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Belgian GLP Compliance Programme Manual

# BELGIAN GLP COMPLIANCE MONITORING PROGRAMME MANUAL

**SCIENTIFIC INSTITUTE OF PUBLIC HEALTH**

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**1 OBJECT**

This manual is the basic document for all Test Facilities requesting verification of compliance to GLP Principles. The aim of this document is to provide detailed practical guidance to the Test Facilities on the structure and the mechanism of the Belgian GLP Compliance Monitoring Programme and the conditions under which Test Facility Inspections and Study Audits are conducted.

**2 SCOPE**

The Belgian GLP Compliance Monitoring Programme is set up to ascertain that Test Facilities apply the Principles of Good Laboratory Practice (GLP) (Annex 2) (7.1, 7.2, 7.7 – 7.12, 7.14, 7.15, 7.17, 7.18) 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, industrial chemicals, biocides, detergents and medical devices. 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 the non-clinical safety testing of 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.

The Royal Decree of 6 March 2002 defines that the Principles of GLP should be applied to all non-clinical health and environmental safety studies required by regulations for the purpose of registering or licensing pharmaceuticals, pesticides, food and feed additives, cosmetic products, veterinary products and similar products, and for the regulation of industrial chemicals (Annex 2)(7.3).

Other important sectors, such as biocides, detergents, industrial preparations and medical devices, are also included in the Belgian GLP Compliance Monitoring Programme, if the non-clinical health and environmental safety studies in this area are carried out according to the Principles of GLP.

### 3 DEFINITIONS (8.1, 8.4)

#### 3.1 *Good Laboratory Practice*

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

#### 3.2 *Terms Concerning the Organization of a Test Facility*

**Test Facility** means the persons, premises and operational unit(s) that are necessary for conducting the non-clinical health and environmental safety study. For multi-site 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(s) at which a phase(s) of a study is conducted.

**Test Facility management** means the person(s) who has the authority and formal responsibility for the organization and functioning of the Test Facility according to these Principles of Good Laboratory Practice.

**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.

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

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

**Principal Investigator** means an individual who, for a multi-site study, acts on behalf of the Study Director and has defined responsibility for delegated phases of the study. The Study Director's

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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.

**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.

**Standard Operating Procedures (SOPs)** means documented procedures, which describe how to perform tests, or activities normally not specified in detail in the study plan or test guidelines.

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

### **3.3 Terms Concerning the Non-Clinical Health and Environmental Safety Study**

**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 safety, intended for submission to appropriate regulatory authorities.

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

*\* Short-term physical/chemical studies are those studies, tests, measurements or observations which are of a short duration (less than one week), employ widely-used techniques and yield easily repeatable results, often expressed by simple numerical values or verbal expressions. Examples of Short-term biological studies are skin absorption tests, bacterial mutagenicity studies, acute ecotoxicological studies, in vitro and ex vivo studies, kinetic studies and some metabolism studies.*

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

**Study plan amendment** means an intended change 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

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study.

**Raw data** means all originally 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 recognized as capable of providing secure storage of information for a time period as stated in section 10, below.

**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.

### **3.4 Terms Concerning the Test Item**

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

**Reference item (“control item”)** means any article used to provide 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 who 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.

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**3.5 Terms Concerning GLP Compliance Monitoring (8.4)**

**GLP Compliance Monitoring:** The periodic inspection of Test Facilities and/or auditing of studies for the purpose of verifying adherence to GLP principles.

**(National) GLP Compliance Programme:** The particular scheme established by a Member country to monitor Good Laboratory Practice compliance by Test Facilities within its territories, by means of inspections and study audits.

**(National) GLP Monitoring Authority:** A body established within a Member country 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 country.

**Test Facility Inspection:** An on-site examination of the Test Facility's procedures and practices to access the degree of compliance with GLP Principles. During inspections, the management structures and operational procedures of the Test Facility are examined, key technical personnel are interviewed, and the quality and integrity of data generated by the facility are assessed and reported.

**Study audit:** A comparison of raw data and associated records with the interim or final report in order to determine whether the raw data has been accurately reported, to determine whether testing was carried out in accordance with the study plan and Standard Operating Procedures, to obtain additional information not provided in the report, and to establish whether practices were employed in the development of data that would impair their validity.

**Inspector:** A person who performs the Test Facility inspections and study audits on behalf of the (National) GLP Monitoring Authority.

**GLP Compliance Status:** The level of adherence of a Test Facility to the GLP principles as assessed by the (National) GLP Monitoring Authority.

**Regulatory Authority:** A national body with legal responsibility for aspects of the control of chemicals.

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**3.6 Terms Concerning Computerized Systems (8.14)**

**Acceptance criteria:** The documented criteria that should be met to successfully complete a test phase or to meet delivery requirements.

**Acceptance testing:** Formal testing of a computerized system in its anticipating operating environment to determine whether all acceptance criteria of the Test Facility have been met and whether the system is acceptable for operational use.

**Back up:** Provisions made for the recovery of data files or software, for the restart of processing or for the use of alternative computer equipment after a system failure or disaster.

**Change control:** Ongoing evaluation and documentation of system operations and changes to determine whether a validation process is necessary following any changes to the computerized system.

**Computerized system:** A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

**Electronic signature:** The entry in the form of magnetic impulses or computer data compilation of any symbol or series of symbols, executed, adapted or authorized by a person to be equivalent to the person's handwritten signature.

**Hardware:** The physical components of a computerized system, including the computer unit itself and its peripheral components.

**Peripheral components:** Any interfaced instrumentation, or auxiliary or remote components such as printers, modems and terminals, etc.

**Recognized technical standards:** Standards as promulgated by national or international standard setting bodies (ISO, IEEE, ANSI, etc.)

**Security:** The protection of computer hardware and software from accidental or malicious access, use, modification, destruction or disclosure. Security also pertains to personnel, data, communications and the physical and logical protection of computer installations.

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**Software (application):** A programme required for or developed, adapted or tailored to the Test Facility requirements for the purpose of controlling processes, data collection, data manipulation, data reporting and/or archiving.

**Software (operating system):** A programme or collection of programmes, routine and sub-routines that controls the operation of a computer. An operating system may provide services such as resource allocation, scheduling, input/output control and data management.

**Source code:** An original computer programme expressed in human-readable form (programming language) which must be translated into machine-readable form before it can be executed by the computer.

**Validation of a computerized system:** The demonstration that a computerized system is suitable for its intended purpose.

## 4 COMPLIANCE MONITORING PROGRAM

### 4.1 *General Information*

Belgium has only one GLP Compliance Monitoring Program legally managed by the Scientific Institute of Public Health. The program covers all the sectors as mentioned in the scope.

The General Director of the Institute is responsible for the GLP Compliance Monitoring Program but the daily management of the program is carried out by the Bureau of Quality Assurance. The activities of the Monitoring Authority concern the management of the documentation system, the organization, performance and follow-up of GLP inspections and study audits, the relationship with the National Receiving Authorities and other GLP Monitoring Authorities, participation at international meetings, the organization of annual meetings, the draft of annual reports and the training of inspectors.

Cooperation with other GLP Monitoring Authorities is carried out by organizing joint inspections of facilities on the request of Receiving Authorities and other GLP Monitoring Authorities. GLP inspections can also be programmed in facilities of non-adherence OECD member countries if they are carried out according to the OECD GLP Principles.

### 4.2 *Administration*

The application of Good Laboratory Practice in safety testing of chemicals is required under several directives or regulations of the European Union (EU)

(Annex 1) [http://ec.europa.eu/enterprise/chemicals/legislation/glp/product\\_en.htm](http://ec.europa.eu/enterprise/chemicals/legislation/glp/product_en.htm)

The application of Good Laboratory Practice in safety testing of chemicals is laid down in different regulations in Belgium. The text and the legal form of this requirement are different in the respective decrees, but finally they have all the same effect: the OECD Principles of Good Laboratory Practice have to be applied where results of safety tests on chemicals are submitted to Regulatory Authorities in Belgium for safety assessment purposes.

The Belgian GLP Compliance Monitoring Program was established in 1988. The Scientific Institute of Public Health (IPH) has been designated by the Royal Decree of 27 October 1988, revised on 6 March 2002 (7.3), as the Belgian GLP Monitoring Authority for GLP compliance assessment. It is a

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governmental non-profit and fully independent organization.

The IPH is a Scientific Institute and is a part of the Federal Department of Public Health, the Food Chain Safety and Environment. The IPH contains several departments and sections. One of these sections is the Bureau of Quality Assurance (BQA), which is responsible for the daily management of the GLP Compliance Monitoring Program. The General Director of the IPH is the responsible person of the GLP Compliance Monitoring Authority and is especially charged with the approval of the "Statement of GLP Compliance" of the Test Facilities. The GLP Monitoring Authority consists of the General Director of the IPH, the Quality Assurance Manager (QAM), the designated GLP inspectors and clerical Staff.

The daily management and operation of the GLP Compliance Monitoring Program are carried out by the BQA and is written down in the Belgian GLP Compliance Monitoring Program Manual which is approved by the General Director of the Institute and the Quality Assurance Manager (QAM). It includes:

- the organization and conduction of GLP inspections and study audits (7.5)
- all inquiries on GLP from Regulatory Authorities and from official GLP Monitoring Authorities in other countries, on matters relating to data generated in Belgium and elsewhere;
- the publication of documents relating to the adoption of GLP principles within its territory;
- the publication of the Belgian GLP Compliance Monitoring Programme Manual containing instructions for GLP verification and accreditation;
- the publication of documents concerning the management and operation of the GLP Compliance Monitoring Programme;
- the update of the website <http://www.iph.fgov.be/GLP/> and the list of Test Facilities with their GLP status;
- the GLP annual reports containing information about the GLP inspections performed;
- the archiving of all the documents concerning the GLP Compliance Monitoring Program.

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According to the article 2 of the Royal Decree, GLP and the criteria of the Belgian GLP Compliance Monitoring Program Manual, GLP Compliance is mandatory and is carried out according to the requirements lay down in the OECD Environment Monographs N° 110, 111 and 115 (7.4, 7.5, 7.13).

The BQA unit also acts as a contact point and provides information, advice and guidance to the chemical industry, Test Facilities or sponsors of studies on any aspect of GLP. In this context, the BQA formed a "GLP working group" represented by the BQA Staff and staff members of the Test Facilities entering in the GLP Monitoring Programme. The BQA Staff yearly organizes a meeting where the national and international GLP Matter is treated and discussed.

The main task of the BQA consists of the introduction and follow-up of the quality system in the different departments of the Institute based on the criteria of the standard ISO 17025, ISO 17020, ISO 9000, ISO 34 and ISO 43. The BQA is also involved in the participation of R&D projects with regard to the quality criteria to be monitored and recorded.

The Monitoring Authority has a very good relationship with the Receiving Authorities.

Oral, paper and electronic communication are regularly maintained with:

1. the Receiving Authority of Dangerous Substances
2. the Receiving Authority of Plant Protection Products
3. the Receiving Authority of Biocides
4. the Receiving Authority of Pharmaceutical Products
5. the Receiving Authority of Veterinary Drugs
6. the Receiving Authority of Detergents
7. the Receiving Authority of Novel Food and Genetic Modified Organisms
8. the Receiving Authority of Cosmetic Products
9. the Receiving Authority of Dangerous Preparations

Meetings, request for study audits, information on files submitted by national and international sponsors, assistance to GLP inspections and availability of GLP inspection reports are the most important activities to strengthen the relationship between the MA and RAs.

There is a close contact with the Higher Council of Health and the Animal Welfare Authority.

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### **4.3 Confidentiality**

During the inspections and study audits the inspectors may require having access to highly confidential, commercially valuable information. The inspectors may not remove these documents from the Test Facility but they can refer to them in detail in their reports. To ensure that maximum confidentiality is maintained:

- The Belgian GLP Monitoring Authority has to communicate the names of inspectors and, if appropriate, of observers of other GLP Monitoring and Regulatory Authorities participating to the Test Facility inspection at least two weeks before the start of the visit. If observers participate to GLP inspections a confidentiality clause should be signed and dated (Annex 4). If the Test Facility considers that a problem of confidentiality or commercial interest can arise with the presence of one or more members of the inspection team the Test Facility can ask to the GLP Monitoring Authority to replace them.
- Information about the Belgian GLP Compliance Monitoring Program is available on the GLP Website (Royal Decrees, GLP Compliance Monitoring Program Manual, annual reports, etc.) <http://www.iph.fgov.be/GLP/> and accessible to anybody. Confidential information such as inspection reports, particular questions and replies, minutes of internal meetings, etc., which is available on paper, hard disks and back up, is only available to the General Director of the Institute, the QA Manager, the GLP inspectors, the secretariat of the Bureau of Quality Assurance and the Receiving Authorities concerned. If computer experts need access to the hard disk to repair a failure a confidential clause have to be signed and dated by them (Annex 4).
- Information about the inspections and study audits undertaken in Test Facilities can be asked by other national Compliance Monitoring Programs. However, paper or electronic information is only available at request and with the extreme permission of the Test Facility.
- Copies of any documents removed from the Test Facility before, during and after the inspections are uniquely marked. The documents removed should be listed on a signed and dated standard form of the facility. The list must be dated and signed by the lead GLP inspector.
- All the original and electronic documents of the Belgian GLP Compliance Monitoring Program are stored in a closed cupboard in the office of the QAM. The General Director of the Institute,

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the QAM, the GLP inspectors and the GLP secretariat has access to the documents. After three years documents can be transferred to the central archives according to the criteria of the SOP 07/NF/18 of the Institute. Only the General Director of the Institute, the QAM, the GLP inspectors, the GLP secretariat and the archivist have access to the documents maintained in the archives of the Institute.

