HELLENIC REPUBLIC - MINISTRY OF FINANCE
SECRETARIAT GENERAL OF TAX & CUSTOMS ISSUES
DIRECTORATE GENERAL OF
GENERAL CHEMICAL STATE LABORATORY
DIVISION OF ENVIRONMENT
SECTION B’ OF DANGEROUS SUBSTANCES, PREPARATIONS & ARTICLES

GREEK G.L.P. COMPLIANCE PROGRAMME

MANUAL. Rev. 2

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1. **AIM**

This text describes the scheme established by Greece to monitor GLP compliance by laboratories within its territory, by means of inspections and study audits.

2. **SCOPE**

The Greek GLP Compliance Programme is set to ascertain that Test Facilities/Sites conducting safety studies on chemicals, the results of which will be submitted to Regulatory Authorities, have been carried out according to the OECD GLP Principles and the respective EU legislation.


The current national law referring to GLP (DSCC No 273/2000) consists a codification of the existing legislation. It implements the whole EU legislation into our national law (including the Dirs 1999/11/EC & 1999/12/EC), describing in the same time the Greek GLP Compliance Programme in greater detail than previously, having taken into account the experience gained in the five (5) years of operation and successful function of the Programme in Greece.

This law is composed by a text consisting of (16) Articles and it is accompanied by (4) Annexes as following:

- Annex I: Good Laboratory Practice Principles
- Annex II: Guidance for the conduct of laboratory Inspections & Study Audits
- Annex III: Guides for compliance monitoring procedures for Good Laboratory Practice (GLP).
- Annex IV: Guidance for a successful application to enter in the Greek GLP Compliance Programme.

3. **FIELD OF APPLICATION**

The Greek GLP Compliance Programme according to the DSCC No 273/00 covers the non-clinical safety testing of all kinds of chemicals (e.g. cosmetics, industrial chemical products, pharmaceuticals, food & feed additives, pesticides) as well as field studies on plant protection products.
It covers non-clinical safety testing of chemicals/articles with final destination /receptor Regulatory Authorities in Greece and abroad.

This legislation is not concerned with the interpretation and evaluation of test results of the studies in question.

4. EU LEGISLATION & GLP

EU legislation requiring the performance of tests and/or studies according to the GLP Principles:

Dir. 67/548/EEC "Classification, labeling & packaging of dangerous substances".
Dir. 1999/45/EC "Classification, labeling & packaging of dangerous preparations".
Reg. 1907/2006/EC “REACH”
Reg. 1272/2008/EC “CLP”
Reg. 648/2004/EC “Detergents”

Dir. 98/8/EC on biocides

Dir. 91/414/EEC on requirements for placing on the market of plant protection products

Receiving/Regulatory Authorities in Greece for the above-mentioned legislation are:
The General Chemical State Laboratory
The Hellenic Ministry of Agricultural Development and Food
The National Drugs Organization.

5. ADMINISTRATION

The Hellenic GLP Monitoring Authority is the General Chemical State Laboratory - Division of Environment. The General Chemical State Laboratory (G.C.S.L.) is a scientific institution of the Ministry of Finance. Most of its staff consists of chemists and chemical engineers supported by administrative staff. The GLP Unit is part of the 2nd Section of the Division of Environment. Head of the GLP Unit and of the Hellenic GLP Monitoring Authority is the Head of the Division of Environment who is especially charged with the selection, among the nominated GLP inspectors, of the ones to perform the specific inspection as well as with the issue of the “Statement of GLP Compliance” to GLP compliant Test Facilities.

The GLP Monitoring Authority is responsible for:
- the "team" of the Greek GLP inspectors
- the publication of documents relating to the adoption of GLP principles in Greece
- the publication of documents concerning the management and operation of the Hellenic GLP Compliance Programme
- the maintenance of the records of the test facilities inspected, of their GLP Compliance Status and of the studies audited
- the preparation of the annual report concerning the monitoring of GLP Compliance in Greece
- all inquiries on GLP from Regulatory Authorities in Greece and abroad and from GLP monitoring Authorities in other countries, on issues relating to data generated in Greece and elsewhere.

