BELGIAN GLP COMPLIANCE
MONITORING PROGRAM
MANUAL

GLP MONITORATE
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1 **OBJECT**

This manual describes the organization of the Belgian Good Laboratory Practice Compliance Monitoring Program, the requirements for the Test Facilities requesting verification of compliance to the OECD Principles of GLP and the mechanism and conditions under which Test Facility Inspections and Study Audits are conducted.

2 **SCOPE**

The Belgian GLP Compliance Monitoring Program is set up to ascertain that Test Facilities apply the OECD Principles of Good Laboratory Practice (GLP) to the non-clinical safety testing of test items.

The Royal Decree of 6 March 2002 defines that the OECD 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. Other products such as biocides, detergents, novel foods, genetic modified organisms and medical devices can also be verified for GLP Compliance if required by national or international legislation.

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 OECD Principles of Good Laboratory Practice include work conducted in the laboratory, in greenhouses, and in the field.

It includes audits of data of physical-chemical studies, toxicity studies, mutagenicity studies, environmental toxicity studies on aquatic and terrestrial
organisms, studies on behaviour in water, soil and air, bioaccumulation studies, studies on effects on mecosoms and natural ecosystems, analytical and clinical chemistry testing, field trials, residue testing of chemicals, pharmacodynamic, pharmacokinetic, biodistribution, toxicokinetic, safety pharmacology, validation studies for virus deactivation or removal, histopathology and other studies as long as clear guidelines for testing are available accepted by the Receiving authorities.

3 ABBREVIATIONS
BQA: Bureau of Quality Assurance
GLP: Good Laboratory Practice
IPH: Scientific Institute of Public Health
MA: Monitoring Authority
OECD: Organization of Economic Development
SOP: Standard Operating Procedures
Website: www.GLP.be or www.wiv-isp.be/glp/
4 COMPLIANCE MONITORING PROGRAM

4.1 Organisation

4.1.1 Legal framework

The Minister of Public Health is the representative of the Government responsible for the designation of the GLP Monitoring Authority in Belgium. The Royal Decree of 27 October 1988, modified by the Royal Decree of 6 March 2002, defines that the Institute of Hygiene and Epidemiology, renamed as “Scientific Institute of Public Health” (IPH), is the only GLP Monitoring Authority in Belgium.

The Compliance Monitoring Program covers all the sectors as mentioned in the scope of the Royal Decree of 6 March 2002.

According to the article 2 of the Royal Decree and the criteria mentioned in 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

• Guidance for GLP Monitoring Authorities – Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice – Environment monograph N°110 (References, 7.4)
• Guidance for GLP Monitoring Authorities – Revised Guidance for the Conduct of laboratory Inspections and Study Audits – Environment monograph No 111 (References, 7.5)
• Guidance for the Preparation of GLP Inspection Reports – Environment monograph No 115 (References, 7.13)
• Council Decision concerning the Adherence of Non-member Countries to the Council Acts related to the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final) and C(89)87(Final)] [C (97) 114/Final] (References, 7.20)
The application of Good Laboratory Practice in safety testing of chemicals is required under several directives or regulations of the European Union (EU) (7.24)

The application of Good Laboratory Practice in safety testing of chemicals is laid down in different regulations in Belgium. The different Regulatory Authorities responsible for the scientific evaluation of the results of testing of chemicals requiring the application of the OCED Principles of GLP are:

- The Committee for the Registration of Dangerous Substances (DG5 – 67/548/EEG –REACH 2006/121/EG)
- The Committee for the Registration of Plant Protection Products (DG4 – 91/414/EC)
- The Committee for the Registration of Biocides (DG5 – 98/8/EC)
- The Committee for the Registration of Pharmaceutical Products (FAMHP – 91/507/EEG)
- The Committee for the Registration of Veterinary Drugs (FAMHP – 92/18/EEG)
- The Committee for the Registration of Detergents (DG5 – Regulation No 648/2004/EC)
- The Committee for the Registration of Novel Foods (DG4 – Regulation No 258/97)
- The Committee for the Registration of Genetic Modified Organisms (DG4 – 2001/18/EC)
- The Committee for the Registration of Cosmetic Products (DG4 – 93/35/EEC)
- The Committee for the Registration of Food Additives (DG4 – 93/99/EEC)
- The Committee for the Registration of Feed additives (DG4 – 87/153/EEC)
- The Committee for the Registration of Medical Devices (FAMHP – 93/42/EG)

The Directive 2004/9/EC (ref. 7.6) specifies further that special test facility inspections/study audits can be placed on the national GLP Monitoring program at the request of a Regulatory Authority, for example, prompted by a query arising from the submission of data to a Regulatory Authority.