#### **4.4 Personnel and Training**

- The Belgian GLP Monitoring Authority is responsible for ensuring that an adequate team of inspectors having the necessary technical/scientific expertise is appointed to carry out inspections and study audits. A team of GLP Inspectors is available to perform Test Facility Inspections and Study Audits in about 25 Test Facilities every two to three years. In audits of specific toxicological and/or physical-chemical experiments, scientists and technical Staff of other departments of the IPH may be integrated as experts in the inspection team, if appropriate. The names of the inspectors and experts and their occupation are specified in the document "Questionnaire on Good Laboratory Practice Belgium" (see website <http://www.iph.fgov.be/GLP> for an up-to-date list). The occupation can increase or decrease in function of the workload and the type of activities in the GLP Compliance Monitoring Program.

Occasionally, the IPH may invite whether or not upon request, official representatives of foreign GLP Monitoring Authorities to participate in an inspection/study audit as joint inspectors or as observers. Personal files of these inspectors or observers are stored at the BQA

- Inspectors are scientifically and academically qualified, with practical experience in toxicology, eco-toxicology, field trials, physical-chemical, analytical and/or clinical chemistry. GLP inspectors are required to have an in-depth knowledge of the OECD GLP Principles of Good Laboratory Practices, and the requirements necessary to comply with those principles.
- Deputy Inspectors are trained at the BAQ. The training program includes the participation to the annual training course, the assistance to internal GLP meetings and the participation to at least 4 Test Facility Inspections and Study Audits. During the inspections and study audits some parts of the inspection are carried out by them under the supervision of the lead

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inspector. They should prepare a report from each inspection. The performance of the inspections and the corresponding reports are evaluated by the QAM. A certificate of qualification (Annex 5) as GLP inspector is signed and dated by the General Director of the Institute if the Deputy Inspector is in compliance with the criteria of the evaluation process.

- Training can also include attendance at formal training courses for GLP inspectors (OECD). Observing inspections and study audits conducted by foreign GLP Monitoring Authorities and eventually, participation in Mutual Evaluation Visits also provides ongoing training for the Belgian GLP inspectors. Internal training sessions according to a pre-established program are given at least once a year. Exchange of information and consultation with staff members of other National GLP Monitoring Authorities are encouraged to promote international harmonization in the interpretation and application of the Principles of GLP, and in the monitoring of compliance with such principles. In this context, inspectors from foreign GLP Monitoring Authorities can be invited to take part in an inspection conducted by the Belgian GLP Monitoring Authority. Consent of the Test Facility will be obtained in advance of such inspections and /or study audits.
- All the personnel associated with the GLP Compliance Monitoring are Civil Servants and are covered by Civil Administration laws with respect to confidentiality. Inspectors may not have financial or other interests in the Test Facilities inspected, the studies audited or the firms sponsoring such studies.
- The name of the Inspectors performing the Test Facility Inspections and Study Audits are communicated to the Test Facility in advance. The Inspector has to show his identity card at the request of the Test Facility.
- Inspectors belong to the permanent Staff of the GLP Monitoring Authority. Experts from other departments of the IPH can be invited by the GLP Monitoring Authority to participate to GLP Inspections and Study Audits, if appropriate. The inspectors present themselves at the Starting Conference of the GLP inspection.

#### **4.5 The National GLP Compliance Monitoring Program**

The GLP Compliance Monitoring Program is intended to ascertain whether Test Facilities have implemented GLP principles for the conduct of studies and are capable of assuring that the resulting data are of adequate quality.

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- Inspections may be conducted at any Test Facility generating health and environmental safety data for regulatory purposes. It includes audits of data of physical-chemical, toxicological and/or ecotoxicological testing of chemicals, such as industrial chemicals and industrial preparations, pharmaceuticals, veterinary drugs, phytopharmaceuticals, food and feed additives and cosmetics. Other sectors such as field trials, biocides, detergents, novel foods, genetic modified organisms and medical devices are also covered by Good Laboratory Practice and inspected by the GLP Monitoring Authority. (Annex 6)
- According to article 5, §1 of the Royal Decree of 6 March 2002 a Test Facility should introduce a request with respect to the verification of GLP compliance to:

**Scientific Institute of Public Health**  
**At the attention of the General Director**  
**Dr. Johan Peeters**  
[Johan.Peeters@iph.fgov.be](mailto:Johan.Peeters@iph.fgov.be)  
**Juliette Wytsmanstreet 14**  
**1050 Brussels**  
**Phone: 0032-2/642.50.03**  
**Fax: 0032-2/642.50.01**

The request is transferred to:

**Bureau of Quality Assurance**  
**Scientific Institute of Public Health**  
**Juliette Wytsmanstreet 14**  
**1050 Brussels**  
[Hedwig.Beernaert@iph.fgov.be](mailto:Hedwig.Beernaert@iph.fgov.be)  
**Phone: 0032-2/642.51.86 (ev. 5228 or 5230)**  
**Fax: 0032-2/642.52.27**

The BQA introduces the Test Facility in the GLP Compliance Programme (Annex 6).

Test Facilities for which a Regulatory Authority asks a request for GLP compliance or Test Facilities from countries without functioning GLP Monitoring Authority asking a request for

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GLP verification are also listed on the master schedule of the GLP Compliance Programme. The BQA charged with the investigation and treatment of the request sends a standard form (Annex 7) to the Test Facility to fill in the sectors and the area of expertise covered by their GLP activities.

Test Facilities can be contract research laboratories, part of industries or government or university related.

- The Test Facilities embodied in the master schedule of the GLP Compliance Programme are in principle monitored on a two to three year cycle. The GLP Compliance Programme includes Pre-inspections, Test Facility Inspections, Study Audits and Re-inspections. Pre-inspections are carried out if the Test Facility has to be inspected for the first time. During the Test Facility Inspection not only the organization of the Test Facility but also on-going and completed studies are verified. Re-inspections are carried out if deviations have been found during the routine inspection for which corrective actions have to be taken which should be verified on the test site

Special Test Facility inspections/study audits may be monitored at the request of a foreign GLP Monitoring Authority or our national Regulatory Authorities. Such requests will normally be for study audits but may sometimes involve Test Facility inspections. However, it is the responsibility of the Regulatory Authority or the foreign Monitoring Authority to identify and justify the need of such inspections and study audits.

- Inspectors will not normally enter Test Facilities, or attempt to gain access to data held by a Test Facility without the written permission of the Test Facility Management and, where appropriate, the sponsors of the studies. However, in cases where national or foreign regulatory authorities and/or foreign monitoring authorities request for verification of data of studies, GLP inspectors may have access to the Test Facility and to the data of studies at any time. In these circumstances, the Test Facility will always be informed of the visit. If the access to the premises and the documents of the GLP quality system and the studies is refused by Test Facility Management the lead inspector can decide to stop the GLP inspection. In such a case the lead inspector submits a proposal to the General Director of the Institute to withdraw the GLP status of the Test Facility. This proposal should be justified by documented facts.

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Some reference to the protection of the health and safety of workers involved in the conduct of Test Facility studies and to the management of Test Facility waste is made in the OECD GLP Principles. If during an inspection there is doubt about the appropriateness of the Test Facility's procedures in these fields, this will be usually referred to the first responsible governmental bodies.

- The Belgian GLP Monitoring Authority will charge fees to the Test Facility or organization seeking compliance in order to cover the costs of the service it renders. Fees are determined according to the Royal Decree of 6 March 2002 (Annex 2). A tender (IPH/GLP/FORMTEND) is sent to the Test Facility with the announcement of the GLP inspection.

**4.5.1 *The inspection process* (Annex 9)**

▪ **Master schedule of GLP inspections**

An inspection plan (annex 8) is yearly established and contains information on the name of the Test Facility, the period of inspection, the composition of the inspection team, the sectors, the area of expertise and remarks. This FORM is signed and dated by the General Director of the Institute and the QAM. Changes in the inspection plan are justified and signed and dated by QAM. Each Test Facility is inspected every two to three years. If serious changes concerning the organization, infrastructure, sector or area of expertise happen in the Test Facility the GLP Monitoring Authority can decide to forward a GLP inspection.

▪ **Pre-inspection**

If the Test Facility has to be inspected for the first time a pre-inspection is always carried out. The pre-inspection is principally carried out by the QA Manager but this task can be delegated to his substitute.

A full Test Facility inspection is programmed if Test Facilities from abroad are requesting GLP verification.

A pre-inspection is planned to familiarize the inspector with the management structure, the physical layout of buildings, the documentation system and the range of studies of

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the Test Facility. The announcement of the GLP pre-inspection and the pre-inspection programme (Annex 10) will be sent by letter to the Test Facility about two weeks before the start of the visit. The BAQ secretariat informs the Test Facility about the date and time of inspector's arrival, the issues to be inspected and discussed and the length of time to be expected for the visit of the premises. It is absolutely necessary that Test Facility Management and QA Staff are present at the pre-inspection. During the pre-inspection documents and records may be asked and copied for examination.

The time required for the pre-inspection is usually **one day**.

The pre-inspection starts with an opening session at which the QA Manager or his substitute outlines the purpose and the scope of the visit. This introduction will be followed by a management's presentation concerning the organization and the activities of the Test Facility. The next phase of the pre-inspection is concerned with the discussion about the scope of GLP activities, which should supply to the Principles of GLP. Principally, only data of pre-clinical testing of chemicals for regulatory purposes (7.3) will be considered in the GLP Compliance Monitoring Programme.

The organization of the Test Facility will be inspected having knowledge about the documentation and operation system of the facility.

Finally, some premises of the Test Facility will be visited whereby a general look is carried out to the type and separation of activities, the environmental conditions and the identification and storage of apparatus, test systems, test and reference items and archives. During this visit of the premises the normal work could be slightly disturbed.

At the exit meeting the GLP Inspector gives a summary of the findings, including the strong and weak points of the Test Facility's GLP system. All the findings observed are written down in a pre-inspection report, which is sent to the Test Facility in a delay of three weeks.

A Test Facility Inspection and study audits are programmed within **a delay of 6 months after the pre-inspection. Another delay of 6 months can be permitted if the Test Facility can justify the delay.** If a Test Facility inspection is not executed within a delay of 12 months after the pre-inspection the whole procedure should be restarted and the Test Facility is removed from the program.

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Before the end of this delay the Test Facility has to elaborate at least 2 *simulated* studies and compile a final report according to the GLP-principles.

▪ **Test Facility Inspection and Study Audit**

The procedures for carrying out Test Facility inspections and study audits for verification of GLP Compliance are in agreement with the Revised Guidance for the Conduct of Laboratory Inspections and Study Audits (7.5).

Inspections and study audits will be carried out at the request of the Test Facility itself or at the request of a national Regulatory Authority or foreign GLP Monitoring Authority. The Test Facility Inspection and Study Audit cannot be realized if the deviations of the pre-inspection are not corrected within the pre-established period. In such a case, the whole procedure must be restarted.

The announcement of the GLP inspection and the inspection programme (Annex 10) will usually be sent to the Test Facility about two weeks before the start of the visit. The inspection programme informs the Test Facility about the date and time of inspector's arrival, the composition of the inspection team, the issues to be inspected and discussed and the length of time to be expected for the visit of the premises. The inspection takes at least 3 days including the opening session and Test Facility inspection (first day), study audits (second day) and the preparation of the inspection report and the exit meeting (last day). The second day can be extended with one or more days depending upon the size of the Test Facility and the number of the GLP studies to be audited.

The Test Facility can ask the replacement of some members of the inspection team if they consider that the impartiality, integrity and confidentiality against the Test Facility cannot be assured. The arguments for replacement have to be addressed in writing to the General Director of the IPH.

With the exception of the master schedule of completed and on-going GLP studies since the last inspection no other documents are asked to prepare the inspection. Therefore, preparation prior to an inspection visit is focused to the information on the master schedule of GLP studies, the selection of the studies to be audited and the

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lecture of the previous inspection report.

It is absolutely necessary that management is present at the opening and closing meeting. During the inspection it is wishful that a member of the QA Staff accompanies the lead inspector. During the study audits GLP inspectors may have interviews with the Study Directors, the scientists and technical staff of the Test Facility. In some particular cases documents or records may be asked and copied for examination.