The GLP Monitoring Authority also acts as a contact point and provides information, advice and guidance to the chemical industry, test facilities or sponsors of studies on any aspect of GLP.
The Greek GLP Monitoring Authority consists of the Head of the Division of Environment and one official of 2nd Section of the Division of Environment. The inspections are performed by four (4) GLP inspectors nominated as such with the No 3023294/12373/29.10.2007 Decision of the Minister of Economy & Finance. All inspectors are chemists, members of the permanent staff of the GCSL and they are all scientifically qualified with practical experience in analytical chemistry. They have all attended training courses on GLP issues in Greece and abroad (OECD Training Courses, MJVs, Joint Inspections with GLP inspectors of other countries e.t.c.).

A candidate has to participate in three (3) inspections as an observer before he/she is nominated as such and can act as a member of the inspection team.

All inspectors work on a part-time basis on GLP inspections and according to the law they should be no conflict of interests between the GLP inspectors and the test facilities inspected, the studies audited or the companies sponsoring such studies.

In inspections or study audits of specific toxicological, ecotoxicological and/or physical-chemical experiments or field studies, specialized experts from other Ministries or Scientific Institutions may be integrated in the inspection team if appropriate.

These specialized experts are included in an official list maintained by the Monitoring Authority and is established after proposals submitted by the relative Ministries or Institutions. The selection is made depending on test facility to be inspected.

All inspectors are supplied with identification cards to use during inspections.

All issues on GLP should be addressed to:

Ministry of Finance  
Secretariat General of Tax & Customs Issues  
Directorate General of  
General Chemical State Laboratory  
Section B’ of Dangerous Substances, Preparations & Articles  
115 21 Athens  
Tel : +30 210 64 79 450  
Fax : +30 210 64 66 917  
e-mail : environment@gcsl.gr

6. THE GLP COMPLIANCE MONITORING PROGRAMME

The GLP Compliance Monitoring Programme is intended to ascertain whether test facilities have implemented GLP Principles for the conduct of studies and are capable of assuring that the resulting data are of an adequate quality.

Inspections may be conducted at any test facility generating health and/or environmental safety data for regulatory purposes. It includes audits of data of physical-chemical, toxicological and/or ecotoxicological testing of chemicals.

Chemicals covered by the GLP Compliance Monitoring Program are:

⇒ industrial chemicals  
⇒ pharmaceuticals  
⇒ pesticides  
⇒ food and feed additives  
⇒ biocides  
⇒ cosmetics
Tests covered:
1. Physical-chemical tests
2. Toxicity studies
3. Mutagenicity studies
4. Ecotoxicological studies on water & soil organisms
5. Studies in the air compartment, in soil and in water; bioaccumulation
6. Residues studies
7. Studies of the effects on the mesocosms and the natural ecosystems
8. Methods of analytical and clinical chemistry
9. Others, to be specified.

Test facilities submitting a request for verification of compliance with the GLP principles are only accepted if health and environmental safety data of non-clinical studies of chemicals are generated for regulatory purposes. Test facilities may be either research laboratories, or laboratories of industrial units, or public laboratories, or laboratories of universities and research institutes.

The master schedule of the GLP Unit is prepared at the beginning of each year and reflects the inspections planned. It supplies information about the test facilities to be inspected, categories of inspections, inspectors, dates of inspections.

Test facilities introduced in the GLP Monitoring Programme are in principle monitored on a two year cycle (routine inspections). The inspection includes a general test facility inspection and a study audit of on-going and completed studies. Special test facility inspections and/or study audits may be performed at the request of a Regulatory Authority from our country or abroad via the GLP Monitoring authority of the particular country. Such requests will normally concern study audits but may sometimes involve test facility inspections. However, it is the responsibility of the Regulatory Authority to identify and justify the need of such inspections and study audits.

The wide diversity of test facilities (in terms both of physical layout and management structure), together with the variety of types of studies encountered by inspectors, means that the inspectors must use their own judgement to assess the degree and extent of compliance with GLP Principles. Nevertheless, inspectors should strive for a consistent approach in evaluating whether, in the case of a particular test facility or study, an adequate level of compliance with GLP Principles has been achieved.

Inspectors will not be concerned with the need for or the suitability of the design of the studies, the interpretation of the findings of the studies, or the suitability of the test systems used for the purposes of the study. Test facility management must be reminded that legislation exists which controls the use of animals in experiments.

Inspectors normally will not enter test facilities, or attempt to gain access to data held by the test facility without the expressed permission of the test facility management. In the case that access is refused, the GCSL (as GLP Compliance Authority) will proceed to the appropriate measures according to the provisions of the Greek legislation.