4.1.2 Organisational structure

The Scientific Institute of Public Health is a part of the Federal Public Service
Health, Food Chain Safety and Environment.

The Institute is a governmental non-profit and fully independent organization. The Director General of the Institute has the final responsibility for the GLP Compliance Monitoring Program. He is especially charged with the approval of the "Statement of GLP Compliance" of the Test Facilities and the treatment of the appeals submitted by the Test Facilities.

The Bureau of Quality Assurance (BQA) directly depends of the Director General. The QA Manager is responsible for the daily management of the Quality Assurance of the IPH and directly reports to the Director General. The position of the BQA in the organization structure of the Scientific Institute is presented in the organization chart (DOC 00/NF/04) of the IPH.

The GLP Compliance Monitoring Program (GLP Monitorate) is integrated in the BQA and is managed by the GLP Coordinator. He directly reports to the Director General and to the QA Manager. The position of the GLP Monitorate is presented in the organization chart of the BQA (DOC 03/NF/0303).

Taking into account that the GLP Compliance Monitoring Program is one of the programs of the BQA the exchange of information with the program Quality Management System (ISO 17025, ISO 9001, ISO 17020) is strongly maintained to innovate and to set quality criteria in the different quality systems of the Institute.

The GLP Monitoring Authority consists of the General Director of the IPH, the GLP Coordinator, and the designated GLP inspectors. The responsibilities of each member of the BQA and deputies in the functioning of the GLP Monitorate are described in DOC 03/NF/0301.

4.1.3 Operation

The daily management and operation of the GLP Compliance Monitoring Program are written down in the Belgian GLP Compliance Monitoring Program Manual which is approved by the General Director of the Institute,
and the GLP Coordinator.

It includes:

- the organization and conduction of GLP inspections and study audits (see § 4.4.2 & § 4.4.3);

- 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 (see § 4.4.1);

- the publication of documents relating to the adoption of GLP principles within its territory;

- the publication of the Belgian GLP Compliance Monitoring Program Manual containing instructions for GLP verification and accreditation;

- the publication of documents concerning the management and operation of the GLP Compliance Monitoring Program;

- the content and update of the Website 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. (see §6. Archives)

The GLP MA also acts as a contact point and provides information, advice and guidance to the industry concerned, Test Facilities, Sponsors of studies on any aspect of GLP.

Cooperation with the GLP Monitoring Authorities of other OECD member countries is carried out by organizing or participating in joint inspections of facilities on the request of national and international Regulatory Authorities and other OECD GLP Monitoring Authorities.

The Monitoring Authority has a good relationship with the Belgian Receiving Authorities. 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 Monitoring Authority and Regulatory Authorities.

4.2 Confidentiality

All the personnel associated with the GLP Compliance Monitoring are permanent members of the Institute of Public Health and are covered by Civil Administration rules with respect to confidentiality. Inspectors may not have direct financial or other interests in the Test Facilities inspected, the studies audited or the firms sponsoring such studies.

During the inspections and study audits the inspectors may require having access to confidential and commercially valuable information.

The Belgian GLP Monitoring Authority maintains a high level of confidentiality in its operations. To ensure this, the following deontological code is applied:

- The Belgian GLP Monitoring Authority has to communicate the test facility manager the names of inspectors and, if appropriate, of observers of other GLP Monitoring and Regulatory Authorities participating to the Test Facility inspection at least three weeks before the start of the visit.
- 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 a demand for replacement can be sent. The arguments for replacement have to be addressed in writing to the Director General of the IPH and justified.
- The inspectors and observers will present themselves at the Starting Conference of the GLP inspection and show their identity card at the request of the Test Facility.
- If observers participate to GLP inspections a confidentiality clause should be signed and dated by them before the start of the inspection. The original will be kept in the Monitoring Authority files, but a copy can be given to the test facility on request.
- Information about the Belgian GLP Compliance Monitoring Program is available on the GLP Website (Royal Decrees, GLP Compliance
Monitoring Program Manual, annual reports, certified test facilities etc.) 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 GLP Coordinator, the GLP inspectors and the Receiving Authorities concerned.

