. Good test substance control is demonstrated by a well documented audit trail, supplemented by checks of operations at critical points.

Demonstration of the concentration, stability and homogeneity of the test, control or reference item in the vehicle might not be possible or practical in short-term studies. Unlike many studies where large batches of material must be prepared and held for some time (for example, feeding studies), most *in vitro* studies involve dilution of the items immediately before use and in relatively small volumes. The study plan must carefully address the preparation and handling requirements of test, control and reference items in the vehicles used to present the substance to the test system. If analysis is not to be performed, its exclusion should be clearly stated in the study plan and study report. It might be appropriate to state this exclusion as part of the GLP compliance statement (see section Reporting of Study Results) in the study report.

In many situations (including prevalidation and validation studies), the laboratory might be testing test, reference and control items which are provided under code from the sponsor. In this case, the sponsor would be responsible for characterization and for providing the laboratory with sufficient information to handle the test and reference items appropriately. Laboratory safety is also an issue when testing coded materials. It is common practice for the sponsor to provide some information directly to the laboratory if there is a particular hazard which must be addressed. Safety instructions (for example, material safety data sheets) may be sent to the laboratory safety officer or another appropriate agency (for example, a poisons control centre) in a sealed envelope which is opened only in the case of an emergency (spill or exposure). It is important that the supplier of the blind coded materials takes on these responsibilities and provides sufficient information to help ensure that the handling of the test items under code does not affect the outcome of the study.

Standard Operating Procedures

The Principles of GLP specific to SOPs are presented in Table 7. SOPs are the written body of procedures that govern the procedural aspects of the GLP-compliant laboratory. They should address all

the categories listed in Table 7. Collectively, they should set the standards by which the test facility operates, reflecting the expectations of Test Facility Management, the Study Director, and QA.

Table 7: Standard Operating Procedures

<p>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 the test facility. Revisions to Standard Operating Procedures should be approved by Test Facility Management.</p> <p>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.</p> <p>7.3 Deviations from Standard Operating Procedures related to the study should be acknowledged by the Study Director and Principal Investigator(s), as applicable.</p> <p>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.</p>
<p>1. <i>Test, Reference and Control Items</i> Receipt, identification, labelling, handling, sampling and storage</p>
<p>2. Apparatus, Materials and Reagents</p> <p>a. <i>Apparatus</i> Use, maintenance, cleaning, <u>performance check</u> and calibration.</p> <p>b. <i>Computerised Systems</i> Validation, operation, maintenance, security, change control and back-up.</p> <p>c. <i>Materials, Reagents and Solutions</i> Preparation and labelling.</p>
<p>3. <i>Record Keeping, Reporting, Storage and Retrieval</i> Coding of studies, data collection, preparation of reports, indexing systems, handling of data, including the use of computerised systems.</p>
<p>4. <i>Test System (where appropriate)</i></p> <p>a. Room, <u>area and equipment</u> preparation and environmental room, <u>area and equipment</u> conditions for the test system.</p> <p>b. Procedures for receipt, transfer, proper placement, characterisation, identification and care of the test system.</p> <p>c. Test system preparation, observations and examinations, before, during and at the conclusion of the study.</p> <p>d. <u>Tests for contamination or defects of the test system. Handling of test system individuals found moribund or dead during the study.</u></p> <p>e. Collection, identification and handling of specimens (including necropsy and histopathology).</p> <p>f. <u>Siting and placement of test systems in test plots.</u></p>
<p>5. <i>Quality Assurance Procedures</i> Operation of Quality Assurance personnel in planning, scheduling, performance, documenting and reporting inspections.</p>

Recommended additions to the text are in bold and underlined. Recommended deletions are in italics and underlined.

The procedure for preparing, distributing and maintaining SOPs should be addressed in an SOP. This SOP should describe SOP format, including section headings and section numbering, in order to promote

consistency. SOPs can be written by a variety of authors, reflecting the expertise of many individuals within the organization. In turn, the SOPs should be reviewed and ultimately approved by the appropriate signatory.

