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COUNCIL DIRECTIVE

►**C1** of 7 June 1988 ◄

on the inspection and verification of Good Laboratory Practice (GLP)

(88/320/EEC)

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COUNCIL DIRECTIVE

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on the inspection and verification of Good Laboratory Practice (GLP)

(88/320/EEC)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100A thereof,

Having regard to the proposal from the Commission [1],

In cooperation with the European Parliament [2],

Having regard to the opinion of the Economic and Social Committee [3],

Whereas the application of standardized organizational processes and conditions under which laboratory studies are planned, performed, recorded and reported for the non-clinical testing of chemicals for the protection of man, animals and the environment, hereinafter referred to as 'Good Laboratory Practice' (GLP), contributes to the reassurance of Member States as to the quality of the test data generated;

Whereas, in Annex 2 to its Decision on 12 May 1981 on the mutual acceptance of data in the assessment of chemicals, the council of the Organization for Economic Cooperation and Development (OECD) adopted principles of good laboratory practice which are accepted within the Community and are specified in Council Directive 87/18/EEC of 18 December 1986 on the harmonization of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances [4];

Whereas, in the conduct of tests on chemicals, it is desirable that specialist manpower and testing laboratory resources should not be wasted owing to the need to duplicate tests because of differences in laboratory practices from one Member State to another; whereas this applies especially for animal protection which requires that the number of experiments on animals be restricted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes [5]; whereas mutual recognition of the results of tests obtained using standard and recognized methods is an essential condition for reducing the number of experiments in this area;

Whereas, however, in order to ensure that test data generated by laboratories in one Member State are also recognized by other Member States, it is necessary to provide for a harmonized system for study audit and inspection of laboratories to ensure that they are working under GLP conditions;

Whereas Member States designate the authorities responsible for carrying out monitoring on compliance with GLP;

Whereas a committee, the members of which will be appointed by the Member States, would be of assistance to the Commission in the technical application of this Directive and would cooperate in its efforts to encourage the free movement of goods by the mutual recognition by Member States of procedures for monitoring compliance with GLP;

(1) OJ No C 13, 17. 1. 1987, p. 5.
(2) OJ No C 156; 15. 6. 1987, p. 190 and OJ No C 122, 9. 5. 1988.
(3) OJ No C 232, 31. 8. 1987, p. 1.
(4) OJ No L 15, 17. 1. 1987, p. 29.
(5) OJ No L 358, 18. 12. 1986, p. 1.

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whereas the committee set up by Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances ([1]), as last amended by Directive 87/432/EEC ([2]), may be used for this purpose;

Whereas this committee may assist the Commission not only in the application of this Directive but also in contributing to the exchange of information and experience in this field,

HAS ADOPTED THIS DIRECTIVE:

Article 1

1. This Directive applies to the inspection and verification of the organizational processes and the conditions under which laboratory studies are planned, performed, recorded and reported for the non-clinical testing, carried out in accordance with the rules and regulations, of all chemicals (e. g. cosmetics, industrial chemicals, medicinal products, food additives, animal feed additives, pesticides) in order to assess the effect of such products on man, animals and the environment.

2. For the purposes of this Directive, the GLP, is described in Directive 87/18/EEC.

3. This Directive is not concerned with the interpretation and evaluation of test results.

Article 2

1. Using the procedure laid down in Article 3, Member States shall verify the compliance with GLP of any testing laboratory within their territory claiming to use GLP in the conduct of tests on chemicals.

2. Where the provisions of paragraph 1 have been complied with, and the results of the inspection and verification are satisfactory, the Member State in question may provide endorsement of a claim by a laboratory that it and the tests that it carries out comply with GLP, using the formula 'Assessment of conformity with GLP according to Directive 88/320/EEC on … (date)'.

Article 3

1. Member States shall designate the authorities responsible for the inspection of laboratories within their territories and for the audit of studies carried out by laboratories to assess compliance with GLP.

2. The authorities referred to in paragraph 1 shall inspect the laboratory and audit the studies in accordance with the provisions laid down in the Annex.

Article 4

1. Each year, Member States shall draw up a report relating to the implementation of GLP within their territory.

This report shall contain a list of laboratories inspected, the date on which such inspection was carried out and a brief summary of the conclusions of the inspections.

2. The reports shall be forwarded to the Commission each year, not later than 31 March. The Commission shall communicate them to the committee referred to in Article 7. The committee may request information in addition to those elements mentioned in paragraph 1.

3. Member States shall ensure that commercially sensitive and other confidential information to which they gain access as a result of GLP compliance monitoring activities is made available only to the Commis-

([1]) OJ No 196, 16. 8. 1967, p. 1/67.
([2]) OJ No L 239, 21. 8. 1987, p. 1.

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sion, to national regulatory and designated authorities and to a laboratory or study sponsor directly concerned with a particular inspection or study audit.

