COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 26.09.2002
COM(2002) 530 final

2002/0231 (COD)

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

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

(codified version)

(presented by the Commission)

EXPLANATORY MEMORANDUM

1. In the context of a people's Europe, the Commission attaches great importance to simplifying and clarifying Community law so as to make it clearer and more accessible to the ordinary citizen, thus giving him new opportunities and the chance to make use of the specific rights it gives him.

   This aim cannot be achieved so long as numerous provisions that have been amended several times, often quite substantially, remain scattered, so that they must be sought partly in the original instrument and partly in later amending ones. Considerable research work, comparing many different instruments, is thus needed to identify the current rules.

   For this reason a codification of rules that have frequently been amended is also essential if Community law is to be clear and transparent.

2. On 1 April 1987 the Commission therefore decided[1] to instruct its staff that all legislative measures should be codified after no more than ten amendments, stressing that this was a minimum requirement and that departments should endeavour to codify at even shorter intervals the texts for which they are responsible, to ensure that the Community rules were clear and readily understandable.

3. The Conclusions of the Presidency of the Edinburgh European Council (December 1992) confirmed this[2], stressing the importance of codification as it offers certainty as to the law applicable to a given matter at a given time.

   Codification must be undertaken in full compliance with the normal Community legislative procedure.

   Given that no changes of substance may be made to the instruments affected by codification, the European Parliament, the Council and the Commission have agreed, by an interinstitutional agreement dated 20 December 1994, that an accelerated procedure may be used for the fast-track adoption of codification instruments.

4. The purpose of this proposal[3] is to undertake the codification of Council Directive 87/18/EEC of 18 December 1986, on the harmonisation of laws, regulations and administrative provisions relating to the principles of good laboratory practice and the verification of their applications for tests on chemical substances. The new Directive will supersede the various Directives incorporated in it[4]; their content is fully preserved, and they are brought together with only such formal amendments as are required by the codification exercise itself.

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1 COM(1987) 868 PV.

2 See Annex 3 to Part A of such conclusions.

3 Carried out pursuant to the Communication from the Commission to the European Parliament and the Council – Codification of the Acquis communautaire, COM(2001) 645 final.

4 See Annex II, Part A of this proposal.

5. The codification proposal was drawn up on the basis of a preliminary consolidation, in all official languages, of Directive 87/18/EEC and the instruments amending it, carried out by the Office of Official Publications of the European Communities, by means of a data-processing system. Insofar as the Articles have been given new numbers, the correlation between the old and the new numbers is shown in a table contained in Annex III to the codified Directive.

↓ 87/18/EEC

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

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

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

↓ 87/18/EEC (adapted)

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 Economic and Social Committee[1],

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

Whereas:

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(1) Council Directive 87/18/EEC of 18 December 1986 on the harmonisation of laws, regulations and administrative provisions relating to the application of principles of good laboratory practice and the verification of their applications for tests on chemical substances[3] has been substantially amended[4]. In the interests of clarity and rationality the said Directive should be codified.

1 OJ C , , p. .
2 OJ C , , p. .
3 OJ L 15, 17. 1. 1987, p. 29. Directive amended by Commission Directive 1999/11/EC (OJ L 77, 23.3.1999, p. 8).
4 See Annex II, Part A.

↓ 87/18/EEC Recital (1)

(2) 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[5] requires tests to be carried out on chemical substances in order to enable their potential risk to man and the environment to be determined.

↓ 87/18/EEC Recital (3) (adapted)

(3) When the active substances in pesticides undergo tests they should do so in accordance with Directive 67/548/EEC.

↓ 87/18/EEC Recital (2) (adapted)

(4) Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products[6] and Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use[7] lay down that non-clinical tests on pharmaceutical products are to be carried out in accordance with the principles of good laboratory practice (GLP) in force in the Community for chemical substances, compliance with which is also required by other Community legislation.

↓ 87/18/EEC Recital (4)

(5) The methods to be used for these tests are laid down in Annex V to Directive 67/548/EEC.

