THE MINISTRY OF HEALTH

1709

Pursuant to Article 10 of the Medicinal Products Act (Official Gazette 71/07, 45/09 and 124/11), the Minister of Health, hereby issues the

ORDINANCE
ON GOOD LABORATORY PRACTICE

Article 1

This Ordinance establishes good laboratory practice (hereinafter: GLP) in test facilities conducting non-clinical studies of properties of medicinal products along with the assessment and supervision of the compliance with the principles of good laboratory practice.

Provisions of this Ordinance do not relate to the interpretation and assessment of the results of studies provided for by paragraph 1 of this Article.

Article 2

This Ordinance contains provisions harmonised with the following acts of the European Union:

- Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (OJ L 50, 20. 2. 2004)

- Directive 2004/9/ EC of the European Parliament and of the Council of 11 February 2004 on the Inspection and Verification of Good Laboratory Practice (GLP)

Article 3

For the purposes of this Ordinance, the following terms have the following meanings:

Good laboratory practice is a quality system concerned with the organisational processes and conditions by means of which non-clinical studies safe for human health and environment (hereinafter: non-clinical studies) are planned, performed, monitored, documented, stored and reported.

Test facility comprises the persons, premises and equipment that are necessary for conducting non-clinical studies. 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.

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

Responsible person of the test facility means the person who has the authority and formal responsibility for the organisation and functioning of the test facility according to these principles of good laboratory practice.

Responsible person of the test site means the person 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.

Sponsor means a legal or natural person who commissions, supports and/or recommends a non-clinical study.

Study director means the individual responsible for the overall conduct of the non-clinical study as well as health of the personnel and environmental safety. The study director cannot delegate responsibility for the overall conduct of non-clinical study to the principal investigator. This includes approval of the study plan and its amendments, approval of the final report, and ensuring that all principles of good laboratory practice are followed.

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.

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

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.

Master schedule is the total of information which are needed as assistance in evaluation when assessing workload and monitoring the studies in the test facility

Non-clinical study safe for health and environment means an experiment or set of experiments in which a test item is examined under laboratory conditions or in the environment in order to obtain data on its properties and/or its safety, intended for submission to appropriate regulatory authorities.

Short-term study means a study of short duration applying widely used routine techniques.

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

Study plan amendments mean any intended changes to the study plan after the study initiation date.

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

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

Raw data means all original test facility records and documentation, or verified copies thereof, which are the result of original observations and activities in the course of a study. Raw data also may include, for example, photographs, microfilm or their copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that enables secure storage of information for a prescribed time period.

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

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

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

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

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

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

Reference item (control item) means any article (standard) used as a basis for comparison with the test item.

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.

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

Assessment of compliance with principles of good laboratory practice conducted by the Ministry of Health (hereinafter: the Ministry) means the monitoring of compliance with GLP principles, i.e. occasional laboratory inspection and/or study audit for the purpose of verifying adherence to GLP principles.

Study audit means 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 the raw data has been presented in a satisfying manner, whether the 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.

Authorised person means an inspector authorised for conducting the test facility inspection and study audit.

GLP compliance status means the level of adherence of a test facility to the GLP principles as assessed by the Ministry.

National GLP compliance programme (hereinafter: the programme) means a special programme issued by the Ministry, the objective of which is to establish a system of monitoring compliance with GLP principles in test facilities in the territory of the Republic of Croatia.

Regulatory Authority means the Ministry of Health.

Article 4

Each responsible person of the test facility should ensure that the principles of good laboratory practice are complied with, in their test facility.

The responsible person of the test facility should at least:

1. ensure that a statement exists which identifies the individuals within a test facility who fulfil the responsibilities of management as defined by these principles of good laboratory practice,

2. ensure that a sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the study,

3. ensure the maintenance of a record of the qualifications, training, experience and job description for each professional and technical individual,

4. ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions,

5. ensure that appropriate and technically valid standard operating procedures are established and followed, and approve all original and revised standard operating procedures,

6. ensure that there is a quality assurance programme with designated personnel and assure that the quality assurance measures are implemented in accordance with the principles of good laboratory practice,

7. ensure that for each study an individual with the appropriate qualifications, training, and experience is designated as the study director before the study is initiated. In the event of replacement of the study director, this should be done according to established procedures and should be documented,

8. ensure, in the event of a multisite study, that a principal investigator is designated, who is appropriately qualified and experienced to supervise the delegated phases of the study. Replacement of a principal investigator should be done according to established procedures, and should be documented,

9. ensure documented and written approval of the study plan by the study director which shall be made available to the quality assessment personnel,

10. ensure the maintenance of a historical file of all standard operating procedures,

11. ensure that an individual is designated as responsible for the management of the archive(s),

12. ensure the maintenance of a master schedule,

13. ensure that test facility supplies meet requirements appropriate to their use in a study,

14. ensure for a multisite study that clear lines of communication exist between the study director, principal investigator, the quality assurance programme personnel and study personnel,

15. ensure that test and reference items are appropriately characterised,

16. establish procedures which ensure that computerised systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with the principles of good laboratory practice.

