BELGIAN GLP COMPLIANCE MONITORING PROGRAMME

MANUAL

M. BAETEN

WHO WE ARE

SCIENSANO can count on more than 700 staff members who commit themselves, day after day, to achieving our motto: Healthy all life long. As our name suggests, science and health are central to our mission. Sciensano's strength and uniqueness lie within the holistic and multidisciplinary approach to health. More particularly we focus on the close and indissoluble interconnection between human and animal health and their environment (the "One health" concept). By combining different research perspectives within this framework, Sciensano contributes in a unique way to everybody's health.
For this, Sciensano builds on the more than 100 years of scientific expertise of the former Veterinary and Agrochemical Research Centre (CODA-CERVA) and the ex-Scientific Institute of Public Health (WIV-ISP).

Sciensano

Services of the managing direction - Quality (bio)safety and environment

GLP

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ABBREVIATIONS

OECD	Organization of Economic Development
MAD	Mutual acceptance of data
BE	Belgium
GLP	Good Laboratory Practices
CMA	Compliance Monitoring Authority
EU	European Union
TFM	Test Facility Management
QA	Quality Assurance
SOP	Standard operating procedure

INTRODUCTION

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1. Object

This manual describes the organization of the Belgian Good Laboratory Practice Compliance Monitoring Programme, 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.
The GLP Compliance Monitoring Programme 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 or ecotoxicological studies, 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.

2. Scope

Good Laboratory Practice (GLP) is concerned with the organisational process and the conditions under which non clinical safety studies are planned, performed, monitored, recorded and reported. The principles of GLP are designed to apply to Test Facilities carrying out health and environmental safety studies on test items, including chemicals , biologicals, synthetic substances, natural, living organisms, transgenic organisms, items from complex industrial or biological processes, complex mixtures or part of them, where the results are to be submitted to Receiving Authorities. These authorities are national or international official government bodies who receive test studies for evaluation and are responsible for the assessment and management of test items. They have the legal responsibility for the registration and licensing of relevant substance. The application of GLP to studies assures the quality and integrity of the data generated and allows this data to be used with confidence by relevant Receiving Authorities in hazard and risk assessment of chemicals, biologicals …

The Belgian GLP Compliance Monitoring Programme 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[1] 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, agrochemicals, industrial chemicals, pesticides, food and feed additives, cosmetic products, veterinary products, medical 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 or preferred by national or international legislation of a OECD member country or MAD full adherent country.

GLP applies 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.. 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, in the field.and animal facilities.
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 mesocosms 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 and accepted by the Receiving authorities.

GLP COMPLIANCE MONITORING PROGRAMME

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1. Organisation

1.1. LEGAL FRAMEWORK

Sciensano originated from an integration of the Centre for Research in Veterinary Medicine and Agrochemistry (CODA-CERVA) and the Scientific Institute of Public Health (WIV-ISP), and was established by Law of 25 February 2018 (Moniteur belge of 21 March 2018) as a sui generis public institution with legal personality. Because of this merge, Sciensano can rely on more than 100 years of expertise in health.

Sciensano falls under the competence of the Minister(s) and the Secretary/Secretaries of State competent for respectively *public health* and the *safety of the food chain and environment*.

The State and Sciensano have entered into a management agreement containing the rules and conditions relating to it to implement the legal and regulatory assignments of Sciensano, as provided in the Law of February 25, 2018 establishing Sciensano.

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[1], defines that the Institute of Hygiene and Epidemiology, renamed as “Wetenschappelijk Instituut Volksgezondheid - Institut Scientifique de Santé Publique” (WIV-ISP), and on February 25, 2018 as “Sciensano” is the only GLP Monitoring Authority in Belgium.

The Compliance Monitoring Programme covers all the sectors mentioned in the scope of the Royal Decree of 6 March 2002[1].

1.2. ORGANISATIONAL STRUCTURE

The General Director of Sciensano has the final responsibility for the GLP Compliance Monitoring Authority (CMA). He/she is especially charged with the approval of the "Statement of GLP Compliance" of the Test Facilities.
The management of the Belgian programme is delegated to the GLP Monitorate especially to the GLP Coordinator.
The GLP Coordinator has the responsibility to organise the GLP programme in accordance to the Royal Decree of 6 March 2002[1], the European Directive EC/09/2004[2] and the OECD MAD agreement[3]

The GLP Monitorate is part of the Quality, (bio)safety and environment (QSE) service at Sciensano General. The head of QSE is responsible for the daily management of the quality, (bio)safety and environment system and security and environment of Sciensano and reports to the General Director. The position of the QSE in the organisational structure of Sciensano is presented in the organisation chart.
The GLP Compliance Monitoring Authority consists of the General Director of Sciensano and the members of the GLP Monitorate (the GLP Coordinator and the designated GLP inspectors).
More information on the organisational structure can be found on www.sciensano.be, where the GLP Monitorate is indicated as GLP.

1.3. OPERATION

The daily management and operation of the GLP Compliance Monitoring Authority are written down in this Belgian GLP Compliance Monitoring Programme Manual which is approved by the General Director of Sciensano, and the GLP Coordinator. Operations specific for the running of the GLP Monitorate are described in procedure SOP 03/02/E and is considered 'for internal use only'.