4. The names of laboratories subject to inspection by a designated authority, their GLP compliance status and the dates upon which laboratory inspections or study audits have been conducted shall not be considered to be confidential.

Article 5

1. Without prejudice to Article 6, the results of laboratory inspections and study audits on GLP compliance carried out by a Member State shall be binding on the other Member States.

2. Where a Member State considers that a laboratory within its territory claiming GLP compliance does not in fact comply with GLP to the extent that the integrity or authenticity of the studies it performs might be compromised, it shall forthwith inform the Commission. The Commission shall inform the other Member States.

Article 6

1. Where a Member State has sufficient reason to believe that a laboratory in another Member State claiming GLP compliance has not carried out a test according to GLP, it may request further information from that Member State and in particular may request a study audit, possibly in conjunction with a new inspection.

Should it not be possible for the Member States concerned to reach agreement, the Member States in question shall immediately inform the other Member States and the Commission, giving reasons for their decision.

2. The Commission shall examine as soon as possible the reasons put forward by the Member States within the Committee; it shall then take the appropriate measures in accordance with procedure laid down in Article 8. It may in this connection ask for expert opinions from the designated authorities in the Member States.

3. If the Commission considers that amendments to this Directive are necessary in order to resolve the matters to in paragraph 1, it shall initiate the procedure laid down in Article 8 with a view to adopting those amendments.

Article 7

1. The committee set up by Article 20 of Directive 67/548/EEC, hereinafter called 'the Committee', may examine any question which is referred to it by its chairman either on his own initiative or at the request of a representative of a Member State, concerning the implementation of this Directive and in particular regarding:

— cooperation between the authorities designated by the Member States in technical and administrative matters arising from the implementation of GLP, and

— the exchange of information on the training of inspectors.

2. The amendments necessary for the adaptation of the formula referred to in Article 2 (2) and of the Annex to this Directive to take account of technical progress shall be adopted in accordance with the procedure set out in Article 8.

Article 8

1. The representative of the Commission shall submit to the Committee a draft of the measures to be adopted. The Committee shall deliver its opinion on the draft within a time limit which the chairman may lay down according to the urgency of the matter. The opinion shall be delivered by the majority laid down in Article 148 (2) of the Treaty in the case of decisions which the Council is required to adopt on a proposal from the Commission. The votes of the representatives of the

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Member States within the Committee shall be weighted in the manner set out in that Article. The chairman shall not vote.

2. The Commission shall adopt the measures envisaged if they are in accordance with the opinion of the Committee.

If the measures envisaged are not in accordance with the opinion of the Committee, or if no opinion is delivered, the Commission shall, without delay, submit to the Council a proposal relating to the measures to be taken. The Council shall act by a qualified majority.

3. If within three months of submission of the proposal the Council has not acted, the proposed measures shall be adopted by the Commission.

Article 9

Member States shall bring into force the laws, regulations or administrative provisions necessary to comply with this Directive not later than 1 January 1989. They shall forthwith inform the Commission thereof.

Article 10

This Directive is addressed to the Member States.

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ANNEX

The provisions for the inspection and verification of GLP which are contained in Annexes A and B to this Directive are those contained in Annexes 1 (guides for compliance monitoring procedures for good laboratory practice) and 2 (guidance for the conduct of laboratory inspections and study audits) respectively to the draft Council recommendation on compliance with principles of good laboratory practice (OECD ENV/CHEM/CM/88/15 (first revision).

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ANNEX A

GUIDES FOR COMPLIANCE MONITORING PROCEDURES FOR GOOD LABORATORY PRACTICE (GLP)

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 Annex 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 recognized 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 concern each of these authorities and compliance programmes, as appropriate.

DEFINITIONS OF TERMS

The definitions of terms in the 'OECD principles of good laboratory practice', adopted in Article 1 of Council Directive 87/18/EEC [1] 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 adopted in Article 1 of Directive 87/18/EEC.

GLP compliance monitoring: The periodic inspection of laboratories 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 laboratories within its territories, by means of inspections and study audits.

(National) GLP monitoring authority: A management body established within a member country with responsibility for monitoring the good laboratory practice compliance of laboratories 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.

Laboratory 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 laboratory 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 laboratory inspections on behalf of the (national) GLP monitoring authority.

GLP compliance status: The level of adherence of a laboratory 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

[1] OJ No L 15, 17. 1. 1987, p. 29.

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Administration

A (national) GLP compliance programme should be the responsibility of a properly constituted, legally identifiable management 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, etc.,

— maintain records of laboratories inspected (and their GLP compliance status) and of studies audited.

To foster international understanding and liaison, member countries should inform the OECD and other member countries (e.g. through the OECD complementary information exchange procedure) of the nature and availability of the documentation on GLP which has been produced, together with the addresses and telephone numbers of the (national) GLP monitoring authorities.