↓ 87/18/EEC Recital (5)

(6) It is necessary to comply with the principles of GLP in carrying out the tests laid down by Directive 67/548/EEC so as to ensure that the results are comparable and of high quality.

[5] OJ 196, 16. 8. 1967, p. 1. Directive as last amended by Commission Directive 2001/59/EC (OJ L 225, 21. 8. 2001, p.1).

[6] OJ L 311, 28. 11. 2001, p. 1.

[7] OJ L 311, 28. 11. 2001, p. 67.

↓ 87/18/EEC Recital (7)

(7) The resources devoted to the tests should not be wasted by having to repeat tests owing to differences in laboratory practice from one Member State to another.

↓ 87/18/EEC Recital (8)
→1 1999/11/EC recital (1)
(adapted)

(8) The Council of the Organisation for Economic Cooperation and Development (OECD) took a Decision on 12 May 1981 on the mutual acceptance of data for the evaluation of chemical products; it issued a recommendation on 26 July 1983 concerning the mutual recognition of compliance with GLP; →1 the principles of GLP have been modified by OECD Council Decision [C(97) 186 (Final)]. ←

↓ 87/18/EEC Recital (9)

(9) Animal protection requires that the number of experiments conducted on animals be restricted; 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.

↓ 87/18/EEC recital (10)

(10) It is necessary to set up a procedure allowing rapid adaptation of the principles of GLP.

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(11) 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:

↓ 87/18/EEC, Art. 1

Article 1

↓ 1999/11/EC, Art. 1 (adapted)

1. Member States shall take all measures necessary to ensure that laboratories carrying out tests on chemical products, in accordance with Directive 67/548/EEC, comply with the principles of good laboratory practice (GLP) as laid down in Annex I to this Directive.

↓ 87/18/EEC, Art.1(2)

2. Paragraph 1 shall apply also where other Community provisions provide for the application of the principles of GLP in respect of tests on chemical products to evaluate their safety for man and/or the environment.

↓ 87/18/EEC, Art. 2 (adapted)

Article 2

When submitting results, the laboratories referred to in Article 1 shall certify that the tests have been carried out in conformity with the principles of GLP referred to in that Article.

↓ 87/18/EEC, Art. 3

Article 3

1. Member States shall adopt the measures necessary for verification of compliance with the principles of GLP. These measures shall include, in particular, inspections and study checks in accordance with the recommendations of the OECD in this area.

2. Member States shall notify to the Commission the name or names of the authority or authorities responsible for verifying compliance with the principles of GLP, as referred to in paragraph 1. The Commission shall inform the other Member States thereof.

↓ 87/18/EEC, Art. 4 (adapted)

Article 4

Any adaptation to the principles of GLP mentioned in Article 1 shall be adopted in accordance with the procedure referred to in Article 29 of Directive 67/548/EEC.

↓ 87/18/EEC, Art. 5

Article 5

1. Where Community provisions require application of the principles of GLP following the entry into force of this Directive for tests on chemical products, Member States may not, on grounds relating to the principles of GLP, prohibit, restrict or impede the placing on the market of chemical products if the principles applied by the laboratories concerned are in conformity with those mentioned in Article 1.

2. Should a Member State establish on the basis of detailed evidence that the application of the principles of GLP and the verification of their application for tests on chemical substances show that, although a chemical substance has been examined in accordance with the requirements of this Directive, it presents a danger to man and the environment, the Member State may provisionally prohibit or make subject to special conditions the marketing of that substance on its territory. It shall immediately inform the Commission and the other Member States thereof and give the grounds for its decision.

   The Commission shall, within six weeks, consult the Member States concerned and then give its opinion and take suitable measures without delay.

   Should the Commission consider that technical adaptations to this Directive are necessary, those adaptations shall be adopted either by the Commission or by the Council in accordance with the procedure referred to in Article 4. In that case, the Member State which adopted the safeguard measures may maintain them until the entry into force of those adaptations.