### 6.1 Inspection Process
#### 6.1.1 Request of Inspection

Test facilities are introduced in the Greek GLP Compliance Monitoring Program after the submission of a request for monitoring compliance with GLP Principles to the GCSL - Division of Environment. Facilities for which a request for monitoring compliance with GLP Principles is submitted by a Regulatory Authority will also be listed on the master schedule of the GLP Compliance Programme.

The procedure to be followed by a test facility for entering the GLP compliance program is:
The authorized person of the test facility submits an application to the Monitoring Authority (the GCSL) accompanied by a Declaration of the law 1599/86.

The application form follows a specific format and contains the following:

- **Applicant** (name, function, address, Tel., Fax, e-mail)
- **Test facility** (name, address, Tel., Fax, e-mail)
- **Firm** (name if different from that of the test facility to be inspected, address, Tel., Fax, e-mail)
- **Contact person for the cooperation with the Monitoring Authority** (name, function, address, Tel., Fax, e-mail)
- **Legal status of the test facility** (S.A. filiations e.t.c.)
- **Precise description of the activities of the test facility**
- **Precise description of the tests and studies for which the test facility requests the monitoring**
- **Annual overall activities**
- **Personnel** (number, function, qualifications, expertise e.t.c.)
- **Any other useful information**

In the Declaration of the law No 1599/86 the authorized person acting as the contact point for the cooperation with the Monitoring Authority declares that:

1. He is aware of:
   - The Decision of the Supreme Chemical Council No 273/2000
   - The OECD documents referring to the GLP Principles (Documents Consensus referring to GLP)
   - The GLP accreditation process and the monitoring of compliance with the GLP principles.

2. He will make available to the nominated inspectors at least two (2) weeks before the agreed date of the inspection any useful information relative to the:
   - nature and the layout of the test facility
   - management structure of the test facility
   - nature and number of the tests and the studies to be monitored

3. He will permit the free access of the inspection team to all the premises, documents and archives related to the GLP activities, the contact with the personnel involved in the planning, realization and archiving of the GLP studies as well as in any other activity promoting the achievement or the maintenance of the GLP status of the test facility.

4. He will make available to the inspection team any information necessary to evaluate the test facility compliance with the GLP principles.

5. He will make available to the inspection team an appropriate room to work in, during the inspection.

6. He will send his written comments on the deviations and/or on the non compliance observations mentioned in the inspection report, as well as the proposed corrective measures to be taken and the time schedule for their realization, to the Monitoring Authority.

7. He will inform in time the Monitoring Authority about any change in the proprietary status, the personnel, the premises or any other change which may influence the quality of the undertaken studies and he will ask for approval.

8. The firm he represents is not under bankruptcy.

9. He will pay the inspection fees.
10. In the case of field studies, he will destroy the crop used, according to the legal dispositions of the Ministry of Agricultural Development and Food.

6.1.2 PRE-INSPECTION

If the test facility has to be inspected for the first time a pre-inspection is usually carried out before.

The pre-inspection is planned so as to familiarize the inspector(s) with the management structure, the physical layout of buildings and the range of studies undertaken by the test facility. A pre-inspection letter will be sent to the test facility about two (2) weeks before the date of the visit informing the test facility about the name(s) of the inspector(s) and the date and time of the inspector(s)'s visit. (The selected inspectors have to fill in a Declaration of the Law No 1599/86 declaring that there is no family or economic relation between them and the test facility to be inspected).

It is absolutely necessary that management and QA staff are present at the pre-inspection, as in some particular cases documents or records may be asked for examination. The time allocated to a pre-inspection is one (1) day.

The pre-inspection starts with an opening session during which the inspector(s) outline(s) 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 studies which should comply to the GLP Principles. Principally, any study can be performed according to the GLP Principles. However, only data of non-clinical testing of chemicals for regulatory purposes will be considered in the GLP Compliance monitoring programme.

The organization of the test facility will be investigated in order the inspector(s) to be informed about the documentation and operation system of the facility.

Finally, some premises of the test facility will be visited while special attention will be paid to the type and separation of activities, the environmental conditions and the identification and storage of apparatus, test systems and test and reference materials. During this visit to the test facility premises the normal work may be slightly disturbed.

At the exit meeting a summary of the findings, including the strong and weak points of the test facility GLP system, is given by the inspector(s) to the test facility management.

6.1.3 INSPECTION AND STUDY AUDIT

Inspections and study audits will be carried out at the request of the test facility itself or at the request of a Regulatory Authority. If the test facility is visited for the first time the inspection and study audit are normally preceded by a pre-inspection.