- Information about the inspections and study audits undertaken in Test Facilities can be asked by other national Compliance Monitoring Programs. However, copies of documents from test facilities are only available at request and with the explicit permission of the Test Facility.

- Copies of any document removed from the Test Facility before, during and after the inspections are uniquely marked. The inspection report should contain in annex a list of copied documents that have been referenced in the report.

- All the original and electronic documents of the Belgian GLP Compliance Monitoring Program are stored in a closed cupboard in the office of the GLP Coordinator for a period of 3 years or one inspection cycle. The Director General of the Institute, the GLP Coordinator and the GLP inspectors has access to the documents. Thereafter, the documents will 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 GLP Coordinator, the GLP inspectors and the archivist has access to the documents maintained in the archives of the Institute.

See further also references 7.21 or 7.22 concerning the deontology of Belgian Civil agents.

4.3 **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. Where necessary, inspectors may be supported by technical experts of operational departments
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 GLP Monitorate.

The required qualifications for the GLP inspectors are the following:

- The inspectors must be employees of the Scientific Institute of Public Health
- The inspectors must be scientifically and academically qualified,
- The inspectors are required to have an in-depth knowledge of the OECD Principles of GLP and the requirements necessary to comply with those principles. New inspectors will follow a theoretical and practical training documented and supervised by the GLP-Coordinator.
- The experts contracted must have knowledge of the OECD Principles of GLP and should be scientifically and academically qualified in the studies to be audited.

4.4 The National GLP Compliance Monitoring Program

4.4.1 Request for verification

The GLP Compliance Monitoring Program is intended to monitor good laboratory practice compliance by test facilities within its territories, by means of inspections and study audits. 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, ecotoxicological, field trials and residue testing of chemicals, such as industrial chemicals and industrial preparations, pharmaceuticals, veterinary drugs, phytopharmaceuticals, food and feed additives and cosmetics. Other sectors such as biocides, detergents, novel foods, genetic modified organisms and medical devices are also covered by
Good Laboratory Practice and inspected by the GLP Monitoring Authority.

According to article 5, §1 of the Royal Decree of 6 March 2002 (Annex 2) a Test Facility, should introduce a request by Test Facility Manager, with regards to the verification of GLP compliance:

via post mail to Scientific Institute of Public Health:

At the attention of the Director General Dr. Johan Peeters,

Rue Juliette Wytsmanstraat 14,
1050 Brussels, Belgium

or by e-mail

to: Johan.Peeters@wiv-isp.fgov.be,

cc: Guido.Jacobs@wiv-isp.fgov.be

A standard form (Annex 2, available on the GLP website) with the sectors and the area of expertise covered by their GLP activities should be included.

The request will internally be transferred to:

The GLP Monitorate (Bureau of Quality Assurance)

Contact info: Guido Jacobs- GLP coordinator; Phone: 0032-(0)2 642.52.30 (or 51.86); Fax: 0032-(0)2 642.52.27

The GLP Coordinator charged with the investigation and treatment of the request will add the Test Facility to the GLP Compliance Monitoring Program.

Special Test Facility inspections/study audits, in Belgium, may be monitored at the request of a foreign GLP Monitoring Authority or national or international Regulatory Authorities. In such cases the Regulatory Authority or the foreign GLP Monitoring Authority shall justify the need of such inspections.
and study audits.

Test Facility inspections/study audits, of test facilities located in non-adherent OECD member countries, may be monitored at the request of a national or international Regulatory Authorities. In such cases the Regulatory Authority shall justify the need of such inspections and study audits.

Test Facilities for which a Regulatory Authority or other OECD GLP Monitoring Authority requests a verification of GLP compliance are also added to the GLP Compliance Monitoring Program.

