SUBSIDIARY LEGISLATION 427.56

GOOD LABORATORY PRACTICE REGULATIONS

30th July, 2004

LEGAL NOTICE 371 of 2004, as amended by Legal Notice 426 of 2012.

Citation.

1. The title of these regulations is the Good Laboratory Practice Regulations.

General provisions. S.L. 427.14

2. (1) Laboratories carrying out tests on chemical products, in accordance with the Dangerous Substances (Notification) Regulations, shall comply with the principles of Good Laboratory Practice as laid down in the First Schedule.

(2) Regulation 2(1) shall apply also where other provisions provide for the application of the principles of Good Laboratory Practice in respect of tests on chemical products to evaluate their safety for man and, or the environment.

(3) These regulations implement the provisions of Directive 2004/9/EC of the European Parliament and of the Council and of Directive 2004/10/EC of the European Parliament and of the Council.

Duties of the competent authority.

3. (1) The National Accreditation Body - Malta Standards Authority (NAB-MSA), hereinafter referred to as the competent authority, shall be responsible for verifying compliance with the principles of Good Laboratory Practice of any testing laboratory in Malta claiming to use Good Laboratory Practice, as referred to in regulation 2(1), in the conduct of tests on chemicals.

(2) Should it be established on the basis of detailed evidence that the application of the principles of Good Laboratory Practice 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 these regulations, it presents a danger to man and, or the environment, the Director responsible for Consumer Affairs may, on the advice of the Head of the Directorate responsible for chemicals within the Malta Standards Authority, provisionally prohibit or make subject to special conditions the marketing of that substance in Malta.

(3) On a yearly basis, the competent authority shall draw up a report relating to the implementation of Good Laboratory Practice in Malta. The 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. The report shall be forwarded to the European Commission each year, not later than 31st March.

Certification of results.

4. Where a laboratory has carried out a test in accordance with regulation 2(1), it shall give a notice in writing to the person

who commissioned the test and to the competent authority, stating that the test has been carried out in conformity with the principles of Good Laboratory Practice.

Inspection and verification of Good Laboratory Practice.

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

(2) This regulation is not concerned with the interpretation and evaluation of test results.

(3) The compliance with Good Laboratory Practice of any testing laboratory claiming to use Good Laboratory Practice in the conduct of tests on chemicals shall be verified using the procedure laid down in this regulation.

(4) Where the provisions of subregulation (3) have been complied with, and the results of the inspection and verification are satisfactory, the competent authority may provide endorsement of a claim by a laboratory that it and the tests that it carries out comply with Good Laboratory Practice, using the formula 'Assessment of conformity with Good Laboratory Practice according to Directive 2004/9/EC on ..... (date)'.

(5) The competent authority shall inspect the laboratory and audit the studies in accordance with the provisions laid down in the Second Schedule.

(6) The competent authority shall ensure that commercially sensitive and other confidential information to which it gains access as a result of Good Laboratory Practice compliance monitoring activities is made available only to those national and international bodies which the Minister may, from time to time, designate, and to a laboratory or study sponsor directly concerned with a particular inspection or study audit.

(7) The names of the laboratories subject to inspection by the competent authority, their Good Laboratory Practice compliance status and the dates upon which laboratory inspections or study audits have been conducted shall not be considered to be confidential.

Recognition of Good Laboratory Practice compliance status in other States.

6. (1) Without prejudice to subregulation (2), the competent authority shall accept the results of laboratory inspections and study audits on Good Laboratory Practice compliance carried out by Member States of the European Community.

(2) Where the competent authority has sufficient reason to believe that a laboratory in another Member State claiming Good Laboratory Practice compliance has not carried out a test according to Good Laboratory Practice, it may request further information from the competent authority of that Member State prior to taking a decision on whether to accept the test results.

FIRST SCHEDULE

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' (Good Laboratory Practice), utilising common managerial and scientific practices and experience from various national and international sources. These principles of Good Laboratory Practice 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 Good Laboratory Practice 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 standardized 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).

SECOND SCHEDULE

Amended by:
L.N. 426 of 2012.

The provisions for the inspection and verification of Good Laboratory Practice 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 Good Laboratory Practice 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 (*) are applicable to this part of the Annex. In addition, the following definitions apply:

- *Good Laboratory Practice 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,

- *Good Laboratory Practice compliance monitoring:* the periodic inspection of test facilities and, or auditing of studies for the purpose of verifying adherence to Good Laboratory Practice principles,

- *(National) Good Laboratory Practice 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) Good Laboratory Practice 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 Good Laboratory Practice 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) Good Laboratory Practice Monitoring Authority,

- *Good Laboratory Practice compliance status:* the level of adherence of a test facility to the Good Laboratory Practice principles as assessed by the (national) Good Laboratory Practice 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) Good Laboratory Practice compliance programme should be the responsibility of a properly constituted, legally identifiable body adequately staffed and working within a defined administrative framework.