SOPs are controlled to ensure that only current authorised SOPs are available. Given that they are controlled documents, it is appropriate for every SOP page to have the SOP identifier and version number. Management should ensure that a responsible individual has been assigned, such as an SOP administrator, who is accountable for ensuring that SOPs are current, authorised, appropriately distributed, and reviewed on a regular basis.

A copy of each superseded or withdrawn SOP should be maintained in a designated archive. In this manner, when reconstructing studies, the SOPs which were current at the time of a study can be referenced.

If common SOPs are to be issued to all laboratories in a multi-site study, it is necessary to establish, before beginning the study, how SOPs are to be authorised, issued and eventually archived. Where there are differences between a study plan and SOPs, it should be clarified whether it is the study plan or the SOPs which are the primary reference for the study. In multi-site studies, it may be helpful for the lead laboratory to provide study SOPs to the other laboratories. This reduces the workload and helps to assure greater uniformity in procedures among the participating laboratories.

Performance of the Study

This section includes discussion on the study plan and performance of a study. The Principles of GLP specific to this area are presented in Table 8.

Table 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 Table 2. 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. <ul style="list-style-type: none"> 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 <u>item(s)</u> , reference <u>item(s)</u> , <u>negative control item(s)</u> , and <u>positive control item(s)</u> : <ul style="list-style-type: none"> a. a descriptive title; b. a statement which reveals the nature and purpose of the study; c. identification of the test <u>item(s)</u> by code or name (IUPAC, CAS number, biological parameters, etc.); d. the reference <u>item(s)</u> to be used (if applicable); e. <u>negative control item(s)</u>; f. <u>positive control item(s)</u>.

<p>2. Information concerning the sponsor and the test facility:</p> <ul style="list-style-type: none"> 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).
<p>3. Dates:</p> <ul style="list-style-type: none"> 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.
<p>4. Test methods. Reference to the OECD Test Guideline or other test guideline or method to be used.</p>
<p>5. Issues (where applicable):</p> <ul style="list-style-type: none"> a. the justification for selection of the test <u>system(s)</u>; b. <u>characterisation of an <i>in vitro</i> test system(s), such as species and tissue of origin, source of supply, cell designation, culture conditions and other pertinent information</u>; c. the method for administration and the reason for its choice; d. the dose levels and/or concentration(s), frequency and duration of administration/application. <u>Numbers of treatment groups and replicate determinations within each treatment group</u>; e. detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, <u>use of positive and negative controls</u>, type and frequency of analysis, measurements, observations and examinations to be performed, and statistical methods to be used; f. <u>assay acceptance criteria for endpoints</u>.
<p>6. Records. A list of records to be retained, <u>including their location</u>.</p>
<p>8.3. Conduct of the Study</p>
<p>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.</p>
<p>2. The study should be conducted in accordance with the study plan.</p>
<p>3. All data generated during the conduct of the study should be recorded directed, promptly, accurately and legibly by the individual entering the data. These entries should be signed or initialled and dated.</p>
<p>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.</p>
<p>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 audits 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 rated (electronic) signatures. Reason for changes should be given.</p>

Recommended additions to the text are in bold and underlined.

Controls and acceptance criteria

One of the major additions to the Principles of GLP proposed by the workshop is the concept of assay acceptance criteria for endpoints (Table 8).

The responses of a test system to control items usually provides the basis for determining the acceptability of an assay. In some assays, both negative and positive control items are used to determine acceptance. In other assays, only positive control responses are used. The observed positive control response is compared to historical values for the assay to determine whether or not the response falls within the predefined limits given in the study plan's acceptance criteria. The range of acceptable values is generally derived as a function of the historical mean and standard deviation for the controls. They must also address the required precision of the assay. Ideally, each endpoint in an assay should be addressed by a positive control and have an acceptable range of values. The performance of the controls also allows comparison of an assay's performance in different laboratories and over time.

Study preparation

Before the commencement of a study, it can be useful for the Study Director to have a pre-study meeting to discuss the proposed study plan. Such a meeting should clarify communications throughout the study. The establishment of open, two-way communication between the Study Director and study personnel is essential to the proper control of a study. In addition to a discussion of the study plan, such a meeting can include practical demonstrations of applicable techniques.

