Directive 2004/9/EC of the European Parliament and of the Council of 11 February 2004 on the inspection and verification of good laboratory practice (GLP) (Codified version) (Text with EEA relevance)

DIRECTIVE 2004/9/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 11 February 2004

on the inspection and verification of good laboratory practice (GLP)

(Codified version)

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Economic and Social Committee[(1)],

Acting in accordance with the procedure laid down in Article 251 of the Treaty[(2)],

Whereas:

(1) Council Directive 88/320/EEC of 7 June 1988 on the inspection and verification of Good Laboratory Practice (GLP)[(3)] has been significantly amended several times. In the interests of clarity and rationality the said Directive should be codified.

(2) The application of standardised organisational 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.

(3) In Annex 2 to its Decision of 12 May 1981 on the mutual acceptance of data in the assessment of chemicals, the Council of the Organisation for Economic Cooperation and Development (OECD) adopted principles of good laboratory practice which are accepted within the Community and are specified in the European Parliament and Council Directive 2004/10/EC of 11 February 2004 on the harmonisation 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)].

(4) 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.

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)]. Mutual recognition of the results of tests obtained using standard and recognised methods is an essential condition for reducing the number of experiments in this area.

(5) However, in order to ensure that test data generated by laboratories in one Member State are also recognised by other Member States, it is necessary to provide for a harmonised system for study audit and inspection of laboratories to ensure that they are working under GLP conditions.

(6) Member States should designate the authorities responsible for carrying out monitoring on compliance with GLP.

(7) 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 through the mutual recognition by Member States of procedures for monitoring compliance with GLP. 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[(6)] should be used for this purpose.

(8) That 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.

(9) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission[(7)].

(10) This Directive should be without prejudice to the obligations of the Member States concerning the time-limits for transposition of the Directives set out in Annex II, Part B,

HAVE ADOPTED THIS DIRECTIVE:

Article 1 U.K.

1 This Directive shall apply to the inspection and verification of the organisational 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, ‘good laboratory practice’ (GLP), shall mean laboratory practice conducted in accordance with the principles set out in Directive 2004/10/EC.

3 This Directive does not concern the interpretation and evaluation of test results.

Article 2 U.K.

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 2004/9/EC on … (date)'.

Article 3 U.K.

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 Annex I.

Article 4 U.K.

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(1). The Committee may request information in addition to those elements mentioned in paragraph 1 of this Article.

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 Commission, 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 U.K.

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 U.K.

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 in accordance with 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 referred to in Article 7(1); it shall then take the appropriate measures in accordance with procedure referred to in Article 7(2). It may in this connection ask for expert opinions from the designated authorities in the Member States.

[[F1]3 The Commission is empowered to adopt delegated acts in accordance with Article 6a amending this Directive in order to resolve the matters referred to in paragraph 1. Amendments to Annex I shall not change its nature of providing guidance for compliance monitoring procedures for GLP and for the conduct of test facility inspections and study audits.**]**

Textual Amendments

F1 Substituted by Regulation (EU) 2019/1243 of the European Parliament and of the Council of 20 June 2019 adapting a number of legal acts providing for the use of the regulatory procedure with scrutiny to Articles 290 and 291 of the Treaty on the Functioning of the European Union (Text with EEA relevance).

I[F2]*Article 6a* U.K.

1 The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2 The power to adopt delegated acts referred to in Article 6(3) and Article 8(2) shall be conferred on the Commission for a period of five years from 26 July 2019. The Commission shall draw up a report in respect of the delegation of power not later than nine months before the end of the five-year period. The delegation of power shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

3 The delegation of power referred to in Article 6(3) and Article 8(2) may be revoked at any time by the European Parliament or by the Council. A decision to revoke shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the *Official Journal of the European Union* or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

4 Before adopting a delegated act, the Commission shall consult experts designated by each Member State in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making[(8)].

5 As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

6 A delegated act adopted pursuant to Article 6(3) and Article 8(2) shall enter into force only if no objection has been expressed either by the European Parliament or by the Council within a period of two months of notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or of the Council.**]**

Textual Amendments

F2 Inserted by Regulation (EU) 2019/1243 of the European Parliament and of the Council of 20 June 2019 adapting a number of legal acts providing for the use of the regulatory procedure with scrutiny to Articles 290 and 291 of the Treaty on the Functioning of the European Union (Text with EEA relevance).

[F3 Article 7 U.K.

1 The Commission shall be assisted by the Committee established by Article 29(1) of Council Directive 67/548/EEC[9], hereinafter 'the Committee'.

2 Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.**]**

F4 3 . . . . . .

Textual Amendments

F3 Substituted by Regulation (EC) No 219/2009 of the European Parliament and of the Council of 11 March 2009 adapting a number of instruments subject to the procedure referred to in Article 251 of the Treaty to Council Decision 1999/468/EC with regard to the regulatory procedure with scrutiny Adaptation to the regulatory procedure with scrutiny — Part Two.

F4 Deleted by Regulation (EU) 2019/1243 of the European Parliament and of the Council of 20 June 2019 adapting a number of legal acts providing for the use of the regulatory procedure with scrutiny to Articles 290 and 291 of the Treaty on the Functioning of the European Union (Text with EEA relevance).

Article 8 U.K.

1 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.

[F1 2 The Commission is empowered to adopt delegated acts in accordance with Article 6a amending:

a the formula in Article 2(2);

b Annex I, to take account of technical progress.**]**

Textual Amendments

F1 Substituted by Regulation (EU) 2019/1243 of the European Parliament and of the Council of 20 June 2019 adapting a number of legal acts providing for the use of the regulatory procedure with scrutiny to Articles 290 and 291 of the Treaty on the Functioning of the European Union (Text with EEA relevance).