If it is necessary for a Test facility (Belgian or abroad) to use a test site that is not included in a national GLP compliance monitoring program or is located in a non-adherent OECD member country, GLP inspections can also be programmed in those facilities. In this case the test facility management has to provide a rationale for this selection. If the test facility is located itself in a non-adherent OECD member country they have to provide evidence that Sponsors of audited studies will send their registration dossiers to a Belgian regulatory authority or to an European Agency.

Inspectors will not enter Test Facilities, or attempt to gain access to data held by a Test Facility without prior agreement with the Test Facility Management and, where appropriate, the sponsors of the studies. However, during the inspections they may ask any kind of information needed to verify the integrity of the study. Also in cases where national or foreign Regulatory Authorities and/or foreign GLP 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 those 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 Director General of the Institute to withdraw the GLP status of the Test Facility. This proposal should be justified by documented facts.

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.

Test Facility Management is also reminded that legislation exists which controls the use of animals in experiments. Test facilities should follow the laws about “animal welfare” of their country.

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. A tender is sent to the Test Facility together with the announcement and agenda of the GLP inspection at least three weeks before the inspection. Urgent remarks or concerns about those documents should be reported (by phone, and/or e-mail) to the GLP coordinator within one week.

4.4.2 The inspection process

4.4.2.1 Master schedule of GLP inspections

An inspection plan is yearly established and contains information on the name of the Test Facility, the period of inspection, the composition of the inspection team, the area of expertise and remarks.

This GLP Compliance Program includes pre-inspections, full inspections including 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.

- During the Test Facility inspection not only the organization of the Test Facility but also on-going and completed studies are verified. If major deviations have been found during an audit of a delegated phase in a test site a verification of the whole study with the study director in the test facility can be programmed.

Each Test Facility is inspected every two to three years. The test facility management has the obligation to inform the GLP Coordinator about any important change in his operational or functional structure (e.g. extension of scope, new test systems, new location, change in TFM, new study directors, change in QAM...). If serious changes concerning the organization, infrastructure, sector or area of expertise happen in the Test Facility the GLP Monitoring Authority can decide to bring forward a GLP inspection.

4.4.2.2 Pre-inspection

If the Test Facility has to be inspected for the first time a pre-inspection is carried out, except when it is not practical relevant (e.g. Test facility is located abroad Belgium).

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 the Test Facility. The announcement of the GLP pre-inspection and the pre-inspection program will be sent by letter to the Test Facility about two weeks before the start of the visit. The GLP coordinator 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 one day.

The pre-inspection starts with an opening session at which the GLP Coordinator 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. Only data of pre-clinical testing of chemicals for regulatory purposes (ref. 7.3) will be considered in the GLP Compliance Monitoring Program.

The Test Facility will be inspected about the documentation and organisation 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.

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 within three weeks. A formalised action plan on this report is not requested, but Test Facility should take appropriate corrective actions before submitting his demand for a full inspection.

A test facility inspection and study audits are programmed within a delay of 6 till 12 months. If the full inspection is not executed within 12 months after the pre-inspection the Test Facility is removed from the program and the whole procedure should be restarted.

For a full test facility inspection to be realised successfully the following conditions should be fulfilled:

- The deviations observed during the pre-inspection should have been corrected

- At least 2 studies (effective or simulated), including at least one study in each area of expertise and the compilation of a final report according to the GLP-principles. If real GLP studies are elaborated, they should be taken up already in the master schedule as GLP studies before the start of the study. However these studies can not be reported as GLP study until the test facility has been declared as GLP compliant.
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 (see 7.5).

Inspections and study audits will be carried out at the request of the Test Facility itself or at the request of a Regulatory Authority or a foreign GLP Monitoring Authority.

A first announcement with dates of the GLP inspection will usually be sent to the Test Facility about eight weeks before the start of the visit. The Test facility will be asked to send his master schedule of the last 3 years, the list of the ongoing studies planned during the inspection period, the key persons that will be absent during this period and the names of their deputy, as well as possible remarks on the proposed date of inspection within 3 weeks after receiving the announcement.