Cooperation with the GLP Compliance Monitoring Authorities of other OECD member countries is carried out by organizing or participating in "On site" evaluations of MAD countries, joint inspections of facilities on the request of national and international Receiving Authorities and other OECD GLP Compliance Monitoring Authorities, and training of new inspectors during OECD training courses.

The GLP CMA maintains a good relationship with the Belgian, European and other international 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 Receiving Authorities.

2. Confidentiality & integrity

All personnel associated with the GLP Compliance Monitoring are employees of Sciensano for undetermined period.
Inspectors may have access to confidential and commercially valuable information whilst conducting inspections and audits and may even need to remove commercially sensitive documents from a Test Facility or to refer to them in detail in their reports.
The Belgian GLP Monitoring Authority maintains a high level of confidentiality in its operations. To ensure this, the Monitoring Authority follows article 4 of European Directive EC/09/2004[2] and the internal deontological code of Sciensano. This can be consulted by external parties upon request. Also, the following steps are applied:

- The inspectors and observers will present themselves at the Starting Conference of the GLP inspection and will show their identity card on 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 Programme is available on the GLP Website (Royal Decrees, GLP Compliance Monitoring Programme Manual, certified Test Facilities etc.) Are

publicly accessible. Confidential information such as inspection reports, particular questions and replies, minutes of internal meetings, etc., is only available to the General Director of the Institute, the GLP Coordinator and the GLP inspectors. Receiving Authorities can require access to specific information only upon request.

- Information about the inspections and study audits undertaken in Test Facilities can be asked by other national Compliance Monitoring Programmes. However, copies of documents from Test Facilities are only available on request and with the explicit permission of the Test Facility.
- Transparency of documents: Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2011 regarding public access to the European Parliament, council and Commission documents (OJ L 145, 31.5.2001, p. 43) is followed.
- All the original and electronic documents of the Belgian GLP Compliance Monitoring Programme are stored in a closed cupboard in the office of the GLP Coordinator or on a secure area of the Sciensano servers for a period of minimum 3 years or one inspection cycle. Only the General Director of the Institute, the GLP Coordinator and the GLP inspectors have access to the documents. Thereafter, the documents are transferred to the central archives according to the criteria of the SOP I/03/43/NF of Sciensano. Only the General Director of the Institute, the GLP Coordinator, the GLP inspectors and the archivist have access to the documents maintained in the archives of Sciensano.

3. Personnel and training

The Belgian GLP Compliance Monitoring Authority consists of the General Director of Sciensano, the GLP coordinator and inspectors who are upfront scientifically qualified (master degree) .
The Belgian GLP Compliance 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. Where necessary, inspectors may be supported by technical experts of scientific departments of Sciensano.
Occasionally, Sciensano may invite whether or not upon request, official representatives from foreign GLP Monitoring Authorities to participate in an inspection/study audit as joint inspectors or as observers. If so, this will always be communicated up front to the test facility.

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, according to the internal procedure.

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. The National GLP Compliance Monitoring Pogramme

4.1. REQUEST FOR VERIFICATION BY A BELGIAN TEST FACILITY

According to the Royal Decree of 6 March 2002[1], a Test Facility Manager should introduce a request on behalf of the Test Facility, with regards to the verification of GLP compliance:

- via post mail to Sciensano:

  At the attention of the Services of the General Director

  Belgian GLP Monitorate

  Rue Juliette Wytsmanstraat 14

  1050 Brussels, Belgium

- or by e-mail to glp@sciensano.be

A standard form of test facilities GLP activities, available on the GLP website[4], with the sectors and the area of expertise covered by their GLP activities should be included. The standard form can be submitted electronically from the GLP website[4].
The GLP Coordinator is charged with the investigation and treatment of the request and will add the Test Facility to the GLP Compliance Monitoring Programme if the request complies with the criteria for uptake (see under chapter 2. Scope)

4.2. REQUEST FOR VERIFICATION OF STUDIES OR STUDY PHASES IN BELGIUM BY A RECEIVING OR MONITORING AUTHORITY

Special Test Facility inspections/study audits in Belgium, may be performed at the request of a foreign GLP Monitoring Authority or a national or international Receiving Authority. In such cases the Receiving Authority or the foreign GLP Monitoring Authority shall justify the need of such inspections and study audits. The Belgian GLP Monitorate will, based on the availability of inspectors and time-limits specified by the requesting authority, propose a time schedule for inspections, inform the Test Facility up front and provide an agenda, unless the requesting Authority refuses that the facility is informed upfront.