When a phase(s) of a study is conducted at a test site, responsible person of the test site (if appointed) shall have the responsibilities of the responsible person of the test facility, with the exceptions provided for by items 7 and 9 of this Article.

Article 5

The study director shall be responsible for the overall conduct of the study and for the final report.

The study director shall at least:

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

b) ensure that the quality assurance personnel receives a copy of the study plan and any amendments in a timely manner and establish efficient communication with the quality assurance personnel during the conduct of the study,

c) ensure that study plans and amendments and standard operating procedures are available to personnel taking part to study,

d) ensure that the study plan and the final report for a multisite study identify and define the role of any principal investigator 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, 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 and thus indicate acceptance of responsibility for the validity of the data and indicate the extent to which the study complies with these principles of good laboratory practice,

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

Article 6

The principal investigator shall ensure that the delegated phases of the study are conducted in compliance with the principles of good laboratory practice.

Article 7

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.

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 act in compliance 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, or to both of them.

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

All measures should be taken with a view of ensuring integrity of the study and protecting the health of the personnel taking part thereto.

The personnel should inform the responsible person of the existence of any health or medical condition that may affect the study. Personnel members displaying such health or medical conditions shall be excluded from the study.

Article 8

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

The quality assurance programme should be carried out by an individual or by individuals familiar with the test procedures who are designated by and directly responsible to the authorised person. These individuals should not be involved in the conduct of the study being assured.

Article 9

Quality assurance personnel are responsible for at least:

a) maintaining and keeping copies of all approved study plans and standard operating procedures in use in the test facility,

b) verification that the study plan contains all the information in accordance with these principles of good laboratory practice. This verification should be documented

c) conducting inspections with the aim to determine whether 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.

As specified by quality assurance programme standard operating procedures, inspections can be of the following types:

- study-based inspections,

- facility-based inspections,

- process (procedure)-based inspections.

Records of such inspections should be retained,

d) inspection of the final reports in order to confirm that the methods, procedures, and observations are accurately and thoroughly described, and that the reported results accurately and completely reflect the raw data of the studies,

e) promptly communicate a written report on the inspection results to the study director, the principal investigator and the responsible persons, when applicable

f) compilation and signing of a statement, to be included with the final report, which specifies types of inspections and their dates, including the phases of the study inspected, and the dates inspection results were communicated to study director, the principal investigator and the responsible persons, when applicable. This statement would also serve to confirm that the final report reflects the raw data.

Article 10

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

The available space of the test facility should provide an adequate degree of separation of the different activities in order to enable the proper conduct of each study.

The test facilities 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 suspected of present a biohazard.

Suitable rooms or areas should be available for the diagnosis, treatment and control of diseases, in order to ensure that the test systems do not deteriorate to unacceptable degree. There should be adequate storage rooms with areas suitable for storing supplies and equipment in the test facility. 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.

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

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

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.

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

Article 11

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.

Apparatus used in a study should be regularly 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.

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

Chemicals, reagents, and solutions should be labelled to indicate properties (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.

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

The proper operation of the physical and chemical test systems must be ensured.

Article 12

When using biological test systems, adequate conditions should be established and maintained for the storage, housing, and care in order to ensure quality of data.

Newly received test animals and plant test systems should be isolated until their health status has been evaluated. In the event of any unusual mortality or morbidity, these lots 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 in the course of a study should be isolated and treated, if that is necessary to maintain the integrity of the study. Any diagnosis and treatment of any disease before or during a study should be recorded.

Article 13

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

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.

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.

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.

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.

Article 14

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

Handling, sampling, and storage procedures should be identified in order to assure the homogeneity and stability to the highest possible degree and preclude contamination and/or mix-up.

The storage container should carry basic identification information, expiry date, and specific storage instructions.

Stability in the conditions of storage and study should be known for each item.

Each test and reference item should be appropriately identified (e.g. code, Chemical Abstracts Service registry number (CAS number), name, and biological parameters).

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

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.

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

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.

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

Article 15

A test facility should have written standard operating procedures approved by the responsible person of the test facility 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 the responsible person of the test facility.

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.

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

Standard operating procedures should be available for, but not be limited to, the following categories of test facility activities:

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 systems.

(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.

Article 16

For each study, a written plan should be prepared 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. The study plan should also be approved by the responsible person of the test facility and the sponsor.

