Decision-Recommendation of the Council on Compliance with Principles of Good Laboratory Practice



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Background Information

The Decision-Recommendation on Compliance with Principles of Good Laboratory Practice was adopted by the OECD Council on 2 October 1989 on the proposal of the Joint Meeting of the Management Committee of the Special Programme on the Control of Chemicals and the Chemicals Group. The Decision-Recommendation establishes procedures for monitoring Good Laboratory Practice compliance through government inspections and study audits as well as a framework for international liaison among monitoring and data-receiving authorities. It is part of the OECD System of Mutual Acceptance of Data (MAD), a multilateral agreement which allows participating countries to share the results of various non-clinical tests done on chemicals. Under MAD, a non-clinical chemical safety study developed using OECD Test Guidelines and OECD Principles of Good Laboratory Practice (GLP) in one Adherent country must be accepted for assessment purposes in all adhering countries.

THE COUNCIL,

HAVING REGARD to Articles 5 a) and 5 b) of the Convention on the Organisation for Economic Co-operation and Development of 14 December 1960,

HAVING REGARD to the Recommendation of the Council of 7 July 1977 Establishing Guidelines in Respect of Procedure and Requirements for Anticipating the Effects of Chemicals on Man and in the Environment [C(77)97(Final)];

HAVING REGARD to the Decision of the Council of 12 May 1981 concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)] and, in particular, the Recommendation that Member countries, in the testing of chemicals, apply the OECD Principles of Good Laboratory Practice, set forth in Annex 2 to that Decision;

HAVING REGARD to the Recommendation of the Council of 26 July 1983 concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95(Final)];

HAVING REGARD to the conclusions of the Third High-Level Meeting of the Chemicals Group (OECD, Paris, 1988);

CONSIDERING the need to ensure that test data on chemicals provided to regulatory authorities for purposes of assessment and other uses related to the protection of human health and the environment are of high quality, valid and reliable;

CONSIDERING the need to minimise duplicative testing of chemicals, and thereby to utilise more effectively scarce test facilities and specialist manpower, and to reduce the number of animals used in testing;

CONSIDERING that recognition of procedures for monitoring compliance with good laboratory practice will facilitate mutual acceptance of data and thereby reduce duplicative testing of chemicals;

CONSIDERING that a basis for recognition of compliance monitoring procedures is an understanding of, and confidence in, the procedures in the Member country where the data are generated;

CONSIDERING that harmonized approaches to procedures for monitoring compliance with good laboratory practice would greatly facilitate the development of the necessary confidence in other countries' procedures;

On the proposal of the Joint Meeting of the Management Committee of the Special Programme on the Control of Chemicals and the Chemicals Group, endorsed by the Environment Committee;

PART I: GLP Principles and Compliance Monitoring

I. **DECIDES** that Member countries in which testing of chemicals for purposes of assessment related to the protection of health and the environment is being carried out pursuant to principles of good laboratory practice that are consistent with the OECD Principles of Good Laboratory Practice as set out in Annex 2 of the Council Decision C(81)30(Final) (hereafter called "GLP Principles") shall:

i) Establish national procedures for monitoring compliance with GLP Principles, based on laboratory inspections and study audits;

ii) Designate an authority or authorities to discharge the functions required by the procedures for monitoring compliance; and

iii) Require that the management of test facilities issue a declaration, where applicable, that a study was carried out in accordance with GLP Principles and pursuant to any other provisions established by national legislation or administrative procedures dealing with good laboratory practice.

II. **RECOMMENDS** that, in developing and implementing national procedures for monitoring compliance with GLP Principles, Member countries apply the "Guides for Compliance Monitoring

Procedures for Good Laboratory Practice" and the "Guidance for the Conduct of Laboratory Inspections and Study Audits", set out respectively in Annexes I and II which are an integral part of this Decision-Recommendation.

PART II: Recognition of GLP Compliance among Member Countries

I. DECIDES that Member countries shall recognise the assurance by another Member country that test data have been generated in accordance with GLP Principles if such other Member country complies with Part I above and Part II paragraph 2 below.

II. DECIDES that, for purposes of the recognition of the assurance in paragraph 1 above, Member countries shall:

i) Designate an authority or authorities for international liaison and for discharging other functions relevant to the recognition as set out in this Part and in the Annexes to this Decision-Recommendation;

ii) Exchange with other Member countries relevant information concerning their procedures for monitoring compliance, in accordance with the guidance set out in Annex III which is an integral part of this Decision-Recommendation; and

iii) Implement procedures whereby, where good reason exists, information concerning GLP compliance of a test facility (including information focussing on a particular study) within their jurisdiction can be sought by another Member country.

III. DECIDES that the Council Recommendation concerning the Mutual Recognition of Compliance with Good Laboratory Practice [C(83)95(Final)] shall be repealed.

PART III: Future OECD Activities

I. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to ensure that the "Guides for Compliance Monitoring Procedures for Good Laboratory Practice" and the "Guidance for the Conduct of Laboratory Inspections and Study Audits" set out in Annexes I and II are updated and expanded, as necessary, in light of developments and experience of Member countries and relevant work in other international organisations.

II. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to pursue a programme of work designed to facilitate the implementation of this Decision-Recommendation, and to ensure continuing exchange of information and experience on technical and administrative matters related to the application of GLP Principles and the implementation of procedures for monitoring compliance with good laboratory practice.

III. INSTRUCTS the Environment Committee and the Management Committee of the Special Programme on the Control of Chemicals to review actions taken by Member countries in pursuance of this Decision-Recommendation.