4.3. REQUEST FOR VERIFICATION OF STUDIES OR STUDY PHASES ABROAD BY A RECEIVING OR MONITORING AUTHORITY

Inspections or study audits of Test Facilities located in non-adherent OECD member countries may be monitored at the request of a national or international Receiving Authority. In such cases the Receiving Authority shall justify the need of such inspections and study audits and a contract with the party responsible for covering the cost of the inspection must be available.
The Monitorate will be, based on the availability of inspectors and in concertation with the requesting authority, propose a time schedule for inspections and provide an agenda. Because the monitoring

authority must give absolute priority to the Belgian inspection programme, inspections abroad can only be accepted as long as it doesn't hamper the national Belgian programme.
Test Facilities for which a Receiving Authority or other OECD GLP Monitoring Authority requests a verification of GLP compliance, are added to the GLP Compliance Monitoring Programme.

4.4. REQUEST FOR VERIFICATION OF TEST FACILITIES ABROAD BY A THIRD PARTY (SPONSOR, TEST FACILITY MANAGER, NGO,…)

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 programme or is located in a non-adherent OECD member country, the Test Facility should file a formal request to the Belgian GLP Monitorate using the Standard Form to notify a non-GLP phase in a study (available on the GLP website[4]). 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 national EU Receiving authority or to an European Agency. This evidence has to be provided before each inspection.

An inspection in non-member economies by OECD inspectors will not guarantee that, if Test Facilities 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.

4.5. FEES

The Belgian GLP Monitoring Authority will charge fees to the Test Facility or organisation requesting for compliance audits in order to cover the costs of the service it renders. Fees are determined according to the Royal Decree of 6 March 2002[1] and are adjusted each year on the Belgian index. A tender is sent to the Test Facility approximately 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.
More information on fees can be found on FAQ page of our GLP website.

5. The inspection process

5.1. MASTER SCHEDULE OF GLP INSPECTIONS

An inspection plan is established yearly and contains information on the name of the Test Facility, a time schedule, the composition of the inspection team, remarks and estimation of the inspection time and cost.

This GLP Compliance Programme includes pre-inspections, full inspections including Test Facility inspections, study audits and re-inspections.

5.2. GENERAL

Inspectors will not enter Test Facilities, or attempt to gain access to data held by a Test Facility without prior agreement from the Test Facility Management.

However, during the inspections they may ask any kind of information needed to verify the integrity of any study placed on the test facility's master schedule and identified as executed *'GLP compliant'* or intended for registration. Even if parts of a GLP study are claimed to be done under non-GLP compliant circumstances, they can also be audited.

Also in cases where national or foreign Receiving Authorities and/or foreign GLP Monitoring Authorities request for verification of data from specific studies, GLP inspectors may have access to the Test Facility and to the data of studies at any time. 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 at any moment to stop the GLP inspection. When this happens, the lead inspector submits a proposal to the General Director of Sciensano to withdraw the GLP status of the Test Facility. This proposal should be evidence-based.

A first announcement with dates of the GLP inspection will usually be sent to the Test Facility approximately 10 weeks in advance. This notification will include:

- the week of inspection
- the estimated duration
- the number and names of the inspectors
- the following information will be requested to the Test Facility:
    - The list of most important structural changes since the last inspection (organogram, new equipment, new key personnel, new scope)
    - An up-to-date list of the SOPs
    - The master schedule of on-going studies and studies carried out since the last inspection, including involved test sites, if appropriate
    - The list of computerised systems used in studies
    - The list of equipment used in studies
    - …

The Test Facility should send all requested information 6 weeks in advance to the Belgian GLP Monitorate. The definitive announcement of the GLP inspection, the inspection programme will be sent to the Test Facility normally 14 days before the start of the visit. The tender will be sent to the Test Facility at least four 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 aspects to be inspected and discussed and the timeframe foreseen for the visit of the premises and the study audits. The inspection includes the opening session and Test Facility inspection, study audits and the exit meeting. The duration of the inspection can be extended with one or more days depending of 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.
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 QA, who verified the report, Study Directors, the scientists and technical staff of the Test Facility.

5.3. EXPECTATIONS

It is the challenge and the obligation of the Test Facility to prove that there is a complete quality assurance system in place based on the principles of the OECD for GLP and that their GLP studies are planned,

monitored, performed, reported and archived according to the OECD Principles of GLP. The Test Facility Management will be evaluated on the promises that in each stage the chemical safety of the test item for the consumer is the final objective. Responsibility, safety and reliability should always predominate the financial and commercial benefits of the company.

This means that the implementation of the GLP quality system of the Test Facility will be inspected to verify that the OECD Principles of GLP have been followed and that the GLP studies have been carried out according to the study plan and standard operating procedures (SOP). The inspection will be combined with study audits of simulated ('mock study') or real GLP studies or test methods under validation. The integrity of the studies is in this content very important to ensure that the data will be accepted by the national and international Monitoring and Receiving Authorities. The inspectors will also verify that the results in the final report completely and accurately reflect the raw data of the study.

At the starting conference, the inspection team is presented to Test Facility Management 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 brief presentation about the organization and the activities of the Test Facility. Then, the inspection programme 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. As a consequence, it is the obligation of the facility to demonstrate it is working according to the principles of GLP and full cooperation during the inspection is expected.
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. Electronic data should be available on demand within a reasonable time and in a human readable way.