Study plan

Sufficient information should be available to prepare a detailed study plan which eliminates as much uncertainty in the execution of the study as possible. It would be hard to over-emphasise the need for careful, detailed preparation of the study plan. The study plan includes the conceptual design of the study (what is tested and how it is tested), the raw data to be obtained, the manipulations of the raw data to produce the study endpoint values, the interpretation scheme for endpoints, and the acceptance criteria for the study. The study plan must be written in such a way as to preclude misinterpretation by the study personnel. This requirement is particularly important when more than one laboratory will use the same study plan.

In a multi-site study, the study plan should include the name and address of the Principal Investigator, the location of the test site(s), the study-part(s) performed, the methods and statistical parameters used, the location where the documentation relating to the part for which the Principal Investigator is responsible is archived, the GLP regulations followed (according to national requirements), and any time schedules necessary for the conduct of the study. A study plan amendment will be necessary if a new Principal Investigator and new test site become involved in the study. The study plan should include procedures for the recording of study data to ensure consistency of data recording at all of the sites in a multi-site study, and to meet the requirements of data management.

In addition to the study plan which identifies the records to be retained or archived, it is also appropriate to address at which locations archived records will be kept.

The study plan becomes an authorised document when it is signed by the Study Director, Test Facility Management and the sponsor, if applicable. The study plan should be distributed to study personnel and QA personnel, who need to be informed of studies so that QA inspections can be planned. Obtaining signatures in a multi-site study can be a lengthy process. It might be acceptable, subject to written procedures, for facsimiled signatures to be used in order to allow the study plan and amendments to be issued in a timely manner.

A study plan is distinct from the trial plan, which is specific to multi-study trials and is discussed later.

Study plan amendments

If a change to the original study plan is proposed, a study plan amendment should be issued before the change occurs. An amendment may also be issued as a result of unexpected occurrences during a study, which will require significant action. Study plan amendments should be sequentially numbered, indicate

the reason for the change, and include the dated signature of the Study Director and, if applicable, those of the Principal Investigators and Test Facility Management. All amendments should be distributed to all recipients of the original study plan.

Notes to file

A note to file provides a means of recording study information, such as a study plan deviation. Notes to file can be initiated by any study personnel, but should be acknowledged by the Study Director, who should approve any corrective action and decide upon the recipients of notes to file. Sequential numbering of notes to file assists study control. Significant deviations from the study plan might be best documented as study plan amendments.

Raw data

Study personnel must have a clear understanding of what constitutes raw data. The definition of raw data (see [Appendix 1](#)) must be documented.

Raw data records should enable the reconstruction of the study. They should also be able to explain who did what, when, by what means, why and where. To do so, data must be generated completely, accurately, legibly and promptly. Entries should be signed or initialled and dated. Corrections should be made without obscuring the original entry. Corrections should also be dated and signed, and the reason for the correction should be given. Raw data not only involve study-specific documentation (performance of a study), but also the more general records concerning apparatus, material and reagents, and handling of test, control and reference items and of test systems. During a study, raw data should be maintained in safe storage areas prior to transfer to archives for long-term secure retention.

Quality control

The conduct of the study should include quality control (QC) steps, undertaken by study personnel, as described in SOPs. QC steps should be undertaken when there is a need for verification, especially at a data interface. For example, manual entry of raw data should be checked by another study member. If the data being checked are critical, i.e. one error in the data could affect study integrity, all such data should be considered for checking. If the data being checked are non-critical, consideration can be given to checking samples of data (for example, a sample from each analytical batch).

Confidentiality issues

In multi-site studies, it should be ensured in advance that confidentiality issues will not impede the flow of information between institutions. It may be appropriate for study personnel to sign confidentiality statements.

Reporting of Study Results

The Principles of GLP specific to the reporting of study results are presented in Table 9. The OECD Principles of GLP employ the term "final report". In the current document, "study report" is used instead of final report, in order to keep study report distinct from the trial report, i.e. the report of a multi-study prevalidation and validation trial (see section Trial Report).