The definitive announcement of the GLP inspection, the inspection program and the tender will be sent to the Test Facility about three weeks before the start of the visit. The inspection program informs the Test Facility about the date and time of inspector’s arrival, the composition of the inspection team, the aspects to be inspected and discussed and the length of time foreseen for the visit of the premises and the study audits. The inspection takes at least 3 days including the opening session and Test Facility inspection, study audits, preparation of the inspection report and the exit meeting. The length of the inspection can be extended during the inspection with one or more days depending upon the size of the Test Facility and the number of study directors and GLP studies to be audited, or in case of unforeseen workload. Alternatively the number of inspector can be increased.

The Test Facility can ask the replacement of some members of the inspection/observers 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 Director General of the IPH and justified.

It is absolutely necessary that a member of the management is present at the
opening and closing meeting. During the inspection it is advisable 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. It is expected that documents asked from the archive will be delivered within a reasonable time. Copies of documents or records may be asked 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. Thereafter, Test Facility Management is asked to give a general presentation about the organization and the activities of the Test Facility. Then, the inspection program is fixed, the selected studies are communicated, the documentation required for the test facility inspection 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. Therefore, inspectors try to obtain a general view of the documentation, organisation and personnel 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. Moreover, it is not the task of the inspection team to perform a scientific evaluation of the data from the studies, their design or the suitability of the test systems used for the purposes of the study. However, if deficiencies are observed from the scientific point of view they will be communicated to the Regulatory Authority which dealt with.

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 items to be inspected according to the guidance for the conduction of Test Facility Inspections and the questions prepared in advance are the basic instruments of the GLP inspectors to notify their findings (7.5). During the inspection the criteria described in the OECD Consensus and Advisory Documents are also taken into consideration, if appropriate (7.8 – 7.12, 7.14 – 7.19). Finally the requirements mentioned in the present Belgian GLP Compliance Monitoring Program Manual Addendum
1, should be applied by the Test Facility and shall be verified by the GLP inspectors.

During or at least within one week after the last day of 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 seriously jeopardise 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 yet resulted in a serious impact on the functioning of the GLP quality or on the integrity of study data, but corrective actions are necessary.
  
  **B*:** the Test Facility should take sufficient corrective action within 30 days after the receipt of the provisional report and justify it by documentary evidence.

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

- **No deviation, (A):** finding written down by the inspector is in compliance with the Principles of GLP.

- **No observation, (D):** the GLP Principle was not applicable and therefore could not be verified.

When several major deviations are observed during the inspection, the lead inspector can decide to close the inspection earlier than planned, to audit supplementary studies or to expand his team with supplementary inspectors or experts. This 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. Generally the studies will be selected to cover as many study director/principle investigators as possible and different test systems. During the inspection the normal work in the Test Facility may be disturbed. Inspectors will try to minimize this disturbance as much as
possible.

The full inspection will be concluded with an exit meeting during which a written list of GLP deviations noted by the inspection team will be presented. The test facility management should acknowledge the inspectors' findings and make a commitment to take corrective actions. The listing is signed and dated by the lead inspector and handed over to the Test Facility Management who signs and dates for receipt.

Within a week after the inspection the findings of the inspection team are written down in a more extensive provisional report, and sent to the Test Facility Management. Not only are the deviations from GLP principles written down, but also the strong points of the GLP system of the Test Facility.

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 (one inspection cycle) in a closed cupboard of the office of the GLP Coordinator and then transferred to the central archives of the Institute where it stays for a period of seven years.

4.4.2.4 Re-inspection

If the Test Facility receives C deviations during the inspection a re-inspection should be programmed. Two types of re-inspection can be carried out:

- Re-inspection by documentation. The reply given by the Test Facility to the deviations written down in the provisional report are justified by documentary evidence and evaluated by the inspection team.

- Re-inspection at the test site. The reply given by the Test Facility requires a visit at the test site to evaluate if the corrective actions are correctly implemented.

For a re-inspection at the test site, the Test Facility receives a re-inspection
program at least three weeks before the visit.

4.4.3 Follow-up to Test Facility Inspections and Study Audits

4.4.3.1 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 GLP inspector.

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.