5.4. PRE INSPECTION

If the Test Facility has to be inspected for the first time, a pre-inspection is carried out. This can be done by an *on-site* visit on premises or, when it is not practical or relevant (e.g. Test Facility is located abroad), by document verification (SOP's, study plan for each scope, organigram, floor plan, CV's, list of apparatus, list of validated equipment …).

A pre-inspection is planned to familiarise the inspector with the management structure, the physical layout of buildings, the documentation system and the range of studies of the Test Facility.
During the pre-inspection, also the scope of GLP activities is discussed.

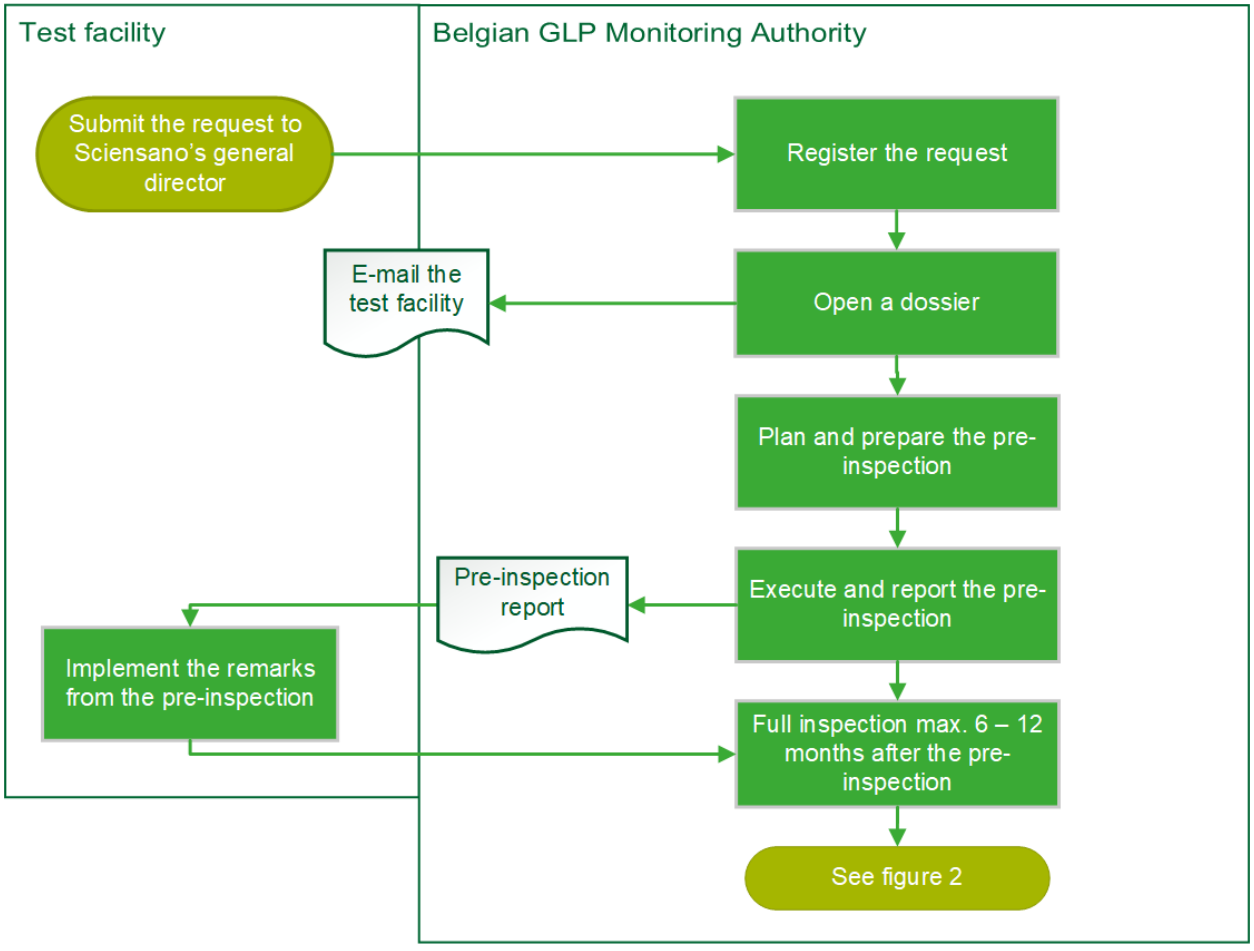
If deviations are observed, a list of these major observations is given to the Test Facility Management at the end of the exit meeting. All the findings observed, minor and major, are written down in a pre-inspection report, which is sent to the Test Facility within three weeks. A formalised action plan on this report is not requested, but the Test Facility should take appropriate corrective actions before submitting a demand for a full inspection.

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

For a full Test Facility inspection to be realised successfully the following conditions should be fulfilled beforehand:

- The deviations observed during the pre-inspection should have been corrected
- At least 2 studies (effective or simulated/mock), including at least one study in each area of expertise and study director 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.