Table 9: Reporting Study Results

9.1 General
1. A study report should be prepared for each study. In the case of short-term studies, a standardised study 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 study report should be signed and dated by the SStudy 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 <u>study</u> 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 <u>study</u> report to comply with the submission requirements of a national registration or regulatory authority does not constitute a correction, addition or amendment to the <u>study</u> report.
9.2 Content of the <u>Study</u> Report
The <u>study</u> report should include, but not be limited to, the following information.
1. Identification of the study, the test <u>item(s)</u> , reference <u>item(s) and control item(s)</u> : <ol style="list-style-type: none"> a descriptive title; identification of the test item(s) by code or name (IUPAC, CAS number, biological parameters, etc.); identification of the reference <u>and control items</u>, by name; characterisation of the test item including purity, stability and homogeneity.
2. Information concerning the sponsor and the test facility: <ol style="list-style-type: none"> name and address of the sponsor; name and address of any test facilities and test sites involved; name and address of the Study Director; name and address of the Principal Investigator(s), and the phase(s) of the study delegated by the Study Director, if applicable; name and address of scientists having contributed reports to the <u>study</u> 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 <u>study</u> report reflects the raw data.
5. Description of materials and test methods: <ol style="list-style-type: none"> description of methods and materials used; reference to OECD Test Guideline or other test guideline or method.
6. Results: <ol style="list-style-type: none"> a summary of results; all information and data required by the study plan; a presentation of the results, including calculations, determinations of statistical significance (if appropriate) and historical control data; an evaluation and discussion of the results and, where appropriate, conclusions.
7. Storage: The location(s) where the study plan, samples of test, reference <u>and control</u> items, specimens, raw data and the <u>study</u> report are to be stored.

Recommended additions to the text are in bold and underlined.

Study reports should be prepared in a timely manner. The Study Director should sign and date the study report to indicate acceptance of responsibility for the validity of the data and that the study report accurately reflects work conducted and all the results obtained. The study report for a multi-site study should identify and define the role of any Principal Investigators and test sites involved in the conduct of the study.

The study report should include a GLP compliance statement, which is a formal record to confirm that the study was conducted and reported in accordance with GLP, clearly identifying, as appropriate, where the study deviated from GLP. The GLP compliance statement is signed and dated by the Study Director and

should address, in particular, the GLP status of any test sites not within a national GLP compliance programme.

In a multi-site study, it might be appropriate for the Principal Investigator to include a signed GLP compliance statement in the contributory report that is forwarded to the Study Director.

The GLP compliance statement should not be confused with the QA statement, also presented in the study report, which is a distinct and separate record of QA study monitoring.

The Study Director should authorise and sign any subsequent corrections and/or additions to the study report.

Storage and Retention of Records and Materials

The principles of GLP specific to records are presented in Table 10.

Table 10: Storage and Retention of Records and Materials

<p>10.1 The following should be retained in the archives for the period specified by the appropriate authorities:</p> <ol style="list-style-type: none">the study plan, raw data, samples of test, reference <u>and control</u> items, specimens and the <u>study</u> report of each study;records of all inspections performed by the Quality Assurance programme, as well as Master Schedules;records of all inspections performed by the Quality Assurance programme, as well as Master Schedules;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;the historical file of all Standard Operating Procedures;environmental monitoring records. <p>In the absence of required retention period, the final disposition of any study materials should be documented. When samples of test, reference <u>and control</u> 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, reference <u>and control</u> items and specimens should be retained only as long as the quality of the preparation permits evaluation.</p>
<p>10.2 Materials retained in the archives should be indexed in order to facilitate orderly storage and retrieval.</p>
<p>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.</p>
<p>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) or the study(s).</p>

Recommended additions to the text are in bold and underlined.

On completion of a study the Study Director is responsible for ensuring that all study data are transferred in a timely manner to the archives, as described in the study report. If study data are archived at several locations, it should be remembered that, if the study is subject to regulatory audit, it could be necessary, at short notice, for all study data to be transferred to one location for the audit.