At the starting conference the inspection team is presented to the management of the Test Facility and the purpose and the scope of the visit is outlined by the lead inspector. Then, the inspection programme is fixed and the persons who have to accompany the inspectors are designated. The Test Facility has to be aware that it is impossible for the inspection team to verify in detail all the elements of the principles of GLP listed in Annex 2 (7.1, 7.2). Therefore, inspectors try to obtain a general view of the documentation and operation system of the Test Facility and use their judgment as to which GLP Principles apply and as to what constitutes an adequate level of compliance with each GLP Principle. *Also the requirements mentioned in Italic in Annex 2* should be applied by the Test Facility and shall be verified by the GLP inspectors. The inspection team will not be concerned with the need for or suitability of the design of studies, the interpretation of the findings of the studies, or the suitability of the test systems used for the purposes of the study. Test Facility management are reminded that legislation exists which controls the use of animals in experiments.

The inspections and study audits are carried out in accordance with the OECD/EU guidance for the conduct of Test Facility inspections and study audits (7.5, 7.6, and 7.7). The criteria described in the OECD Consensus and Advisory Documents are also taken into consideration during the Test Facility Inspections and Study Audits, if appropriate (7.8 – 7.12, 7.14 – 7.18). The guidance for the conduction of Test Facility Inspections gives an indication of the major GLP aspects which inspectors will examine during Test Facility Inspections and Study Audits.

During the inspection the observed findings are written down in a provisional report. The findings are classified as follows:

- Major deviation, **C**: the observation made by the inspector means that the deficiency is not in compliance with the Principles of GLP. The deficiency seriously

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influences the good functioning of the GLP quality system or the integrity of study data.

- Minor deviation, **B\* or B**: the observation made by the inspector means that the deficiency does not have a serious impact on the functioning of the GLP quality or on the integrity of study data.

**B\***: the Test Facility should justify the corrective action by document evidence within **30 days** after the receipt of the provisional report

**B**: The Test Facility should apply a corrective action that will be verified at the next inspection

- No deviation, **A**: the observation made by the inspector is totally in compliance with the Principles of GLP.
- No observation, **D**: the GLP Principle was not applicable and therefore, not observed.

When major deviations are observed during the inspection, the inspection can be interrupted. On the other side, the inspection team may decide to audit more studies than programmed, which can prolong the period of inspection. At least one on-going and two completed studies have to be verified by the inspector(s) during their visit. During the inspection the normal work in the Test Facility may be disturbed. Inspectors will try to minimize this disturbance as much as possible, however.

The inspection and study audits will be concluded with an exit meeting during which the management and other personnel are informed of the findings of the inspection. Not only the deviations from GLP principles are communicated, but also the strong points of the GLP system of the Test Facility. All the findings are written down in a provisional report, which is signed and dated by the inspectors and handed over to the Test Facility Management who signs and dates the report for receipt. All the records concerning the observations and examinations and copies of documents or materials requested during the inspection and study audits are retained for three years in a closed cupboard of the QAM office and then transferred to the central archives of the Institute.

- **Re-inspection**

If the Test Facility receives C deviations during the inspection a re-inspection should

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be programmed. Two types of re-inspection can be carried out:

1. Re-inspection by documentation. The reply given by the Test Facility to the deviations written down in the provisional report are justified by document evidence and evaluated by the inspection team.
2. Re-inspection on the test site. The reply given by the Test Facility requires a visit to the test site to evaluate if the corrective actions are correctly implemented.

**The re-inspection should be carried out within a maximum delay of six months after the date of the GLP inspection.** The Test Facility receives a re-inspection programme at least two weeks before the visit of the GLP Inspector(s) at the test site.

The re-inspection includes three phases: the opening meeting explaining the purpose of the visit, the inspection verifying the corrective actions and the exit meeting communicating the findings observed.

**4.5.2 Follow-up to Test Facility Inspections and Study Audits**

- **Pre-inspection**

The GLP Inspector prepares a pre-inspection report within a delay of three weeks after the visit. This report contains:

- name and address of the Test Facility;
- name of Test Facility Management;
- name of the inspector(s);
- sectors and area of expertise which can be taken into account for inspection;
- date of pre-inspection;
- deviations observed concerning the issues inspected;
- date of the report;
- signature of the reporter.

The Test Facility should take corrective actions with regard to the deviations observed during the pre-inspection but the action plan should not be sent to the GLP Monitoring Authority.

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A Test Facility Inspection and study audits are programmed within a **delay of 6 months after the pre-inspection. Another delay of 6 months can be permitted if the Test Facility can justify the delay.** If a Test Facility inspection is not executed within a delay of 12 months after the pre-inspection the whole procedure should be restarted and the Test Facility is removed from the program.

Before the end of this delay the Test Facility has to elaborate at least 2 *simulated* studies and compile a final report according to the GLP-principles.

- ***Test Facility Inspection, Study Audit and Re-inspection***

A provisional inspection report (7.13) is prepared at the last day of the Test Facility inspection, study audit or re-inspection and handed over to the Test Facility Management for receipt. The provisional report is established according to the instructions of the OECD Environment Monograph N°115 "Guidance for the preparation of GLP inspection reports" and contains, but not limited to, the following information:

- name and address of the Test Facility;
- name of the responsible of the Test Facility;
- date of inspection;
- name of inspectors;
- narrative headings including summary, introduction, narrative, exit discussion and annexes as specified in the GLP consensus document "Guidance for the preparation of GLP inspection reports". A **bold** text is used to indicate the type of findings, the criterion of the GLP Principle and the initials of the inspector noticing the finding. Codes **A** (in compliance), **B or B\*** (minor deviation), **C** (major deviation) and **D** (not applicable) are used by the inspectors or experts to classify categorise the findings;
- date of the report;
- signature of the principal GLP inspector and other inspectors, if appropriate

The Test Facility should give its comments to the deviations in writing a reply within **30 days** after the inspection. The reply should be sent to the inspection team by e-mail and also on paper to the lead inspector. The reply should contain an **action plan** describing the corrective actions taken with regard to the major and minor deviations written down in the provisional inspection report.

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The corrective actions taken for the **C** deviations should be justified by document evidence. If the corrective actions proposed for the major deviations **C** cannot be accepted by the inspector a re-inspection on the site will be programmed.

The corrective action proposed for the minor deviations **B\*** should be justified by documents evidence within **30 days** after the receipt after the provisional report. The corrective action proposed for the minor deviations **B** will be verified for implementation at the next inspection.

The inspector should give his comments to each corrective action taken by the Test Facility. These comments and the decision taken by the inspector are integrated in the final report.

The final inspection report will be prepared within a delay of **three weeks** after receiving the comments of the Test Facility to the provisional report or **two weeks** after the re-inspection. The final inspection report is established according to the instructions of the OECD Environment Monograph N°115 "Guidance for the preparation of GLP inspection reports" and contains, but not limited to, the following information:

- name and address of the Test Facility;
- name of the responsible of the Test Facility;
- date of inspection;
- name of inspectors;
- narrative headings including summary, introduction, narrative, exit discussion and annexes as specified in the GLP consensus document "Guidance for the preparation of GLP inspection reports". A **bold** text is used to indicate the type of findings, the criterion of the GLP Principle and the initials of the inspector making the finding. Codes **A** (in compliance), **B** or **B\*** (minor deviation), **C** (major deviation) and **D** (not applicable) are used by the inspectors or experts to judge the findings;
- date of the report;
- signature of the principal GLP inspector and eventually of other inspectors.

The final inspection report, including the conclusions of the inspection, is sent to the Test Facility and the national relevant receiving authority. If a special request for inspection or study audit from a national or foreign receiving authority is received final reports of this inspection or study audit(s) are also drafted according to the requirements of the OECD Environment Monograph N°115.

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- **GLP Statement**

If no or only minor deviations (**B, A**) remain in the final report, the GLP Monitoring Authority will issue a statement that the Test Facility has been inspected and found to be operating **in compliance** with GLP principles. The statement of GLP compliance (Annex 11) will include:

- the GLP logo of the Belgian GLP Monitoring Authority;
- name and address of the Test Facility;
- identification number of the Test Facility;
- date of inspection;
- sector of chemicals and area of expertise for which the Test Facility is in compliance with GLP principles;
- signature of the General Director of the IPH;
- date of signature.

This statement is sent to the Test Facility together with the final report.

If major deviations **C** are observed during the Test Facility inspection, Test Facility receives the GLP status of “**pending**” until acceptable corrective actions have been taken. This statement is valid for a maximum period of 6 months. If the corrective actions taken by the Test Facility are in compliance with the GLP Principles the status “**pending**” is changed into “**In Compliance**”.

***During the period of “pending” no Study Reports can be signed by the Study Director(s) as being in compliance with the GLP Principles.***

When major deviations (**C**) have been found during the Test Facility inspection and remain after a re-inspection, the Belgian GLP Monitoring Authority:

- issues a statement of “**Not in Compliance**” in the summary of the inspection report, giving details of the inadequacies or faults found which might affect the validity of the studies conducted in the Test Facility;
- removes the Test Facility from the GLP Compliance Programme;
- requires from the Test Facility that a statement detailing the deviations is attached to study reports of chemicals for regulatory purposes.

When major deviations (**C**) are observed during the Study Audits concerning specific

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study(ies) and remain in the final report, that study(ies) will be judged as not in compliance onto the GLP principles and the Belgian GLP Monitoring Authority will acknowledges the non compliance GLP studies to the OECD Monitoring Authorities and the national and foreign relevant receiving authorities. If the deviations are limited to a small number of studies, they don't necessarily jeopardise the GLP status of the Test Facility.

**4.5.3 Rights and Duties**

- The Bureau of Quality Assurance archives the original of the final reports. A copy of them is sent to the Test Facility, the Responsible of the GLP Monitoring Authority and to the Regulatory Authority(ies) concerned. Copies can be available on request but with the permission of the Test Facility concerned.
- It is in the interest of the Test Facility to be in compliance with the requirements of GLP Principles and to produce data of adequate quality for assessment and decision-making by Regulatory Authorities. Failure to do so may lead to non-acceptance of test results by Regulatory Authorities.
- If the Test Facility management, the QA Staff, Study Directors, the personnel and the infrastructure of the Test Facility, or the types of studies conducted is significantly extended or changed, the Test Facility has the obligation to inform these changes to the GLP Monitoring Authority within one month.
- The acceptability of a study is decided by the responsible Regulatory Authority and not by the GLP Monitoring Authority. However, following the OECD decision on the Mutual Acceptance of Data (7.1), a Regulatory Authority of an OECD member country will accept a study on GLP grounds where a facility inspection and/or study audit has been conducted and where the facility and/or study has been found to be in compliance with GLP Principles. If a study has not been performed according to the GLP Principles the GLP Monitoring Authority will inform its Regulatory Authorities and the GLP Monitoring Authorities of the OECD Member Countries.
- In order to facilitate the communication between sponsors, Test Facilities,

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Regulatory and Monitoring Authorities from this country or abroad the IPH provide information on inspections to interested parties in three forms :

- the conclusions of an inspection and a "Statement of GLP compliance", where the inspection reveals an adequate compliance with GLP, are given to the Test Facility, this information will also be given to the Belgian Regulatory Authorities concerned;
  - list of Belgian Test Facilities (annex 13) in compliance with GLP is available via the website ([www.iph.fgov.be/GLP](http://www.iph.fgov.be/GLP));
  - the annual GLP monitoring report, (Annex 14) including the Test Facilities inspected and their GLP statement, are sent to the OECD and EU Organizations and to the GLP Monitoring Authorities of each OECD member country or EU Member State.  
[http://www.oecd.org/document/56/0,2340,en\\_2649\\_34381\\_1935800\\_1\\_1\\_1\\_1,00.html](http://www.oecd.org/document/56/0,2340,en_2649_34381_1935800_1_1_1_1,00.html)  
[http://ec.europa.eu/enterprise/chemicals/legislation/glp/national\\_en.htm](http://ec.europa.eu/enterprise/chemicals/legislation/glp/national_en.htm)
- Annually, a master schedule with Test Facilities to be inspected is drafted (annex 8).

#### **4.6 Appeals Procedures**

Any disagreement or difference of opinion between the inspectors and Test Facility Management, arising from an inspection or study audit, will normally be resolved during the inspection or at the exit meeting. However, where problems persist and agreement on differences cannot be reached during the inspection process, Test Facility Management may make representations against the findings observed and communicated by the inspectors. Such representations against those findings must be addressed, in writing, to the General Director of the IPH within 30 days after the date of his decision taken. The General Director of the IPH will then take appropriate steps to achieve a mutually acceptable resolution. Therefore, he can ask the advice of independent internal or external experts. Based on this advice the General Director will take a final decision.

## 5 INTERNATIONAL ACCEPTANCE OF INSPECTION RESULTS

Studies can be submitted to several Regulatory Authorities in different countries. Based on the criteria of the EU Directives 2004/09/EC and 2004/10/EC the inspection results of the Belgian GLP Monitoring Authority (e.g. statements of compliance and inspection reports) and the data of the laboratories of their program are accepted by the Regulatory Authorities of the EU member states.