After submission by the test facility of the request for GLP compliance monitoring, the Monitoring Authority (the Head of the Division of Environment) selects among the nominated inspectors those who will perform the pre-inspection and the initial inspection of the test facility. Usually the inspection team consists of two (2) inspectors but in particular cases where specific expertise may be needed specialized experts may be integrated in the inspection team. The date of inspection is defined after consultation with the test facility management. The same procedure is followed in the case of a routine inspection with the difference that in this occasion no application is needed as it is the obligation of the
Monitoring Authority to schedule and perform the routine inspections. The test facility has in any case to pay the relative inspection fees.

An inspection letter will be sent to the test facility about two (2) weeks before the start of the visit, indicating the name(s) of the inspector(s) and the date and the time of the inspection, which normally takes three (3) days. However, when major deviations are observed during the inspection, the inspection can be interrupted. On the other side, the inspection team may conclude to audit more studies than programmed which can prolong the period of inspection. 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 inspections and study audits are carried out in accordance with the OECD Guidance for the Conduct of Test Facility inspections and study audits. This Guidance provides an indication of the major GLP aspects which inspectors should examine during inspections and study audits. The checklist used by the inspectors is based upon the aspects listed in the guidance, but is not limited to.

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 are outlined by the responsible of the inspection team. Then, the inspection programme is fixed and the test facility persons who have to accompany the inspectors are designated.

The inspection and study audit will be concluded with an exit meeting during which the test facility management and other personnel is informed about the findings of the inspection. Not only the deviations from GLP Principles are communicated, but also the strong points of the GLP system of the test facility. The deviations are written down after the exit meeting and after discussion with the test facility management are concluded and signed both by the inspectors and the test facility management. This summary of the findings with possible arguments of the test facility management is prepared in two (2) copies, one for the inspectors and one for the test facility management. All deviations found and reported in the summary of the exit meeting, are reported in the inspection report too, at the relative section.

The test facility has to sent its comments on the observations made by the inspector(s), the proposed corrective measures to be taken and the time foreseen for the realization of these measures in writing, as soon as possible (not later than (20) working days after the receipt of the inspection report) to the GLP Monitoring Authority. These comments will be annexed to the inspection report and will be taken into account for the evaluation of the GLP status of the test facility by the Monitoring Authority. The inspection team may visit the test facility again to investigate if the corrective actions are taken.

6.1.4 INSPECTION REPORT

The inspector(s) soon after the completion of the inspection prepare(s) the inspection report which must be sent to the GLP Monitoring Authority within thirty (30) working days after the completion of the inspection. The inspection report is prepared in two (2) copies. One copy is archived by the GLP Monitoring Authority and the second one is sent to the test facility management for comments.

The inspections reports are treated as confidential documents and copies of them can be submitted only to Regulatory Authorities of Greece or from abroad after an official and justified request with aim the safety evaluation of a product and/or its licensing to be placed on the market.

The inspection report follows a specific format and contains the following:
- name and address of the test facility
- units inspected
- type of inspection (initial, routine e.t.c.)
- date of inspection
- persons interviewed during the inspection
- inspectors (name, function)
- specialized experts*(name, function), *when integrated in the inspection team
- an overview of the inspected test facility
- results of the GLP inspection
- observed deviations from the GLP Principles
- annexes

6.2 GLP COMPLIANCE

It is in the interest of the test facility to comply with the requirements of GLP and to produce data of an adequate quality for assessment and decision making by the Regulatory Authorities. Failure to do so may lead to rejection of test results by them.

Depending on the content of the inspection report and the written arguments of the inspected test facility, the Evaluation Committee nominated by the Monitoring Authority evaluates the GLP Status of the test facility. The Evaluation Committee consists of three (3) members and can be assisted in its work by the specialized experts integrated in the inspection team when necessary.

Where no or only minor deviations have been found, the proposed by the test facility corrective measures have been assessed as satisfactory and after the positive proposal of the Evaluation Committee, the GLP Monitoring Authority will issue a statement that the test facility has been inspected and has been found to be operating in compliance with the GLP Principles. The GLP Compliance Statement (Annex 3) will include:

- name and address of the test facility
- identification number of the GLP statement
- date of inspection
- sector of chemicals covered by the GLP statement
- categories of tests for which the test facility is in compliance with the GLP Principles
- signature of the Head of the Division of Environment of the GCSL
- date of signature

Where major deviations have been found during the test facility inspection and/or the study audit the Greek GLP Monitoring Authority requires specific corrective actions to be taken by the test facility management and characterizes the GLP status of the test facility as "pending". When the appropriate corrective actions have been completed by the test facility, a new inspection is scheduled by the Monitoring Authority.

