National GLP Programme
Principles of monitoring compliance with Good Laboratory Practice

Administration

Introduction


This procedure is based on inspections of the test facilities and on audits of GLP studies, carried out by national Monitoring Authorities (State Institute for Drug Control and National GLP Inspection Authority, Centre for Assessment of Laboratories ASLAB, T. G. Masaryk Water Research Institute, public research institution established by the Ministry of Environment), and, thus, it creates conditions for mutual acceptance of results of studies among the individual EU/EEA and OECD states.

State administration

Competence of state administration authorities in management of chemical substances is divided in the following way:

The state administration authority for the field of pharmaceuticals is the State Institute for Drug Control (hereinafter SUKL).

The state administration authority for the field of chemical substances and chemical preparations is the Ministry of Environment (hereinafter MŽP).

Monitoring Authorities

In accordance with provisions of recital 6 of the Directive 2004/9/EC, two Monitoring Authorities exist in the Czech Republic:

I. Field of pharmaceuticals

The Monitoring Authority for the field of pharmaceuticals is the State Institute for Drug Control (Státní ústav pro kontrolu léčiv; SUKL). This field is regulated by the following regulations:

Act No. 79/1997 Coll., on pharmaceuticals and amendment and modification of certain other acts, as amended.

* The document was prepared jointly by the representatives of national GLP monitoring authorities for the sphere of pharmaceuticals (the State Institute for Drug Control), and for the sphere of chemical substances and chemical products, (NIA SLP). Identical texts of the document were published in the Bulletin of SUKL and the Bulletin of the Ministry of Environment.
Act No. 552/1991 Coll., on state control, as amended

Decree of the Ministry of Health and Ministry of Agriculture No. 504/2000 Coll., laying down the Good Laboratory Practice in the field of pharmaceuticals. Translation of the document "Decision of the OECD Council [C(97)186 (final)]" ("OECD Principles of Good Laboratory Practice") forms an annex to this Decree.

National GLP Programme, in actual wording


After the carried out inspection, the SUKL GLP inspectors issue a protocol on inspection. If the test facility complies with the GLP principles, the SUKL issues a certificate, on the basis of a request of the test facility. During the period when a test facility is included in the GLP Programme, it may ask SUKL for issuance of a new certificate, for example in the case of request of a sponsor. A condition for issuance of this certificate may be a preceding inspection. The procedure of issuance is described below (Chapter VII, paragraph 3).

II. Field of chemical substances and chemical preparations

The Monitoring Authority for the field of chemical substances and chemical preparations is the National GLP Inspection Authority, Centre for Assessment of Laboratories ASLAB, T. G. Masaryk Water Research Institute, public research institution (hereinafter "NIA GLP"). The field of monitoring includes chemical substances and chemical preparations according to the Act No. 356/2003 Coll., as amended, cosmetics according to the Act No. 258/2000 Coll., as amended, pesticides according to the Decree No. 91/2002 Coll., as amended and biocides according to the Act No. 120/2002 Coll., as amended.

This field is regulated by the following regulations:

Act No. 356/2003 Coll., on chemical substances and chemical preparations and on amendment of certain acts, as amended.

Act No. 552/1991 Coll., on state control, as amended

Decree of the Ministry of Environment No. 219/2004 Coll., as amended (hereinafter "Decree No. 219/2004 Coll."), on principles of Good Laboratory Practice. Translation of the document "Decision of the OECD Council [C(97)186 (final)]" (i.e., "OECD Principles of Good Laboratory Practice") forms annex No. 1 to this Decree.

National GLP Programme in the actual wording.

After the carried out inspection, the NIA GLP inspectors issue a report on inspection results. The structure of the document is identical with the SUKL protocol, and it is described below (see Chapter IV, paragraph 4).

If the test facility complies with the GLP principles at the time of the inspection, the Ministry of Environment issues a certificate on compliance with the Principles in the field of chemical substances and chemical preparations (on the basis of recommendation stated in the report on inspection results). The procedure of issuance of this document is described below (Chapter VII, paragraph 3).