Since 1989 bilateral arrangements on the mutual acceptance of GLP inspection results between EU and non-EU member states are excluded. Due to this fact there is no Memorandum of understanding between Belgium and non-European Union OECD member countries, such as Switzerland, Norway, the United States, Canada, Australia, New-Zealand, Korea and Japan.

In the mean time European Union has concluded Mutual Recognition Agreements in the area of GLP with Israel, Japan and Switzerland. By means of the Treaty of the European Economic Area (EEA) of 13 December 1993, the European Regulations and Directives also apply to Iceland, Liechtenstein and Norway

Following Decision C(97)186/Final of the OECD Council, data generated in the testing of chemicals in an OECD Member Country, in accordance with OECD Test Guidelines and the Principles of Good Laboratory Practice, are accepted in other OECD Member Countries (e.g. Australia, Canada, Korea and USA).

If non-European Union countries do not accept data from Test Facilities in Belgium, which are in compliance with GLP, on grounds relating to GLP, the IPH may be asked to give further information to such authorities to facilitate the acceptance of data.

In accordance with the EU directive 2004/09/EC Belgium gives a statement of GLP compliance to Test Facilities which are in compliance with GLP principles. Test Facility Management may only use this statement of GLP compliance if studies according to the article 1 of the EU directive 2004/09/EC are contracted with sponsors.

## **6 COOPERATION WITH THE BELAC ACCREDITATION SYSTEM**

BELAC is in Belgium the official body to accredit Test Facilities working in compliance with the criteria of the standard ISO 17025. The activities of such Test Facilities are mostly routine-based. This standard is not mandatory and, therefore, the Test Facilities can ask an accreditation for their technical competence and for testing of characteristics on a voluntary basis.

Test Facilities which are interested to obtain a GLP and a BELAC certificate for the same scope of activities (e.g. physical-chemical parameters) can separately introduce a request to both organizations. In such a situation, the possibility of a joint inspection or audit is investigated. Some aspects as the separation of activities, identification, storage and handling of test and reference materials, identification, maintenance and calibration of equipment, etc. can be inspected in common. The findings concerning this part of inspection can be used by both organizations.

The GLP Monitoring Authority will also accept audit results of BELAC concerning the above-mentioned aspects if the Test Facility can prove that Standard Operating Procedures, a Quality Assurance Program and Archives are applied according to GLP Principles.

## **7 ARCHIVES**

The GLP monitoring authority retains the following records in his archives for at least ten years:

- records of qualifications and experience, training and job descriptions of inspectorate personnel
- documents submitted by Test Facilities for the preparation of inspections
- correspondence with Test Facilities relating to inspections and study audits
- all notes taken during the course of inspections and study audits
- copies of documents or materials gathered during the course of, or after, an inspection
- original inspection reports issued at the discretion of the authority
- copies of all GLP statements
- documents of correspondence with foreign authorities
- further relevant GLP documents, if appropriate.
- the original GLP compliance monitoring programme containing the original documents, if available

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- historical file of replaced documents (documents that have been superseded by new versions) from the Belgian GLP compliance monitoring programme
- historical file of the annual reports of the inspections and study audits performed
- protocols and working documents relating to the OECD Panel on GLP

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- 8.3 Royal Decree of 2 March 2002 concerning the application of the principles of GLP and the verification of their application to testing of chemical substances
- 8.4 Revised guides for compliance monitoring procedures for Good Laboratory Practice N°2, 1995. OECD Environment Monograph N°110, OECD/GD(95)66, 14 Jun 1995.
- 8.5 Revised guidance for the conduct of laboratory inspections and study audits N°3, 1995. OECD Environment Monograph N°111, OECD/GD(95)67, 14 Jun 1995
- 8.6 The EU directive 88/320/EEC, adapted by the directives 99/12/EC and 2004/9/EC, concerning the inspection and verification of Good Laboratory Practice. Official Journal of EU N° L145 of 11/6/88, p.35.
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- 8.9 Consensus Document: Compliance of laboratory suppliers with GLP principles N°5 (revised), 1999. OECD Document ENV/JM/MONO(99)21, 28 Sep 2000
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- 8.15 Advisory Document: The Role and Responsibilities of the Sponsor in the application of the Principles of GLP N°11, 1998. ENV/MC/CHEM(98)16, 6 Mar 1998
- 8.16 The OECD Advisory Document N°12, 2002: Requesting and Carrying out inspections and study audits in another country. OECD Document ENV/JM/MONO(2000)3, 25 Jun 2002
- 8.17 The OECD Consensus Document N°13, 2002: The application of the OECD Principles of GLP to the organization and management of multi-site studies. OECD Document ENV/MJ/MONO(2002)9, 3 Oct 2002
- 8.18 The OECD Advisory Document N°14, 2004: The application of the Principles of GLP to in vitro studies. OECD Document ENV/JM/MONO(2004)26, 30 Nov 2004

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**ANNEX 1 : DIRECTIVES AND REGULATIONS REQUIRING GLP CONFORM  
STUDY REPORTS**

Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of **dangerous substances**

Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of **dangerous preparations**

Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to **cosmetic products** (the "Cosmetics Directive")

Council Directive 91/414/EEC of 15 July 1991 concerning the placing of **plant protection products** on the market

Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of **biocidal products** on the market

Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on **additives for use in animal nutrition** (Text with EEA relevance)

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to **medicinal products for human use**

Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning **novel foods and novel food ingredients**

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to **veterinary medicinal products**

Regulation (EC) No 648/2004 of the European Parliament and of the Council of 31 March 2004 on **detergents** (Text with EEA relevance) .....

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**ANNEX 2 : OECD/EU PRINCIPLES OF GOOD LABORATORY PRACTICE**

**CHAPTER 1. INTRODUCTION**

**1. Scope**

The Belgian GLP compliance monitoring programme is set up to ascertain that test facilities apply the Principles of Good Laboratory Practice (GLP) 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 the non-clinical safety testing of 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 GLP apply to all non-clinical health and environmental safety studies required by regulations for the purpose of registering or licensing pharmaceuticals, pesticides, food and feed additives, cosmetic products, veterinary products and similar products, and for the regulation of industrial chemicals.

**2. Definitions of terms (see point 3 "Definitions")**

**CHAPTER 2. GOOD LABORATORY PRACTICE PRINCIPLES**

**1. Test Facility Organization 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

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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 appropriate qualifications, training and experience is designated by the management as the Study Director before the study is initiated. Replacement of the Study Director should be done according to established procedures, and should be documented;
- h) ensure, in the event of a multi-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 approved study plan available to the Quality Assurance personnel;
- k) ensure the maintenance of an historical file of all Standard Operating Procedures;

***The test facility should have a list of SOP's with version number and date of application \****

- l) ensure that an individual is identified as responsible for the management of the archives;
- m) ensure the maintenance of a master schedule;

***This master schedule should contain, but not limited, the following items: study number, study director's name, name of sponsor, test item, test system, type of administration, initiation date, experimental starting date, experimental completion date and date of final report. In case of multi-site studies the following items (but not limited to) should be added: name of test site manager(s), Principal Investigator(s)... \****

- n) ensure that Test Facility supplies meet requirements appropriate to their use in a study;
  - o) ensure for a multi-site 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 characterized;
  - q) establish procedures to ensure that computerized 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).

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**1.2 Study Director's Responsibilities**

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 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 the actual versions of the study plans, amendments and Standard Operating Procedures are available to study personnel;
  - d) ensure that the study plan and the final report for a multi-site 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 computerized 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).

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3. All study personnel 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 minimize 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 study being assured.

**2.2 *Responsibilities of the Quality Assurance Personnel***

1. 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

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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 inspection 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 will 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 minimize disturbances 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 and 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 substances***

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 jeopardize the integrity of studies. This includes provision for appropriate collection, storage and disposal facilities

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and decontamination and transportation procedures.

**4. Apparatus, materials and reagents**

**4.1 Apparatus**

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 procedures 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**

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.

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.

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

Biological test systems should be acclimatized 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, where possible.

During use, housing or containers for test systems should be cleaned and sanitized at appropriate

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levels. 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.

**6. Test and Reference Items**

**6.1 *Receipt, Handling, Sampling and Storage***

1. Records including test item and reference item characterization, 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 is assured to the degree possible and contamination and mix-up are precluded.
3. Storage container(s) should carry identification information, expiry date and specific storage instructions.

**6.2 *Characterization***

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 and reference item should be known.
3. In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation 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**

- 7.1. A Test Facility should have written Standard Operating Procedures approved by Test Facility management that are intended to ensure the quality and integrity of data generated by that Test Facility. Revisions to Standard Operating Procedures should be approved by Test Facility management.

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7.2. Each separate Test Facility unit or area should have immediately available current Standard Operating Procedures relevant to the activities being performed therein. Published textbooks, analytical methods, articles and manuals may be used as supplements to these Standard Operating Procedures.

***These documents have to be identified as a document of the quality system.\****

7.3. 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).

7.4. Standard Operating Procedures should be available for, but not 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 substance*

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

2. *Apparatus, Materials and Reagents*

a) *Apparatus*

Use, maintenance, cleaning and calibration.

b) *Computerized systems*

Validation, operation, maintenance, security, changes 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 computerized systems.

4. *Test systems (where appropriate)*

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

b) Procedures for receipt, transfer, proper placement, characterization, identification and care of 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 necroscopy and histopathology.

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

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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 in a written form prior to initiation of the study. The study plan should be approved by dated signature of the Study Director and verified for GLP compliance by Quality Assurance personnel as specified in Section 2.2.1.b, above.

***The Belgian GLP compliance program requires that Study Plans are also approved by test facility management and sponsor. \****

***For multi-site studies, the Study Plans should also be approved by the test site management(s) and the Principal Investigators. \****

***Furthermore, it is recommended that the Study Plan is signed and dated by the QA officer as proof of verification. \****

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.

***The Belgian GLP compliance program requires that the amendments to the Study Plans are also approved by Test Facility Management and sponsor. \****

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 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 the 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 Facility and test sites involved;

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- 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 OECD test guidelines, or other test guidelines, or method to be used.

5. *Issues (where applicable)*

- a) The justification for selection of the test system;
- b) Characterization 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, 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, measurement, observations and examinations to be performed, and statistical methods to be used (if any).

***The study plan or protocol should refer to the standard operating procedures used, including their version. \****

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 conform their origin. Such identification should enable traceability, as appropriate for the specimen and the study.
- 2. The study should be conducted in accordance with the study plan.

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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, and 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.

With regard to the methods used, the protocol or study plan should refer to the standard operating procedures used including the used version.

## **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 Investigator(s) 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 additions and should be signed and dated by the Study Director.

### **9.2 *Content of the Final Report***

The final report should include, but not 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, EC number, biological parameters, etc.)
  - c) Identification of the reference item by name;
  - d) Characterization of the test item including purity, stability and homogeneity.

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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 Guidelines or other test guidelines or method.

6. *Results*

- a) A summary of results;
- b) All information and data required in 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 material**

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

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- a) The study plans, 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 qualification, 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 rapid retrieval.
- 10.3 Only personnel authorized 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).

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**ANNEX 3 : ROYAL DECREE OF 6 MARCH 2002 CONCERNING THE APPLICATION OF PRINCIPLES OF GLP**

6 MAART 2002. - Koninklijk besluit tot vaststelling van de beginselen van goede laboratoriumpraktijken en het toezicht op de uitvoering ervan bij proeven op scheikundige stoffen

ALBERT II, Koning der Belgen,  
Aan allen die nu zijn en hierna wezen zullen, Onze Groet.

Gelet op de wet van 30 december 2001 houdende sociale en diverse bepalingen, inzonderheid op artikel 47;

Gelet op het koninklijke besluit van 27 oktober 1988 betreffende de toepassing van de beginselen van goede laboratoriumpraktijken en het toezicht op de uitvoering ervan bij proeven op scheikundige stoffen;

Gelet op de richtlijn 1999/11/EG van de Commissie van 8 maart 1999 tot aanpassing aan de vooruitgang van de techniek van de beginselen van goede laboratoriumpraktijken als uiteengezet in Richtlijn 87/18/EEG van de Raad betreffende de onderlinge aanpassing van de wettelijke en bestuursrechtelijke bepalingen inzake de toepassing van de beginselen van goede laboratoriumpraktijken en het toezicht op de toepassing ervan voor tests op chemische stoffen;

Gelet op de richtlijn 1999/12/EG van de Commissie van 8 maart 1999 tot tweede aanpassing aan de vooruitgang van de techniek van de bijlage bij Richtlijn 88/320/EEG van de Raad inzake de inspectie en de verificatie van goede laboratoriumpraktijken (GLP);

Gelet op het advies van de Inspecteur van Financiën, gegeven op 12 februari 2002;

Gelet op de akkoordbevinding van de Minister van Begroting, gegeven op 1 maart 2002;

Gelet op de wetten op de Raad van State, gecoördineerd op 12 januari 1973, inzonderheid op artikel 3, § 1, vervangen bij de wet van 4 juli 1989 en gewijzigd bij de wet van 4 augustus 1996;

Gelet op de dringende noodzakelijkheid gemotiveerd door het feit dat :

- dit ontwerp strekt tot omzetting van de richtlijnen 1999/11/EG en 1999/12/EG van de Commissie van

6 MARS 2002. - Arrêté royal fixant les principes de bonnes pratiques de laboratoire et la vérification de leur mise en application pour les essais effectués sur les substances chimiques

ALBERT II, Roi des Belges,  
A tous, présents et à venir, Salut.