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Article 6

Directive 87/18/EEC, as amended by the Directive set out in Annex II, Part A, is hereby repealed, without prejudice to the obligations of the Member States concerning the time-limits for transposition of the said Directive as set out in Annex II, Part B.

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

Article 7

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

↓ 87/18/EEC, Art. 7

Article 8

This Directive is addressed to the Member States.

Done at Brussels, […]

For the European Parliament	*For the Council*
The President	*The President*

↓ 1999/11/EC Art. 2

ANNEX I

THE OECD PRINCIPLES OF GOOD LABORATORY PRACTICE (GLP)

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Section I

INTRODUCTION

Preface

Government and industry are concerned about the quality of non-clinical health and environmental safety studies upon which hazard assessments are based. As a consequence, OECD Member countries have established criteria for the performance of these studies.

To avoid different schemes of implementation that could impede international trade in chemicals, OECD Member countries have pursued international harmonisation of test methods and good laboratory practice. In 1979 and 1980 an international group of experts, established under the special programme on the control of chemicals, developed the «OECD principles of good laboratory practice» (GLP), utilising common managerial and scientific practices and experience from various national and international sources. These principles of GLP were adopted by the OECD Council in 1981, as an Annex to the Council Decision on the mutual acceptance of data in the assessment of chemicals. [C(81)30(Final)].

In 1995 and 1996, a new group of experts was formed to revise and update the principles. The current document is the result of the consensus reached by that group. It cancels and replaces the original principles adopted in 1981.

The purpose of these principles of good laboratory practice is to promote the development of quality test data. Comparable quality of test data forms the basis for the mutual acceptance of data among countries. If individual countries can confidently rely on test data developed in other countries, duplicative testing can be avoided, thereby saving time and resources. The application of these principles should help to avoid the creation of technical barriers to trade, and further improve the protection of human health and the environment.

1. **Scope**

These principles of good laboratory practice should be applied to the non-clinical safety testing of test items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives, and industrial chemicals. These test items are frequently synthetic chemicals, but may be of natural or biological origin and, in some circumstances, may be living organisms. The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment.

Non-clinical health and environmental safety studies covered by the principles of good laboratory practice include work conducted in the laboratory, in greenhouses, and in the field.

Unless specifically exempted by national legislation, these principles of good laboratory practice apply to all non-clinical health and environmental safety studies required by regulation for the purpose of registering or licensing pharmaceuticals, pesticides, food and feed additives, cosmetic products, veterinary drug products and similar products, and for the regulation of industrial chemicals.

2. **Definition of terms**

2.1. *Good laboratory practice*

Good laboratory practice (GLP) is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

2.2. *Terms concerning the organisation of a test facility*

1. *Test facility* means the persons, premises and operational unit(s) that are necessary for conducting the non-clinical health and environmental safety study. For multisite studies, those which are conducted at more than one site, the test facility comprises the site at which the study director is located and all individual test sites, which individually or collectively can be considered to be test facilities.

2. *Test site* means the location(s) at which a phase(s) of a study is conducted.

3. *Test facility management* means the person(s) who has the authority and formal responsibility for the organisation and functioning of the test facility according to these principles of good laboratory practice.

4. *Test site management* (if appointed) means the person(s) responsible for ensuring that the phase(s) of the study, for which he is responsible, are conducted according to these principles of good laboratory practice.

5. *Sponsor* means an entity which commissions, supports and/or submits a non-clinical health and environmental safety study.

6. *Study director* means the individual responsible for the overall conduct of the non-clinical health and environmental safety study.

7. *Principal investigator* means an individual who, for a multisite study, acts on behalf of the study director and has defined responsibility for delegated phases of the study. The study director's responsibility for the overall conduct of the study cannot be delegated to the principal investigator(s); this includes approval of the study plan and its amendments, approval of the final report, and ensuring that all applicable principles of good laboratory practice are followed.

8. *Quality assurance programme*: means a defined system, including personnel, which is independent of study conduct and is designed to assure test facility management of compliance with these principles of good laboratory practice.