ANNEX I

GUIDES FOR COMPLIANCE MONITORING PROCEDURES FOR GOOD LABORATORY PRACTICE

To facilitate the mutual acceptance of test data generated for submission to Regulatory Authorities of OECD Member countries, harmonization of the procedures adopted to monitor good laboratory practice compliance, as well as comparability of their quality and rigour, are essential. The aim of this document is to provide detailed practical guidance to OECD Member countries on the structure, mechanisms and procedures they should adopt when establishing national Good Laboratory Practice compliance monitoring programmes so that these programmes may be internationally acceptable.

It is recognised that Member countries will adopt GLP Principles and establish compliance monitoring procedures according to national legal and administrative practices, and according to priorities they give to, e.g., the scope of initial and subsequent coverage concerning categories of chemicals and types of testing. Since Member countries may establish more than one Good Laboratory Practice Monitoring Authority due to their legal framework for chemicals control, more than one Good Laboratory Practice Compliance Programme may be established. The guidance set forth in the following paragraphs concerns each of these Authorities and Compliance Programmes, as appropriate.

DEFINITIONS OF TERMS

The definitions of terms in the "OECD Principles of Good Laboratory Practice" [Annex 2 to Council Decision C(81)30 (Final)] are applicable to this document. In addition, the following definitions apply:

GLP Principles: Principles of good laboratory practice that are consistent with the OECD Principles of Good Laboratory Practice as set out in Annex 2 of Council Decision C(81)30(Final).

GLP Compliance Monitoring: The periodic inspection of test facilities and/or auditing of studies for the purpose of verifying adherence to GLP Principles.

(National) GLP Compliance Programme: The particular scheme established by a Member country to monitor good laboratory practice compliance by test facilities within its territories, by means of inspections and study audits.

(National) GLP Monitoring Authority: A body established within a Member country with responsibility for monitoring the good laboratory practice compliance of test facilities within its territories and for discharging other such functions related to good laboratory practice as may be nationally determined. It is understood that more than one such body may be established in a Member country.

Test Facility Inspection: An on-site examination of the test facility's procedures and practices to assess the degree of compliance with GLP Principles. During inspections, the management structures and operational procedures of the test facility are examined, key technical personnel are interviewed, and the quality and integrity of data generated by the facility are assessed and reported.

Study audit: A comparison of raw data and associated records with the interim or final report in order to determine whether the raw data have been accurately reported, to determine whether testing was carried out in accordance with the study plan and Standard Operating Procedures, to obtain additional information not provided in the report, and to establish whether practices were employed in the development of data that would impair their validity.

Inspector: A person who performs the test facility inspections and study audits on behalf of the (National) GLP Monitoring Authority.

GLP Compliance Status: The level of adherence of a test facility to the GLP Principles as assessed by the (National) GLP Monitoring Authority.

Regulatory Authority: A national body with legal responsibility for aspects of the control of chemicals.

COMPONENTS OF GOOD LABORATORY PRACTICE COMPLIANCE MONITORING PROCEDURES

Administration

(National) GLP Compliance Programme should be the responsibility of a properly constituted, legally identifiable body adequately staffed and working within a defined administrative framework.

Member countries should:

- Ensure that the (National) GLP Monitoring Authority is directly responsible for an adequate "team" of inspectors having the necessary technical/scientific expertise or is ultimately responsible for such a "team"
- Publish documents relating to the adoption of GLP Principles within their territories;
- Publish documents providing details of the (National) GLP Compliance Programme, including information on the legal or administrative framework within which the programme operates and references to published acts, normative documents (e.g., regulations, codes of practice), inspection manuals, guidance notes, periodicity of inspections and/or criteria for inspection schedules, etc.;
- Maintain records of test facilities inspected (and their GLP Compliance Status) and of studies audited for both national and international purposes.

Confidentiality

(National) GLP Monitoring Authorities will have access to commercially valuable information and, on occasion, may even need to remove commercially sensitive documents from a test facility or refer to them in detail in their reports.

Member countries should:

- Make provision for the maintenance of confidentiality, not only by Inspectors but also by any other persons who gain access to confidential information as a result of GLP Compliance Monitoring activities;
- Ensure that, unless all commercially sensitive and confidential information has been excised, reports of Test Facility Inspections and Study Audits are made available only to Regulatory Authorities and, where appropriate, to the test facilities inspected or concerned with Study Audits and/or to study sponsors.

Personnel and Training

(National) GLP Monitoring Authorities should:

- **Ensure that an adequate number of Inspectors is available**

  The number of Inspectors required will depend upon:

  i) The number of test facilities involved in the (National) GLP Compliance Programme;

  ii) The frequency with which the GLP Compliance Status of the test facilities is to be assessed:

  iii) The number and complexity of the studies undertaken by those test facilities;

  iv) The number of special inspections or audits requested by Regulatory Authorities.

- **Ensure that Inspectors are adequately qualified and trained**

  Inspectors should have qualifications and practical experience in the range of scientific disciplines relevant to the testing of chemicals. (National) GLP Monitoring Authorities should:

i) Ensure that arrangements are made for the appropriate training of GLP Inspectors, having regard to their individual qualifications and experience;

ii) Encourage consultations, including joint training activities where necessary, with the staff of (National) GLP Monitoring Authorities in other Member countries in order to promote international harmonization in the interpretation and application of GLP Principles, and in the monitoring of compliance with such Principles.

- **Ensure that inspectorate personnel, including experts under contract, have no financial or other interests in the test facilities inspected, the studies audited or the firms sponsoring such studies**

- **Provide Inspectors with a suitable means of identification (e.g., an identity card)**

  Inspectors may be:

  - On the permanent staff of the (National) GLP Monitoring Authority;
  - On the permanent staff of a body separate from the (National) GLP Monitoring Authority; or
  - Employed on contract, or by another way, by the (National) GLP Monitoring Authority to perform Test Facility Inspections or Study Audits.