Vu la loi du 30 décembre 2001 portant des dispositions sociales et diverses, notamment l'article 47;

Vu l'arrêté royal du 27 octobre 1988 relatif à l'application des principes de bonnes pratiques de laboratoire et à la vérification de sa mise en application pour les essais effectués sur les substances chimiques;

Vu la directive 1999/11/CE de la Commission du 8 mars 1999 portant adaptation au progrès technique des principes de bonnes pratiques de laboratoire visés dans la directive 87/18/CEE du Conseil concernant de rapprochement des dispositions législatives, réglementaires et administratives relatives à l'application des principes de bonnes pratiques de laboratoire et au contrôle de leur application pour les essais sur les substances chimiques;

Vu la directive 1999/12/CE de la Commission du 8 mars 1999 portant deuxième adaptation au progrès technique de l'annexe de la directive 88/320/CEE du Conseil, concernant l'inspection et la vérification de bonnes pratiques de laboratoire (BPL);

Vu l'avis de l'Inspecteur des Finances, donné le 12 février 2002;

Vu l'accord du Ministre du Budget, donné le 1<sup>er</sup> mars 2002;

Vu les lois sur le Conseil d'Etat, coordonnées le 12 janvier 1973, notamment l'article 3, § 1<sup>er</sup>, remplacé par la loi du 4 juillet 1989 et modifié par la loi du 4 août 1996;

Vu l'urgence motivée par la circonstance que :  
- ce projet porte la transposition des directives 1999/11/CE et 1999/12/CE de la Commission du 8 mars 1999 relatives aux principes de bonnes pratiques de laboratoire;

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8 maart 1999 betreffende de beginselen van goede laboratoriumpraktijken;  
- de termijn voor de omzetting van deze richtlijnen reeds verstreken is;  
- dit ontwerp reeds werd voorgelegd aan het advies van de Raad van State;  
- de Raad van State het advies nr. 31.066/3 van 2 februari 2001 verstrekt heeft waaruit bleek dat onvoldoende wettelijke basis voor de omzetting van deze richtlijnen bestond;  
- de Europese Commissie op 18 juli 2001 een met redenen omkleed advies heeft uitgevaardigd wegens het nog niet omzetten van bovenvermelde richtlijnen;  
- bij de wet van 30 december 2001 houdende sociale en diverse bepalingen rechtsgrond werd gegeven voor de omzetting van deze richtlijnen;  
- de nodige maatregelen tot omzetting van deze richtlijnen zonder verwijl dienen genomen te worden;

Op de voordracht van Onze Minister van Consumentenzaken, Volksgezondheid en Leefmilieu,  
Hebben Wij besloten en besluiten Wij :

**HOOFDSTUK I. - Definities**

Artikel 1. Voor de toepassing van dit besluit wordt verstaan onder :

1° Beginselen van goede laboratoriumpraktijken : een kwaliteitssysteem dat betrekking heeft op de wijze waarop studies over de eigenschappen van chemische stoffen in laboratoria worden georganiseerd en op de voorwaarden waaronder deze studies worden gepland, uitgevoerd, gecontroleerd, geregistreerd, gerapporteerd, verdeeld en gearhiveerd;

2° Toezicht op de naleving van de beginselen van goede laboratoriumpraktijken : de inspectie van laboratoria en/of studie-audits om na te gaan of de beginselen van goede laboratoriumpraktijken worden nageleefd;

3° Programma voor de naleving van de beginselen van goede laboratoriumpraktijken : een specifiek programma opgesteld voor het toezicht op de naleving van de beginselen van goede laboratoriumpraktijken door laboratoria door middel van inspecties en verificatie van studies;

4° Instantie voor het toezicht op de naleving van goede laboratoriumpraktijken : een organisme dat belast is met het toezicht op de naleving van de beginselen van goede laboratoriumpraktijken door laboratoria en met andere taken die verband houden met de beginselen van goede

- le délai de transposition de ces directives est déjà dépassée;  
- ce projet a été soumis à l'avis du Conseil d'Etat;  
- le Conseil d'Etat a donné son avis n° 31.066/3 le 2 février 2001 dont il ressortait qu'il y avait une base légale insuffisante pour la transposition de ces directives;  
- la Commission européenne a émis le 18 juillet 2001 un avis motivé pour non transposition des directives sus-mentionnées;  
- par la loi du 30 décembre 2001 portant des dispositions sociales et diverses le fondement légal a été donné pour la transposition de ces directives;  
- les dispositions nécessaires pour la transposition de ces directives doivent être prises sans délai;  
Sur la proposition de Notre Ministre de la Protection de la Consommation, de la Santé publique et de l'Environnement,  
Nous avons arrêté et arrêtons :

**CHAPITRE I<sup>er</sup>. - Définitions**

Article 1<sup>er</sup>. Pour l'application du présent arrêté, il faut entendre par :

1° Principes de bonnes pratiques de laboratoire : un système de qualité se rapportant au mode d'organisation des études relatives aux caractéristiques des substances chimiques dans les laboratoires et aux conditions dans lesquelles ces études sont planifiées, réalisées, contrôlées, enregistrées, rapportées, diffusées et archivées;

2° Vérification de la mise en conformité des principes de bonnes pratiques de laboratoire : l'inspection de laboratoires et/ou la vérification d'études réalisées afin de s'assurer du respect des principes de bonnes pratiques de laboratoire;

3° Programme de mise en conformité aux principes de bonnes pratiques de laboratoire : un dispositif particulier établi pour vérifier la mise en conformité aux principes de bonnes pratiques de laboratoire effectué par des laboratoires au moyen d'inspections et de vérification d'études;

4° Autorité de vérification en matière de bonnes pratiques de laboratoire : un organisme chargé de contrôler la mise en conformité aux principes de bonnes pratiques de laboratoire par les laboratoires et de remplir d'autres tâches relatives aux principes de bonnes pratiques de

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laboratoriumpraktijken;  
5° Inspectie van goede laboratoriumpraktijken : een onderzoek ter plaatse van de werkwijzen en praktijken van het laboratorium, om te beoordelen in welke mate de beginselen van goede laboratoriumpraktijken worden nageleefd;  
6° Studie-audit : een vergelijking van de onbewerkte gegevens met het voorlopig of eindverslag, om na te gaan of de onbewerkte gegevens juist in het verslag zijn verwerkt, om na te gaan of de studies zijn uitgevoerd in overeenstemming met het studieplan en de standaardwerkvoorschriften, om aanvullende informatie te verkrijgen die niet in het verslag is vermeld en om vast te stellen of bij het verkrijgen van de gegevens methodes zijn toegepast die de geldigheid ervan in vraag kunnen stellen;  
7° Inspecteur van goede laboratoriumpraktijken : de persoon die de inspecties uitvoert namens de instantie bevoegd voor het toezicht op de naleving van goede laboratoriumpraktijken;  
8° Status van conformiteit met de goede laboratoriumpraktijken : de mate waarin, volgens de bevoegde instantie, een laboratorium de beginselen van goede laboratoriumpraktijken, het toepassingsgebied, de testen en de geldigheidsdatum naleeft;  
9° Bevoegde instantie voor het toezicht op de naleving van goede laboratoriumpraktijken : het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur is belast met het toezicht op de naleving van de beginselen van goede laboratoriumpraktijken in de laboratoria;  
10° Conformiteitsverklaring van goede laboratoriumpraktijken : het document, ondertekend en gedateerd door de Directeur van het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur, vermeldend dat het laboratorium studies volgens de beginselen van goede laboratoriumpraktijken uitvoert in een toepassingsgebied dat gespecificeerd is in artikel 1 van de richtlijn 88/320/EEG van de Raad inzake de inspectie en de verificatie van goede laboratoriumpraktijken (GLP);  
11° Veldstudie : een proef of een geheel van proeven waarbij een chemische stof wordt onderzocht om gegevens te bekomen over zijn eigenschappen en veiligheid met betrekking tot de gezondheid van mens en dier en/of het leefmilieu.

laboratoire;  
5° Inspection de bonnes pratiques de laboratoire : un examen sur place des procédures et des méthodes appliquées dans le laboratoire, afin d'évaluer le degré de conformité aux principes de bonnes pratiques de laboratoire;  
6° Vérification d'étude : une comparaison des données brutes qui y sont associées avec le rapport provisoire ou final, en vue de déterminer si les données brutes ont été traitées avec exactitude, de vérifier si les essais ont été menés conformément au plan d'étude et aux modes opératoires normalisés, d'obtenir des informations complémentaires ne figurant pas dans le rapport et d'établir si les méthodes utilisées pour obtenir les données ne risquaient pas d'entacher leur validité;  
7° Inspecteur de bonnes pratiques de laboratoire : la personne qui réalise les inspections du laboratoire pour le compte de l'autorité compétente de vérification en matière de bonnes pratiques de laboratoire;  
8° Degré de conformité aux bonnes pratiques de laboratoire : le degré d'adhésion aux principes de bonnes pratiques de laboratoire, au domaine d'application, aux essais et à la date de validité d'un laboratoire, qui est évalué par l'autorité compétente de vérification en la matière;  
9° Autorité compétente de vérification en matière de bonnes pratiques de laboratoire : l'Institut scientifique de la Santé publique - Louis Pasteur est chargé de contrôler la mise en conformité aux principes de bonnes pratiques de laboratoire dans les laboratoires;  
10° Déclaration de conformité en matière de bonnes pratiques de laboratoire : le document, signé et daté par le Directeur de l'Institut scientifique de la Santé publique - Louis Pasteur, mentionnant que le laboratoire réalise des études selon les principes de bonnes pratiques de laboratoire dans un domaine d'application spécifié dans l'article 1<sup>er</sup> de la directive 88/320/CEE du Conseil concernant l'inspection et la vérification de bonnes pratiques de laboratoire (BLP);  
11° Etude sur le terrain : un essai ou un ensemble d'essais au cours duquel est examinée une substance chimique en vue d'obtenir des données sur ses propriétés et sur sa sécurité du point de vue de la santé humaine, animale et/ou l'environnement.

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HOOFDSTUK II - Toepassingsgebied van de beginselen van goede laboratoriumpraktijken  
Art. 2. De beginselen van goede laboratoriumpraktijken moeten worden toegepast op niet klinische veiligheidsproeven van teststoffen aanwezig in farmaceutische, cosmetische en fytofarmaceutische producten, diergeneesmiddelen, industriële chemicaliën, voedings- en veevoederadditieven. Deze teststoffen zijn synthetisch chemische producten, producten van natuurlijke of biologische oorsprong of levende organismen. Deze proeven hebben tot doel gegevens te bekomen over de eigenschappen van teststoffen en over hun schadelijkheid met betrekking tot de gezondheid van mens, dier of het leefmilieu.

De beginselen van goede laboratoriumpraktijken moeten eveneens worden toegepast bij proeven die kaderen in veldstudies.

De beginselen van goede laboratoriumpraktijken zijn van toepassing op niet-klinische veiligheidsproeven, vereist door de bevoegde overheid, ten einde de erkenning van farmaceutische, cosmetische en fytofarmaceutische producten, diergeneesmiddelen, industriële chemicaliën, voedings- en veevoederadditieven toe te staan of te weigeren.

HOOFDSTUK III. - Conformiteitsverklaring van goede laboratoriumpraktijken

Art. 3. Bij het voorleggen van de resultaten moet het laboratorium, dat de in artikel 2 van dit besluit bedoelde proeven heeft uitgevoerd, bevestigen dat de uitvoering van de proeven is gebeurd overeenkomstig de beginselen van goede laboratoriumpraktijken bedoeld in artikel 1 van dit besluit.

HOOFDSTUK IV. - Toezicht op de naleving van de beginselen van goede laboratoriumpraktijken

Art. 4. Het toezicht op de naleving van de beginselen van goede laboratoriumpraktijken wordt uitgeoefend door uitvoering van inspecties van laboratoria en studie-audits door de bevoegde instantie voor het toezicht op de naleving van goede laboratoriumpraktijken als beschreven in artikel 5 van dit besluit.