Figure 1: Process for new test facilities



5.5. 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[5] and in accordance with the OECD/EU guidance for the conduct of Test Facility inspections and study audits [2 5 6 7]

Inspections and study audits will be carried out at the request of the Test Facility itself or at the request of a Receiving Authority or a foreign GLP Monitoring Authority.
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[5].
During the inspection the criteria described in all OECD Consensus and Advisory Documents, as published on the OECD public website[8] are also taken into consideration, if appropriate.
Finally the requirements mentioned on FAQ page of the Belgian GLP website[4], the FAQ on GLP of the OECD[9] and the Q&A of the EU working group on GLP[10] should be applied by the Test Facility and shall be verified by the GLP inspectors.
During the Test Facility inspection not only the organization of the Test Facility but also on-going (if there is any) and completed studies are verified.
For multisite studies, if major deviations have been found during an audit of a delegated phase in a Test Site, an audit of the whole study within the Test Facility can be programmed (in Belgium) or requested (outside Belgium).
Each Test Facility is inspected normally every two to three years, depending on the size/capacity of the Test Facility, number of studies performed since last inspection, outcome of last inspection ... 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 Test Facility Management, new study directors, change in Quality assurance management…. If serious changes concerning the organization, infrastructure, sector or area of expertise take place in the Test Facility, the GLP Monitoring Authority can decide to expedite the following programmed inspection **.**
The full inspection will be concluded with an exit meeting. During this meeting, a written list of major (if any) 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 approximately two weeks after the last day of inspection all, the observed findings, major and minor, 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 system 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 end 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 (if available) and one completed study per granted scope ha to be verified by the inspector(s) during their visit. Generally the studies will be selected to cover as many study directors/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. However, daily work in the facility should continue, this to allow the inspection of on-going studies as well.

All the records concerning the observations and examinations and copies of documents or materials requested during the inspection and study audits are retained for at least 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. Electronic received information will be stored on a secured part of the Sciensano server for a non-defined period.

5.6. RE-INSPECTION

If the Test Facility receives “C” deviations during the inspection, a re-inspection can 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 documented evidence and evaluated by the inspection team remotely.
- Re-inspection *on-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 *on-site*, the Test Facility receives a re-inspection programme approximately three weeks before the visit.

5.7. EXTENSION OF THE SCOPE

When an extension of the scope is foreseen, the GLP Monitoring Authority should be contacted. The GLP monitoring authority will perform a documentary audit and/or inspection based on the received information. At least one effective or simulated study according to the new area of expertise should be elaborated. The study plan in advance together with the inspection days foreseen by the Quality Assurance of the critical phases should be sent to the GLP coordinator. Based on this information, 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 GLP studies are truly elaborated, they should be included in the master schedule as GLP studies before the start of the study. However, these studies cannot be reported as GLP study until the Test Facility has received an update of the GLP statement including the new area of expertise.

5.8. 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 no longer plans to do studies 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.
If the Test Facility decides to remove itself from the Belgian GLP monitoring programme because all GLP activities are permanently stopped or due to closure of the Test Facility, the GLP Monitoring Authority should be alerted as soon as possible to schedule a final GLP inspection to audit studies executed since last inspection.

In case the final inspection cannot be scheduled, all studies since last inspection will be declared as non-compliant with the GLP principles.

5.9. EXCEPTIONAL CIRCUMSTANCES

When it is not possible to perform a normal onsite inspection due to exceptional circumstances, an alternative inspection approach can be performed (documentation inspection remotely, inspection via teleconference, …). If an remote inspection of a facility is conducted, an on-site facility inspection will then be scheduled once the regular inspection programme resumes.
In case an alternative inspection approach is needed, the GLP Compliance Monitoring Authority will justify this approach in a risk assessment, documented in the introduction of the inspection report.
Follow-up of remote inspections is similar to a normal on-site inspection.

6. Follow-up to Test Facility Inspections and Study Audits

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”[11] 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” [11] will be coded, scanned and stored as a pdf-file or on paper, but will be sent only on demand.