  In the latter two cases, the (National) GLP Monitoring Authority should have ultimate responsibility for determining the GLP Compliance Status of test facilities and the quality/acceptability of a Study Audit, and for taking any action based on the results of Test Facility Inspections or Study Audits which may be necessary.

(National) GLP Compliance Programmes

GLP Compliance Monitoring is intended to ascertain whether test facilities have implemented GLP Principles for the conduct of studies and are capable of assuring that the resulting data are of adequate quality. As indicated above, Member countries should publish the details of their (National) GLP Compliance Programmes. Such information should, *inter alia*:

- **Define the scope and extent of the Programme**

  A (National) GLP Compliance Programme may cover only a limited range of chemicals, e.g., industrial chemicals, pesticides, pharmaceuticals, etc., or may include all chemicals. The scope of the monitoring for compliance should be defined, both with respect to the categories of chemicals and to the types of tests subject to it, e.g., physical, chemical, toxicological and/or ecotoxicological.

- **Provide an indication as to the mechanism whereby test facilities enter the Programme**

  The application of GLP Principles to health and environmental safety data generated for regulatory purposes may be mandatory. A mechanism should be available whereby test facilities may have their compliance with GLP Principles monitored by the appropriate (National) GLP Monitoring Authority.

- **Provide information on categories of Test Facility Inspections/Study Audits**

  A (National) GLP Compliance Programme should include:

  i) Provision for Test Facility Inspections. These inspections include both a general Test Facility Inspection and a Study Audit of one or more on-going or completed studies;

  ii) Provision for special Test Facility Inspections/Study Audits at the request of a Regulatory Authority - e.g., prompted by a query arising from the submission of data to a Regulatory Authority.

- **Define the powers of Inspectors for entry into test facilities and their access to data held by test facilities (including specimens SOP's, other documentation, etc.)**

  While Inspectors will not normally wish to enter test facilities against the will of the facility's management, circumstances may arise where test facility entry and access to data are essential to protect public health or the environment. The powers available to the (National) GLP Monitoring Authority in such cases should be defined.

- **Describe the Test Facility Inspection and Study Audit procedures for verification of GLP compliance**

  The documentation should indicate the procedures which will be used to examine both the organisational processes and the conditions under which studies are studies are planned, performed, monitored and recorded. Guidance for such procedures is available in Guidance for Conduct of Test Facility Inspections and Study Audits (No.3 in the OECD series on Principles of GLP and Compliance Monitoring).

- **Describe actions that may be taken as follow-up to Test Facility Inspections and Study Audits**

Follow-up to Laboratory Inspections and Study Audits

When a Test Facility Inspection or Study Audit has been completed, the Inspector should prepare a written report of the findings.

Member countries should take action where deviations from GLP Principles are found during or after a Test Facility Inspection or Study Audit. The appropriate actions should be described in documents from the (National) GLP Monitoring Authority.

If a Test Facility Inspection or Study Audit reveals only minor deviations from GLP Principles, the facility should be required to correct such minor deviations. The Inspector may need, at an appropriate time, to return to the facility to verify that corrections have been introduced.

Where no or where only minor deviations have been found, the (National) GLP Monitoring Authority may:

- Issue a statement that the test facility has been inspected and found to be operating in compliance with GLP Principles. The date of inspections and, if appropriate, the categories of tests inspected in the test facility at that time should be included. Such statements may be used to provide information to (National) GLP Monitoring Authorities in other Member countries;

  and/or

- Provide the Regulatory Authority which requested a Study Audit with a detailed report of the findings.

Where serious deviations are found, the action taken by (National) GLP Monitoring Authorities will depend upon the particular circumstances of each case and the legal or administrative provisions under which GLP Compliance Monitoring has been established within their countries. Actions which may be taken include, but are not limited to, the following:

- Issuance of a statement, giving details of the inadequacies or faults found which might affect the validity of studies conducted in the test facility;
- Issuance of a recommendation to a Regulatory Authority that a study be rejected;
- Suspension of Test Facility Inspections or Study Audits of a test facility and, for example and where administratively possible, removal of the test facility from the (National) GLP Compliance Programme or from any existing list or register of test facilities subject to GLP Test Facility Inspections;
- Requiring that a statement detailing the deviations be attached to specific study reports;

- Action through the courts, where warranted by circumstances and where legal/administrative procedures so permit.

Appeals Procedures

Problems, or differences of opinion, between Inspectors and test facility management will normally be resolved during the course of a Test Facility Inspection or Study Audit. However, it may not always be possible for agreement to be reached. A procedure should exist whereby a test facility may make representations relating to the outcome of a Test Facility Inspection or Study Audit for GLP Compliance Monitoring and/or relating to the action the GLP Monitoring Authority proposes to take thereon.

ANNEX II

GUIDANCE FOR THE CONDUCT OF TEST FACILITY INSPECTIONS AND STUDY AUDITS

INTRODUCTION

The purpose of this document is to provide guidance for the conduct of Test Facility Inspections and Study Audits which would be mutually acceptable to OECD Member countries. It is principally concerned with Test Facility Inspections, an activity which occupies much of the time of GLP Inspectors. A Test Facility Inspection will usually include a limited Study Audit or "review" as a part of the inspection, but Study Audits will also have to be conducted from time to time at the request, for example, of a Regulatory Authority. General guidance for the conduct of Study Audits will be found at the end of this document.

Test Facility Inspections are conducted to determine the degree of conformity of test facilities and studies with GLP Principles and to determine the integrity of data to assure that resulting data are of adequate quality for assessment and decision-making by national Regulatory Authorities. They result in reports which describe the degree of adherence of a test facility to the GLP Principles. Test Facility Inspections should be conducted on a regular, routine basis to establish and maintain records of the GLP Compliance Status of test facilities.