4.4.3.2 Test Facility Inspection, Study Audit and Re-inspection

A provisional inspection report is prepared within a week after the Test Facility inspection, study audit or re-inspection and sent to the Test Facility Management. The provisional inspection report is established according to the instructions of the OECD Environment Monograph N°115 “Guidance for the preparation of GLP inspection reports” (7.13) 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 date; and a list of copies of documents that have been referenced in the report. Annexes to the report as specified in the GLP consensus document "Guidance for the preparation of GLP inspection reports" (ref 7.13) will be coded, scanned and stored as a pdf-file but will be sent only on demand.

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 to categorise the findings;

The Test Facility should give its comments to the deviations in writing a reply within 30 days after the receipt of the inspection report. The reply should be sent to the GLP coordinator (by e-mail, CD-rom or on paper). 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.

- The corrective actions taken for the C and B* deviations should be justified by documentary evidence within 30 days after the receipt of the inspection report. The inspector should give his comments to each corrective action proposed by the Test Facility. The inspector will re-contact the TFM in the cases for which he expects more specific evidence.

If 3 months after the inspection the proposed documentary evidence is still not sufficient to assess the corrective action a final report of the inspection will be made but a re-inspection at the Test Facility will be programmed.

- The corrective action proposed for the minor deviations B will be verified for implementation at the next inspection.

The comments and the decision taken by the inspector are integrated in the inspection report, version 3 (= final inspection report).

The final inspection report will be prepared within four weeks after receiving satisfying corrective actions of the Test Facility to the inspection report.

The final inspection report, including the conclusions of the inspection, is signed by the GLP Coordinator and sent to the Test Facility and the national Receiving Authority concerned. If a special request for inspection or study audit from a national or foreign Receiving or Monitoring Authority is received a final inspection shall be drafted according to the requirements of the OECD Environment Monograph No.115.(7.13)
4.4.3.3 GLP Statement

The three following categories of compliance status are used:
- test facility in pending
- test facility not in compliance
- test facility in compliance

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”. The GLP Coordinator or lead inspector can decide that 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 final 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 Program;

When major deviations (C) are observed during the Study Audits for which corrective actions cannot be taken by the Test Facility and/or test site the GLP Monitoring Authority shall judge the study as not in compliance with the OECD Principles of GLP. In such cases the Belgian GLP Monitoring Authority shall acknowledge the non compliance of the GLP study to the OECD and EU secretariat and to the national and foreign receiving authorities concerned. The Test Facility is obliged to make within one week an amendment to the GLP statement of the study report, detailing the deviations.
A non-compliance GLP study doesn’t necessarily mean that the GLP quality system of the Test Facility is not functioning anymore. It should be evaluated case by case.

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 OECD Principles of GLP.

The statement of GLP compliance (see annex 3) will include: the GLP logo of the Belgian GLP Monitoring Authority; name and address of the Test Facility; identification number of the Test Facility in the GLP Compliance Program; periods or dates of inspection; area of expertise for which the Test Facility is in compliance with GLP principles; signature of the General Director of the IPH (Head of the GLP Monitoring Authority); date of signature.

This statement is sent to the Test Facility together with the final inspection report. The statement is valid for 3 years after the date of signature, unless otherwise indicated. The test facility has the right to refer to the statement on his website or official documents, or to make a reference to the official website of the Belgian Monitoring Authority (www.GLP.be/Labs.htm) where the GLP statements are reported.
4.4.3.4 Extension of the scope

When an extension of the scope is foreseen, the GLP Monitoring authority should be contacted. At least one effective or simulated study according to the new area of expertise should be elaborated. The study plan should be sent to the GLP coordinator together with the inspection days foreseen by the Quality Assurance of the critical phases. Based on this info, experience of test facility and type of study, the GLP Monitoring Authority will decide if an inspection of the test facility is needed during the execution of this study. After the study a study report should be sent to the GLP coordinator for auditing. If effective GLP studies are elaborated, they should be taken up in the master schedule as GLP studies before the start of the study. However these studies can not be reported as GLP study until the test facility has received an update of the GLP statement including the new area of expertise.

4.4.3.5 Reduction of the scope

A test facility has to show at each inspection that enough experience remains in all certified areas of expertise. If the test facility management doesn’t plan to do studies anymore in a specific area of expertise, this should be documented and reported promptly to the Monitoring Authority. At the next inspection the remaining studies within this area will be verified, after which the scope will be adapted.