6.1. FIRST FULL GLP INSPECTION

For initial inspection, the Test Facility should give its comments to the deviations in writing within 30 days after the receipt of the inspection report. This 30 days-delay can exceptionally be extended in consultation with the GLP coordinator The reply should be sent to the GLP coordinator. 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 report with the proposed corrective actions will constitute the version 2 of the inspection report.
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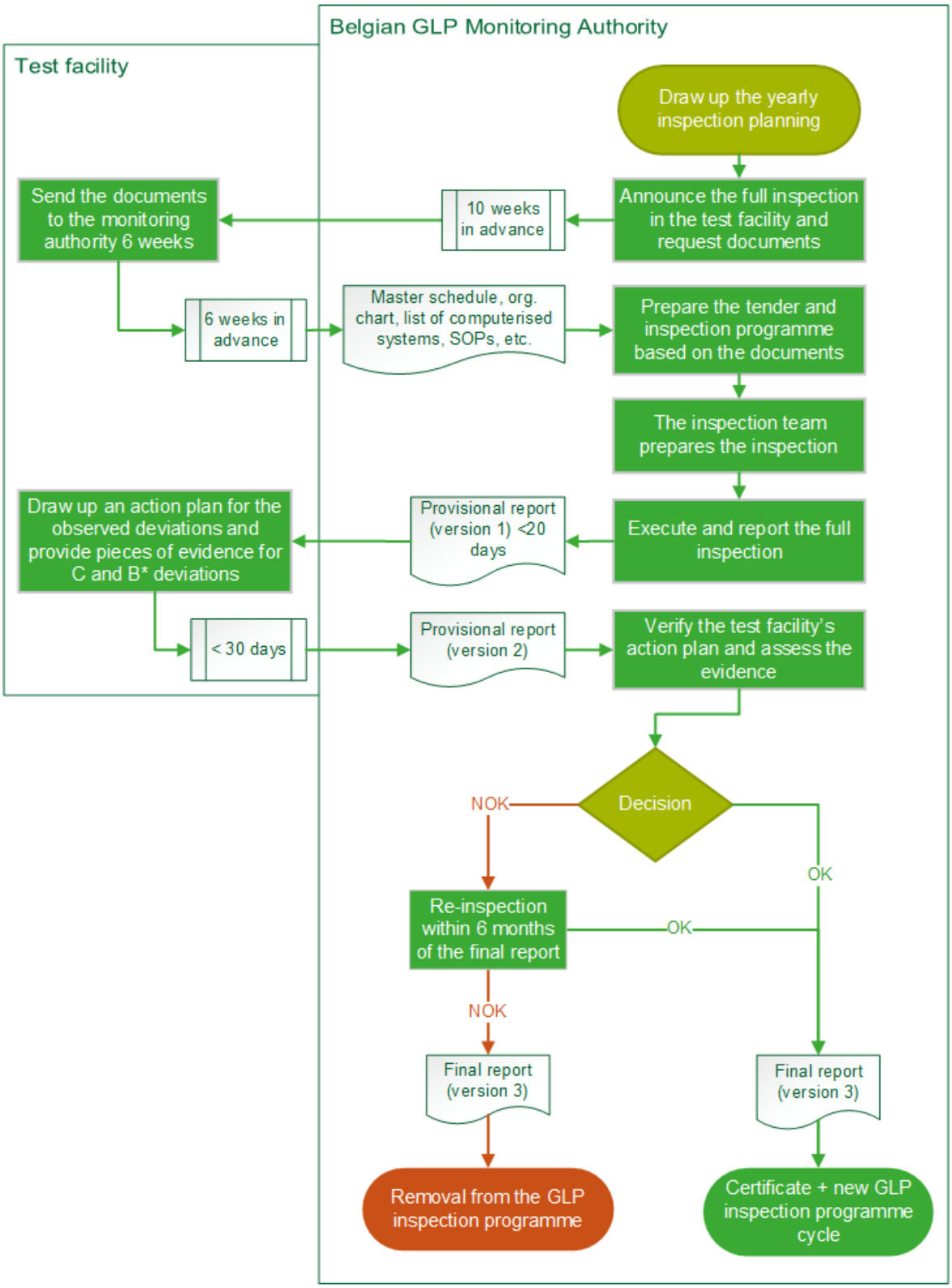
The corrective actions taken for the C and B* deviations should be justified by documentary evidence within 6 months after the receipt of the inspection report.
The inspector will give his comments to each corrective action proposed by the Test Facility. The inspector will re-contact the Test Facility Management if more specific evidence is required for some corrective actions.
The final inspection report will be prepared within 30days after receiving satisfying corrective actions of the Test Facility to the inspection report.
Implementation of the corrective action proposed for the minor deviations B will be verified at the next inspection.

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

If 6 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.(see paragraph 5.6 on re-inspection)

The final inspection report, including the conclusions of the inspection, is signed by the GLP Coordinator and sent to the Test Facility.
(see figure 2)

Figure 2: Inspection process for first full GLP inspection for test facilities entering the Belgian GLP Compliance monitoring programme



6.2. ROUTINE GLP INSPECTION FOR TEST FACILITIES BELONGING TO THE BELGIAN GLP COMPLIANCE MONITORING PROGRAMME

The Test Facility should give its comments to the deviations in writing within 30 days after the receipt of the inspection report. This 30 days-delay can exceptionally be extended in consultation with the GLP coordinator The reply should be sent to the GLP coordinator. 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 report with the proposed corrective actions will constitute the version 2 of the 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 will give his comments to each corrective action proposed by the Test Facility. The inspector will re-contact the Test Facility Management if more specific evidence is required for some corrective actions.