Further clarification of many of the points in this document may be obtained by referring to the OECD Consensus Documents on GLP (on, e.g., the role and responsibilities of the Study Director).

DEFINITIONS OF TERMS

The definitions of terms in the "OECD Principles of Good Laboratory Practice" [Annex II to Council Decision C(81)30 (Final)] and in the "Guides for Compliance Monitoring Procedures for Good Laboratory Practice" [Annex I to Council Decision-Recommendation C(89)87(Final)] are applicable to this document.

TEST FACILITY INSPECTIONS

Inspections for compliance with GLP Principles may take place in any test facility generating health or environmental safety data for regulatory purposes. Inspectors may be required to audit data relating to the physical, chemical, toxicological or ecotoxicological properties of a substance or preparation. In some cases, Inspectors may need assistance from experts in particular disciplines.

The wide diversity of facilities (in terms both of physical layout and management structure), together with the variety of types of studies encountered by Inspectors, means that the Inspectors must use their own judgement to assess the degree and extent of compliance with GLP Principles. Nevertheless, Inspectors should strive for a consistent approach in evaluating whether, in the case of a particular test facility or study, an adequate level of compliance with each GLP Principle has been achieved.

In the following sections, guidance is provided on the various aspects of the testing facility, including its personnel and procedures, which are likely to be examined by Inspectors. In each section, there is a statement of purpose, as well as an illustrative list of specific items which could be considered during the course of a Test Facility Inspection. These lists are not meant to be comprehensive and should not be taken as such.

Inspectors should not concern themselves with the scientific design of the study or the interpretation of the findings of studies with respect to risks for human health or the environment. These aspects are the responsibility of those Regulatory Authorities to which the data are submitted for regulatory purposes.

Test Facility Inspections and Study Audits inevitably disturb the normal work in a facility. Inspectors should therefore carry out their work in a carefully planned way and, so far as practicable, respect the wishes of the management of the test facility as to the timing of visits to certain sections of the facility.

Inspectors will, while conducting Test Facility Inspections and Study Audits, have access to confidential, commercially valuable information. It is essential that they ensure that such information is seen by

authorised personnel only. Their responsibilities in this respect will have been established within their (National) GLP Compliance Monitoring Programme.

INSPECTION PROCEDURES

Pre-Inspection

PURPOSE: To familiarise the Inspector with the facility which is about to be inspected in respect of management structure, physical layout of buildings and range of studies.

Prior to conducting a Test Facility Inspection or Study Audit, Inspectors should familiarise themselves with the facility which is to be visited. Any existing information on the facility should be reviewed. This may include previous inspection reports, the layout of the facility, organisation charts, study reports, protocols and curricula vitae (CVs) of personnel. Such documents would provide information on:

- The type, size and layout of the facility;
- The range of studies likely to be encountered during the inspection;
- The management structure of the facility.

Inspectors should note, in particular, any deficiencies from previous Test Facility Inspections. Where no previous Test Facility Inspections have been conducted, a pre-inspection visit can be made to obtain relevant information.

Test Facilities may be informed of the date and time of Inspectors' arrival, the objective of their visit and the length of time they expect to be on the premises. This could allow the test facility to ensure that the appropriate personnel and documentation are available. In cases where particular documents or records are to be examined, it may be useful to identify these to the test facility in advance of the visit so that they will be immediately available during the Test Facility Inspection.

Starting Conference

PURPOSE: To inform the management and staff of the facility of the reason for the Test Facility Inspection or Study Audit that is about to take place, and to identify the facility areas, study(ies) selected for audit, documents and personnel likely to be involved.

The administrative and practical details of a Test Facility Inspection or Study Audit should be discussed with the management of the facility at the start of the visit. At the starting conference, Inspectors should:

- Outline the purpose and scope of the visit;
- Describe the documentation which will be required for the Test Facility Inspection, such as lists of on-going and completed studies, study plans, standard operating procedures, study reports, etc. Access to and, if necessary, arrangements for the copying of relevant documents should be agreed upon at this time;
- Clarify or request information as to the management structure (organisation) and personnel of the facility;
- Request information as to the conduct of studies not subject to GLP Principles in the areas of the test facility where GLP studies are being conducted;
- Make an initial determination as to the parts of the facility to be covered during the Test Facility Inspection;
- Describe the documents and specimens that will be needed for on-going or completed study(ies) selected for Study Audit;
- Indicate that a closing conference will be held at the completion of the inspection.

Before proceeding further with a Test Facility Inspection, it is advisable for the Inspector(s) to establish contact with the facility's Quality Assurance (QA) unit.

As a general rule, when inspecting a facility, Inspectors will find it helpful to be accompanied by a member of the QA unit.

Inspectors may wish to request that a room be set aside for examination of documents and other activities.

Organisation and Personnel

PURPOSE: To determine whether: the test facility has sufficient qualified personnel, staff resources and support services for the variety and number of studies undertaken; the organisational structure is appropriate; and management has established a policy regarding training and staff health surveillance appropriate to the studies undertaken in the facility.

The management should be asked to produce certain documents, such as:

- Floor plans;
- Facility management and scientific organisation charts;
- CVs of key personnel involved in the type(s) of studies selected for the Study Audit;
- List(s) of on-going and completed studies with information on the type of study, initiation/completion dates, test system, method of application of test substance and name of Study Director;
- Staff health surveillance policies;
- Staff job descriptions and staff training programmes and records;
- An index to the facility's Standard Operating Procedures (SOPs);
- Specific SOPs as related to the studies or procedures being inspected or audited;
- List(s) of the Study Directors and sponsors associated with the study(ies) being audited.

