

ANNEX I

PART B

REVISED GUIDANCE FOR THE CONDUCT OF TEST FACILITY INSPECTIONS AND STUDY AUDITS

Introduction

The purpose of this part of this Annex 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 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 Annex.

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 part of this Annex 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 GLP adopted in Article 1 of Directive 2004/10/EC and in Part A of this Annex are applicable to this part of this Annex.

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 judgment 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

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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 inspector's 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 on 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 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 director(s), 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 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,

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- 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 procedure 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 updating of SOPs.

Facilities

Purpose: to determine if the test facility, whether indoor or outdoor, is of suitable size, 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, for example, 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, for example, 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 judgment, 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 is 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, for example, 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,
- in 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,

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- 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 tests 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 its 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;

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- (ii) use, maintenance, cleaning, calibration and validation of measuring apparatus, computerised systems 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 are reliable, accurate and have been 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 cooperating disciplines are included,

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- 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 review 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 judgment 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, for example, 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) logbooks, laboratory notebooks, files, worksheets, print-outs of computer-stored data, etc.; checking of calculations, where appropriate;
- (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 on 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.