Amendments to the study plan should be justified and approved by dated signature of the study director. The amendments should be maintained with the study plan. Deviations from the study plan should be described, explained, acknowledged and dated in a timely fashion by the study director or principal investigator. and maintained with the study raw data.

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

The study plan should contain at least 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 investigators, and the phases 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 accompanied by the signature of the study director. The date of approval of the study plan accompanied by the signature of the responsible person of the test facility and the sponsor,

(b) The proposed experimental starting and completion dates.

4. Test methods

It is necessary to follow instructions contained in the test guidelines of the Organisation for Economic Cooperation and Development (hereinafter: OECD) or other test guidelines or methods to be used.

5. Other issues (where applicable)

(a) justification for the 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) method of administration and the reason for its choice,

(d) dose levels and/or concentrations, 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.
Along with the said information, the study plan may contain other information.

Article 17

A unique identification should be given to each study which shall be used on any document, information, or specimen used in that study. Specimens from the study should be identified in such a way as to confirm their origin. The identification should enable traceability, as appropriate for the specimen and study.

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

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 and dated.

Any change in the raw data should be made so as not to obscure the previous entry and the reason for change should be indicated. The individual making the change should confirm the change by their dated signature.

Data generated as a direct computer input should be identified at the time of data input by the individuals 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.

Article 18

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

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.

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

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

Article 19

The final report should include at least the following information:

a) identification of the study, of the test item and of the reference item,

b) a descriptive title,

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

d) identification of the reference item,

e) characterisation of the test item including purity, stability and homogeneity,

f) name and address of the sponsor,

g) name and address of any test facilities and test sites involved,

h) name and address of the study director,

i) name and address of the principal investigator(s) and the phases of the study delegated to the principal investigator by the study director,

j) names and addresses of scientists having contributed to the final report,

k) experimental starting and completion dates,

l) a quality assurance programme statement listing the types of inspections conducted and the dates thereof, including the phases inspected, and the dates any inspection results were reported to the responsible person of the test facility, to the study director, and the principal investigator, if applicable. This statement would also serve to confirm that the final report reflects the raw data,

m) description of materials and test methods,

n) description and argumentation of a certain modality of use of the tested substance,

o) reference to OECD test guidelines or other test guidelines or methods,

p) methods and schedule of evaluation, recording, and parameter analysis,

r) a description of the statistical methods used,

s) a summary of the results,

t) all information and data required by the study plan,

u) a presentation of the results, including calculations and determinations of statistical significance,

v) an evaluation and discussion of the results and, where appropriate, conclusions,

z) the location where the documentation, data, and samples are to be stored.

Article 20

The following shall be retained in the archives for the period prescribed:

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 the study plan, raw data, test items or documentation 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 should be retained only as long as the quality of the preparation permits evaluation.

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

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

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 of the study or a third person.

GLP COMPLIANCE ASSESSMENT AND MONITORING PROCEDURES

Article 21

The Ministry shall be responsible for GLP compliance assessment and monitoring procedures of all test facilities in the territory of the Republic of Croatia which conduct non-clinical studies.

The Ministry shall inform the European Commission of its competence referred to in paragraph 1 of this Article.

When the Ministry, after having conducted the inspection, determines that the test facilities and the studies conducted therein are in compliance with GLP principles, it shall issue the „Confirmation of GLP principles compliance“ which is enclosed in Annex I to this Ordinance and forms its constituent part.

Article 22

GLP compliance monitoring shall be conducted by inspectors fulfilling requirements under Article 94 of the Medicinal Products Act and familiar with good laboratory practice principles and other documents necessary for alignment with good laboratory practice principles, with comprehensive knowledge of the rules regulating good laboratory practice, adequately trained for inspection of GLP and holding a special authorisation of the Minister competent for the health sector (hereinafter: the Minister).

Persons referred to in paragraph 1 of this Article shall have the rights and responsibilities to:

1. enter the premises of the test facility at any time,

2. on the premises of the test facility, conduct checks, studies, and analyses they deem necessary for the assessment of the test facility's compatibility for studies in accordance with provisions laid down in this Ordinance,

3. inspect, request the preparation or take copies or excerptions of any documentation relevant to the compliance assessment,

4. ask for assistance of any employee of the test facility while the compliance assessment is in progress.

While conducting the monitoring, the Ministry may, if applicable, invite representatives of other competent bodies or representatives of competent bodies of other countries which are in charge of good laboratory practice, to be present to the test facility inspection and study audit.

Article 23

While conducting the inspection, an inspector may gain access to confidential information, remove documents labelled as confidential from the test facility or make use of them in reports.