The Inspector should check, in particular:

- Lists of on-going and completed studies to ascertain the level of work being undertaken by the test facility;
- The identity and qualifications of the Study Directors, the Head of the Quality Assurance unit and other personnel;
- Existence of SOPs for all relevant areas of testing.

Quality Assurance Programme

PURPOSE**:** To determine whether the mechanisms used to assure management that studies are conducted in accordance with GLP Principles are adequate.

The Head of the Quality Assurance (QA) unit should be asked to demonstrate the systems and methods for QA inspection and monitoring of studies, and the system for recording observations made during QA monitoring. Inspectors should check:

- The qualifications of the Head of QA, and of all QA staff;
- That the QA unit functions independently from the staff involved in the studies;
- How the QA unit schedules and conducts inspections, how it monitors identified critical phases in a study, and what resources are available for QA inspections and monitoring activities;
- That where studies are of such short duration that monitoring of each study is impracticable, arrangements exist for monitoring on a sample basis;
- The extent and depth of QA monitoring during the practical phases of the study;

- The extent and depth of QA monitoring of routine test facility operation;
- The QA procedures for checking the final report to ensure its agreement with the raw data;
- That management receives reports from QA concerning problems likely to affect the quality or integrity of a study;
- The actions taken by QA when deviations are found;
- The QA role, if any, if studies or parts of studies are done in contract laboratories;
- The part played, if any, by QA in the review, revision and up-dating of SOPs.

Facilities

PURPOSE: To determine whether the test facility, whether indoor or outdoor, is of suitable size, construction, design and location to meet the demands of the studies being undertaken.

The Inspector should check that:

- The design enables an adequate degree of separation so that, e.g., test substances, animals, diets, pathological specimens, etc. of one study cannot be confused with those of another;
- Environmental control and monitoring procedures exist and function adequately in critical areas, e.g., animal and other biological test systems rooms, test substance storage areas, laboratory areas;
- The general housekeeping is adequate for the various facilities and that there are, if necessary, pest control procedures.

Care, Housing and Containment of Biological Test Systems

PURPOSE: To determine whether the test facility, if engaged in studies using animals or other biological test systems, has support facilities and conditions for their care, housing and containment, adequate to prevent stress and other problems which could affect the test system and hence the quality of data.

A test facility may be carrying out studies which require a diversity of animal or plant species as well as microbial or other cellular or sub-cellular systems. The type of test systems being used will determine the aspects relating to care, housing or containment that the Inspector will monitor. Using his judgement, the Inspector will check, according to the test systems, that:

- There are facilities adequate for the test systems used and for testing needs;
- There are arrangements to quarantine animals and plants being introduced into the facility and that these arrangements are working satisfactorily;
- There are arrangements to isolate animals (or other elements of a test system, if necessary) known to be, or suspected of being, diseased or carriers of disease;
- There is adequate monitoring and record-keeping of health, behaviour or other aspects, as appropriate to the test system;
- The equipment for maintaining the environmental conditions required for each test system is adequate, well maintained, and effective;
- Animal cages, racks, tanks and other containers, as well as accessory equipment, are kept sufficiently clean;
- Analyses to check environmental conditions and support systems are carried out as required;
- Facilities exist for removal and disposal of animal waste and refuse from the test systems and that these are operated so as to minimise vermin infestation, odours, disease hazards and environmental contamination;

- Storage areas are provided for animal feed or equivalent materials for all test systems; that these areas are not used for the storage of other materials such as test substances, pest control chemicals or disinfectants, and that they are separate from areas in which animals are housed or other biological test systems are kept;
- Stored feed and bedding are protected from deterioration by adverse environmental conditions, infestation or contamination.

Apparatus, Materials, Reagents and Specimens

PURPOSE: To determine whether the test facility has suitably located, operational apparatus in sufficient quantity and of adequate capacity to meet the requirements of the tests being conducted in the facility and that the materials, reagents and specimens are properly labelled, used and stored.

The Inspector should check that:

- Apparatus are clean and in good working order;
- Records have been kept of operation, maintenance, verification, calibration and validation of measuring equipment and apparatus (including computerised systems);
- Materials and chemical reagents are properly labelled and stored at appropriate temperatures and that expiry dates are not being ignored. Labels for reagents should indicate their source, identity and concentration and/or other pertinent information;
- Specimens are well identified by test system, study, nature and date of collection;
- Apparatus and materials used do not alter to any appreciable extent the test systems.

Test Systems

PURPOSE: To determine whether adequate procedures exist for the handling and control of the variety of test systems required by the studies undertaken in the facility, e.g., chemical and physical systems, cellular and microbic systems, plants or animals.

Physical and Chemical Systems

The Inspector should check that:

- Where required by study plans, the stability of test and reference substances was determined and that the reference substances specified in test plans were used;
- Iin automated systems, data generated as graphs, recorder traces or computer print-outs are documented as raw data and archived.

Biological Test Systems

Taking account of the relevant aspects referred to above relating to care, housing or containment of biological test systems, the Inspector should check that:

- Test systems are as specified in study plans;
- Test systems are adequately and, if necessary and appropriate, uniquely identified throughout the study; and that records exist regarding receipt of the test systems and document fully the number of test systems received, used, replaced or discarded;
- Housing or containers of test systems are properly identified with all the necessary information;
- There is an adequate separation of studies being conducted on the same animal species (or the same biological test systems) but with different substances;
- There is an adequate separation of animal species (and other biological test systems) either in space or in time;

- The biological test system environment is as specified in the study plan or in SOPs for aspects such as temperature, or light/dark cycles;
- The recording of the receipt, handling, housing or containment, care and health evaluation is appropriate to the test systems;
- Written records are kept of examination, quarantine, morbidity, mortality, behaviour, diagnosis and treatment of animal and plant test systems or other similar aspects as appropriate to each biological test system;
- There are provisions for the appropriate disposal of test systems at the end of tests.