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 laboratory 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 laboratory inspections and study audits are made available only to regulatory authorities and, where appropriate, to the laboratories inspected or concerned with study audits and/or to study sponsors.

The names of laboratories subject to laboratory 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 to national) GLP monitoring authorities in other member countries upon request.

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:

(a) the number of laboratories involved in the (national) GLP compliance programme;

(b) the frequency with which the GLP compliance status of the laboratories is to be assessed;

(c) the number and complexity of the studies undertaken by those laboratories;

(d) 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:

(a) ensure that arrangements are made for the appropriate training of Inspectors, having regard to their individual qualifications and experience,

(b) 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

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interpretation and application of GLP principles, and in the monitoring of compliance with such principles,

— *ensure that inspectorate personnel have no financial or other interests in the laboratories 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 laboratory 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 laboratories and the quality/acceptability of a study audit, and for taking any action based on the results of laboratory inspections or study audits which may be necessary.

(National) GLP compliance programmes

GLP compliance monitoring is intended to ascertain whether laboratories 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 laboratories 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 laboratories may have their compliance with GLP principles monitored by the appropriate (national) GLP monitoring authority,

— *provide information on categories of laboratory inspections/study audits*

A (national) GLP compliance programme should include:

(a) routine laboratory inspections — i.e. the regular monitoring of laboratories, in principle on a two-year cycle. These inspections include both a general inspection of the laboratory and a (limited) study audit of an on-going or completed study;

(b) special laboratory 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 laboratories and their access to data held by laboratories*

While inspectors will not normally wish to enter laboratories against the will of the laboratory management, circumstances may arise where 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 laboratory inspection and study audit procedures for verification of GLP compliance*

The documentation should indicate the procedures which will be used to examine both the organizational processes and the conditions under which laboratory studies are planned, performed, monitored and recorded. Guidance for such procedures is available in Annex B to this Directive,

— *describe actions that may be taken as follow-up to laboratory inspections and study audits*

Follow-up to laboratory inspections and study audits

When a laboratory 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 laboratory inspection or study audit. The appropriate

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actions should be described in documents from the (national) GLP monitoring authority.

If a laboratory inspection or study audit reveals only minor deviations from GLP principles, the laboratory 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 laboratory has been inspected and found to be operating in compliance with GLP principles. The date of inspection and, if appropriate, the categories of tests inspected in the laboratory at that time should be included. Such statements may be used to provide information to (national) GLP monitoring authorites 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 laboratory,

— suspension of laboratory inspections or study audits of a laboratory and, for example and where administratively possible, removal of the laboratory from the (national) GLP compliance programme or from any existing list or register of laboratories subject to GLP laboratory inspections,

— the requirement 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.

Where serious deviations are found which may have affected specific studies, the (national) GLP monitoring authority should consider the need to inform relevant regulatory authorities or (national) GLP monitoring authorities in other member countries of their findings.

Appeals procedures

Problems, or differences of opinion, between inspectors and laboratory management will normally be resolved during the course of an laboratory inspection or study audit. However, it may not always be possible for agreement to be reached. A procedure should exist whereby a laboratory may make representations relating to the outcome of a laboratory inspection or study audit for GLP compliance monitoring and/or relating to the action the GLP monitoring authority proposes to take thereon should exist.

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ANNEX B

GUIDANCE FOR THE CONDUCT OF LABORATORY INSPECTIONS AND STUDY AUDITS

INTRODUCTION

The purpose of this Annex is to provide guidance for the conduct of laboratory inspections and study audits which would be mutually acceptable to the OECD member countries. It is principally concerned with laboratory inspections, an activity which occupies much of the time of GLP inspectors. A laboratory 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 Annex.

Laboratory inspections are conducted to determine the degree of conformity of test facilities and laboratory 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. Laboratory inspections result in reports which describe the degree of adherence of a test facility of the GLP principles. Laboratory inspections should be conducted on a regular, routine basis to establish and maintain a record of the GLP compliance status of a test facility.

DEFINITIONS OF TERMS

The definitions of terms in the 'OECD principles of good laboratory practice', adopted in Article 1 of Directive 87/18/EEC and in the Annex A to this Directive, are applicable to this Annex.

LABORATORY 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 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 laboratory 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 laboratory inspection. These lists are not meant to be comprehensive and should not be taken as such.

Inspectors should not concern themselves with the need for, or objectives 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.

Laboratory inspections and study audits inevitably disturb the normal work in a laboratory. 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 laboratory as to the timing of visits to certain sections of the facility.

Inspectors will, while conducting laboratory inspections and study audits, have access to confidential, commercially valuable information. It is essential that they ensure that such information is seen by authorized personnel only. Their responsibilities in this respect will have been established within their (national) GLP compliance monitoring programme.