The confidentiality of information should be ensured by:

1. an inspector submitting for consideration a special authorisation by the Minister,

2. labelling all confidential information collected by the inspector and/or information retained in the Ministry as confidential and treating them in accordance with rules regulating information confidentiality,

3. appropriately labelling all the copies of documents removed from the test facility and establishing the level of their confidentiality.

Inspectors for GLP compliance monitoring and other persons authorised by the Ministry shall have access to information and reports stored at the Ministry.

The following information may not be labelled as confidential:

1. information on the test facilities which are currently or have been previously included in the GLP programme,

2. dates of test facility inspections or dates of study audits and the decision on compliance,

3. types of inspections,

4. areas of the test facility's specialisation,

5. test facility GLP compliance assessments,

6. main defects, the situation established between the inspection and the decision.

Confidential information to which, in terms of this Ordinance, only authorised persons have access in the course of monitoring compliance, shall be accessible only to the European Commission, to competent bodies of other member states of the European Union, and to the test facility to which a certain inspection or study audit apply.

Article 24

The Ministry shall guarantee fulfilment of obligations deriving from international agreements referring to the application of GLP principles. This shall apply primarily the following activities:

1. exchange of information regarding assessment and GLP compliance procedures, such as:

a) nationally recognised GLP principles,

b) the scope of GLP principles assessment in relation to the type of substances and preparations, as well as the studies being conducted,

c) information on the organisation and competences of the Ministry,

d) test facility inspection procedures, the decision on studies, and parameters for the inspection planning,

e) number of inspectors and their qualifications,

f) the measures to be taken by the Ministry in the event of lack of compliance, including informing the bodies competent for GLP in other countries, where applicable, on the results of test facility inspections and of the decisions on the studies,

g) measures for the protection of information confidentiality,

h) test facility inspection procedures and the decision on the studies upon requests of third countries,

i) procedures of obtaining information on test facilities inspected by the body of another member country competent for GLP, including the compliance assessment of that test facility, and

j) the type of decision confirming that the study has been conducted in accordance with GLP procedures,

2. the exchange of annual reports on test facility inspections conducted,

3. reporting information on test facility inspections and decisions on the study upon request of competent bodies of third countries,

4. test facility inspections and decisions on the study from competent bodies of third countries

5. requesting information on test facility inspections and decisions on the study from competent bodies of third countries,

6. requesting test facility inspections by competent bodies of other countries, upon request of other competent bodies, if applicable in the presence of observers,

7. participation in operations of international bodies competent for GLP,

8. participation in international inspections aiming at aligning the application of GLP principles in the test facility,

9. reporting on possible international disputes and their settling in front of international bodies.

Article 25

When the body of another country competent for GLP wishes only to conduct the test facility inspection or the decision on the study in the territory of the Republic of Croatia, the test facility shall have to procure approval of the Minister and enable the presence of persons authorised by the Ministry as observers.

Article 26

GLP principles compliance assessment includes the testing facility conducting the study of characteristics of substances or preparations:

1. the results of which enable the assessment of their possible hazardous effects on humans and the environment, and which are used in the marketing, registration, application, and reporting procedures,

2. for which the application of GLP principles is required in accordance with special regulations for certain substances or preparations.

The assessment referred to in paragraph 1 of this Article shall be conducted in accordance with provisions referring to GLP principles laid down in this Ordinance and corresponding OECD publications on good laboratory practice principles and compliance monitoring.

It is necessary for the test facility to provide for each inspection a written statement proving that it was conducted in line with GLP principles.

The test facility reporting the inspection results to the competent body shall have to prove that the inspections on which the results submitted are based corresponds to GLP principles. The proof shall have to comprise:

1. a copy of the confirmation of compliance with GLP principles enclosed in Annex I to this Ordinance and

2. a written statement referred to in paragraph 3 of this Article.

Article 27

The assessment of compliance with GLP principles includes test facilities dealing in non-clinical studies.

The areas of the test facility's specialisation are divided into:

1. physical and chemical studies,

2. toxicological studies,

3. studies of mutagenic properties,

4. environmental toxicological studies on water and land organisms,

5. the study of behaviour in water, land, and air; bioaccumulation,

6. the study of residues,

7. the study of the effect on the mesocosmos and natural ecosystems,

8. analytical and clinical chemical studies and

9. other.

Article 28

Monitoring of test facility compliance with GLP principles encompasses the following types of inspection:

1. pre-inspection of the test facility which is carried out in the course of inclusion in the GLP programme prior to the first compliance inspection of the test facility.

2. periodical test facility inspection conducted every second year and consists of the general inspection of the test facility and the assessment of one or more completed or on-going inspections,

3. a special test facility inspection or study audit upon request of national or foreign competent bodies, which is based on e.g. the inspection of documentation submitted to the competent body

4. verification inspection of the test facility.