Test and Reference Substances

PURPOSE: To determine whether the test facility has procedures designed i) to ensure that the identity, potency, quantity and composition of test and reference substances are in accordance with their specifications, and ii) to properly receive and store test and reference substances.

The Inspector should check that:

- There are written records on the receipt (including identification of the person responsible), and for the handling, sampling, usage and storage of test and reference substances;
- Test and reference substances containers are properly labelled;
- Storage conditions are appropriate to preserve the concentration, purity and stability of the test and reference substances;
- There are written records on the determination of identity, purity, composition, stability, and for the prevention of contamination of test and reference substances, where applicable;
- There are procedures for the determination of the homogeneity and stability of mixtures containing test and reference substances, where applicable;
- Containers holding mixtures (or dilutions) of the test and reference substances are labelled and that records are kept of the homogeneity and stability of their contents, where applicable;
- When the test is of longer than four weeks' duration, samples from each batch of test and reference substances have been taken for analytical purposes and that they have been retained for an appropriate time;
- Procedures for mixing substances are designed to prevent errors in identification or cross-contamination.

Standard Operating Procedures

PURPOSE: To determine whether the test facility has written SOPs relating to all the important aspects of the operations, considering that one of the most important management techniques for controlling facility operations is the use of written SOPs. These relate directly to the routine elements of tests conducted by the test facility.

The Inspector should check that:

- Each test facility area has immediately available relevant, authorised copies of SOPs;
- Procedures exist for revision and updating of SOPS;
- Any amendments or changes to SOPs have been authorised and dated;
- Historical files of SOPs are maintained;
- SOPs are available for, but not necessarily limited to, the following activities:
    i) Receipt; determination of identity, purity, composition and stability; labelling, handling, sampling, usage and storage of test and reference substances;

ii) Use, maintenance, cleaning, calibration and validation of measuring apparatus and environmental control equipment;

iii) Preparation of reagents and dosing formulations;

iv) Record-keeping, reporting, storage and retrieval of records and reports;

v) Preparation and environmental control of areas containing the test systems;

vi) Receipt, transfer, location, characterisation, identification and care of test systems;

vii) Handling of the test systems before, during and at the termination of the study;

viii) Disposal of test systems;

ix) Use of pest control and cleaning agents;

x) Quality Assurance programme operations.

Performance of the Study

PURPOSE: To verify that written study plans exist and that the plans and the conduct of the study are in accordance with GLP Principles.

The Inspector should check that:

- The study plan was signed by the Study Director;
- Any amendments to the study plan were signed and dated by the Study Director.
- The date of the agreement to the study plan by the sponsor was recorded (where applicable);
- Measurements, observations and examinations were in accordance with the study plan and relevant SOPs;
- The results of these measurements, observations and examinations were recorded directly, promptly, accurately and legibly and were signed (or initialled) and dated;
- Any changes in the raw data, including data stored in computers, did not obscure previous entries, included the reason for the change and identified the person responsible for the change and the date it was made;
- Computer-generated or stored data have been identified and that the procedures to protect them against unauthorised amendments or loss are adequate;
- The computerised systems used within the study is reliable, accurate and can be validated;
- Any unforeseen events recorded in the raw data have been investigated and evaluated;
- The results presented in the reports of the study (interim or final) are consistent and complete and that they correctly reflect the raw data.

Reporting of Study Results

PURPOSE: To determine whether final reports are prepared in accordance with GLP Principles.

When examining a final report, the Inspector should check that:

- It is signed and dated by the Study Director to indicate acceptance of responsibility for the validity of the study and confirming that the study was conducted in accordance with GLP Principles;
- It is signed and dated by other principal scientists, if reports from co-operating disciplines are included;
- A Quality Assurance statement is included in the report and that it is signed and dated;
- Any amendments were made by the responsible personnel;

- It lists the archive location of all samples, specimens and raw data.

Storage and Retention of Records

PURPOSE: To determine whether the facility has generated adequate records and reports and whether adequate provision has been made for the safe storage and retention of records and materials.

The Inspector should check:

- That a person has been identified as responsible for the archive;
- The archive facilities for the storage of study plans, raw data (including that from discontinued GLP Studies), final reports, samples and specimens and records of education and training of personnel;
- The procedures for retrieval of archived materials;
- The procedures whereby access to the archives is limited to authorised personnel and records are kept of personnel given access to raw data, slides, etc.;
- That an inventory is maintained of materials removed from, and returned to, the archives;
- That records and materials are retained for the required or appropriate period of time and are protected from loss or damage by fire, adverse environmental conditions, etc.

STUDY AUDITS

Test Facility inspections will generally include, inter alia, Study Audits, which reviews on-going or completed studies. Specific Study Audits are also often requested by Regulatory Authorities, and can be conducted independently of Test Facility Inspections. Because of the wide variation in the types of studies which might be audited, only general guidance is appropriate, and Inspectors and others taking part in Study Audits will always need to exercise judgement as to the nature and extent of their examinations. The objective should be to reconstruct the study by comparing the final report with the study plan, relevant SOPs, raw data and other archived material.

In some cases, Inspectors may need assistance from other experts in order to conduct an effective study audit, e.g., where there is a need to examine tissue sections under the microscope.