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INSPECTION PROCEDURES

Pre-inspection

Purpose: To familiarize 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 laboratory inspection or study audit, Inspectors should familiarize 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, organization charts, study reports, protocols and curricula vitae (CVs) of key 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 laboratory inspections. Where no previous laboratory inspections have been conducted, a pre-inspection visit can be made to obtain relevant information.

Laboratories should 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 will allow the laboratory 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 laboratory in advance of the visit so that they will be immediately available during the laboratory inspection.

Starting conference

Purpose: To inform the management and staff of the facility of the reason for the laboratory inspection or study audit that is about to take place, and to identify the laboratory areas, study(ies) selected for audit, documents and personnel likely to be involved.

The administrative and practical details of a laboratory 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 laboratory 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 (organization) and personnel of the facility,

— request information as to the conduct, side-by-side, of studies subject to GLP principles with others for which they are not applied,

— make an initial determination as to the parts of the facility to be covered during the laboratory inspection,

— describe the documents and specimens that will be needed for on-going or completed study(ies) selected for study audit.

Before proceeding further with a laboratory inspection, it is advisable for the inspector to establish contact with the laboratory'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.

Organization 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 organizational structure is appropriate; and management has established a policy regarding training and staff health surveillance appropriate to the studies undertaken in the facility.

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The management should be asked to produce certain documents, for example:

— 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, route of administration and name of study director,

— staff training and health surveillance policies, where such policies have been established,

— staff training records where available,

— 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 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 laboratory,

— the identity and qualifications of the study directors, the head of the quality assurance unit and other key personnel,

— existence of SOPs for all relevant areas of testing.

Quality assurance programme

Purpose: To determine whether the mechanisms used to assure management that laboratory 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 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 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.

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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 laboratory 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 apparatus operation, maintenance, standardization and calibration,

— 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 interfere with 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.

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Physical and chemical systems

The inspector should check that:

— where required by study plans, the stability of test and reference substances were determined and that the reference substances specified in test plans were used,

— SOPs exist to cover laboratory activities and that their provisions are observed,

— 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 identified,

— animals are adequately and, if necessary and appropriate, uniquely identified throughout the study,

— 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 laboratory 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 SOPs for recording the receipt, 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 SOPs for the determination of identity, purity, composition, stability, and for the prevention of contamination of test and reference substances, where applicable,

— records are kept of the composition, characterisation, concentration, and stability 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 laboratory has written standard operating procedures (SOPs) relating to all the important aspects of the laboratory's operations, considering that one of the most important management techniques for

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controlling laboratory operations is the use of written SOPs. These relate directly to the routine elements of tests conducted by the laboratory.

The inspector should check that:

— each laboratory area has immediately available relevant, authorized copies of SOPs,
— procedures exist for revision and updating of SOPs,
— any amendments or changes to SOPs have been authorized and dated,
— historical files of SOPs are maintained,
— SOPs are available for, but not necessarily limited to, the following activities:

(i) receipt, identification, labelling, handling, sampling, usage and storage of test and reference substances;
(ii) maintenance, cleaning and calibration 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, characterization, 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,
— 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 were signed and dated,
— computer-generated or stored data have been identified and that the procedures to protect them against unauthorized amendments or loss are adequate,
— the computer software 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 a final report is available, the inspector should check that:

— it is signed and dated by the study director and by other principal scientists,
— the study director has signed a statement indicating acceptance of responsibility for the validity of the study and confirming that the study was conducted in accordance with GLP principles,
— a quality assurance statement is included in the report and that it is signed and dated,

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— 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:

— the archive facilities for the storage of study plans, raw data, final reports, samples and specimens,

— the procedures for retrieval or archived materials,

— the procedures whereby access to the archives is limited to authorized 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

Laboratory inspections will generally include *inter alia* (limited) study audits. These may be brief reviews of on-going or completed studies. When specific study audits are requested by regulatory authorities, the conduct and reporting of the study should be subjected to a detailed examination. 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 from the study plan using 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 laboratory to autopsy. They should pay particular attention to the records relating to:

— animal body weight, food/water intake, dose formulation and administration, etc.,

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— clinical observations and autopsy findings,
— clinical chemistry,
— pathology.

COMPLETION OF INSPECTION OR STUDY AUDIT

When a laboratory inspection or study audit has been completed, the inspector should be prepared to discuss his findings with representatives of the test facility and should prepare a written report, i.e. the inspection report.

A laboratory inspection of any large laboratory 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 laboratory. In such cases, it is reasonable for an inspector to report that the laboratory 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 laboratory and assurances sought from its senior management that action will be taken to remedy them. The inspector may need to revisit the laboratory 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 laboratory 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 will depend upon the nature and extent of the non-compliance and the legal and/or administrative provisions within the GP 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.