9. *Standard operating procedures (SOPs)* means documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines.

10. *Master schedule* means a compilation of information to assist in the assessment of workload and for the tracking of studies at a test facility.

2.3. *Terms concerning the non-clinical health and environmental safety study*

1. *Non-clinical health and environmental safety study*, henceforth referred to simply as «study», means an experiment or set of experiments in which a test item is examined under laboratory conditions or in the environment to obtain data on its properties and/or its safety, intended for submission to appropriate regulatory authorities.

2. *Short-term study* means a study of short duration with widely used, routine techniques.

3. *Study plan* means a document which defines the objectives and experimental design for the conduct of the study, and includes any amendments.

4. *Study plan amendment* means an intended change to the study plan after the study initiation date.

5. *Study plan deviation* means an unintended departure from the study plan after the study initiation date.

6. *Test system* means any biological, chemical or physical system or a combination thereof used in a study.

7. *Raw data* means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in

a study. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognised as capable of providing secure storage of information for a time period as stated in section 10 below.

8. *Specimen* means any material derived from a test system for examination, analysis, or retention.

9. *Experimental starting date* means the date on which the first study specific data are collected.

10. *Experimental completion date* means the last date on which data are collected from the study.

11. *Study initiation date* means the date the study director signs the study plan.

12. *Study completion date* means the date the study director signs the final report.

2.4. *Terms concerning the test item*

1. *Test item* means an article that is the subject of a study.

2. *Reference item* («control item») means any article used to provide a basis for comparison with the test item.

3. *Batch* means a specific quantity or lot of a test item or reference item produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character and should be designated as such.

4. *Vehicle* means any agent which serves as a carrier used to mix, disperse, or solubilise the test item or reference item to facilitate the administration/application to the test system.

Section II

GOOD LABORATORY PRACTICE PRINCIPLES

1. **Test facility organisation and personnel**

1.1. *Test facility management's responsibilities*

1. Each test facility management should ensure that these principles of good laboratory practice are complied with, in its test facility.

2. At a minimum it should:

(a) ensure that a statement exists which identifies the individual(s) within a test facility who fulfil the responsibilities of management as defined by these principles of good laboratory practice;

(b) ensure that a sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the study;

(c) ensure the maintenance of a record of the qualifications, training, experience and job description for each professional and technical individual;

(d) ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions;

(e) ensure that appropriate and technically valid standard operating procedures are established and followed, and approve all original and revised standard operating procedures;

(f) ensure that there is a quality assurance programme with designated personnel and assure that the quality assurance responsibility is being performed in accordance with these principles of good laboratory practice;

(g) ensure that for each study an individual with the appropriate qualifications, training, and experience is designated by the management as the study director before the study is initiated. Replacement of a study director should be done according to established procedures, and should be documented;

(h) ensure, in the event of a multisite study, that, if needed, a principal investigator is designated, who is appropriately trained, qualified and experienced to supervise the delegated phase(s) of the study. Replacement of a principal investigator should be done according to established procedures, and should be documented;

(i) ensure documented approval of the study plan by the study director;

(j) ensure that the study director has made the approval study plan available to the quality assurance personnel;

(k) ensure the maintenance of a historical file of all standard operating procedures;

(l) ensure that an individual is identified as responsible for the management of the archive(s);

(m) ensure the maintenance of a master schedule;

(n) ensure that test facility supplies meet requirements appropriate to their use in a study;

(o) ensure for a multisite study that clear lines of communication exist between the study director, principal investigator(s), the quality assurance programme(s) and study personnel;

(p) ensure that test and reference items are appropriately characterised;

(q) establish procedures to ensure that computerised systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with these principles of good laboratory practice.

3. When a phase(s) of a study is conducted at a test site, test site management (if appointed) will have the responsibilities as defined above with the following exceptions: 1.1.2(g), (i), (j) and (o).

1.2. *Study director's responsibilites*

1. The study director is the single point of study control and has the responsibility for the overall conduct of the study and for its final report.