Article 29

The Ministry shall inform the test facility of the date of the inspection or assessment and the names of authorised persons that are going to conduct the inspection or study audit.

The provision laid down in paragraph 1 of this Article does not refer to inspections referred to in Article 28, item 4 of this Ordinance.

The test facility may object to the choice of the authorised person with a valid argumentation. If necessary, the Ministry may request additional information from the test facility prior to the periodical or special inspection.

The Ministry conducts inspections of the test facility and the study audit in accordance with instructions laid down in Annex II printed with this Ordinance and being an integral part thereof.

Article 30

Upon the completion of the inspection or assessment, the inspector is required to prepare a written report consisting of:

1. general information on the test facility,

2. inspection results referring to GLP principles,

3. opinion on compliance and a suggestion of possible improvements.

The Ministry shall communicate a draft of the report referred to in paragraph 1 of this Article for the information of the test facility and shall set a 30 days deadline from the receipt of the draft report for the submission of objections to the draft report.

Objections may be taken into consideration when drawing up the inspection report and shall be enclosed to the report.

The Ministry shall communicate the final report on the inspection or study audit to the test facility.

Article 31

On the basis of the inspection report, the Ministry shall decide on the compliance of the test facility with GLP principles.

The assessment referred to in paragraph 1 of this Article may be:

1. the test facility conducts the testing in accordance with GLP principles,

2. the test facility does not conduct the testing in accordance with GLP principles and

3. no final rating was assigned.

The Ministry may reach the assessment referred to in paragraph 3, item 2 of this Article in the event of deviations from GLP principles, in the event referred to in Article 32, paragraph 4, item 2 and Article 33, paragraph 1 of this Ordinance, or in the course of the assessment procedure.

Article 32

When, in the course of the test laboratory inspection, compliance with GLP principles is established, the Minister shall issue a written decision of compliance with GLP principles, enclosed in Annex I to this Ordinance.

When, in the course of the test laboratory inspection, compliance with GLP principles, or only minor deviations which do not affect its validity, have been established, the Minister shall issue a written confirmation of compliance with GLP principles enclosed in Annex I to this Ordinance.

When only minor deviations which do not affect the validity of the tests run by the test facility are detected in the course of the inspection, the Minister may:

1. issue a written confirmation of compliance with GLP principles enclosed in Annex I to this Ordinance, providing that the test laboratory confirms in written form its willingness to remove forthwith the established defects, or

2. set an appropriate deadline for the removal of the defects and call for a written notice on the measures taken.

The Minister issues a written confirmation of compliance with GLP principles or decides on the necessity for repeating the part of the inspection where the deviations were detected.

Article 33

When major deviations that may affect the validity of the tests conducted by the test facility are detected in the course of the test facility inspection or assessment, the Ministry may:

1. set an appropriate deadline for the implementation of measures and, within 6 months at the latest, conduct another complete or partial inspection. When in the course of the repeated inspection, the authorised person establishes that the irregularities have been removed, the Minister issues the confirmation of compliance with GLP principles,

2. remove the test facility from the list of test facilities.

3. issue a statement which in detail describes the irregularities or faults detected which may influence on the validity of tests in a certain test facility,

4. request that the assessment on non-compliance issued by the Ministry be enclosed to a certain study,

5. issue a recommendation to reject the study to the competent bodies,

6. inform competent international bodies and bodies in charge of GLP monitoring in other countries of major deviations.

Article 34

Notwithstanding the implementation of the provision laid down in Article 35 of this Ordinance, the results of laboratory tests and assessments regarding GLP compliance conducted in the territory of the Republic of Croatia are legally binding for the competent bodies of other member states of the European Union.

Results of test facility inspections and audits of studies regarding GLP compliance conducted in the territory of another member state of the European Union are legally binding for the Ministry.

When the Ministry considers that a test facility in the territory of the Republic of Croatia claiming to be in compliance with GLP principles, actually does not respect GLP principles to such an extent that the integrity and credibility of the conducted test may be challenged, the Ministry shall forthwith inform the European Commission. The European Commission shall inform other member states of the European Union thereof.

The Ministry shall temporarily prohibit the marketing of the dangerous chemical which has been proved to present a hazard for health and the environment and the dangerous characteristics of which have been tested at the test facility for which compliance with GLP principles was established.

Article 35

When the Ministry determines that a test facility in another EU member state claiming to be in compliance with GLP principles does not conduct tests in accordance with GLP principles, it may ask additional information from this EU member state and, particularly, it may call for an assessment referring to a new inspection, if applicable.