Cooperation between SUKL and NIA GLP

GLP inspections according to the Act No. 79/1997 Coll., as amended, are carried out by SUKL, and inspections according to the Act No. 356/2003 Coll. as amended, are carried out by NIA GLP. If both these acts apply to the test facility, the inspections are usually carried out by the both Monitoring Authorities together. A separate certificate is issued for each field (pharmaceuticals and chemical substances).
Procedure for carrying out the inspections is identical for the both Monitoring Authorities. It is regulated by valid legislation and relevant OECD documents**, and it is described in this National Programme.

The both Monitoring Authorities cooperate on training of the staff of test facilities, and on preparation of new documents.

**Inspection teams and frequency of inspections**

The SUKL GLP inspectors are authorised to carry out inspections according to Section 54 of the Act No. 79/1997 Coll., as amended.

The NIA GLP inspectors are authorised to carry out inspections according to Section 9 paragraph 3 of the Act No. 356/2003 Coll., as amended, and of the Decree No. 219/2004 Coll.

Both Monitoring Authorities have sufficient number of inspectors.

The interval between inspections of the test facilities included in the National Programme is determined by the inspectors, and it is usually two, or, at most, three years.

**Published documents**

Acts, Decrees and other documents are mentioned above. New documents are published either in the SUKL Bulletin (instructions of the GLP-xx series or information), or in the Bulletin of the Ministry of Environment.

**Contact of the GLP Monitoring Authorities with the test facilities**

1. If necessary, the both Monitoring Authorities organise seminars for the test facilities, especially in the case of changes of legislation and documents.

2. Before their issuance, proposals of new instructions of SUKL and NIA GLP are published on internet pages of SUKL or ASLAB, respectively. The test facilities may express their opinion concerning wording of the new documents. The test facilities do not express their opinion concerning translations of EU or OECD documents.

3. Valid documents, list of test facilities included in the National GLP Programme, and other information, are available on internet pages of SUKL http://www.sukl.cz (field of pharmaceuticals) and on internet pages of ASLAB http://aslab.vuv.cz/ (field of chemical substances and chemical preparations).

**Keeping of records on the test facilities**

All documents concerning the test facilities are kept by the Monitoring Authorities. The documents include copies of the issued certificates, protocols on inspections or reports on inspections, corrective actions adopted by the test facilities, and correspondence with the test facilities. The records are kept for at least 10 years.

**Confidentiality**

SUKL: SUKL employees are state administration workers. They are obliged to act and make decisions without prejudice, and to maintain confidentiality (Section 12, paragraph 2, letter f) of the Act on State Control, Act No. 552/1991 Coll., as amended).

NIA GLP: The same legislation applies to the NIA GLP employees.

External experts: By signing a contract before each inspection or audit, they confirm that they have neither financial nor other interest in the test facility to be inspected, and they are not aware of conflict of interests in connection with their activity during the inspection or audit.

**Staff and training**

** See SUKL Instruction SLP-5
Position of the inspectors

All the GLP inspectors are either permanent employees of SUKL or NIA GLP or inspectors under contract.

Qualification - qualification preconditions

Inspectors: university education in natural science, chemistry, pharmacy, or human or veterinary medicine kind, practice in the field at least 5 years, knowledge of national legislation concerning GLP and of relevant OECD and EU regulations.
External experts: university education of the relevant specialisation, at least 3 years of experimental practice in the field, knowledge of national legislation and GLP Directives.

Appointment of the inspectors

Identity cards of inspectors are issued by the Director of SUKL. Appointment documents of the NIA GLP inspectors are issued by the Ministry of Environment, identity cards of inspectors are issued by ASLAB.

Independence

- According to the section 10 of the Act No. 552/1991 Coll., as amended the inspection must not conduct those inspectors by who may be doubtful about unbiassednes.

Training of inspectors

The training has two levels:
- Introductory training for new inspectors, including national legislation and OECD (EU) regulations, introductory GLP training, and gradual involvement into work of the inspection group; the inspection authority draws up an individual training plan for the new inspector;
- Continuous training for all inspectors, including, for example, participation in OECD GLP courses, and, optionally, other national, as well as international, audits, and exchange of experience with other Monitoring Authorities of the Member States.

External experts

The leader of the inspection group may appoint an external expert as a member of the inspection group.