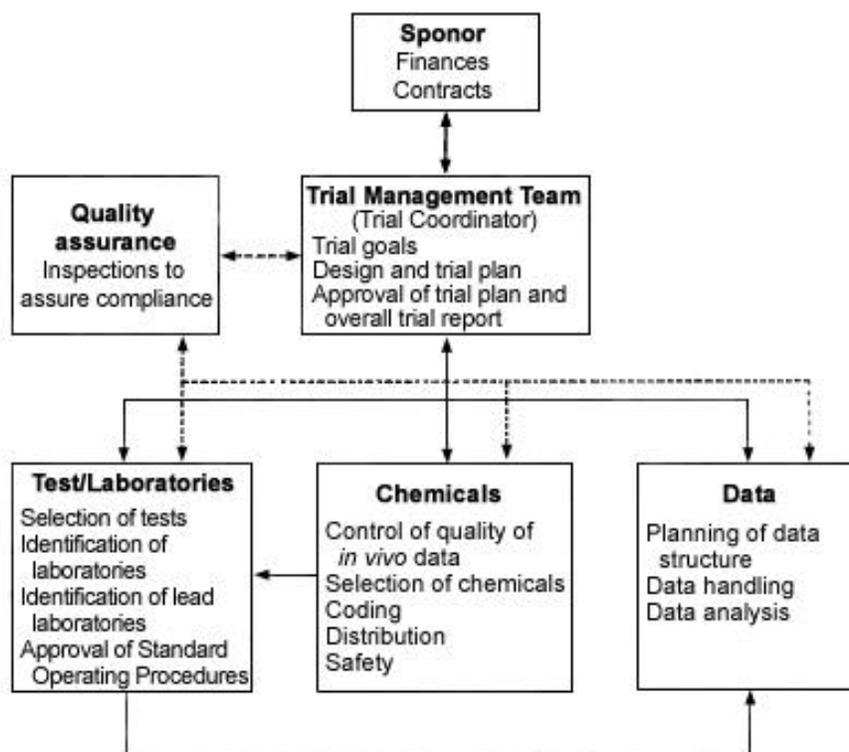
Once archived, the responsibility for the safe keeping of study data passes from the Study Director to Test Facility Management, which has responsibility for ensuring that there are designated personnel responsible for the archives, and that the archives are secure areas with the contents indexed in an orderly manner. The duration of archiving should be in accordance with regulatory requirements or as specified by Test Facility Management.

Multi-Study Trials

Trial Management Team

The sponsor of a multi-study trial appoints a Trial Management Team to have responsibility for overseeing the organization, conduct and reporting of the trial (6, 15). The Trial Management Team does not have immediate responsibility for ensuring GLP compliance, since it is Test Facility Management which has direct GLP responsibility. However, there are some Principles of GLP which can be usefully applied to the Trial Management Team. For example, the trial plan should identify the key responsibilities of specific members of the Trial Management Team, including that of the chairperson and Trial Coordinator. It might be appropriate to designate an individual in the Trial Management Team to coordinate GLP compliance issues, however, the responsibility for GLP at a test facility remains with Test Facility Management. Some of the required responsibilities of the Trial Management Team are illustrated in Figure 4 (6, 13). The Trial Management Team is responsible for the selection of participating laboratories, but not for the appointment of Study Directors who are appointed by Test Facility Management.

Figure 4: Overview of Management for a Multi-Study Validation Trial



Dashed lines indicate quality assurance staff involvement

Trial Plan

The trial plan outlines the trial goals and proposed time-scales, and identifies the studies, all the participating facilities and the names of Test Facility Management, Study Directors and Principal Investigators. Where there is no formal Study Director or Principal Investigator, as might be the case for facilities undertaking test item supply, data management and statistics, the person responsible for the technical conduct of the work should be identified.

The trial plan should include:

- a. the identity of the Trial Coordinator;
- b. SOP administration, if common SOPs are to be used across studies;
- c. arrangements for QA monitoring of study activities, including any pre-trial inspections; and
- d. the identity of archiving locations.

The trial plan must be signed by at least the chairperson of the Trial Management Team. The final trial plan should be identified as final, be fully authorised, and issued on a need-to-know basis. Any changes to the trial plan should result in a trial plan amendment, in the same manner that any changes to a study plan result in a study plan amendment. Trial plan amendments must be numbered, sequentially, and should be issued to all the original recipients of the trial plan.