When the Ministry and the competent body of this EU member state cannot reach an agreement, they shall forthwith inform other member states of the European Union thereof, expounding their decision.

Article 36

The Ministry keeps a list of test facilities conducting tests in compliance with GLP principles.

The list referred to in paragraph 1 of this Article shall be published once a year in the Official Gazette.

Article 37

When the test facility stops conducting tests in accordance with GLP principles, it is required to forthwith inform the Ministry thereof.

In the event referred to in paragraph 1 of this Article, the Ministry shall remove the test facility from the list of test facilities and this shall be published in the Official Gazette.

Article 38

The aim of the programme referred to in Article 3, item 32 of this Ordinance is to establish whether the test facilities have implemented GLP principles during the conduct of the tests and whether they are capable of ensuring appropriate quality of the information obtained.

The programme referred to in Article 3, item 32 of this Ordinance shall be published annually in the Official Gazette and shall comprise the following information on:

1. the implementation area and scope of the programme (whether it includes only a restricted number of chemicals or medicinal products, implementation extent of the compliance inspection, both in relation to categories of chemicals or medicinal products and types of inspections they are subject to, for instance, physical, chemical, toxicological and/or eco-toxicological),

2. the mechanism by which test facilities take part in the programme (the implementation of GLP principles may be mandatory for information on health and environmental safety, obtained for regulatory purposes). It is necessary to establish a mechanism by means of which the Ministry monitors compliance with GLP principles,

3. information on categories of test facility inspections/ study audits,

4. provisions relating to test facility inspections (these inspections also comprise the general inspection of the test facility and a study audit of one or more on-going or completed inspections, on special test facility inspections/ study audits, upon request of the regulatory authority, for instance, initiated by issues arising from information submitted to the regulatory authority),

5. on the authorities of inspectors regarding entry in the laboratory and access to information available to the laboratory (including specimens, SOPs (standard operating procedures), other documentation, etc.), especially in cases of exceptional circumstances when the entry in the test facility and access to data are necessary for the protection of public health and the environment. In such cases it is necessary to define the competence of the Regulatory Authority,

6. describe procedures of test facility inspections and procedures of study audits in order to monitor compliance with GLP procedures (the documentation shall have to demonstrate procedures to be used for the inspection of organisation processes and conditions under which inspections are planned, conducted, monitored, and recorded). Instructions for such procedures are listed in Annex II to this Ordinance,

7. on the measures likely to be taken as a consequence of the test facility inspection and study audit.

Article 39

Each year the Ministry shall prepare a report on the implementation of GLP principles in the territory of the Republic of Croatia.

The report referred to in paragraph 1 of this Article shall comprise a list of inspected laboratories, the date of the inspection and a short outline of the conclusion of the inspection.

The report referred to in paragraph 1 of this Article shall be communicated to the European Commission each year not later than 31 March.

Article 40

On the day of entry into force of this Ordinance, the Ordinance on good laboratory practice (Official Gazette 51/06) shall cease to be valid.

Article 41

This Ordinance shall enter into force on the eighth day after its publication in the Official Gazette, save the provisions laid down in Article 21, paragraph 2, Article 23 paragraph 5, Article 34, Article 35 and Article 39, paragraph 3 of this Ordinance which shall enter into force on the day of the accession of the Republic of Croatia to the European Union.

Class: 011-02/12-02/77
Reg. No: 534-10-1-1-1/1-12-1
Zagreb 20 June 2012

The Minister
Rajko Ostojić

ANNEX I

CONFIRMATION OF COMPLIANCE WITH PRINCIPLES
OF GOOD LABORATORY PRACTICE

REPUBLIC OF CROATIA
MINISTRY OF HEALTH
CONFIRMATION OF COMPLIANCE
WITH PRINCIPLES OF GOOD
LABORATORY PRACTICE

It is hereby confirmed that the test facility _____ (name and seat of the legal person) was inspected on _____ (date and year) and it has been established that it conducts testing in compliance with the principles of good laboratory practice.

Test facility
_____

Area of specialisation
_____

It has been found that, at the time of the inspection, the aforementioned test facility was operating in compliance with OECD principles of good laboratory practice

(Place and date)
THE MINISTER

ANNEX II

GUIDANCE FOR THE CONDUCT OF TEST FACILITY INSPECTIONS AND STUDY AUDITS

Test facility inspections

Inspections for compliance with GLP principles may take place at 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 test facilities, together with the variety of types of studies encountered, inspectors must use their own judgment to assess the degree and extent of compliance with GLP principles. Inspectors should strive for a consistent approach in evaluating whether, in the case of a particular test facility or study, an adequate level of compliance with each GLP principle has been achieved.