Before each inspection or study audit, the external experts confirm in a contract that they are not aware of conflict of interests. In the same way, they confirm also that they will maintain confidentiality of the gained information.

Independence of external experts is also confirmed by a written consent of the test facility with participation of the appointed expert.

Identification of the inspectors

The SUKL inspectors prove their identity by identity cards of inspectors according to Section 9 of the Act No. 552/1991 Coll., as amended, on state control. A specimen of the certificate, and authorisation of the inspectors, may be verified on the internet address www.sukl.cz.

In the case of the introductory inspection, the NIA GLP inspectors show authorisation for the inspection, letter of appointment from the Ministry of Environment, and identity cards of inspector. During the periodical inspections, they prove their identity by identity cards of inspectors.

Contents of the GLP Monitoring Programme
I. Framework and scope of the Programme

Pharmaceuticals: On the basis of results of the inspection, the SUKL issues certificates to the test facilities carrying out non-clinical studies in the field of pharmaceuticals. By means of the certificates, it confirms compliance with the GLP conditions (Section 9 paragraph 1 letter a) item 4 of the Act No. 79/1997 Coll., as amended). Also the kind of studies which formed the subject-matter of the inspections, and which comply with the GLP, is stated in the certificates. In the case that the test facility was already included in the National GLP Programme, and less than two years passed from the last inspection, the SUKL GLP Inspectorate may, after considering the case, issue a renewed certificate without carrying out an inspection on the spot.

Chemical substances and chemical preparations: The Ministry of Environment issues certificates to test facilities carrying out studies in the field of chemical substances and chemical preparations. By means of the certificates, it certifies compliance with the GLP conditions (Section 9 paragraph 2 of the Act No. 356/2003 Coll., Decree No. 219/2004 Coll.), on the basis of recommendation of the NIA GLP.

The scope of the Programme is based on the following facts:
- It covers chemical substances and preparations according to the Act No. 356/2003 Coll., pharmaceuticals according to the Act No. 79/1997 Coll., as amended, cosmetic preparations according to the Act No. 258/2000 Coll., as amended, pesticides according to the Decree No. 91/2002 Coll., and biocides according to the Act No. 120/2002 Coll.;
- It covers methods described in the "OECD Guidelines for the Testing of Chemicals";
- Reference to the OECD Test Guideline or other test guideline or method to be used;
- Test facilities comply with GLP conditions laid down by the Decree No. 504/2000 Coll. for the field of pharmaceuticals, and by the Decree No. 219/2004 Coll. for the field of chemical substances and chemical preparations. By this, the test facilities comply with requirements specified in the document "OECD Principles of Good Laboratory Practice".

II. Procedure for inclusion of test facilities into the Programme

1. The test facility applying for inclusion into the National Programme submits, according to the specialisation, either an application for issuance of a GLP certificate to the SUKL GLP Inspectorate, or an application for issuance of a GLP certificate to the Ministry of Environment, with a copy to the National GLP Inspection Authority. The Ministry of Environment authorises, in writing, the National GLP Inspection Authority to carry out the introductory inspection.
2. The test facility applying for inclusion into the National Programme submits a completed "Questionnaire for Test Facility" to the SUKL Inspectorate or to the National GLP Inspection Authority. A template of this questionnaire is published on internet pages both of SUKL and the NIA GLP.
3. Inspectors assess the received documents, and, if necessary, they request further information, or visit the test facility.
4. The test facility is informed by the Monitoring Authority about the date of inspection by means of a letter.
5. Inspection of the test facility (see Chapter IV).
6. Protocol or report on inspection (see Chapter VII).
7. The test facility describes the corrective actions to eliminate possible non-compliance, found out during the inspection.
8. After implementation of the corrective actions, the test facility works in compliance with the GLP. Subsequently, the SUKL GLP Inspectorate, or the Ministry of Environment, respectively issues a certificate to the test facility, and includes it into the National GLP Programme.
9. The public is informed of the newly included test facility by means of the SUKL Bulletin or the Bulletin of the Ministry of Environment, and internet pages of both these authorities. Details are described in Chapter VII, paragraph 5.
III. Categories of inspections and study audits of test facilities

**Full-routine inspection of the test facility** is carried out in the case that the test facility applies for inclusion into the National Programme (i.e., issuance of the GLP certificate) or in the case of a periodical inspection taking place every two or three years, according to decision of the inspectors.