*OJ L 15, 17.1.1987, p.29.

Member States should:

- ensure that the (national) Good Laboratory Practice 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 Good Laboratory Practice principles within their territories,
- publish documents providing details of the (national) Good Laboratory Practice 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 Good Laboratory Practice compliance status) and of studies audited for both national and international purposes.

Confidentiality

(National) Good Laboratory Practice 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 Good Laboratory Practice 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) Good Laboratory Practice 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) Good Laboratory Practice compliance programme;

  (*b*) the frequency with which the Good Laboratory Practice 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) Good Laboratory Practice Monitoring Authorities should:

(*a*) ensure that arrangements are made for the appropriate training of Good Laboratory Practice inspectors, having regard to their individual qualifications and experience;

(*b*) encourage consultations, including joint training activities where necessary, with the staff of (national) Good Laboratory Practice Monitoring Authorities in other OECD member countries in order to promote international harmonisation in the interpretation and application of Good Laboratory Practice 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., a legally valid identification document).

Inspectors may be:

- on the permanent staff of the (national) Good Laboratory Practice Monitoring Authority,
- on the permanent staff of a body separate from the (national) Good Laboratory Practice Monitoring Authority, or
- employed on contract, or in another way, by the (national) Good Laboratory Practice Monitoring Authority to perform test facility inspections or study audits.

In the latter two cases, the (national) Good Laboratory Practice Monitoring Authority should have ultimate responsibility for determining the Good Laboratory Practice 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) Good Laboratory Practice compliance programmes

Good Laboratory Practice compliance monitoring is intended to ascertain whether test facilities have implemented Good Laboratory Practice 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) Good Laboratory Practice compliance programmes.

Such information should, *inter alia:*

- define the scope and extent of the programme.

A (national) Good Laboratory Practice 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 Good Laboratory Practice 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 Good Laboratory Practice principles monitored by the appropriate (national) Good Laboratory Practice Monitoring Authority,

- provide information on categories of test facility inspections/study audits.

A (national) Good Laboratory Practice 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) Good Laboratory Practice Monitoring Authority in such cases should be defined,

- describe the test facility inspection and study audit procedures for verification of Good Laboratory Practice compliance.

The documentation should indicate the procedures which will be used to examine both the organizational 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 Good Laboratory Practice principles are found during or after a test facility inspection or study audit. The appropriate actions should be described in documents from the (national) Good Laboratory Practice Monitoring Authority.

If a test facility inspection or study audit reveals only minor deviations from Good Laboratory Practice 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) Good Laboratory Practice Monitoring Authority may:

- issue a statement that the test facility has been inspected and found to be operating in compliance with Good Laboratory Practice 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) Good Laboratory Practice 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) Good Laboratory Practice Monitoring Authorities will depend on the particular circumstances of each case and the legal or administrative provisions under which Good Laboratory Practice 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) Good Laboratory Practice compliance programme or from any existing list or register of test facilities subject to Good Laboratory Practice 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 Good Laboratory Practice compliance monitoring and/or relating to the action the Good Laboratory Practice 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 Good Laboratory Practice 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 Good Laboratory Practice 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 Good Laboratory Practice principles. Test facility inspections should be conducted on a regular, routine basis to establish and maintain records of the Good Laboratory Practice 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 Good Laboratory

Practice (on, e.g., the role and responsibilities of the study director).

Definitions of terms

The definitions of terms in the OECD principles of Good Laboratory Practice adopted in Article 1 of Directive 87/18/EEC and in part A of the Annex to this Directive are applicable to this part of the Annex.

Test facility inspections

Inspections for compliance with Good Laboratory Practice 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 Good Laboratory Practice 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 Good Laboratory Practice 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 authorized personnel only. Their responsibilities in this respect will have been established within their (national) Good Laboratory Practice 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 Good Laboratory Practice principles in the areas of the test facility where Good Laboratory Practice 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 Good Laboratory Practice principles are adequate.

The head of the quality assurance (QA) unit should be asked to demonstrate the systems and methods for QA inspection and monitoring of studies, and the system for recording observations made during QA monitoring.

Inspectors should check:

- the qualifications of the head of QA, and of all QA staff,
- that the QA unit functions independently from the staff involved in the studies,
- how the QA unit schedules and conducts inspections, how it monitors identified critical phases in a study, and what resources are available for QA inspections and monitoring activities,
- that where studies are of such short duration that monitoring of each study is impracticable, arrangements exist for monitoring on a sample basis,
- the extent and depth of QA monitoring during the practical phases of the study,

- the 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 Good Laboratory Practice 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 Good Laboratory Practice 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 Good Laboratory Practice 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 Good Laboratory Practice 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 Good Laboratory Practice 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 Good Laboratory Practice principles according to the criteria established by the (national) Good Laboratory Practice 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 Good Laboratory Practice 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) Good Laboratory Practice 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 Good Laboratory Practice 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) Good Laboratory Practice Monitoring Authority.