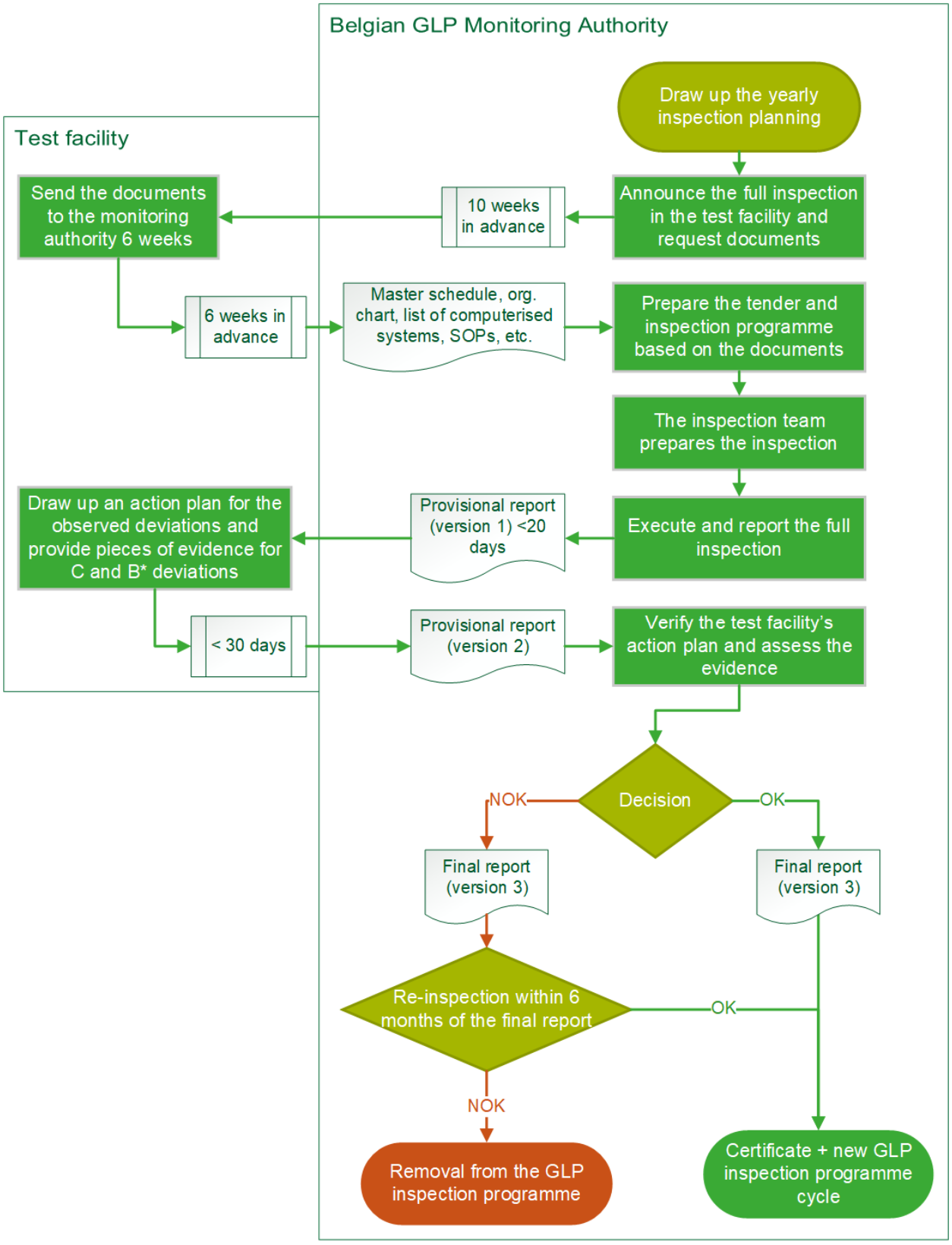
The Belgian GLP CMA recognises that in exceptional circumstances, it might not be possible for the test facility to provide all documentary evidence within 30 days after reception of the inspection report. In this case, the facility should alert the Belgian GLP CMA and discuss acceptable timelines to deliver all required documentary evidences.

The final inspection report will be prepared within 30days after receiving satisfying corrective actions of the Test Facility to the inspection report.
Implementation of the corrective action proposed for the minor deviations B will be verified at the next inspection.
The comments and the decision taken by the inspector are integrated in the inspection report, version 3 (= final inspection report).

If 6 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.(see paragraph 5.6 on re-inspection)

The final inspection report, including the conclusions of the inspection, is signed by the GLP Coordinator and sent to the Test Facility. **(see figure 3)**

Figure 3: Routine GLP Inspection process for test facilities belonging the Belgian GLP Compliance monitoring programme



7. GLP Statement (GLP certificate)

The three following categories of compliance status are used:
- Test Facility with status pending
- Test Facility not in compliance
- Test Facility in compliance

If major deviations “C” are observed during the Test Facility inspection, the 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 to continue 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 and integrity of the studies conducted in the Test Facility;
- removes the Test Facility from the GLP Compliance Programme

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 will judge the study as not in compliance with the OECD Principles of GLP. In such cases the Belgian GLP Monitoring Authority will 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 month, an amendment to the GLP statement of the study report, detailing the deviations. Documented evidences, including that the sponsor was contacted, must be send to the GLP Compliance Monitoring Authority.
A non-compliant 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 none or only minor deviations (B, B*) 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.

As stated in the European Directive 2004/9/EC[2] article 1 & 2, an endorsement (certificate) of compliance can only be granted after a successful inspection and verification of organisational processes and the conditions under which laboratory studies are planned, performed, recorded and reported for the non-clinical testing, carried out in accordance with the rules and regulations, of all chemicals (e.g. cosmetics, industrial chemicals, medicinal products, food additives, animal feed additives, pesticides) in order to assess the effect of such products on man, animals and the environment.
This means that an endorsement of compliance can only be granted after a successful inspection including study audits of actual GLP studies, as required by the regulation.