Inspectors do not assess the scientific design of the study or the interpretation of the findings of studies with respect to risks for human health or the environment. These aspects are the responsibility of those regulatory authorities to which the data are submitted for regulatory purposes.

Test facility inspections and study audits inevitably disturb the normal work in a facility. Inspectors should therefore carry out their work in a carefully planned way and, so far as practicable, respect the wishes of the management of the test facility as to the timing of visits to certain sections of the facility.

Inspectors will, while conducting test facility inspections and study audits have access to confidential, commercially valuable information. It is essential that they ensure that such information is seen by authorised personnel only. Their responsibilities in this respect will have been established by the programme provided for by Article 2, item 32 of this Ordinance.

Types of inspection

Pre-inspection

Purpose: to familiarise the inspector with the test facility management structure, physical layout of the 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. All information on the facility, including previous inspection reports, the layout of the facility, organisation charts, study reports, protocols and curricula vitae (CVs) of personnel, should be reviewed. Such documents would provide information on:

– the type, size and layout of the test 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 the inspectors' 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 made available. In cases where particular documents or records are to be examined, it is recommended to notify the test facility thereof in advance so that they will be immediately available during the test facility inspection.

Starting conference

Purpose: to inform the management bodies 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, studies 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 bodies of the facility at the start of the visit. At the starting conference, authorised persons should:

– state 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 and organisation of the personnel of the facility,

– request information as to the conduct of studies not subject to GLP principles in the areas of the test facility where GLP studies are being conducted,

– initially determine which parts of the facility are to be covered during the test facility inspection,

– describe the documents and specimens that will be needed for on-going or completed studies selected for study audit,

– announce a closing conference that will be held at the completion of the inspection.

Before proceeding further with the test facility inspection, it is advisable for the authorised persons to establish contact with the test facility's quality assurance (QA) unit.

As a general rule, when inspecting a test 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 in support services for the variety and number of studies undertaken; whether the organisational structure is appropriate, and whether the management bodies have established a policy regarding training and staff health surveillance appropriate to the studies undertaken at the test facility.

The management body shall be asked to produce certain documents, such as:

– floor plans,

– test facility management and scientific organisation charts,

– CVs of personnel involved in the types of studies selected for 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 the study director,

– staff health surveillance data,

– 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 studies 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 directors, 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 provided by the authorised persons, the aim of which is to assure that that studies are conducted in accordance with GLP principles, are adequate.

The head of the QA unit should be asked to demonstrate the systems and methods for QA inspection and monitoring of studies, and the system for recording observations made during QA monitoring. The inspector should check:

–qualifications of the head of the QA unit, and of all QA staff ,

– whether the QA unit functions independently from the staff involved,

– 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,

– whether arrangements exist for monitoring on a sample basis where studies are of such short duration that monitoring of each study is impracticable,

– the extent and scope of QA monitoring during the practical phases of the study,

– the extent and scope of QA monitoring of routine test facility operation,

– the QA procedure for checking the final report to ensure its compliance with the raw data,

– that management receives reports from the QA unit concerning problems likely to affect the quality or integrity of a study,

– the security measures taken by QA when deviations are found,

– the role of the QA unit, if any, if studies or parts of studies are done in contract laboratories,

– the part played, if any, by the QA unit in the review, revision and updating of SOPs.

Test 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 whether:

– 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 whether there are, if necessary, pest control procedures.

Supply, 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 supply, 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 supply, housing, and containment that the authorised person will monitor. Depending on the type of test system, the inspector will check whether:

– there are facilities adequate for the test systems used and for testing needs,

– there are animal or plant quarantines and whether these quarantines 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 due to 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 test facility and that the materials, reagents and specimens are properly labelled, used and stored.

The inspector should check whether:

– the apparatus is clean and in good working order,

– records are being 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,

– the apparatus and materials used do not alter to any appreciable extent other test systems.

Test systems

Purpose: to determine whether adequate procedures exist for the handling of the variety of test systems required by the studies undertaken in the test facility and for their control, for example, chemical and physical systems, cellular and microbial systems, plants or animals.

Physical and chemical systems

The inspector should check whether:

- the stability of test and reference substances has been determined and whether the reference substances specified in test plans were used, where this is required by study plans,

- data generated as graphs or computer print-outs are documented and archived as raw data.