When conducting a Study Audit, the Inspector should:

- Obtain names, job descriptions and summaries of training and experience for selected personnel engaged in the study(ies) such as the Study Director and principal scientists;
- Check that there is sufficient staff trained in relevant areas for the study(ies) undertaken;
- Identify individual items of apparatus or special equipment used in the study and examine the calibration, maintenance and service records for the equipment;
- Review the records relating to the stability of the test substances, analyses of test substance and formulations, analyses of feed, etc.;
- Attempt to determine, through the interview process if possible, the work assignments of selected individuals participating in the study to ascertain if these individuals had the time to accomplish the tasks specified in the study plan or report;
- Obtain copies of all documentation concerning control procedures or forming integral parts of the study, including:
  - i) The study plan;
  - ii) SOPs in use at the time the study was done;
  - iii) Log books, laboratory notebooks, files, worksheets, print-outs of computer-stored data, etc.;
  - iv) The final report.

In studies in which animals (i.e., rodents and other mammals) are used, the Inspectors should follow a certain percentage of individual animals from their arrival at the test facility to autopsy. They should pay particular attention to the records relating to:

- Animal body weight, food/water intake, dose formulation and administration, etc.;
- Clinical observations and autopsy findings;
- Clinical chemistry;
- Pathology.

COMPLETION OF INSPECTION OR STUDY AUDIT

When a Test Facility Inspection or Study Audit has been completed, the Inspector should be prepared to discuss his findings with representatives of the test facility at a Closing Conference and should prepare a written report, i.e., the Inspection Report.

A Test Facility Inspection of any large facility is likely to reveal a number of minor deviations from GLP Principles but, normally, these will not be sufficiently serious to affect the validity of studies emanating from that test facility. In such cases, it is reasonable for an Inspector to report that the facility is operating in compliance with GLP Principles according to the criteria established by the (National) GLP Monitoring Authority. Nevertheless, details of the inadequacies or faults detected should be provided to the test facility and assurances sought from its senior management that action will be taken to remedy them. The Inspector may need to revisit the facility after a period of time to verify that necessary action has been taken.

If a serious deviation from the GLP Principles is identified during a Test Facility Inspection or Study Audit which, in the opinion of the Inspector, may have affected the validity of that study, or of other studies performed at the facility, the Inspector should report back to the (National) GLP Monitoring Authority. The action taken by that Authority and/or the regulatory authority, as appropriate, will depend upon the nature and extent of the non-compliance and the legal and/or administrative provisions within the GLP Compliance Programme.

Where a Study Audit has been conducted at the request of a Regulatory Authority, a full report of the findings should be prepared and sent via the relevant (National) GLP Monitoring Authority to the Regulatory Authority concerned.

ANNEX III

GUIDANCE FOR THE EXCHANGE OF INFORMATION CONCERNING NATIONALPROGRAMMES FOR MONITORING OF COMPLIANCE WITH PRINCIPLES OF GOOD LABORATORY PRACTICES

Part II, paragraph 2 of the Council Act contains a Decision that Member countries exchange information related to their programmes for monitoring of compliance with GLP Principles. This Annex provides guidance concerning the types of information which should be exchanged. While information concerning all of the aspects covered in the "Guides for Compliance Monitoring Programmes procedures for Good Laboratory Practice" (Annex I) are relevant to an understanding of other Member countries' procedures for GLP Compliance Monitoring, certain types of information are of particular importance. These include:

- The GLP Principles adopted nationally;
- The scope of the national programme for monitoring compliance with GLP Principles in terms of the types of chemicals and tests covered;
- The identity, legal status, and organisational structure of the (National) GLP Monitoring Authority(ies);
- The procedures followed during Test Facility Inspections and Study Audits, and the periodicity of inspections and/or criteria for inspection schedules;
- The number and qualifications of Inspectors;
- The actions available to the (National) GLP Monitoring Authority(ies) in cases of non-compliance, including the ability to inform other Member countries, when necessary, of the results of Laboratory Inspections and Study Audits;
- The arrangements for protecting confidentiality of information;
- The procedures for initiating, conducting and reporting on Test Facility Inspections and Study Audits at the request of other Member countries;
- The procedures for obtaining information on test facilities which have been inspected by a (National) GLP Monitoring Authority of another Member country, including such facilities' compliance status; and
- The nature of test facility certifications that studies were carried out following GLP Principles.

Where serious deviations which may have affected specific studies are found, the (National) GLP Monitoring Authority should consider the need to inform relevant (National) GLP Monitoring Authorities in other Member countries of their findings.

The names of test facilities subject to Test Facility Inspections within a (National) GLP Compliance Programme, their levels of compliance with the national GLP Principles and the date(s) the Inspections were conducted should be made available annually to (National) GLP Monitoring Authorities in other Member countries upon request (see "Guidance for GLP Monitoring Authorities for the Preparation of Annual Overviews of Test Facilities Inspected" set out in the Appendix to this Annex.)

Recognition of national programmes for monitoring compliance with GLP Principles may not be immediately forthcoming from other Member countries. Member countries should be prepared to meet genuine concerns in a co-operative way. It may be that a Member country is unable to judge the acceptability of the GLP Compliance Monitoring programmes of another solely on the basis of the exchange of written information. In such cases, Member countries may seek the assurance they require through consultation and discussion with relevant (National) GLP Monitoring Authorities. In this context, OECD provides a forum for the discussion and solving of problems relating to the international harmonization and acceptance of GLP Compliance Monitoring programmes.

To facilitate international liaison and the continuing exchange of information, the establishment of a single GLP Monitoring Authority covering all good laboratory practice activities within a Member country has obvious advantages. Where more than one Authority exist, a Member country should ensure that

they operate in a consistent way, and have similar GLP Compliance Programmes. The Authority or Authorities with responsibilities for international contacts should be identified by Member countries.