**Target inspection** serves, in particular, for checking how the incompliances detected during the routine inspection in the case of conclusion “pending”, on request of the Czech regulatory authorities (for example, Ministry of Environment, Registration Department, or Department of Clinical Assessment and Pharmacovigilance of SUKL, Institute for State Control of Veterinary Biologicals and Medicaments) or of regulatory authorities of the other OECD or EU member states, in the case of higher number of minor deviations, the target inspection may be prescribed by the leader of the inspection group.

A **study audit** forms always a part of the overall inspection of the test facility, or it may by carried out separately. It may be requested by the relevant regulatory authorities or regulatory authorities of the other OECD or EU member states.

IV. Conduct of inspections

The basic steps are stated also in Chapter II of this document "Procedure for inclusion of test facilities into the Programme”.

1. The Monitoring Authorities carry out inspections as defined by the above-mentioned regulations (see Chapter Administration).

2. Preparation of the inspection

   2.1. Setting-up of an inspection group.
   2.2. Study of documents of the test facility, requesting further documents, visit of the test facility, as appropriate.
   2.3. Planning the programme of the inspection.
   2.4. The Monitoring Authority usually informs the test facility management about the inspection by means of a letter. In the letter, it informs the test facility of the names of the inspectors, date of the inspection, preliminary programme of the inspection, and requirement that all staff which the inspection concerns be present at the time of the inspection.
   The inspection may be carried out without previous notification.

3. Procedure of the inspection

   3.1. Starting conference, including:
   - Proving of identity of the inspectors;
   - Informing about reason and extent of the inspection or study audit;
   - Familiarization of the inspectors with organisation of the test facility, master schedule;
   - Information about premises of the facility, staff and activities which will form the subject-matter of the inspection;
   - Information on non-GLP activities, and those where exists danger of negative influencing of studies within the framework of GLP;
   - Requirement of inspectors on documents which the inspection concerns;
   - Information on studies to be audited;
   - Approval of approximate time schedule;
   - Specification of persons who will accompany the inspectors.

   3.2. Conduct of the inspection (for categories of inspections please see Chapter III) – maximum extent
   - Organisation and staff;
   - Quality assurance programme;
   - Premises;
   - Biological test systems: care, housing and handling thereof;
   - Apparatuses, materials and samples of test systems;
• Test and reference items;
• Standard operating procedures;
• Performance of the study;
• Final report;
• Retention and storage of records, archiving
• Audit of at least one finished study.

3.3. Closing conference:
• The inspectors prepare a draft inspection protocol or list of findings or draw up their final copy comprising deficiencies found out during the inspection or study audit. The inspectors inform the management of the test facility (or a representative appointed) and the responsible employees about these findings;
• The management of the test facility and the key personnel are informed about serious deficiencies, and about deadlines set for their elimination;
• The inspectors inform the management of the test facility about the decision on compliance with the Principles – in compliance, pending or not in compliance.

4. Protocol on inspection or report on inspection results
4.1. The inspectors draw up the protocol on inspection or report on inspection results within five weeks from finishing the inspection, at the latest, and ensure its delivery to the management of the test facility.

4.2. The protocol or report on inspection results comprises:
4.2.1. Names of the inspectors;
4.2.2. Name, address, identification number of the test facility, in the case of study audit title of the study;
4.2.3. Extent of activities of the test facility;
4.2.4. Names of key personnel of the test facility who participated in the inspection;
4.2.5. Declaration that the inspectors communicated start of the inspection, and proved their authorisation;
4.2.6. Place and time of the inspection;
4.2.7. Reason, subject-matter and extent of the inspection;
4.2.8. Legislation on the basis of which the inspection was carried out;
4.2.9. Summary of the inspection (comprises serious, systematic and repeated deviations);
4.2.10. Introductory information on the inspected subject
4.2.11. Process of the inspection and inspection findings (see item 3.2);
4.2.12. Overall assessment comprising the statement of the inspectors concerning compliance with the GLP, and, optionally, notification on, or proposal for, granting or withdrawal of the certificate:
  • in compliance (no or minor deviations);
  • pending (serious defects which do not have influence on integrity of the study, subsequent inspection required );
  • not in compliance (serious defects which have influence on integrity of the study);
4.2.13. Information on appeal procedures (stated in Chapter VII);
4.2.14. Date and signatures of the inspectors and the test facility management (or another authorised person). Statement of the management of the test facility is an annex to the NIA GLP report.