The statement of GLP compliance will include at least: the logo of Sciensano; name and address of the Test Facility; identification number of the Test Facility in the GLP Compliance Programme; periods or dates of inspection; area of expertise for which the Test Facility is in compliance with GLP principles; signature of the General Director Sciensano (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 contains no validity date, unless otherwise indicated. As stated in the European Directive 2004/9/EC[2], during a GLP inspection, the monitoring authority verifies what is done since last inspection. The certificate states that a GLP inspection has been conducted to verify the GLP compliance and the level of GLP compliance at the end of the inspection process for the test facility and the studies completed until the dates of the inspection. This is not an approval about activities undertaken after the inspection; GLP inspections are a retrospective assessment. The Test Facility has the right to refer to the statement on his website, or to make a reference to the official website of the Belgian Monitoring Authority, where GLP facilities, granted with a valid certificate, are reported under the category " GLP facilities".

When the facility has undergone a full Test Facility inspection successfully, but the facility had no real GLP studies to be inspected but only simulated studies, a certificate cannot be granted, based on the legislation laid down in the European Directive 2004/9/EC[2]. However, a positive inspection report will be issued which can be used to attract sponsors in order to start actual GLP studies, in accordance with the relevant rules and regulations. The summary of the inspection report will indicate that:

- the facility is able to perform studies according to the OECD principles of GLP
- it is the responsibility of the facility to contact the Belgian GLP CMA the moment the first actual study will start and when it is finalized
- the first study must be finalized within 3 years after the inspection
- a certificate will be granted after successful study audit of an actual GLP study

8. Claiming GLP

As indicated in the Q&A of the EU working group on GLP[10], a claim to GLP constitutes any claim of having conducted a non-clinical study in accordance with or in compliance with the principles of GLP (or using any other expression with the same meaning), as outlined in Annex I to Directive 2004/10/EC, as transposed into national legislation under the relevant national GLP Compliance Monitoring Programme.

A claim to GLP can of course only be made to studies that fall within the scope for which the test facility requested a GLP inspection and successfully passed this inspection (certificate granted). The test facility can of course perform other scientific activities outside the scope of GLP, but reports of those studies can never make any reference to GLP certification in a general way, as these studies are not within the verified GLP scope of the facility.

Any vague or confusing reference that the test facility might be GLP certified for studies out of scope, could be considered as a false claim of GLP, in which case it will be notified to the receiving authorities by the Belgian GLP compliance Monitoring Authority.

9. International acceptance of inspection results

The GLP Monitoring Authority is responsible for ensuring that studies have been performed in compliance with the OECD Principles of GLP. The responsible Receiving Authority decides if a study is acceptable after scientific evaluation. However, following the OECD decision on the Mutual Acceptance of Data[3] a Receiving 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 Receiving Authorities and the GLP Monitoring Authorities of the OECD Member Countries.
Studies can be submitted to several Receiving Authorities in different countries. Based on the criteria of the EU Directives 2004/09/EC [2] and 2004/10/EC[12] 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 programme are accepted by the Receiving Authorities of the EU member states.
Following Decision C(97)186/Final of the OECD Council [3] 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.

OECD inspections of Test Facilities located in non-adherent OECD member countries
The Belgian Monitoring Authority can send inspectors at the request of Receiving 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 Test Facilities 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. (see also 4.4)

10. Appeal procedures

Any disagreement or difference in 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 an 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 ”Administrative Council of Sciensano within 30 days after the date of this decision taken. The Board of Directors of Sciensano will then take appropriate steps to achieve a mutually acceptable resolution. Therefore, the board can ask the advice of the GLP Coordinator, independent internal or external experts or a request a second opinion of inspectors from other monitoring authorities. Based on this advice the Board of Directors of Sciensano will take a final decision.

11. References

1. [1] 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
2. [2] 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.
3. [3] 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];
4. [4] https://www.sciensano.be/en/belgian-glp-monitoring-authority
5. [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
6. [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.
7. [7] The EU Council Decision 89/569/EEC of 28 July 1989 on the acceptance by the European Economic Community of an OECD decision/recommendation on compliance with Principles of Good Laboratory Practice. Official Journal of EU N° L315 of 28/10/1989, p.1.
8. [8]http://www.oecd.org/chemicalsafety/testing/oecdseriesonprinciplesofgoodlaboratorypracticeglpandcompliancemonitoring.htm
9. [9] http://www.oecd.org/chemicalsafety/testing/glp-frequently-asked-questions.htm
10. [10] Questions and answers concerning the implementation of Directives 2004/9/EC and 2004/10/EC on Good Laboratory Practices(GLP)
11. [11] Guidance for the preparation of GLP inspection reports N°9, 1995. OECD Environment Monograph N°115, OECD/GD(95)114, 5 Oct 1995
12. [12] 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.

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MORE INFORMATION

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