Biological test systems

Taking account of the relevant aspects referred to above relating to the supply, housing, and containment of biological test systems, the inspector should check whether:

– test systems correspond to those specified in study plans,

– test systems are adequately and, if necessary and appropriate, uniquely identified throughout the whole study, and whether 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 between 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 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 (1) to ensure that the identity, potency, quantity and composition of test and reference substances are in accordance with their specifications, and (2) to properly receive and store test and reference substances. The inspector should check whether:

– there are written records of the receipt (including identification of the person responsible), and of the handling, sampling, usage, and storage of tests and reference substances,

– containers where test and reference substances are kept 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 whether records are kept of the homogeneity and stability of their contents, where applicable,

– when the test is of longer duration than four weeks, samples from each batch of test and reference substances have been taken for analytical purposes and whether 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 whether:

– 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:

(1) receipt; determination of identity, purity, composition and stability, labelling, handling, sampling, usage, and storage of test and reference substances,

(2) use, maintenance, cleaning, calibration, and validation of measuring apparatus, computerised systems and environmental control equipment,

(3) preparation of reagents and dosing formulations,

(4) record-keeping, reporting, storage and retrieval of records and reports,

(5) preparation and environmental control of areas containing the test systems,

(6) receipt, transfer, location, characterisation, identification and supply of test systems,

(7) handling of the test systems before, during and after the termination of the study,

(8) disposal of test systems,

(9 use of pest control and cleaning agents,

(10) quality assurance programme operations.

Performance of the study

Purpose: to verify whether written study plans exist and whether the plans and the conduct of the study are in accordance with GLP principles.

The inspector should check whether:

– the study plan has been signed by the study director,

– any amendments to the study plan have been signed and dated by the study director,

– the date of the agreement to the study plan by the sponsor was recorded (where applicable),

– the results of measurements, observations, and examinations were in accordance with the study plan and relevant SOPs,

– the results of these measurements, observations, and examinations have been recorded directly, promptly, accurately and legibly and signed (or initialled) and dated,

–any changes in the raw data, including the reason for the change, data stored in computers, whether the change obscured previous entries, and whether the person responsible for the change signed and dated these changes,

– computer-generated or stored data have been identified and whether the procedures for their protection 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 whether they correctly reflect the raw data.

Reporting of study results

Purpose: to determine whether final reports are prepared in accordance with GLP principles. When examining a final report, the inspector should check whether:

– it has been signed and dated by the study director to indicate acceptance of responsibility for the validity of the study and confirm that the study was conducted in accordance with GLP principles,

– it has been signed and dated by other scientists, if reports from cooperating disciplines are included,

– a quality assurance statement is included in the report and whether it has been signed and dated,

– any amendments have been 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 test 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:

– whether a person has been identified as responsible for the archive,

– the archive facilities for the storage of study plans, raw data (including that from discontinued GLP studies), final reports, samples and specimens and records of education and training of personnel,

– the procedures for retrieval of archived materials,

– the procedures whereby access to the archives is limited only to authorised personnel and records are kept of personnel given access to raw data, slides, etc.,

– whether an inventory is maintained of materials removed from, and returned to, the archives,

– whether records and materials are retained for the required or appropriate period of time and whether they are protected from loss or damage by fire, adverse environmental conditions, etc.

Study audit

Test facility inspections will generally include, *inter alia*, study audits, which consist of a review of on-going or completed studies. Regulatory Authorities often request study audits which 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 their own 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, in order to conduct an effective study audit, beside inspector other experts may need to take part in the study (for instance, 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, such as the study director and principal scientists,

– check whether there is sufficient staff trained in relevant areas for the studies 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.

– through the interview process, determine 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:

(1) the study plan,

(2) SOPs in use at the time the study was conducted,

(3) logbooks, laboratory notebooks, files, worksheets, print-outs of computer-stored data, etc.; checking of calculations, where appropriate,

(4) the final report.

In studies in which animals (i.e., rodents or other mammals) are used, the inspector must follow a certain percentage of individual animals from their arrival at the test facility to the 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 authorised person should be prepared to discuss his/her findings with representatives of the test facility at a closing conference and should prepare a written report, i.e., the inspection report.

A test facility inspection of any large facility is likely to reveal a number of minor deviations from GLP principles but, normally, these will not affect the validity of studies conducted in that test facility. In such cases, it is expected from the inspector to mention in his/her report that the test facility is operating in compliance with GLP principles according to the criteria established by the Regulatory Authority.

Nevertheless, the inspector should provide details of the inadequacies or faults detected seek assurances from its management bodies that action will be taken to fix them.

The inspector may need to revisit the test facility after a certain period of time to verify that necessary action has been taken.

If a serious deviation from the GLP principles is identified during a test facility inspection or study audit which, in the opinion of the inspector, may have affected the validity of that study, or of other studies performed at that facility, the inspector should report back immediately to the Regulatory Authority. Actions taken will depend on the nature and extent of the non-compliance and the legal and/or administrative provisions within the GLP compliance programme.

Where a study audit has been conducted at the request of a Regulatory Authority, the authorised person should prepare a detailed report to be sent to the Regulatory Authority.