HOOFDSTUK V. - Inspectie van goede laboratoriumpraktijken en studie-audits

Art. 5. § 1. Het verzoek tot toezicht op de naleving

CHAPITRE II. - Domaine d'application des principes de bonnes pratiques de laboratoire  
Art. 2. Les principes de bonnes pratiques de laboratoire doivent être appliqués aux essais de sécurité non cliniques sur des substances d'essais présentes dans les produits pharmaceutiques, cosmétiques, vétérinaires, phytopharmaceutiques, chimiques industriels, les additifs alimentaires et pour la nourriture du bétail. Ces substances d'essais sont des produits chimiques synthétiques, des produits d'origine naturelle ou biologique ou des organismes vivants. Le but de ces essais est de fournir des données sur les propriétés des substances d'essais et sur l'innocuité de celles-ci du point de vue de la santé humaine, animale ou de l'environnement.

Les principes de bonnes pratiques de laboratoire doivent également être appliqués aux essais menés dans le cadre d'études sur le terrain.

Les principes de bonnes pratiques de laboratoire s'appliquent aux essais de sécurité non cliniques, exigés par l'autorité compétente, en vue d'agréer ou licencier les produits pharmaceutiques, cosmétiques, vétérinaires, phytopharmaceutiques, chimiques industriels, les additifs alimentaires et pour la nourriture du bétail.

CHAPITRE III. - Déclaration de conformité de bonnes pratiques de laboratoire

Art. 3. Lors de la remise des données, le laboratoire qui a effectué des essais, visés à l'article 2 du présent arrêté, doit certifier que l'exécution des essais a été effectuée conformément aux principes de bonnes pratiques de laboratoire visées à l'article 1<sup>er</sup> du présent arrêté.

CHAPITRE IV. - Vérification de la mise en conformité aux principes de bonnes pratiques de laboratoire

Art. 4. La vérification de la mise en conformité aux principes de bonnes pratiques de laboratoire est effectuée par l'exécution d'inspections de laboratoires et de vérifications d'études par l'autorité compétente de vérification en matière de bonnes pratiques de laboratoire comme décrit à l'article 5 du présent arrêté.

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van de beginselen van goede laboratoriumpraktijken door de laboratoria die proeven uitvoeren bedoeld in artikel 2 van dit besluit, moet gericht worden aan de Directeur van het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur, Juliette Wytsmanstraat 14, 1050 Brussel. In dat verzoek moeten de sectoren van producten, bedoeld in artikel 2 van dit besluit, en het type van proeven, waarvoor de conformiteitsverklaring wordt gevraagd, duidelijk zijn omschreven.

§ 2. Het laboratorium moet kunnen aantonen dat het de proeven, waarvoor een conformiteitsverklaring wordt aangevraagd, uitvoert volgens de beginselen van goede laboratoriumpraktijken. Het laboratorium moet er zich toe verbinden :

1° alle inlichtingen te verstrekken die nodig zijn voor het uitvoeren van inspecties en studie-audits;  
2° aan de in artikel 5, § 5, 2°, van dit besluit bedoelde agenten toegang te verlenen tot het laboratorium.

§ 3. In het raam van dit besluit stelt het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur een programma voor de naleving van de beginselen van goede laboratoriumpraktijken op en voert dit uit in de laboratoria die de in artikel 2 van dit besluit bepaalde proeven uitvoeren, overeenkomstig de instructies beschreven in het handboek van het Belgisch bewakingsprogramma voor de naleving van de beginselen van goede laboratoriumpraktijken. Het Instituut beheert de administratie betreffende dit programma en besteedt vooral aandacht aan de vertrouwelijkheid van de informatie en resultaten verstrekt door de laboratoria. Het programma kan aangevraagd worden bij het Bureau Kwaliteitszorg van het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur.

§ 4. Het programma voor de naleving van de beginselen van goede laboratoriumpraktijken omvat:

1° de inspecties van laboratoria bestaande uit een algemene inspectie van het laboratorium en de verificatie van tenminste twee beëindigde studies. De inspectie van de laboratoria zal om de twee tot drie jaar uitgevoerd worden. De inspecties mogen vaker gebeuren wanneer er een vermoeden van niet-conformiteit bestaat;  
2° de inspecties en studie-audits op verzoek van een federale overheid op het ogenblik dat aan deze overheid gegevens worden voorgelegd;  
3° de inspecties en studie-audits op verzoek van

CHAPITRE V. - Inspection de bonnes pratiques de laboratoire et vérification des études  
Art. 5. § 1<sup>er</sup>. La demande de vérification de conformité aux principes de bonnes pratiques de laboratoire par les laboratoires effectuant des essais visés à l'article 2 du présent arrêté, doit être adressée au Directeur de l'Institut scientifique de la Santé publique - Louis Pasteur, rue Juliette Wytsman 14, 1050 Bruxelles. La demande doit clairement spécifier les secteurs de produits visés à l'article 2 du présent arrêté et le type d'essais pour lesquels la déclaration de conformité est demandée.

§ 2. Le laboratoire demandeur doit pouvoir justifier qu'il effectue les essais, pour lesquels la déclaration de conformité est revendiquée, conformément aux principes de bonnes pratiques de laboratoire. Le laboratoire doit s'engager à :

1° fournir tous les renseignements nécessaires aux inspections et vérification des études;  
2° permettre l'accès du laboratoire aux agents visés à l'article 5, § 5, 2°, du présent arrêté.

§ 3. Dans le cadre du présent arrêté, l'Institut scientifique de la Santé publique - Louis Pasteur rédige un programme de vérification de conformité aux principes de bonnes pratiques de laboratoire et réalise ce programme dans les laboratoires effectuant des essais prévus par l'article 2 du présent arrêté, conformément aux instructions décrites dans le manuel du programme belge de vérification de conformité aux principes de bonnes pratiques de laboratoire. L'Institut gère l'administration afférente à ce programme et donne surtout une attention particulière aux questions de confidentialité relative aux informations et résultats donnés par le laboratoire. Le programme peut être demandé au Bureau Assurance Qualité de l'Institut scientifique de la Santé publique - Louis Pasteur.

§ 4. Le programme de vérification de la mise en conformité aux principes de bonnes pratiques de laboratoire comprend :

1° les inspections de laboratoires comprenant une inspection générale du laboratoire et une vérification de deux études terminées au moins. L'inspection des laboratoires sera effectuée tous les deux à trois ans. Des inspections plus rapprochées peuvent avoir lieu s'il y a suspicion de non conformité;  
2° les inspections et les vérifications d'études faites à la demande d'une autorité fédérale,

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een buitenlandse overheid. Deze verzoeken moeten behoorlijk worden verrechtvaardigd en hun draagwijdte moet duidelijk worden gepreciseerd.

§ 5. De inspecties en studie-audits worden uitgevoerd door inspecteurs van goede laboratoriumpraktijken. Deze worden voor de duur van de inspectie en van de studie-audits door het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur aangeduid.

Indien het dossier van de aanvraag behoort tot één of meerdere gereguleerde sectoren, kunnen vertegenwoordigers van de betrokken departementen de inspecties en studie-audits bijwonen.

In bepaalde omstandigheden kan het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur beroep doen op federale, communautaire, gewestelijke of internationale experts om bepaalde deelaspecten van studies te verifiëren.

§ 6. De samenstelling van het inspectieteam en het programma van de inspectie worden normaliter 14 dagen vóór het uitvoeren van de inspectie aan de aanvrager meegedeeld.

§ 7. Na afloop van de inspecties en controles van studies stellen de inspecteurs van goede laboratoriumpraktijken, bedoeld in artikel 5, § 5, van dit besluit, op basis van hun bevindingen een geschreven rapport op over de staat van conformiteit van het laboratorium en van de beoordeelde studies.

Dit rapport wordt binnen de 20 dagen aan de aanvrager overgemaakt, die binnen de 30 dagen, door middel van een aangetekend schrijven, zijn opmerkingen en commentaren kan laten worden aan het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur.

§ 8. De Directeur van het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur beslist op basis van het eindverslag en de opmerkingen en commentaren van het laboratorium of het laboratorium conform is met de beginselen van goede laboratoriumpraktijken, bedoeld in artikel 1 van dit besluit.

De beslissing en een kopie van het eindverslag worden bij een ter post aangetekende brief naar het laboratorium opgestuurd. Indien de beslissing gunstig is, bevat het certificaat dat verklaart dat het laboratorium de beginselen van goede laboratoriumpraktijken naleeft minstens de volgende elementen:

- de identiteit van het laboratorium;
- het identificatienummer van het laboratorium;
- de handtekening van de Directeur van het

formulée à la suite de la soumission de données à cette autorité;

3° les inspections et les vérifications d'études faites à la demande d'une autorité étrangère. Ces demandes devraient être dûment justifiées et leur portée précisée.

§ 5. Les inspections et les vérifications d'études sont effectuées par des inspecteurs de bonnes pratiques de laboratoire. Ceux-ci sont désignés par l'Institut scientifique de la Santé publique - Louis Pasteur pour la durée de l'inspection et de la vérification d'études.

Lorsque la demande concerne un ou plusieurs secteurs réglementés, des représentants des départements concernés peuvent assister aux inspections et vérification d'études.

Dans certaines circonstances, l'Institut scientifique de la Santé publique - Louis Pasteur peut faire appel aux experts fédéraux, communautaires, régionaux ou internationaux afin de vérifier quelques aspects partiels d'études.

§ 6. La composition de l'équipe d'inspection et le programme d'inspection sont normalement communiqués au demandeur au plus tard 14 jours avant l'exécution de l'inspection.

§ 7. A l'issue des inspections et vérifications d'études et sur base de leurs observations, les inspecteurs de bonnes pratiques de laboratoire, visés à l'article 5, § 5, du présent arrêté, préparent un rapport écrit sur l'état de conformité du laboratoire et des études vérifiées.

Ce rapport est communiqué dans les 20 jours au demandeur qui peut, dans les 30 jours, faire valoir par lettre recommandée ses remarques et commentaires auprès de l'Institut scientifique de la Santé publique - Louis Pasteur.

§ 8. Sur base du rapport d'inspection et des remarques et commentaires du laboratoire, le Directeur de l'Institut scientifique de la Santé publique - Louis Pasteur prend une décision relative à la conformité du laboratoire aux principes de bonnes pratiques de laboratoire visés à l'article 1<sup>er</sup> du présent arrêté.

La décision ainsi qu'une copie du rapport d'inspection sont envoyées au laboratoire par pli recommandé à la poste. Quand la décision est favorable, le certificat déclarant que le laboratoire respecte les principes de bonnes pratiques de laboratoire contient au moins les renseignements suivants :

- l'identité du laboratoire;

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Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur en de datum van de handtekening;  
- de datum waarop de inspectie en de studie-audits werden uitgevoerd;

- het toepassingsgebied van de conformiteitsverklaring van goede laboratoriumpraktijken.

Indien de beslissing ongunstig is, beschikt het laboratorium, vanaf de ontvangst van de beslissing van de Directeur van het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur, over 30 dagen om deze laatste ervan in kennis te stellen of :

- hij afziet van het verzoek tot toezicht op de naleving van de beginselen van goede laboratoriumpraktijken; in dit geval wordt de aanvraag zonder gevolg geklasseerd;  
- hij zijn verzoek weerhoudt; in dit geval wordt de verdere behandeling van het aanvraagdossier geschorst totdat de aanvrager van oordeel is dat hij klaar is voor een tweede inspectie en verificatie van studies.

Bij onstentenis van deze kennisgeving wordt de beslissing definitief bij het verstrijken van deze termijn. Deze beslissing wordt meegedeeld aan het laboratorium bij een ter post aangetekend schrijven.

**HOOFDSTUK VI. - Duur, behoud, uitbreiding en intrekking van de conformiteitsverklaring van goede laboratoriumpraktijken**

Art. 6. § 1. De status van conformiteit met de goede laboratoriumpraktijken wordt toegekend voor maximum drie jaar, tenzij anders bepaald in de conformiteitsverklaring van goede laboratoriumpraktijken. De status van conformiteit heeft uitsluitend betrekking op de in de conformiteitsverklaring van goede laboratoriumpraktijken vermelde toepassingsgebieden.

§ 2. Onverminderd de in de artikelen 2, 3, 4 en 5 van dit besluit vermelde algemene voorwaarden moeten de laboratoria, om conform te blijven met de beginselen van goede laboratoriumpraktijken, voldoen aan de volgende voorwaarden :

- het vereffenen van de vergoedingen die vastgesteld zijn in het koninklijk besluit van 6 maart 2002 tot vaststelling van de vergoedingen in het kader van het toezicht op de naleving van de beginselen van goede laboratoriumpraktijken van laboratoria voor proeven bedoeld in artikel 2 van dit besluit;

- het schriftelijk meedelen aan de Directeur van het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur van elke wijziging van organisatorische of

- le numéro d'identification du laboratoire;

- la signature du Directeur de l'Institut scientifique de la Santé publique - Louis Pasteur et la date de la signature;

- la date à laquelle l'inspection et la vérification des études ont été exécutées;

- le domaine d'application de la déclaration de conformité de bonnes pratiques de laboratoire.