V. Procedures for inspections and study audits carried out on request of a regulatory authority
1. The request of a regulatory authority of the Czech Republic (SUWL - Registration Department or Department of Clinical Assessment and Pharmacovigilance, Institute for State Control of Veterinary Biologicals and Medicaments, State Veterinary Administration, Ministry of Health, Ministry of Agriculture; NIA GLP - Ministry of Environment) comprises a requirement of inspection or study audit, including the subject it concerns (for example, title and specification of the study) and the requested extent of the inspection. Representatives of the regulatory authorities, and, optionally, other experts, may participate in the inspection or study audit as observers or as invited persons. (Section 54 paragraph 2 letter d) of the Act No. 79/1997 Coll., as amended).
1.1. Notification of the test facility on inspection or study audit (including reasons, if appropriate).
1.2. Execution of the inspection or study audit (stated in Chapter IV).
1.3. Protocol or report on result of the inspection or study audit (stated in Chapter VII), comprising statement of the inspectors (see 4.2.12).
1.4. A counterpart of the protocol or report on inspection result is sent to the regulatory authority.

2. Request of a regulatory authority of an OECD/EU/EEA country.
The procedure is identical as in item 1, only the protocol or report on inspection or study audit is written in the English language. Representatives of the administrative authorities of the OECD and EU/EEA member states may participate at the inspection or study audit as observers or as invited persons. (Section 54 paragraph 2 letter d) of the Act No. 79/1997 Coll., as amended).

VI. Jurisdiction of inspectors to enter the test facilities

The scope of authorisation of the SUKL inspectors is laid down in the Section 54 of the Act No. 79/1997 Coll., as amended, and in the section 11 of the Act No. 552/1991 Coll., and that of NIA GLP inspectors in the Section 9 paragraph 3 of the Act No. 356/2003 Coll.

1. The inspectors are authorised to assess compliance with the above-mentioned acts and their implementing regulations.

2. Inspectors are authorised pending the inspections pursuant to Act No. 552/1991 Coll., i.a.:
   - to enter objects, facilities and plants, plots and other areas of the legal entities inspected, bearing on the subject of inspection; immunity of residences being guaranteed,
   - to ask inspected persons for presenting authentic documents and other papers, electronic records and their printouts, and programme source codes, product samples, or another commodities in due terms,
   - to get acquainted with classified matters provided they are certified for the particular degree of security according to special Act,
   - to require inspected persons to provide with true and complete information about investigated and related facts,
   - to safeguard documents in reasonable cases; their receipt shall be confirmed in writing and copies of the respective documents retained to the inspected person,
   - require the inspected persons to deliver a written report on rectification of deficiencies in a due time limit,
   - to impose disciplinary fines in cases set out by Act No. 552/1991 Coll.,
   - to use telecommunication devices of inspected persons provided the necessity of their using to secure the inspection.

VII. Procedures following-up the inspection

1. Proceedings on objections of the inspected persons are described in Section 17 and 18 of the Act No. 552/1991 Coll. In the field of pharmaceuticals, the final decision is issued by the SUKL Director, and in the field of chemical substances and chemical preparations by the ASLAB Director.

2. In the case of objections to the decision of the ASLAB Director, the inspected subject may seek remedy in front of the court, or claim objections (only in the case of NIA GLP report on inspection result) in administrative proceedings before the Ministry of Environment.