2. These responsibilities should include, but not be limited to, the following functions. The study director should:

(a) approve the study plan and any amendments to the study plan by dated signature;

(b) ensure that the quality assurance personnel have a copy of the study plan and any amendments in a timely manner and communicate effectively with the quality assurance personnel as required during the conduct of the study;

(c) ensure that study plans and amendments and standard operating procedures are available to study personnel;

(d) ensure that the study plan and the final report for a multisite study identify and define the role of any principal investigator(s) and any test facilities and test sites involved in the conduct of the study;

(e) ensure that the procedures specified in the study plan are followed, and assess and document the impact of any deviations from the study plan on the quality and integrity of the study, and take appropriate corrective action if necessary; acknowledge deviations from standard operating procedures during the conduct of the study;

(f) ensure that all raw data generated are fully documented and recorded;

(g) ensure that computerised systems used in the study have been validated;

(h) sign and date the final report to indicate acceptance of responsibility for the validity of the data and to indicate the extent to which the study complies with these principles of good laboratory practice;

(i) ensure that after completion (including termination) of the study, the study plan, the final report, raw data and supporting material are archived.

1.3. *Principal investigator's responsibilities*

The principal investigator will ensure that the delegated phases of the study are conducted in accordance with the applicable principles of good laboratory practice.

1.4. *Study personnel's responsibilities*

1. All personnel involved in the conduct of the study must be knowledgeable in those parts of the principles of good laboratory practice which are applicable to their involvement in the study.

2. Study personnel will have access to the study plan and appropriate standard operating procedures applicable to their involvement in the study. It is their responsibility to comply with the instructions given in these documents. Any deviation from these instructions should be documented and communicated directly to the study director, and/or if appropriate, the principal investigator(s).

3. All study personnel are responsible for recording raw data promptly and accurately and in compliance with these principles of good laboratory practice, and are responsible for the quality of their data.

4. Study personnel should exercise health precautions to minimise risk to themselves and to ensure the integrity of the study. They should communicate to the appropriate person any relevant known health or medical condition in order that they can be excluded from operations that may affect the study.

2. **Quality assurance programme**

2.1. *General*

1. The test facility should have a documented quality assurance programme to assure that studies performed are in compliance with these principles of good laboratory practice.

2. The quality assurance programme should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.

3. This individual(s) should not be involved in the conduct of the study being assured.

2.2. *Responsibilities of the quality assurance personnel*

The responsibilities of the quality assurance personnel include, but are not limited to, the following functions. They should:

(a) maintain copies of all approved study plans and standard operating procedures in use in the test facility and have access to an up-to-date copy of the master schedule;

(b) verify that the study plan contains the information required for compliance with these principles of good laboratory practice. This verification should be documented;

(c) conduct inspections to determine if all studies are conducted in accordance with these principles of good laboratory practice. Inspections should also determine that study plans and standard operating procedures have been made available to study personnel and are being followed.

Inspections can be of three types as specified by quality assurance programme standard operating procedures:

– study-based inspections,

– facility-based inspections,

– process-based inspections.

Records of such inspections should be retained;

(d) inspect the final reports to confirm that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the studies;

(e) promptly report any inspection results in writing to management and to the study director, and to the principal investigator(s) and the respective management, when applicable;

(f) prepare and sign a statement, to be included with the final report, which specifies types of inspections and their dates, including the phase(s) of the study inspected, and the dates inspection results were reported to management and the study director and principal investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

3. **Facilities**

3.1. *General*

1. The test facility should be of suitable size, construction and location to meet the requirements of the study and to minimise disturbance that would interfere with the validity of the study.

2. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study.

3.2. *Test system facilities*

1. The test facility should have a sufficient number of rooms or areas to assure the isolation of test systems and the isolation of individual projects, involving substances or organisms known to be or suspected of being biohazardous.

2. Suitable rooms or areas should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems.

3. There should be storage rooms or areas as needed for supplies and equipment. Storage rooms or areas should be separated from rooms or areas housing the test systems and should provide adequate protection against infestation, contamination, and/or deterioration.

