COMMISSION DIRECTIVE 1999/12/EC

of 8 March 1999

adapting to technical progress for the second time the Annex to Council Directive 88/320/EEC on the inspection and verification of good laboratory practice (GLP)

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 88/320/EEC of 9 June 1988 on the inspection and verification of good laboratory practice (GLP) ([1]) as amended by Commission Directive 90/18/EEC ([2]), and in particular Article 7(2) thereof,

Whereas, on 9 March 1995, the OECD Council adopted a Decision amending the Annexes to the Council Decision-Recommendation on compliance with principles of good laboratory practice which affects the texts included in the Annex to Directive 88/320/EEC;

Whereas it is necessary to adapt for a second time the Annex to Directive 88/320/EEC so as to take account of the OECD Council Decision of 9 March 1995, and, by publishing the full text of the annexes on the inspection and verification of good laboratory practice, to facilitate the uniform interpretation thereof;

Whereas the measures provided for in this Directive are in accordance with the opinion of the Committee for the adaptation to technical progress of the Directives concerning the elimination of technical barriers to trade in dangerous substances and preparations,

HAS ADOPTED THIS DIRECTIVE:

Article 1

The Annex to Directive 88/320/EEC is replaced by the Annex hereto.

Article 2

1. Member States shall adopt the laws, regulations and administrative provisions necessary in order to comply with this Directive not later than 30 September 1999 and shall forthwith inform the Commission thereof.

2. When Member States adopt these provisions, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States.

Article 3

This Directive is addressed to the Member States.

Done at Brussels, 8 March 1999.

For the Commission

Martin BANGEMANN

Member of the Commission

([1]) OJ L 145, 11. 6. 1988, p. 35.
([2]) OJ L 11, 13. 1. 1990, p. 37.

ANNEX

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

REVISED GUIDES FOR COMPLIANCE MONITORING PROCEDURES FOR GOOD LABORATORY PRACTICE

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 good laboratory practice compliance, as well as comparability of their quality and rigour, are essential. The aim of this part of the Annex is to provide detailed practical guidance to the Member States on the structure, mechanisms and procedures they should adopt when establishing national good laboratory practice compliance monitoring programmes so that these programmes may be internationally acceptable.

It is recognised that Member 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 Good Laboratory Practice Monitoring Authority due to their legal framework for chemicals control, more than one good laboratory practice compliance programme may be established. The guidance set forth in the following paragraphs concerns each of these Authorities and compliance programmes, as appropriate.

Definitions of terms

The definitions of terms in the OECD principles of good laboratory practice adopted in Article 1 of Council Directive 87/18/EEC [1] are applicable to this part of the 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 87/18/EEC,

— *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 good laboratory practice compliance by test facilities within its territories, by means of inspections and study audits,

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

[1] OJ L 15, 17. 1. 1987, p. 29.

— *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

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

Introduction

The purpose of this part of the 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 the Annex may be obtained by referring to the OECD consensus documents on GLP (on, e.g., the role and responsibilities of the study director).