3. GLP certificate and National GLP Programme
   3.1. The certificate confirm that the test facility complied with the GLP principles at the time of the inspection. Such test facility is included into the National GLP Programme.
   3.2. The certificate is issued after the performance requirements GLP and inspection conducted on the basis of application for inclusion into the National Programme only, with the exception of cases described in Chapter I. Framework and scope of the Programme, section Field of pharmaceuticals.
   3.3. The list in the National GLP Programme confirms that the test facilities listed therein comply with the Decree of the Ministry of Health and Ministry of Agriculture No. 504/2000 Coll. and/or
the Decree of the Ministry of Environment No. 219/2004 Coll. It also means that these test facilities comply with the "OECD Principles of Good Laboratory Practice" and the relevant EU legislation. These Principles form annexes to the both decrees.

3.4. The certificate is issued on the basis of the conducted inspection at the test facility.

3.5. Test facilities included into the National GLP Programme are subject to GLP inspections (for details please see Chapter IV).

4. Decision on GLP non-compliance

4.1. When a test facility included National GLP Programme is found non-compliant with GLP Principles during the inspection, the inspectors decides “not in compliance” (serious defects influencing integrity of the study were found).

4.2. In the case of “not in compliance” in the field of pharmaceuticals, SUKL terminates the validity of the issued GLP certificate according to Section 9 paragraph 1 letter e) item 3 of the Act No. 79/1997 Coll., as amended. In the field of chemical substances and chemical preparations, the Ministry of Environment withdraws the certificate on the basis of recommendation of the National Inspection Authority, according to Section 9 paragraph 6 of the Act No. 356/2003 Coll.

5. Methods of informing and publishing

5.1. Information on the test facilities included into the National GLP Programme (i.e., facilities to which a certificate was issued) is published a) for the field of pharmaceuticals in the SUKL Bulletin and on SUKL internet pages at least once a year. It contains the following data: name and address of the test facility, extent of activities, date of the first and the last GLP inspection, result of the last inspection (compliance, non-compliance); b) regularly in the Bulletin of the Ministry of Environment, for the field of chemical substances and chemical preparations. It contains the following data: name and address of the test facility, extent of activities, date of the first and the last GLP inspection, result of the last inspection (compliance, non-compliance).

5.2. Information on the test facilities newly included into the National GLP Programme is published in the SUKL Bulletin and on SUKL internet pages in the extent mentioned in item 5.1 within three months from the date of issuance of the certificate, at the latest, and similarly, in the Bulletin of the Ministry of Environment for the field of chemical substances and chemical preparations.

5.3. Information on test facilities which were expelled from the National Programme (i.e., the ones from which the certificate was withdrawn) is published, for the field of pharmaceuticals, in the SUKL Bulletin and on SUKL internet pages in the extent mentioned in item 5.1 within three months from the date of termination of validity of the certificate, at the latest, and similarly, in the Bulletin of the Ministry of Environment for the field of chemical substances and chemical preparations. Simultaneously, in accordance with the requirements of Article 5 of the Directive 2004/9/EC, the European Commission and OECD are informed. The procedure is the same in the case of an audit of a study which does not comply with GLP principles.

5.4. In view of membership of the Czech Republic in OECD, the both Monitoring Authorities inform (using one report form) the GLP Monitoring Authorities of the OECD countries in the extent mentioned in item 5.1 once per year. In the same extent they inform the European Commission, Chemicals Department.

6. Removal from and resignation on the National GLP Programme.

6.1. If a test facility does not wish to be included in the National GLP Programme any longer, it asks, in writing, the competent GLP authority - i.e., SUKL for the field of pharmaceuticals, or the Ministry of Environment for the field of chemical substances and chemical preparations, for withdrawal from the National GLP Programme. Withdrawal is published in the SUKL Bulletin or the Bulletin of the Ministry of Environment, and also on the SUKL internet pages. This fact is also included into the next annual information (items 5.1 and 5.4).

6.2. A test facility withdrawn from the National GLP Programme (6.1) is regarded as a facility not in compliance with the GLP requirements.

6.3. A test facility, regarded as not in compliance by the inspectors, is expelled from the National GLP Programme. After making the information public according to item 6.1 on expulsion from the National GLP Programme, such facility is not henceforth listed in the National Programme list (5.1 and 5.4).

6.4. An expelled or withdrawn test facility may re-enter the National GLP Programme via the above-mentioned procedure (Chapter II).