3.3. *Facilities for handling test and reference items*

1. To prevent contamination or mix-ups, there should be separate rooms or areas for receipt and storage of the test and reference items, and mixing of the test items with a vehicle.

2. Storage rooms or areas for the test items should be separate from rooms or areas containing the test systems. They should be adequate to preserve identity, concentration, purity, and stability, and ensure safe storage for hazardous substances.

3.4. *Archive facilities*

Archive facilities should be provided for the secure storage and retrieval of study plans, raw data, final reports, samples of test items and specimens. Archive design and archive conditions should protect contents from untimely deterioration.

3.5. *Waste disposal*

Handling and disposal of wastes should be carried out in such a way as not to jeopardise the integrity of studies. This includes provision for appropriate collection, storage and disposal facilities, and decontamination and transportation procedures.

4. **Apparatus, material, and reagents**

1. Apparatus, including validated computerised systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.

2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to standard operating procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement.

3. Apparatus and materials used in a study should not interfere adversely with the test systems.

4. Chemicals, reagents, and solutions should be labelled to indicate identity (with concentration if appropriate), expiry date and specific storage instructions. Information concerning source, preparation date and stability should be available. The expiry date may be extended on the basis of documented evaluation or analysis.

5. **Test systems**

5.1. *Physical/chemical*

1. Apparatus used for the generation of physical/chemical data should be suitably located and of appropriate design and adequate capacity.

2. The integrity of the physical/chemical test systems should be ensured.

5.2. *Biological*

1. Proper conditions should be established and maintained for the storage, housing, handling and care of biological test systems, in order to ensure the quality of the data.

2. Newly received animal and plant test systems should be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, this lot should not be used in studies and, when appropriate, should be humanely destroyed. At the experimental starting date of a study, test systems should be free of any disease or condition that might interfere with the purpose or conduct of the study. Test systems that become diseased or injured during the course of a study should be isolated and treated, if necessary to maintain the integrity of the study. Any diagnosis and treatment of any disease before or during a study should be recorded.

3. Records of source, date of arrival, and arrival condition of test systems should be maintained.

4. Biological test systems should be acclimatised to the test environment for an adequate period before the first administration/application of the test or reference item.

5. All information needed to properly identify the test systems should appear on their housing or containers. Individual test systems that are to be removed from their housing or containers during the conduct of the study should bear appropriate identification, wherever possible.

6. During use, housing or containers for test systems should be cleaned and sanitised at appropriate intervals. Any material that comes into contact with the test system should be free of contaminants at levels that would interfere with the study. Bedding for animals should be changed as required by sound husbandry practice. Use of pest control agents should be documented.

7. Test systems used in field studies should be located so as to avoid interference in the study from spray drift and from past usage of pesticides.

6. **Test and reference items**

6.1. *Receipt, handling, sampling and storage*

1. Records including test item and reference item characterisation, date of receipt, expiry date, quantities received and used in studies should be maintained.

2. Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured to the degree possible and contamination or mix-up are precluded.

3. Storage container(s) should carry identification information, expiry date, and specific storage instructions.

6.2. *Characterisation*

1. Each test and reference item should be appropriately identified (e.g. code, chemical abstracts service registry number (CAS number), name, biological parameters).

2. For each study, the identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test or reference items should be known.

3. In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in cooperation between the sponsor and the test facility, to verify the identity of the test item subject to the study.

4. The stability of test and reference items under storage and test conditions should be known for all studies.

5. If the test item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined. For test items used in field studies (e.g. tank mixes), these may be determined through separate laboratory experiments.

6. A sample for analytical purposes from each batch of test item should be retained for all studies except short-term studies.

7. **Standard operating procedures**

1. A test facility should have written standard operating procedures approved by test facility management that are intended to ensure the quality and integrity of the data generated by that test facility. Revisions to standard operating procedures should be approved by test facility management.

