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Number 6 (Revised)

Consensus Document
THE APPLICATION OF THE GLP PRINCIPLES TO FIELD STUDIES

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REVISED CONSENSUS DOCUMENT

OECD SERIES
ON
PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE MONITORING

Number 6 (revised)

GLP Consensus Document

**THE APPLICATION OF THE GLP
PRINCIPLES TO FIELD STUDIES**

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

Paris 1999

FOREWORD

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

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

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

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

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GLP Consensus Document

THE APPLICATION OF THE GLP PRINCIPLES TO FIELD STUDIES

Background

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

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

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

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

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

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

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

Interpretations Related to Definitions of Terms

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

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

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

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

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

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

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

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

“Test system” could also include complex ecological systems.

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

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

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

Interpretations Related to Test Facility Organisation and Personnel

Test Facility Management's Responsibilities

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

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

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

There are likely to be some test sites where aspects of study conduct are indirectly (or directly) carried out by non-permanently employed personnel. Where these persons have generated or entered raw data, or have performed unsupervised activities relevant to the conduct of the study, records of their qualifications, training and experience should be maintained. Where these individuals have carried out routine maintenance operations such as crop thinning, weeding, fertilisation, etc. subject to supervision by more highly qualified staff, no such personnel records need be maintained.

Study Director's Responsibilities

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

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

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

Principal Investigator's Responsibilities

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

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

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

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

Interpretations Related to the Quality Assurance Programme

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

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

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

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

Interpretations Related to Facilities

General

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

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

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

Facilities for Handling Test and Reference Items

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

Waste Disposal

Of particular concern at field sites is the storage and disposal of excess pesticide dilutions (or tank mixes). The minimum volume of such dilutions should be prepared. In addition to assuring that these potentially hazardous wastes are not endangering human health or the environment, these materials also need to be controlled in such a way that there is no impact on test systems, specimens or other

materials or equipment used in studies. It should also be assured that unused test and reference items are returned to the sponsors or suppliers, or are disposed of in a legal and responsible manner.

Interpretations Related to Apparatus, Material and Reagents

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

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

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

Interpretations Related to Test Systems

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

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

Interpretations Related to Test and Reference Items and Reference Items

Receipt, Handling, Sampling and Storage

The following documentation should be present at the test site:

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

Mode of transfer, with retention of shipping documents;

Date of receipt;

Condition of substance on receipt;

Storage location and conditions;

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

Characterisation

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

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

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

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

Interpretations Related to Standard Operating Procedures

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

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

Interpretations Related to Performance of the Study

Study Plan

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

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

Conduct of the Study

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

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

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

Interpretations Related to Reporting of Study Results

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

Interpretations Related to Storage and Retention of Records and Materials

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