Quand la décision est défavorable, le laboratoire dispose de 30 jours, à dater de la réception de la décision du Directeur de l'Institut scientifique de la Santé publique - Louis Pasteur, pour faire savoir à celui-ci :

- s'il renonce à la demande de vérification de conformité aux principes de bonnes pratiques de laboratoire; dans ce cas, cette dernière est classée sans suite;

- s'il maintient sa demande; dans ce cas, l'instruction du dossier de demande est suspendue et reprend son cours quand le demandeur estime être prêt à recevoir une seconde inspection et vérification d'études.

A défaut de cette communication, la décision devient définitive à l'expiration de ce délai. Cette décision est communiquée au laboratoire par lettre recommandée à la poste.

**CHAPITRE VI. - Durée, maintien, extension et retrait de la déclaration de conformité de bonnes pratiques de laboratoire**

Art. 6. § 1<sup>er</sup>. Le degré de conformité aux bonnes pratiques de laboratoire est accordé pour une durée maximum de trois ans sauf disposition contraire exprimée dans la déclaration de conformité de bonnes pratiques de laboratoire.

Le degré de conformité couvre uniquement les domaines spécifiés dans la déclaration de conformité de bonnes pratiques de laboratoire.

§ 2. Sans préjudice des dispositions générales, reprises aux articles 2, 3, 4 et 5 du présent arrêté, les laboratoires doivent, pour rester conforme aux principes de bonnes pratiques de laboratoire, remplir les conditions suivantes :

- s'acquitter des redevances fixées par l'arrêté royal du 6 mars 2002 fixant les redevances appliquées par le système de contrôle de conformité aux principes de bonnes pratiques de laboratoire des laboratoires effectuant des essais visés à l'article 2 du présent arrêté;  
- communiquer immédiatement par écrit au Directeur de l'Institut scientifique de la Santé publique - Louis Pasteur, tout changement de nature organisationnelle ou technique

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technische aard, die van invloed kan zijn op de status van conformiteit met de goede laboratoriumpraktijken;  
- het indienen van een aanvraag tot verlenging aan de Directeur van het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur, ten laatste drie maanden voor het verstrijken van de termijn bepaald in de conformiteitsverklaring, volgens de procedure bepaald in artikel 5, § 1, van dit besluit.  
§ 3. Elke aanvraag tot uitbreiding van de naleving van de beginselen van goede laboratoriumpraktijken dient de procedure, bepaald in artikel 5, § 1 van dit besluit te volgen.  
Een laboratorium kan op ieder ogenblik, geheel of gedeeltelijk, aan zijn naleving van de beginselen van goede laboratoriumpraktijken verzaken, door het sturen van een aangetekende brief aan de Directeur van het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur.  
Dit verzaken ontslaat het laboratorium, gedurende de periode van de status van naleving van de goede laboratoriumpraktijken, niet van de aangegane verplichtingen ten opzichte van de instantie bevoegd met het toezicht op de naleving van goede laboratoriumpraktijken.  
§ 4. Wanneer niet meer voldaan wordt aan de beginselen van goede laboratoriumpraktijken, beslist de Directeur van het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur, die het programma voor de naleving van goede laboratoriumpraktijken onder zijn bevoegdheid heeft, op basis van een met redenen omkleed advies, tot de gehele of gedeeltelijke, tijdelijke of definitieve intrekking van de status van conformiteit met de goede laboratoriumpraktijken.  
De beslissing wordt bij een ter post aangetekende brief aan het laboratorium megedeeld en heeft onmiddellijk uitwerking.

HOOFDSTUK VII. - De instantie bevoegd voor het toezicht op de naleving van goede laboratoriumpraktijken  
Art. 7. § 1. Het secretariaat van de bevoegde instantie voor toezicht op de naleving van goede laboratoriumpraktijken wordt verzekerd door het Bureau Kwaliteitszorg van het Wetenschappelijk Instituut Volksgezondheid - Louis Pasteur.  
§ 2. De bevoegde instantie voor toezicht op de naleving van goede laboratoriumpraktijken stelt zijn reglement van inwendige orde op.  
§ 3. Benevens het uitvoeren van de taken beschreven in artikel 5, § 3 van dit besluit is de bevoegde instantie voor toezicht op de naleving van

susceptible de modifier le respect de conformité aux bonnes pratiques de laboratoire;  
- introduire une demande de prolongation au Directeur de l'Institut scientifique de la Santé publique - Louis Pasteur au moins trois mois avant le terme de la période de validité de déclaration de conformité, selon la procédure prévue à l'article 5, § 1<sup>er</sup>, du présent arrêté.  
§ 3. Toute demande d'extension de la conformité aux principes de bonnes pratiques de laboratoire doit suivre la procédure prévue à l'article 5, § 1<sup>er</sup> du présent arrêté.  
Un laboratoire peut, à tout moment, renoncer totalement ou partiellement à sa conformité aux principes de bonnes pratiques de laboratoire, en le notifiant par lettre recommandée au Directeur de l'Institut scientifique de la Santé publique - Louis Pasteur.  
Cette renonciation ne le dégage pas des obligations vis-à-vis de l'autorité compétente de vérification en matière de bonnes pratiques de laboratoire durant la période du degré de conformité aux bonnes pratiques de laboratoire.  
§ 4. Lorsque les conditions des principes de bonnes pratiques de laboratoire ne sont plus remplies, le Directeur de l'Institut scientifique de la Santé publique - Louis Pasteur qui a autorité pour la déclaration de conformité de bonnes pratiques de laboratoire, sur base d'un avis motivé, décide du retrait du degré de conformité aux bonnes pratiques de laboratoire, totalement, partiellement, temporairement ou définitivement.  
La décision est notifiée par lettre recommandée à la poste au laboratoire et prend effet immédiatement.

CHAPITRE VII. - L'autorité compétente pour la vérification en matière de bonnes pratiques de laboratoire  
Art. 7. § 1<sup>er</sup>. Le secrétariat de l'autorité compétente pour la vérification en matière de bonnes pratiques de laboratoire est assurée par le Bureau Assurance Qualité de l'Institut scientifique de la Santé publique Louis Pasteur.  
§ 2. L'autorité compétente pour la vérification en matière de bonnes pratiques de laboratoire rédige son règlement d'ordre intérieur.  
§ 3. Outre l'exécution de tâches décrites à l'article 5, § 3 du présent arrêté, l'autorité compétente pour la vérification en matière de bonnes pratiques de laboratoire est chargée notamment :

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goede laboratoriumpraktijken inzonderheid belast met :

- het voorstellen van leidraden voor de toepassing van de beginselen van goede laboratoriumpraktijken;
- het voorstellen van de vorm en de minimale inhoud van de aanvraagformulieren tot naleving van de beginselen met de goede laboratoriumpraktijken en de inspectierapporten;
- het voorstellen van de criteria betreffende de kwalificatie en opdrachten van de inspecteurs en de technische experten;
- het beheren van de lijst van inspecteurs en technische experten;
- het beheer van de lijst van laboratoria met status van naleving van de beginselen van de goede laboratoriumpraktijken. De wijzigingen aan deze lijst worden jaarlijks bekendgemaakt in het Belgisch Staatsblad;
- het deelnemen aan inspecties met andere internationale monitoring autoriteiten belast met het toezicht op de naleving van goede laboratoriumpraktijken;
- het ter beschikking stellen van inspectierapporten van de laboratoria en van de controles van studies aan andere bevoegde overheden en/of opdrachtgevers van studies indien dit kan verechvaardigd worden.

Art. 8. Het koninklijk besluit van 27 oktober 1988 betreffende de toepassing van de beginselen van goede laboratoriumpraktijken en het toezicht op de uitvoering ervan van de proeven op scheikundige stoffen wordt opgeheven.

Art. 9. Onze Minister van Consumentenzaken, Volksgezondheid en Leefmilieu is belast met de uitvoering van dit besluit.

Gegeven te Brussel, 6 maart 2002.  
ALBERT  
Van Koningswege :  
De Minister van Consumentenzaken,  
Volksgezondheid en Leefmilieu,  
Mevr. M. AELVOET

6 MAART 2002. - Koninklijk besluit tot vaststelling van de vergoedingen verschuldigd in het kader van het toezicht op de uitvoering van goede laboratoriumpraktijken bij proeven op scheikundige stoffen

ALBERT II, Koning der Belgen,  
Aan allen die nu zijn en hierna wezen zullen, Onze

- de la proposition de directives portant sur l'application des principes de bonnes pratiques de laboratoire;
- de la proposition de la forme et du contenu minimal des formulaires de demande de mise en conformité des principes de bonnes pratiques de laboratoire et des rapports d'inspection;
- de la proposition des critères de qualification et des tâches des inspecteurs et des experts techniques;
- de la gestion de la liste des inspecteurs et des experts techniques et de leurs qualifications;
- de la gestion des listes des laboratoires ayant un degré de mise en conformité des principes de bonnes pratiques de laboratoire. Les modifications à cette liste sont publiées annuellement au Moniteur belge;
- de la participation aux inspections avec autres autorités internationales de vérification en matière de bonnes pratiques de laboratoire;
- de la mise à la disposition aux autres autorités compétentes et/ou aux commettants d'études des rapports d'inspections des autres laboratoires et de vérification d'études et seulement sur demande dûment justifiée.

Art. 8. L'arrêté royal du 27 octobre 1988 relatif à l'application des principes de bonnes pratiques de laboratoire et à la vérification de sa mise en application pour les essais effectués sur les substances chimiques est abrogé.

Art. 9. Notre Ministre de la Protection de la Consommation, de la Santé publique et de l'Environnement est chargé de l'exécution du présent arrêté.

Donné à Bruxelles, le 6 mars 2002.  
ALBERT  
Par le Roi :  
La Ministre de la Protection de la  
Consommation, de la Santé publique et de  
l'Environnement,  
Mme M. AELVOET

6 MARS 2002. - Arrêté royal fixant les redevances dues dans le cadre de la vérification de la mise en application des bonnes pratiques de laboratoire pour les essais effectués sur les substances chimiques

ALBERT II, Roi des Belges,  
A tous, présents et à venir, Salut.

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Groet.

Gelet op de wet van 30 december 2001 houdende sociale en diverse bepalingen, inzonderheid op artikel 47;

Gelet op het koninklijk besluit van 6 maart 2002 betreffende de toepassing van de beginselen van goede laboratoriumpraktijken en het toezicht op de uitvoering ervan bij proeven op scheikundige stoffen;

Gelet op het advies van de Inspecteur van Financiën, gegeven op 12 februari 2002;

Gelet op de akkoordbevinding van de Minister van Begroting, gegeven op 1 maart 2002;

Gelet op de wetten op de Raad van State, gecoördineerd op 12 januari 1973, inzonderheid op artikel 3, § 1, vervangen bij de wet van 4 juli 1989 en gewijzigd bij de wet van 4 augustus 1996;

Gelet op de dringende noodzakelijkheid gemotiveerd door het feit dat :

- dit ontwerp strekt tot financiering van de maatregelen die genomen worden in het kader van de omzetting van de richtlijnen 1999/11/EG en 1999/12/EG van de Commissie van 8 maart 1999 betreffende de beginselen van goede laboratoriumpraktijken;
- de maatregelen tot omzetting van deze richtlijnen alsook dit ontwerp reeds werden voorgelegd aan het advies van de Raad van State;
- de Raad van State de adviezen nr. 31.066/3 en nr. 31.068/3 van 2 februari 2001 verstrekt heeft waaruit bleek dat onvoldoende wettelijke basis voor de omzetting van deze richtlijnen bestond;
- bij de wet van 30 december 2001 rechtsgrond werd gegeven voor de omzetting van deze richtlijnen;
- de nodige maatregelen tot omzetting van deze richtlijnen zonder verwijl dienen genomen te worden;
- de omzetting van deze richtlijnen niet effectief kan zijn zonder tevens de nodige maatregelen te nemen tot financiering van de opdrachten voortvloeiend uit de omzetting van deze richtlijnen;

Op voordracht van Onze Minister van Consumentenzaken, Volksgezondheid en Leefmilieu,  
Hebben Wij besloten en besluiten Wij :

Artikel 1. § 1. Het bekomen, de verlenging, de uitbreiding en de controle van conformiteit met de beginselen van goede laboratoriumpraktijken overeenkomstig de bepalingen van het koninklijk

Vu la loi du 30 décembre 2001 portant des dispositions sociales et diverses, notamment l'article 47;

Vu l'arrêté royal du 6 mars 2002 relatif à l'application des principes de bonnes pratiques de laboratoire et de la vérification de sa mise en application pour les essais effectués sur les substances chimiques;

Vu l'avis de l'Inspecteur des Finances, donné le 12 février 2002;

Vu l'accord du Ministre du Budget, donné le 1<sup>er</sup> mars 2002;

Vu les lois sur le Conseil d'Etat, coordonnées le 12 janvier 1973, notamment l'article 3, § 1<sup>er</sup>, remplacé par la loi du 4 juillet 1989 et modifié par la loi du 4 août 1996;

Vu l'urgence motivée par la circonstance que :

- ce projet touche au financement des dispositions prises dans le cadre de la transposition des directives 1999/11/CE et 1999/12/CE de la Commission du 8 mars 1999 relatives aux principes de bonnes pratiques de laboratoire;
- les dispositions pour la transposition de ces directives ainsi que le présent projet ont déjà été soumis à l'avis du Conseil d'Etat;
- le Conseil d'Etat a donné les avis n° 31.066/3 et n° 31.068/3 le 2 février 2001 dont il ressortait qu'il y avait une base légale insuffisante pour la transposition de ces directives;
- par la loi du 30 décembre 2001 le fondement légal a été donné pour la transposition de ces directives;
- les dispositions nécessaires pour la transposition de ces directives doivent être prises sans délai;
- la transposition de ces directives ne peut pas être effective sans que soient également prises les mesures nécessaires au financement des tâches découlant de la transposition de ces directives;

Sur la proposition de Notre Ministre de la Protection de la Consommation, de la Santé publique et de l'Environnement,  
Nous avons arrêté et arrêtons :

Article 1<sup>er</sup>. § 1<sup>er</sup>. L'obtention, la prolongation, l'extension et la vérification de conformité aux principes de bonnes pratiques de laboratoire conformément aux impositions de l'arrêté royal du 6 mars 2002 fixant les principes de bonnes pratiques de laboratoire et la vérification de sa

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besluit van 6 maart 2002 tot vaststelling van de beginselen van goede laboratoriumpraktijken en het toezicht op de uitvoering ervan bij proeven op scheikundige stoffen, zijn onderworpen aan voorafgaandelijk door de aanvrager te betalen vergoedingen.