Situations will arise where a national Regulatory Authority of a Member country will need to request information on the GLP Compliance Status of a test facility located in another Member country. On rare occasions, and where good reason exists, a particular Study Audit may be requested by a Regulatory Authority of another Member country. Arrangements should be provided whereby these requests may be fulfilled and the results reported back to the requesting Regulatory Authority.

Formal international contact should be established for the exchange of information between GLP Monitoring Authorities. However, this should not be understood to prevent informal contacts between Regulatory Authorities and the GLP Monitoring Authority in another Member country, to the extent that such contacts are accepted by the Member countries concerned.

National authorities should note that authorities from another Member country may wish to be present at a Test Facility Inspection or Study Audit that they have specifically requested; or they may wish that representative(s) from the Member country seeking a special Test Facility Inspection or Study Audit be present at that Inspection or Audit. In these cases, Member countries should enable Inspectors from another Member country to participate in facility Inspections and Study Audits carried out by their GLP Monitoring Authority.

APPENDIX TO ANNEX III

GUIDANCE FOR GOOD LABORATORY PRACTICE MONITORING AUTHORITIES FOR THE PREPARATION OF ANNUAL OVERVIEWS OF TEST FACILITIES INSPECTED

Overviews of GLP inspections should be circulated to Members of the OECD Panel on GLP and the OECD Secretariat annually before the end of March. The following minimum set of information should allow harmonisation of the overviews exchanged among national GLP monitoring authorities:

1. Identification of the Facility Inspected: Sufficient information should be included to make the identification of the facility unequivocal, i.e. the name of the test facility the city and country in which it is located, including inspections abroad.

2. Dates of Inspections and Decisions: month and year of inspection, and, if appropriate, date of final decision on GLP compliance status.

3. Nature of Inspection: A clear indication should be given of whether a full GLP inspection or only a study audit was carried out, as well as whether the inspection was routine or not and any other authorities which were involved.

4. Areas of Expertise of the Facility Inspected: Since GLP compliance is related to the tests performed by a facility, the area(s) of expertise of the test facilities inspected should be included in the annual overviews, using the following broad categories:

1) Physical-chemical testing
2) Toxicity studies
3) Mutagenicity studies
4) Environmental toxicity studies on aquatic and terrestrial organisms
5) Studies on behaviour in water, soil and air; bioaccumulation
6) Residue studies
7) Studies on effects on mesocosms and natural ecosystems
8) Analytical and clinical chemistry testing
9) Other studies, specify

It is emphasised that these categories are to be used in a flexible manner on a case-by-case basis and that the aim is to provide information related to GLP compliance of test facilities that will be useful for other national monitoring authorities.

5. Compliance Status: The three following categories should be used to report the compliance status of facilities:

- In compliance
- Not in compliance
- Pending (with explanation)

In light of the fact that "pending" is interpreted differently by Member countries and that the varying legal and administrative systems do not allow for harmonised use of the term, explanations must accompany the use of the "pending" status in the national overview of test facilities inspected. Such explanations could include, e.g., "pending reinspection", "pending responses from test facility", "pending completion of administrative procedures". etc.

6. **Comments**: If appropriate, further comments can be made.

7. **Major Deficiencies**: At a minimum, individual studies for which a study audit has revealed serious GLP deficiencies and which have consequently been rejected by receiving authorities should be reported in the annual overviews of test facilities inspected. Since many studies are submitted to authorities in several countries at the same time, however, it is recommended that this kind of information be circulated among national authorities as rapidly as possible on an ad hoc basis, when necessary in addition to the annual overviews.

8. **Statements of Compliance**: When statements of compliance are provided to facilities by national monitoring authorities, they should use the same terminology and categories as the annual overviews.

9. **Circulation of Annual Overviews**: Overviews should be circulated annually before the end of March to the Members of the GPL Panel and the OECD Secretariat. This information can be released to the public on request.

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The OECD is a unique forum where governments work together to address the economic, social and environmental challenges of globalisation. The OECD is also at the forefront of efforts to understand and to help governments respond to new developments and concerns, such as corporate governance, the information economy and the challenges of an ageing population. The Organisation provides a setting where governments can compare policy experiences, seek answers to common problems, identify good practice and work to co-ordinate domestic and international policies.

The OECD Member countries are: Australia, Austria, Belgium, Canada, Chile, Colombia, Costa Rica, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, the Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Türkiye, the United Kingdom and the United States. The European Union takes part in the work of the OECD.

OECD Legal Instruments

Since the creation of the OECD in 1961, around 460 substantive legal instruments have been developed within its framework. These include OECD Acts (i.e. the Decisions and Recommendations adopted by the OECD Council in accordance with the OECD Convention) and other legal instruments developed within the OECD framework (e.g. Declarations, international agreements).

All substantive OECD legal instruments, whether in force or abrogated, are listed in the online Compendium of OECD Legal Instruments. They are presented in five categories:

- **Decisions** are adopted by Council and are legally binding on all Members except those which abstain at the time of adoption. They set out specific rights and obligations and may contain monitoring mechanisms.

- **Recommendations** are adopted by Council and are not legally binding. They represent a political commitment to the principles they contain and entail an expectation that Adherents will do their best to implement them.

- **Substantive Outcome Documents** are adopted by the individual listed Adherents rather than by an OECD body, as the outcome of a ministerial, high-level or other meeting within the framework of the Organisation. They usually set general principles or long-term goals and have a solemn character.

- **International Agreements** are negotiated and concluded within the framework of the Organisation. They are legally binding on the Parties.

- **Arrangement, Understanding and Others**: several other types of substantive legal instruments have been developed within the OECD framework over time, such as the Arrangement on Officially Supported Export Credits, the International Understanding on Maritime Transport Principles and the Development Assistance Committee (DAC) Recommendations.