Trial Coordinator's Responsibilities

The name and location of the Trial Coordinator should be identified in each of the individual study plans as the person responsible for coordinating the supply and analysis of test, reference and control items and the coordination and preparation of the trial report. It should be clarified whether the Trial Coordinator has direct access to the test item coding.

The Trial Coordinator's responsibilities include:

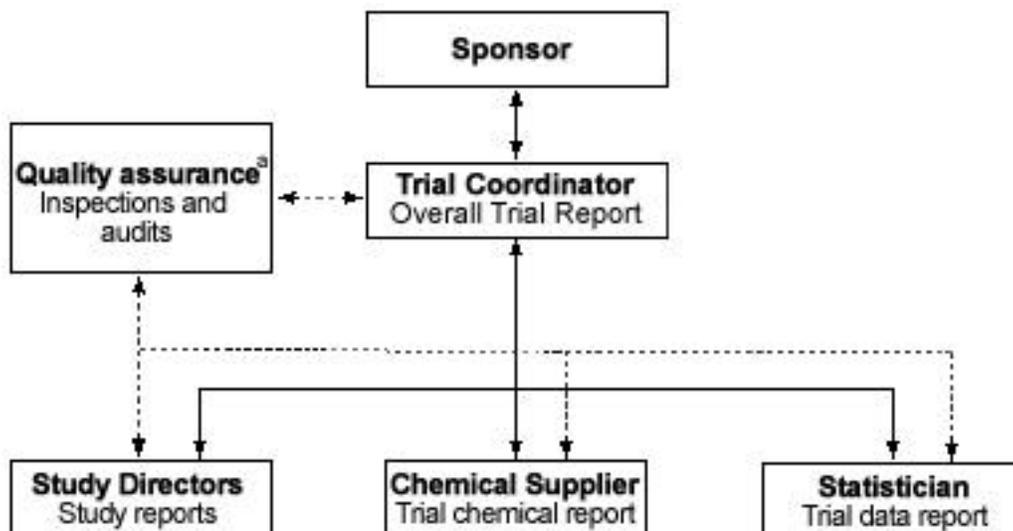
1. Responsibility for the coordination and communication network for test, reference and control item supply and analysis, data management and statistics for all the studies in a multi-study trial.
2. Ensuring that document and data flow between facilities are recorded.
3. Ensuring that QA monitoring is being undertaken in accordance with the trial plan.
4. Assessing and documenting the impact of any amendments and/or deviations from the trial plan and study plans on the quality and integrity of the multi-study trial.
5. Ensuring that the individual study reports are forwarded, in a timely manner, for data and statistical analysis.
6. Preparing the trial report, which can be allocated to a Study Director or an independent person.
7. Ensuring that the trial report is an accurate reflection of the overall multi-study trial. The Trial Coordinator signs and dates the final trial report to confirm that the trial report is an accurate account of the multi-study trial.
8. Ensuring that the trial documentation is properly archived.

Trial Report

The trial report summarises the trial goals, procedures, results and conclusions of a multi-study trial. This represents the whole multi-study trial, including archiving and, as such, will cover several study reports, as well as reports for test item supply, data management and statistics. The preparation of the trial report is outlined in Figure 5. The Trial Coordinator oversees the preparation of the trial report. The Trial Coordinator might also be responsible for preparation of the scientific conclusions. Signatories to the trial report include the Trial Coordinator, the chairperson of the Trial Management Team, the statistician, and the Study Directors. Although the Study Directors may not be involved with the preparation of the trial

report, their signatures confirm that the trial report is an accurate reflection of study events. The trial report should contain a statement, signed by the Trial Coordinator, commenting on the accuracy and completeness of the trial report and identifying any significant issues which could have affected the integrity of the trial, including matters of GLP compliance. A QA statement could be included in the trial report, in order to identify what QA monitoring was done and to confirm whether or not the trial report is an accurate reflection of the study data.

Figure 5: Preparation of the Trial Report



^aSeveral Quality Assurance units might be involved in a multi-study trial. Dashed lines indicate assurance staff involvement.