2. Each separate test facility unit or area should have immediately available current standard operating procedures relevant to the activities being performed therein. Published text books, analytical methods, articles and manuals may be used as supplements to these standard operating procedures.

3. Deviations from standard operating procedures related to the study should be documented and should be acknowledged by the study director and the principal investigator(s), as applicable.

4. Standard operating procedures should be available for, but not be limited to, the following categories of test facility activities. The details given under each heading are to be considered as illustrative examples.

    1. Test and reference items

        Receipt, identification, labelling, handling, sampling and storage.

2. Apparatus, materials and reagents

(a) Apparatus:

use, maintenance, cleaning and calibration.

(b) Computerised systems:

validation, operation, maintenance, security, change control and back-up.

(c) Materials, reagents and solutions:

preparation and labelling.

3. Record keeping, reporting, storage, and retrieval

Coding of studies, data collection, preparation of reports, indexing systems, handling of data, including the use of computerised systems.

4. Test system (where appropriate)

(a) Room preparation and environmental room conditions for the test system.

(b) Procedures for receipt, transfer, proper placement, characterisation, identification and care of the test system.

(c) Test system preparation, observations and examinations, before, during and at the conclusion of the study.

(d) Handling of test system individuals found moribund or dead during the study.

(e) Collection, identification and handling of specimens including necropsy and histopathology.

(f) Siting and placement of test systems in test plots.

5. Quality assurance procedures

Operation of Quality Assurance personnel in planning, scheduling, performing, documenting and reporting inspections.

8. **Performance of the study**

8.1. *Study plan*

1. For each study, a written plan should exist prior to the initiation of the study. The study plan should be approved by dated signature of the study director and verified for GLP compliance by quality assurance personnel as specified in 2.2(b) of Section II. The study plan should also be appproved by the test facility management and the sponsor, if required by national regulation or legislation in the country where the study is being performed.

2. (a) Amendments to the study plan should be justified and approved by dated signature of the study director and maintained with the study plan.

(b) Deviations from the study plan should be described, explained, acknowledged and dated in a timely fashion by the study director and/or principal investigator(s) and maintained with the study raw data.

3. For short-term studies, a general study plan accompanied by a study specific supplement may be used.

8.2. *Content of the study plan*

The study plan should contain, but not be limited to the following information:

1. Identification of the study, the test item and reference item:

(a) a descriptive title;

(b) a statement which reveals the nature and purpose of the study;

(c) identification of the test item by code or name (IUPAC; CAS number, biological parameters, etc.);

(d) the reference item to be used.

2. Information concerning the sponsor and the test facility:

(a) name and address of the sponsor;

(b) name and address of any test facilities and test sites involved;

(c) name and address of the study director;

(d) name and address of the principal investigator(s), and the phase(s) of the study delegated by the study director and under the responsibility of the principal investigator(s).

3. Dates:

(a) the date of approval of the study plan by signature of the study director. The date of approval of the study plan by signature of the test facility management and sponsor if required by national regulation or legislation in the country where the study is being performed;

(b) the proposed experimental starting and completion dates.

4. Test methods:

Reference to the OECD test guideline or other test guideline or method to be used.

5. Issues (where applicable):

   (a) the justification for selection of the test system;

   (b) characterisation of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age and other pertinent information;

   (c) the method of administration and the reason for its choice;

   (d) the dose levels and/or concentration(s), frequency, and duration of administration/application;

   (e) detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed, and statistical methods to be used (if any).

6. Records:

   a list of records to be retained.

8.3. *Conduct of the study*

1. A unique identification should be given to each study. All items concerning this study should carry this identification. Specimens from the study should be identified to confirm their origin. Such identification should enable traceability, as appropriate for the specimen and study.

2. The study should be conducted in accordance with the study plan.

3. All data generated during the conduct of the study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialled and dated.

4. Any change in the raw data should be made so as not to obscure the previous entry, should indicate the reason for change and should be dated and signed or initialled by the individual making the change.