4.4.4 Rights and Duties

The Bureau of Quality Assurance archives their GLP documents, the original version of the final inspection report and accompanying documents at least for 10 years. After this period it can be decided which documents shall be further archived and which ones will be destroyed.

A copy of the final inspection report is sent to the Test Facility, the Responsible of the GLP Monitoring Authority and to the Regulatory Authority.
concerned. Copies can be available on request to observers but only 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 the OECD Principles of GLP 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 Test Facility Management, QA Management, Study Directors, infrastructure of the Test Facility, or scope of studies conducted is significantly changed or extended, Test Facility has the obligation to inform these changes to the GLP Monitoring Authority within one month.

The GLP Monitoring Authority is responsible to accept studies performed according to the OECD Principles of GLP. The responsible Regulatory Authority decides if a study is acceptable after scientific evaluation. 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 found to be in compliance with OECD Principles of GLP. If a study has not been performed according to the OECD Principles of GLP the GLP Monitoring Authority will inform its Regulatory Authorities and the GLP Monitoring Authorities of the OECD Member Countries.

4.4.5 Communication and information

In order to facilitate the communication between sponsors, Test Facilities, OECD and EU secretariat, Regulatory and Monitoring Authorities inlands or abroad the Belgian GLP Monitoring Authority can provide information on inspections to the interested parties in three forms:

- the conclusions of an GLP 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;
- the list of Belgian Test Facilities in compliance with GLP principles (see website www.glp.be/Labs.htm);
- the Annual GLP monitoring report including the Test Facilities inspected and their GLP status.

4.5 Appeal 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 Director General of the IPH within 30 days after the date of this decision taken. The Director General of the IPH will then take appropriate steps to achieve a mutually acceptable resolution. Therefore, he can ask the advice of the GLP Coordinator, independent internal or external experts. Based on this advice the Director General of the IPH 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.

Following Decision C(97)186/Final of the OECD Council (ref. 7.20), 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 all other OECD Member Countries.

Non-OECD Member countries can apply for Adherence to the OECD System for Mutual Acceptance of Data. An up-to-date list of full adherents to the MAD-system can be found on the OECD website. (ref 7.24)

OECD inspections of test facilities located in non-adherent OECD member countries

The Belgian Monitoring Authority can send inspectors at the request of regulatory authorities or test facilities to verify the accuracy of a compliance statement of a test facility in a non-member country.

An inspection in non-member economies by OECD inspectors will not guarantee that, if they are found to be in compliance, their data will be accepted in other member countries than the one to which they are submitting data and which has thus sent inspectors to verify the accuracy of their compliance statement.
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
- relevant 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
- relevant documents of correspondence with foreign authorities
- historical file of replaced documents (documents that have been superseded by new versions) from the Belgian GLP Compliance Monitoring Program
- historical file of the annual reports of the inspections and study audits performed
7 REFERENCES


7.2 The EU directive 87/18/ EEC, adapted by the directives 99/11/EC and 2004/10/EC, concerning the application of Good Laboratory Practice and the verification of their application to testing of chemicals. Official Journal of EU N° L 15 of 17/01/87, p.29.

7.3 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


7.15 Advisory Document: The Role and Responsibilities of the Sponsor in the


7.20 Council Decision concerning the Adherence of Non-member Countries to the Council Acts related to the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final) and C(89)87(Final)] [C (97) 114/Final]; http://webdomino1.oecd.org/horizontal/oecdacts.nsf/linkto/C(81)30

7.21 Omzendbrief nr. 573 van 17 augustus 2007 met betrekking tot het deontologische kader van de leden van het federaal administratief openbaar ambt." (Belgisch Staatsblad 27.08.2007, 44406-44413)

7.22 Circulaire n° 573 du 17 Aout 2007 relative au cadre déontologique des agents de la fonction publique administrative fédérale » (Moniteur Belge 27.08.2007, 44406-44413)

7.23 Non-Member Adherents to the OECD System for Mutual Acceptance of Chemical Safety Data http://www.oecd.org/document/53/0,3343,fr_2649_34365_38457461_1_1_1_1,00.html

8.1.1. 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.