Quality Assurance of Multi-Study Trials

Multi-study trials can involve independent facilities which are not formally GLP-compliant, such as facilities for test item analyses. However, the QA monitoring of such facilities is advised, to assure compliance with the relevant principles of GLP. Also, this presents the opportunity for QA personnel to monitor data exchange between facilities.

QA reports should be forwarded to the relevant facilities and also to the Trial Coordinator. In addition, the production of summary and periodic QA reports, that would be issued to the Trial Management Team and sponsor should be considered. QA review of the trial report is appropriate, to provide independent assurance that the trial report is an accurate reflection of the study reports and also the trial data and trial chemical reports.

Conclusions and Recommendations

Good Laboratory Practice Promotes Confidence in the Data

1. The primary GLP reference for this workshop, the OECD Principles of GLP, describes a quality system concerned with the organization and the conditions under which regulatory studies are planned, performed, monitored, recorded, archived and reported. Undertaking studies in

compliance with GLP demonstrates to the regulatory authorities that studies were undertaken in a manner which promotes confidence in the data and reporting.

Good Laboratory Practice Compliance

2. A test facility might only be able to claim formal GLP compliance if it is within a compliance programme run by the relevant national GLP monitoring authority. The QA monitoring of a facility not within a compliance programme, does not confer GLP compliance. Study reports and trial reports must clearly identify facilities which did not adhere to formal GLP and address any impact this might have had on study or trial integrity.
3. If a test facility has designated GLP-compliant areas and non-GLP areas, it is essential that GLP compliance in the GLP areas is not compromised by the non-GLP areas. Maintenance of GLP and non-GLP areas in the same facility requires constant vigilance to ensure compliance of the GLP areas.
4. A test facility might conduct both "regulatory studies", intended for review by the regulatory authorities, and "non-regulatory" studies, which are not intended for submission to the regulatory authorities. Where this is the practice in the same GLP area, it will be necessary for the non-regulatory work to also be conducted in compliance with GLP. Essentially, the main differences between such regulatory and non-regulatory studies are that the latter may be subject to reduced QA monitoring and have a reduced amount of specific GLP documentation requirements.

Study Conduct

5. The management of single-site and multi-site studies, including the key roles of Study Director and Principal Investigator, as described in the OECD Principles of GLP, are considered relevant to the conduct of *in vitro* studies.
6. To ensure the applicability of GLP to *in vitro* studies, some additions are necessary to the OECD Principles of GLP, most notably with respect to:
 - a. definition of test system facilities, with special reference to handling and storage of test items;
 - b. characterization and care of test systems;
 - c. the required use of positive and negative control items; and
 - d. acceptance criteria.
7. The concept of acceptance criteria is one of the major additions to the Principles of GLP proposed by the workshop. The responses of a test system to control items usually provides the basis for determining the acceptability of an assay. The observed control response is compared to historical values for the assay, to determine whether or not the response falls within predefined limits given in the study plan acceptance criteria. The performance of the controls also allows comparison of the performance of an assay among laboratories and over time.

Quality Assurance

8. The principles of GLP include the requirement for QA monitoring by personnel independent of the procedures being inspected. QA is based on organisational rather than scientific procedures. Therefore, QA does not interfere with the technical and scientific conduct of studies.

Validation and Multi-Study Trials

9. The validation of *in vitro* tests is undertaken as multi-study trials, consisting of a number of separate studies, with each study, having its own study plan and Study Director. Each study within a formal validation multi-study trial, is conducted and reported without knowledge of the test item randomization code.

10. Multi-study trials are overseen by a Trial Management Team which is responsible for the selection of participating facilities. However, it is the Test Facility Managements of the participating laboratories who have responsibility for the GLP compliance of facilities, including the appointment of Study Directors.
11. A trial plan serves to outline the multi-study trial and includes trial goals and time-scales, and identifies participating facilities and key personnel. The trial plan becomes a formal document when it is signed by the chairperson of the Trial Management Team, and the Trial Coordinator.
12. The Trial Coordinator undertakes a pivotal role in ensuring compliance of the multi-study trial with the trial plan, including preparation of the trial report.

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[Appendix 1](#)