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Consensus Document of the Working Group on Good Laboratory Practice

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

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No. 13

Consensus Document of the Working Group on Good Laboratory Practice

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

Environment Directorate

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

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

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

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

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

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

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

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

FOREWORD

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

In the framework of the second OECD Consensus Workshop on Good Laboratory Practice, held 21st – 23rd May 1991, in Vail, Colorado, experts discussed and reached consensus on the application of the GLP Principles to field studies. An OECD Consensus Document on "The Application of the GLP Principles to Field Studies" was subsequently published in 1992 and revised in 1999 [ENV/JM/MONO(99)23]. Among other aspects, this document introduced the concept of a "Principal Investigator" who could assume delegated responsibility for a phase of a field study being conducted at a test site that was remote from the Study Director. Although the concept of a Principal Investigator had originally been developed to assist in the conduct of field studies that included trials being conducted at several different locations, the concept is equally applicable to any other type of multi-site study.

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

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

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

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

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INTRODUCTION

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

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

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

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

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

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

MANAGEMENT AND CONTROL OF MULTI-SITE STUDIES

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

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

The decision to conduct a multi-site study should be carefully considered by the sponsor in consultation with test facility management assigned by the sponsor before study initiation. The use of multiple test sites increases the complexity of study design and management tasks, resulting in additional risks to study integrity. It is therefore important that all of the potential threats to study integrity presented by a multi-site configuration are evaluated, that responsibilities are clear and that risks are minimised. Full

consideration should be given to the technical/scientific expertise, GLP compliance status, resources and commercial viability of all of the test sites that may be used.

Communication

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

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

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

Study management

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

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

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

Roles and Responsibilities

Sponsor

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

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

Test Facility Management

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

Test Site Management

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

Study Director

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

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

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

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

Throughout the conduct of the study, the Study Director should be readily available to the Principal Investigators. The Study Director should facilitate the co-ordination and timing of events and

movement of samples, specimens or data between sites, and ensure that Principal Investigators understand chain of custody procedures.

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

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

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

Principal Investigator

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

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

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

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

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

Study Personnel

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

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

QUALITY ASSURANCE

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

Responsibilities of Lead Quality Assurance

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

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

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

Responsibilities of Test Site Quality Assurance

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

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

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

MASTER SCHEDULES

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

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

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

STUDY PLAN

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

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

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

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

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

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

PERFORMANCE OF THE STUDY

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

Facilities

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

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

Equipment

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

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

Control and accountability of study materials

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

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

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

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

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

REPORTING OF STUDY RESULTS

A single final report should be issued for each multi-site study. The final report should include data from all phases of the study. It may be useful for the Principal Investigators to produce a signed and dated report of the phase delegated to them, for incorporation into the final report. If prepared, such reports

should include evidence that appropriate quality assurance monitoring was performed at that test site and contain sufficient commentary to enable the Study Director to write a valid final report covering the whole study. Alternatively, raw data may be transferred from the Principal Investigator to the Study Director, who should ensure that the data are presented in the final report. The final report produced in this way should identify the Principal Investigator(s) and the phase(s) for which they were responsible.

The Principal Investigators should indicate the extent to which the work for which they were responsible complies with the GLP Principles, and provide evidence of the quality assurance inspections performed at that test site. This may be incorporated directly into the final report, or the required details may be extracted and included in the Study Director's compliance claim and Quality Assurance statement in the final report. When details have been extracted the source should be referenced and retained.

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

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

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

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

STANDARD OPERATING PROCEDURES (SOPs)

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

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

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

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

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

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

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

STORAGE AND RETENTION OF RECORDS AND MATERIALS

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

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

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