**Interpretation:**

- **As soon as the study plan is signed by the study director, the study can start.**

- **It is recommended that Study Plans are also approved by Test Facility Management to comply with the following requirements:**
  - What means that they « approve » the selection of test sites. (Ref. 7.17)
  - “The overall management must have before signing the study plan a firm understanding and working agreement with the test site management as to how and by whom the quality assurance Programme will be carried out”. (Ref. 7.6)

- **It is recommended that the Study Plan is signed and dated by the Quality Assurance officer(s) (lead and test site QA) to comply with the following requirement:**
  - Verify that the study plan contains the information required for compliance with the Principles of Good Laboratory Practice. This verification should be documented. (II, 2.2.1b)

- **It is recommended that for multi-site studies, the Study Plan should also be approved by the Principal Investigators and Test Site Management to comply with the following requirement:**
  - There should be a documented agreement that the Principal Investigator will conduct the delegated phase in accordance with the study plan and the Principles of GLP. (ref. 7.17)

- **It is recommended that when the Sponsor is involved in the study, it**
is recommended that Study Plans are also approved by Sponsor to comply with the following requirements:

- 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. (ref 7.15)

- The sponsor should be aware that, if its site acts as a test site undertaking a phase(s) of a multisite study, its operations and staff involved in the study are subject to control of the Study Director. The Study director has to indicate the extent to which the study complies with GLP, including any work conducted by the sponsor. here (ref. 7.17)

- If parts of the study are contracted out to subcontractors by the sponsor, the sponsor should be aware that the responsibility for the whole study remains with the Study Director, including the validity of the raw data and the report (Ref. 7.15)

- If the characterisation of the test item will be conducted by the sponsor, this fact should be explicitly mentioned in the study plan. (ref 7.17)

8.1.2.a) Amendments to the study plan should be justified and approved by dated signature of the Study Director and maintained with the study plan.

Interpretation:

- **As soon as the amendment is signed by the study director, it can be applied.**

- **It is recommended that the amendments to the Study Plans are approved in the same way as the study plan.**

8.2.5 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).

Interpretation:

- **It is recommended to refer in the study plan to the standard operating procedures used related to the activities described in the**
**experimental design.**

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.

*Interpretation:*

- *It is recommended that on return to the archive, the records and materials should be verified by the archivist to be “complete and unaltered”. (ref. 7.19)*

- *It is recommended that the movement/transfer of documents should be monitored by the conduct of directed QA inspections (ref. 7.19)*
### ANNEX 2: STANDARD FORM OF TEST FACILITIES GLP ACTIVITIES

<table>
<thead>
<tr>
<th>Identity of chemicals (categories)</th>
<th>Industrial chemicals</th>
<th>Pharmaceuticals</th>
<th>Veterinary Medical Products</th>
<th>Pesticides</th>
<th>Food/Food Additives</th>
<th>Cosmetics</th>
<th>Blockers</th>
<th>Detergents</th>
<th>Novel Food</th>
<th>Genetic Modified Organism</th>
<th>Medical devices</th>
<th>Other Products (specify)</th>
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<td>Physical-chemical testing</td>
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<td>Environmental toxicity studies on aquatic and terrestrial organisms</td>
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<td>Other studies: (specify) pharmacodynamic, pharmacokinetic, pharmacogenomic, bio distribution, toxicokinetic, safety pharmacology, validation studies for virus deactivation or removal, histopathology</td>
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<td>Other GLP linked activities: (specify) Contract Archiving, Animal Breeding &amp; mating house, Electronic datamanagement, Computer program validation, Clinical Analysis, Bioanalytical part of bioequivalence trials</td>
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STATEMENT OF
GLP COMPLIANCE

Registration No: (code)

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

Date of inspection: (period of inspection)

According to the criteria specified in the article 5, § 8 of the Royal Decree of March 6, 2002 the General Director of the Scientific Institute of Public Health, endorses on the advice of the GLP Monitorate, that the Test Facility, Test Facility Address

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

The Test Facility will be regularly inspected within a cycle of 2 to 3 years.

Brussels, (date)

Dr. J. Peeters
General Director

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