§ 2. Het bedrag van de vergoedingen is afhankelijk van de aard en het volume van de inspecties en andere noodzakelijke activiteiten.

Art. 2. Elke aanvraag voor het bekomen of de verlenging van een certificaat die verklaart dat de goede laboratoriumpraktijken worden nageleefd, ingediend door een laboratorium, is onderworpen aan de betaling van een vast en niet terugvorderbaar dossierrecht van 375 euro.

Art. 3. Het uurtarief op basis waarvan de federale autoriteit voor het toezicht op de naleving van goede laboratoriumpraktijken de te betalen vergoeding voor het uitvoeren van inspecties en studie-audits bepaalt, is vastgesteld op 90 euro per persoon.

Het bovenvermeld uurtarief is van toepassing bij het uitvoeren van inspecties en studie-audits inzake elk verzoek tot het bekomen, het verlengen of het uitbreiden van certificaten die verklaren dat de goede laboratoriumpraktijken nageleefd worden, alsmede op de verificatie waaraan de laboratoria met een status van naleving van de goede laboratoriumpraktijken zijn onderworpen.

Voor elke aanvraag maakt de federale instantie bevoegd voor het toezicht op naleving van de goede laboratoriumpraktijken een gedetailleerde prijsofferte.

Art. 4. De reiskosten veroorzaakt ter gelegenheid van een inspectie van goede laboratoriumpraktijken zijn ten laste van de aanvrager en worden berekend op basis van de bedragen die door het koninklijk besluit van 20 juli 2000 houdende algemene regeling inzake reiskosten voorzien zijn.

Art. 5. Onze Minister van Consumentenzaken, Volksgezondheid en Leefmilieu is belast met de uitvoering van dit besluit.

Gegeven te Brussel, 6 maart 2002.

mise en application pour les essais effectués sur les substances chimiques, sont soumises à des redevances payables, anticipativement, par le demandeur.

§ 2. Le montant des redevances dépend de la nature et du volume des inspections et autres activités nécessaires.

Art. 2. Toute demande d'obtention ou de prolongation d'un certificat démontrant l'application des bonnes pratiques de laboratoire, introduite par un laboratoire, est soumise au paiement d'un droit de dossier, fixe et non récupérable, de 375 euros.

Art. 3. Le tarif horaire sur base duquel l'autorité fédérale de vérification en matière de bonnes pratiques de laboratoire détermine la redevance à payer pour l'exécution d'inspections et de vérifications d'études, est fixé à 90 euros par personne.

Le tarif horaire ci-dessus est d'application pour l'exécution d'inspections de laboratoire et de vérification d'études relatives à toute demande d'obtention, de prolongation ou d'extension des certificats pour l'application des bonnes pratiques de laboratoire ainsi que pour la vérification à laquelle sont soumis les laboratoires ayant un statut d'application des bonnes pratiques de laboratoire.

Chaque demande fait l'objet d'une offre de prix détaillée émanant de l'autorité fédérale de vérification en matière de bonnes pratiques de laboratoire.

Art. 4. Les frais de parcours engagés à l'occasion d'une inspection de bonnes pratiques de laboratoire sont à charge du demandeur et sont calculés sur la base des montants prévus par l'arrêté royal du 20 juillet 2001 portant réglementation générale en matière de frais de parcours.

Art. 5. Notre Ministre de la Protection de la Consommation, de la Santé publique et de l'Environnement est chargée de l'exécution au présent arrêté.

Donné à Bruxelles, le 6 mars 2002.

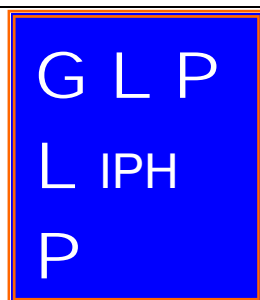
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**ANNEX 4 : CONFIDENTIALITY CLAUSE**



GLP INSPECTOR / EXPERT  
SUPPLIER

**THIS CONFIDENTIALITY CLAUSE MUST BE COMPLETED PRIOR TO TAKING PART IN ANY PREPARATION FOR OR ACTUAL GLP INSPECTION ACTIVITY OR TO HAVE ACCESS TO ANY DOCUMENT OF THE GLP COMPLIANCE MONITORING PROGRAM**

I, ..... (Name) do hereby declare that I will not disclose any information gained during the execution of my duties to any person or organization. I also declare that I am fully aware of the "Ownership and Confidentiality" and "Disclosure, Competition and Private work" provisions of the "Independent Contractor Agreement" concluded between myself and the Belgian GLP Monitoring Authority IPH.

**Organization:**  
**Location:**

**Name, date and signature of IPH responsible:**

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**ANNEX 5 : CERTIFICATE OF GLP INSPECTOR**

**Certificaat van een gekwalificeerd GLP inspector**  
**Certificat d'un inspecteur BPL qualifié**



**WETENSCHAPPELIJK INSTITUUT VOLKGEZONHEID**  
**INSTITUT SCIENTIFIQUE DE SANTE PUBLIQUE**

**VORMINGSCERTIFICAAT / CERTIFICAT DE FORMATION**

**Met betrekking tot de evaluatie van de conformiteit van laboratoria met de  
criteria van de OESO Principes van GLP**  
**Concernant l'évaluation de conformité des laboratoires avec les critères des  
Principes de BPL de l'OECD**

**BEVRET VAN GEKWALIFICEERD GLP INSPECTEUR**  
**BREVET D'UN INSPECTEUR BPL QUALIFIE**

**OVERGEMAAKT AAN**  
**OCTROYE A**

**NAAM INSPECTEUR**  
**NOM DE L'INSPECTEUR**

**DATUM**  
**DATE**

**Dr. J. PEETERS**  
**General Director**



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**ANNEX 7: STANDARD FORM OF TEST FACILITY'S GLP ACTIVITIES**

Identity of chemicals (categories)	Industrial chemicals	Pharmaceuticals	Veterinary Medicinal Products	Pesticides	Food Additives	Feed Additives	Cosmetics	Biocides	Other Products (specify)
Physical-chemical testing  Toxicity studies  Mutagenicity studies  Environmental toxicity studies on aquatic and terrestrial organisms  Studies on behaviour in water, soil and air; bioaccumulation  Residue studies  Studies on effects on mesocosms and natural ecosystems  Analytical and clinical chemistry testing  Other studies; specify :									

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**ANNEX 8: MASTER SCHEDULE OF ANNUAL GLP MONITORING PROGRAMME**

TEST FACILITY	AREA OF EXPERTISE	INSPECTIONS		REMARKS
		Date and period of inspection	Composition Inspection Team	
Name and address Former name (if applicable) and date of name change	1 - 9 If 9 (other) please specify			

Approved by Dr. Johan Peeters  
General Director IPH



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**ANNEX 10 : STANDARD FORM GLP PRE-INSPECTION PROGRAMME**

**GLP PRE-INSPECTION PROGRAMME**

Test Facility  
date of pre-inspection

**09h00-09h30 : STARTING CONFERENCE**

- \* Introduction
- \* Outline of purpose and scope of the visit
- \* Presentation by Test Facility's management
- \* Designation of accompanying persons

**09h30-10h00 : SCOPE OF GLP ACTIVITIES**

**10h00-12h30 : MANAGEMENT STRUCTURE OF THE TEST FACILITY**

- \* Organization chart
- \* Documentation :
  - Master schedule studies
  - Study plans
  - SOPs
  - Study reports
  - Master schedule QA programme

**12h30-13h30 : LUNCH**

**13h30-16h30 : VISIT TO THE FACILITY**

- \* Infrastructure
- \* Archives
- \* Equipment
- \* Test and reference substances
- \* Test systems

**16h30-17h00 : EXIT MEETING**

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**ANNEX 11 : STANDARD FORM GLP INSPECTION PROGRAMME**

**GLP INSPECTION/STUDY AUDIT PROGRAMME**

Test Facility

date of GLP inspection

**FIRST DAY**

**09h00-09h30 : STARTING CONFERENCE**

- \* Introduction
- \* Outline of purpose and scope of visit
- \* Approval of inspection/study audit program
- \* Designation of accompanying persons

**09h30-12h00 : INSPECTION and STUDY AUDITS**

- \* Organization and personnel
- \* Documentation
- \* QA program
- \* Archives

**12h00-12h30 : INTERNAL DISCUSSION INSPECTION TEAM**

**12h30-13h30 : LUNCH**

**13h30-16h30 : INSPECTION and STUDY AUDITS (continue)**

- \* Facilities
- \* Equipment
- \* Test and reference substances
- \* Test systems
- \* Performance

**16h30-17h00 : INTERNAL DISCUSSION INSPECTION TEAM**

**17h00-17h30 : INTERIM EXIT MEETING WITH MANAGEMENT (if necessary)**

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**ANNEX 11 : STANDARD FORM GLP INSPECTION PROGRAMME**

**GLP INSPECTION PROGRAMME**  
Test Facility  
date of GLP inspection

**SECOND and FOLLOWING DAYS**

09h00-12h00 : STUDY AUDIT  
12h00-12h30 : INTERNAL DISCUSSION INSPECTION TEAM  
12h30-13h30 : LUNCH  
13h30-16h00 : STUDY AUDIT (continue)  
16h00-16h30 : INTERNAL DISCUSSION INSPECTION TEAM  
16h30-17h00 : INTERIM EXIT MEETING WITH MANAGEMENT

**LAST DAY**

09h00-12h30 : PREPARATION OF THE GLP INSPECTION REPORT  
12h30-13h30 : LUNCH  
13h30-16h30 : PREPARATION OF THE GLP INSPECTION REPORT  
16h30-17h00 : FINAL EXIT MEETING WITH MANAGEMENT

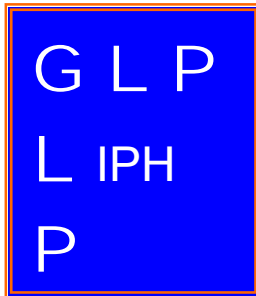
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ANNEX 12 : STANDARD FORM GLP COMPLIANCE STATEMENT



## STATEMENT OF GLP COMPLIANCE

### Registration number

*Date of inspection:*

Assessment of conformity with GLP according to the directive 2004/9/EEC on .....

According to the criteria specified in the article 9 of the Royal Decree of March 6, 2002 the General Director of the Scientific Institute of Public Health, endorses on the advice of the Bureau of Quality Assurance, that the Test Facility

## NAME AND ADDRESS OF THE TEST FACILITY

carries out (*scope*) and (*area of expertise*) with respect to the OECD and the EU principles of Good Laboratory Practices.

Brussels,  
Date

Dr. J. Peeters  
Head of GLP Monitoring Authority

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*Scientific Institute of Public Health, Juliette Wytsmanstreet 14, 1050 Brussels*  
*Phone : 0032-2/642.51.11*  
*Fax : 0032-2/642.50.01*



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**ANNEX 14: ANNUAL GLP MONITORING REPORT**

TEST FACILITY	AREA OF EXPERTISE	INSPECTIONS		CURRENT STATUS	REMARKS
		First	Last		
<b>Name and address</b> Former names (if applicable) and dates of name change	1 - 9 If 9 (other) please specify	Date of inspection Nature of inspection Status after inspection	Date of inspection Nature of inspection Status after inspection	Current status	explanation about pending status, details about particular inspection, date of modification of the area of expertise, date of removal from monitoring programme, other