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Consensus Document
THE APPLICATION OF THE GLP PRINCIPLES TO SHORT TERM STUDIES

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REVISED CONSENSUS DOCUMENT

OECD SERIES
ON
PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE MONITORING

Number 7 (revised)

GLP Consensus Document

THE APPLICATION OF THE GLP PRINCIPLES TO SHORT-TERM STUDIES

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

Paris 1999

FOREWORD

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

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

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

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

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

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

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

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

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

CONTENTS

GLP CONSENSUS DOCUMENT

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

Background

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

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

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

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

NOTES TO THE GLP PRINCIPLES

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

II.1. TEST FACILITY ORGANISATION AND PERSONNEL

II.1.2. Test Facility Management's Responsibilities

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

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

II.2. QUALITY ASSURANCE PROGRAMME

II.2.1. General

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

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

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

> **"*Study-based inspections*: These are scheduled according to the chronology of a given study, usually by first identifying the critical phases of the study.**
>
> ***Facility-based inspections*: These are not based upon specific studies, but cover the general facilities and activities within a laboratory (installations, support services, computer system, training, environmental monitoring, maintenance, calibration, etc.).**

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

***Process-based inspections*: Again these are performed independently of specific studies. They are conducted to monitor procedures or processes of a repetitive nature and are generally performed on a random basis. These inspections take place when a process is undertaken very frequently within a laboratory and it is therefore considered inefficient or impractical to**

undertake study-based inspections. It is recognised that performance of process-based inspections covering phases which occur with a very high frequency may result in some studies not being inspected on an individual basis during their experimental phases."

II.2.2. Responsibilities of the Quality Assurance Personnel

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

a) maintain copies of all approved study plans and Standard Operating Procedures in use in the test facility and have access to an up-to-date copy of the master schedule;

b) verify that the study plan contains the information required for compliance with these Principles of Good Laboratory Practice. This verification should be documented;

c) conduct inspections to determine if all studies are conducted in accordance with these Principles of Good Laboratory Practice. Inspections should also determine that study plans and Standard Operating Procedures have been made available to study personnel and are being followed.

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

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

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

II..3. FACILITIES

II.3.1. General

II.3.1.1. The test facility should be of suitable size, construction and location to meet the requirements of the study and to minimise disturbances that would interfere with the validity of the study.

II.3.1.2. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study.

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

II.4. APPARATUS, MATERIAL AND REAGENTS

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

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

II.5 TEST SYSTEMS

II.5.1. Physical/Chemical

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

II.5.2. Biological

II.5.2.1. Proper conditions should be established and maintained for the storage, housing, handling and care of biological test systems, in order to ensure the quality of the data.

II.5.2.2. Newly received animal and plant test systems should be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, this lot should not be used in studies and, when appropriate, should be humanely destroyed. At the experimental starting date of a study, test systems should be free of any disease or condition that might interfere with the purpose or conduct of the study. Test systems that become diseased or injured during the course of a study should be isolated and treated, if necessary to maintain the integrity of the study. Any diagnosis and treatment of any disease before or during a study should be recorded.

II.5.2.3. Records of source, date of arrival, and arrival condition of test systems should be maintained.

II.5.2.4. Biological test systems should be acclimatised to the test environment for an adequate period before the first administration/application of the test or reference item.

II.5.2.5. All information needed to properly identify the test systems should appear on their housing or containers. Individual test systems that are to be removed from their housing or containers during the conduct of the study should bear appropriate identification, wherever possible.

II.5.2.6. During use, housing or containers for test systems should be cleaned and sanitised at appropriate intervals. Any material that comes into contact with the test system should be free of contaminants at levels that would interfere with the study. Bedding for animals should be changed as required by sound husbandry practice. Use of pest control agents should be documented.

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

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

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

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

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

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

II.6 TEST AND REFERENCE ITEMS

II.6.2. Characterisation

II.6.2.1. Each test and reference item should be appropriately identified (e.g., code, Chemical Abstracts Service Registry Number [CAS number], name, biological parameters).

II.6.2.2. For each study, the identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test or reference items should be known.

II.6.2.3. In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation between the sponsor and the test facility, to verify the identity of the test item subject to the study.

II.6.2.4. The stability of test and reference items under storage and test conditions should be known for all studies.

II.6.2.5. If the test item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined. For test items used in field studies (e.g., tank mixes), these may be determined through separate laboratory experiments.

II.6.2.6. A sample for analytical purposes from each batch of test item should be retained for all studies except short-term studies.

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

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

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

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

II.7 STANDARD OPERATING PROCEDURES

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

II.8. PERFORMANCE OF THE STUDY

II.8.1. *Study Plan*

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

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

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

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

II.8.2. Content of the Study Plan

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

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

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

a) A descriptive title;

b) A statement which reveals the nature and purpose of the study;

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

c) Identification of the test item by code or name (IUPAC; CAS number, biological parameters etc);

d) The reference item to be used.

II.8.2.5. *Issues (where applicable)*

a) The justification for selection of the test system;

b) Characterisation of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age, and other pertinent information;

c) The method of administration and the reason for its choice;

d) The dose levels and/or concentration(s), frequency, and duration of administration/application.

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

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

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

II.9 REPORTING OF STUDY RESULTS

II.9.1. General

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

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

II.9.2. Content of the Final Report

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

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

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

a) A descriptive title;

b) Identification of the test-item by code or name (IUPAC; CAS number, biological parameters, etc.);

c) Identification of the reference item by chemical name;

d) Characterisation of the test item including purity, stability and homogeneity.

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

II.9.2.4. *Statement*

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

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