Article 9 U.K.

Directive 88/320/EEC is hereby repealed, without prejudice to the obligations of the Member States concerning the time limits for transposition of the said Directives as set out in Annex II, Part B.

References made to the repealed Directive shall be construed as being made to this Directive and shall be read in accordance with the correlation table in Annex III.

Article 10 U.K.

This Directive shall enter into force on the 20th day following that of its publication in the *Official Journal of the European Union*.

Article 11 U.K.

This Directive is addressed to the Member States.

ANNEX I U.K.

The provisions for the inspection and verification of GLP which are contained in Parts A and B are those contained in Annexes I (Guides for compliance monitoring procedures for good laboratory practice) and II (Guidance for the conduct of test facility inspections and study audits) respectively of the OECD Council Decision-Recommendation on compliance with principles of good laboratory practice (C(89)87(Final)) of 2 October 1989 as revised by the OECD Council Decision amending the Annexes to the Council Decision-Recommendation on compliance with principles of good laboratory practice of 9 March 1995 (C(95)8(Final)).

PART A U.K.

REVISED GUIDES FOR COMPLIANCE MONITORING PROCEDURES FOR GLP

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

It is recognised that Member States will adopt GLP principles and establish compliance monitoring procedures according to national legal and administrative practices, and according to priorities they give to, for example the scope of initial and subsequent coverage concerning categories of chemicals and types of testing. Since Member States may establish more than one GLP Monitoring Authority due to their legal framework for chemicals control, more than one GLP 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 adopted in Article 1 of Directive 2004/10/EC of the European Parliament and of the Council are applicable to this part of this Annex. 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 2004/10/EC,
— 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 State to monitor GLP compliance by test facilities within its territories, by means of inspections and study audits,
— (national) GLP Monitoring Authority	:	a body established within a Member State with responsibility for monitoring the GLP compliance of test facilities within its territories and for discharging other such functions related to GLP as may be nationally determined. It is understood that more than one such body may be established in a Member State,
— 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

A (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 States 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 States 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 on:

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

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

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

(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 GLP 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 OECD member countries in order to promote international harmonisation 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 in 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 States 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, for example, 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, for example, 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:

(a) 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;

(b) provisions for special test facility inspections/study audits at the request of a Regulatory Authority, for example, 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, SOPs (standard operating procedures) 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 planned, performed, monitored and recorded. Guidance for such procedures is available in part B of this Annex,

— describe actions that may be taken as follow-up test facility inspections and study audits.

Follow-up to test facility 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 States 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 the inspections and, if appropriate, the categories of test 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 OECD 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 on 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.

PART B U.K.

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 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,
— 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,

— 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;

(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,
— 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.

ANNEX II U.K.

PART A U.K.

REPEALED DIRECTIVE AND ITS AMENDMENTS

(Article 9)

Council Directive 88/320/EEC	(OJ L 145, 11.6.1988, p. 35)
Commission Directive 90/18/EEC	OJ L 11, 13.1.1990, p. 37)
Commission Directive 1999/12/EC	(OJ L 77, 23.3.1999, p. 22)
Regulation (EC) No 1882/2003 of the European Parliament and of the Council, Annex III, point 8 only	(OJ L 284, 31.10.2003, p. 1)

PART B U.K.

DEADLINES FOR TRANSPOSITION INTO NATIONAL LAW

(Article 9)

Directive	**Deadline for transposition**
88/320/EEC	1.1.1989
90/18/EEC	1.7.1990
1999/12/EC	30.9.1999

ANNEX III U.K.

CORRELATION TABLE

Directive 88/320/EEC	**This Directive**
Articles 1 to 6	Articles 1 to 6
Article 7	Article 8
Article 8	Article 7
Article 9	—

—	Article 9
—	Article 10
Article 10	Article 11
Annex	Annex I
—	Annex II
—	Annex III

(**1**) OJ C 85, 8.4.2003, p. 137.

(**2**) Opinion of the European Parliament of 1 July 2003 (not yet published in the Official Journal) and Decision of the Council of 20 January 2004.

(**3**) OJ L 145, 11.6.1988, p.35. Directive as last amended by Regulation (EC) No 1882/2003 of the European Parliament and of the Council (OJ L 284, 31.10.2003, p. 1).

(**4**) See page 44 of this Official Journal.

(**5**) OJ L 358, 18.12.1986, p. 1.

(**6**) OJ 196, 16.8.1967, p. 1. Directive as last amended by Council Regulation (EC) No 807/2003 (OJ L 122, 16.5.2003, p. 36).

(**7**) OJ L 184, 17.7.1999, p. 23.

(**8**) **[**[F2]OJ L 123, 12.5.2016, p. 1.**]**

(**9**) **[**[F3]OJ 196, 16.8.1967, p. 1.**]**

Textual Amendments

F2 Inserted by Regulation (EU) 2019/1243 of the European Parliament and of the Council of 20 June 2019 adapting a number of legal acts providing for the use of the regulatory procedure with scrutiny to Articles 290 and 291 of the Treaty on the Functioning of the European Union (Text with EEA relevance).

F3 Substituted by Regulation (EC) No 219/2009 of the European Parliament and of the Council of 11 March 2009 adapting a number of instruments subject to the procedure referred to in Article 251 of the Treaty to Council Decision 1999/468/EC with regard to the regulatory procedure with scrutiny Adaptation to the regulatory procedure with scrutiny — Part Two.