5. Data generated as a direct computer input should be identified at the time of data input by the individual(s) responsible for direct data entries. Computerised system design should always provide for the retention of full audit trails to show all changes to the data without obscuring the original data. It should be possible to associate all changes to data with the persons having made those changes, for example, by use of timed and dated (electronic) signatures. Reason for changes should be given.

9. **Reporting of study results**

9.1. *General*

1. A final report should be prepared for each study. In the case of short-term studies, a standardised final report accompanied by a study specific extension may be prepared.

2. Reports of principal investigators or scientists involved in the study should be signed and dated by them.

3. The final report should be signed and dated by the study director to indicate acceptance of responsibility for the validity of the data. The extent of compliance with these principles of good laboratory practice should be indicated.

4. Corrections and additions to a final report should be in the form of amendments. Amendments should clearly specify the reason for the corrections or additons and should be signed and dated by the study director.

5. Reformatting of the final report to comply with the submission requirements of a national registration or regulatory authority does not constitute a correction, addition or amendment to the final report.

9.2. *Content of the final report*

The final report should include, but not be limited to, the following information:

1. Identification of the study, the test item and reference item:

   (a) a descriptive title;

   (b) identification of the test item by code or name (IUPAC, CAS number, biological parameters, etc.);

   (c) identification of the reference item by name;

   (d) characterisation of the test item including purity, stability and homogeneity.

2. Information concerning the sponsor and the test facility:

   (a) name and address of the sponsor;

   (b) name and address of any test facilities and test sites involved;

   (c) name and address of the study director;

   (d) name and address of the principal investigator(s) and the phase(s) of the study delegated, if applicable;

   (e) name and address of scientists having contributed reports to the final report.

3. Dates:

experimental starting and completion dates.

4. Statement:

a quality assurance programme statement listing the types of inspections made and their dates, including the phase(s) inspected, and the dates any inspection results were reported to management and to the study director and principal investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

5. Description of materials and test methods:

(a) description of methods and materials used;

(b) reference to OECD test guideline or other test guideline or method.

6. Results:

(a) a summary of results;

(b) all information and data required by the study plan;

(c) a presentation of the results, including calculations and determinations of statistical significance;

(d) an evaluation and discussion of the results and, where appropriate, conclusions.

7. Storage:

the location(s) where the study plan, samples of test and reference items, specimens, raw data and the final report are to be stored.

10. **Storage and retention of records and materials**

10.1. The following should be retained in the archives for the period specified by the appropriate authorities:

(a) the study plan, raw data, samples of test and reference items, specimens, and the final report of each study;

(b) Records of all inspections performed by the quality assurance programme, as well as master schedules;

(c) records of qualifications, training, experience and job descriptions of personnel;

(d) records and reports of the maintenance and calibration of apparatus;

(e) validation documentation for computerised systems;

(f) the historical file of all standard operating procedures;

(g) environmental monitoring records.

In the absence of a required retention period, the final disposition of any study materials should be documented. When samples of test and reference items and specimens are disposed of before the expiry of the required retention period for any reason, this should be justified and documented. Samples of test and reference items and specimens should be retained only as long as the quality of the preparation permits evaluation.

10.2. Material retained in the archives should be indexed so as to facilitate orderly storage and retrieval.

10.3. Only personnel authorised by management should have access to the archives. Movement of material in and out of the archives should be properly recorded.

10.4. If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archives of the sponsor(s) of the study(s).

ANNEX II

Part A
Repealed Directive and its amendment
(Article 6)

Council Directive 87/18/EEC	(OJ L 15, 17.1.1987, p.29)
Commission Directive 1999/11/EC	(OJ L 77, 23.3.1999, p. 8)

Part B
Deadlines for transposition into national law
Article 6)

Directive	Deadline for transposition
87/18/EEC	30 June 1988
1999/11/EC	30 September 1999

ANNEX III

CORRELATION TABLE

Directive 87/18/EEC	This Directive
Articles 1 – 5	Articles 1 – 5
Article 6	———
———	Article 6
———	Article 7
Article 7	Article 8
Annex	Annex I
———	Annex II
———	Annex III

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