If the test facility management denies to proceed to these corrective actions and the outcome of the appeal procedure is not in favor of the test facility, then the Monitoring Authority does not issue or withdraws the GLP Compliance Statement and informs all interested parties.(GLP Monitoring Authorities and Regulatory Authorities in Greece and abroad, sponsors e.t.c.)

The Monitoring Authority can withdraw the issued GLP Compliance Statement in the following cases:
- When a test facility has submitted false or falsified information
- When a test facility performs tests and/or studies not covered by the dispositions of the DSCC No 273/2000
- When a test facility does not respect the responsibilities it has declared on the Declaration of the law No 1599/86
- When a test facility does not pay the defined inspection fees
- When a test facility refuses to the inspectors the access to its premises, archives e.t.c.

If the management, the QA staff, the personnel and the infrastructure of the test facility, or the type of studies conducted is significantly extended or changed, the test facility has the obligation to make these changes known to the GCSL, Division of Environment and to ask for approval.

The acceptability of a study is decided only by the particular Regulatory Authority and not by the GCSL (as the Greek GLP Monitoring Authority). However, according to the OECD decision on the Mutual Acceptance of Data, a Regulatory Authority of an OECD/EC Member Country will accept a study on GLP grounds where a facility inspection and/or a study audit has been conducted and the facility and/or the study has been found to be in compliance with the GLP Principles.

In order to facilitate the communication between sponsors, test facilities, regulatory and monitoring authorities from Greece or abroad the GCSL provides information on inspections to interested parties in three forms:

- the inspection report and a "Statement of GLP Compliance", where the inspection reveals an adequate compliance with GLP, are sent to the test facility; the inspection report may also be given to the Greek Regulatory Authorities upon official and justified request;
- list of test facilities in compliance with GLP is available to test facilities and sponsors upon request; this list is sent as well to the Regulatory Authorities in Greece for their information once per year;
- an annual report, including the test facilities inspected and their GLP status, is sent to the OECD and the EU.

The test facilities inspections are not free of charge. Test facilities have to pay the inspection fees defined by the Decision of the Minister of Finance No 3002640/1552 (O.J. 161/B'/14.02.2002) as follows:

- Pre-inspection 293 EUROS
- Initial inspection 1.457 EUROS
- Preparation of the inspection report, evaluation of the GLP compliance of the test facility and issuance of the GLP Statement 293 EUROS
- Routine inspection (every two years) 880 EUROS
- Test facility inspection after request of another GLP Monitoring Authority or national Regulatory Authority (in the case of non-compliance found) 586 EUROS

7. CONFIDENTIALITY

Before, during and after the inspections and study audits the inspectors may have access to highly confidential, commercially valuable information. To ensure that maximum confidentiality is maintained:

- The Greek GLP Monitoring Authority treats any information on GLP inspections (e.g. applications, declarations of the law No 1599/86, documents e.t.c.) as highly confidential material. The staff of the GLP Monitoring Authority, the GLP inspectors and the specialized experts who may be integrated in the inspection team, are all civil servants and have to respect the very strict dispositions on confidentiality defined in the Greek Law about the Civil Administration (No 3258/2007 published in the O.J. 26/A/9.02.2007).

- All information acquired by inspectors or held by the GCSL, Division of Environment, is restricted to the staff of the Greek GLP Monitoring Authority.
- Copies of any documents removed from the test facility before, during and after the inspections are given an identification number and are handled as confidential documents.

- Study audit and inspection reports are considered confidential material and will only be made available to the test facility inspected and/or the relevant Greek Regulatory Authorities upon request.

Overviews of test facilities with indication of their GLP status are not considered as confidential.

8. APPEAL PROCEDURES

Any disagreements or differences of opinion between the inspectors and the test facility management, arising from an inspection or study audit, are normally resolved during the inspection or at the exit meeting. However, where problems persist and agreement on differences cannot be reached during the inspection process, the test facility management may appeal against the findings observed and communicated by the inspectors. Such appeal must be addressed in writing to the Head of the Monitoring Authority. The test facility representative may be present at the conference of the Evaluation Committee and may present his arguments there.

If the resolution by this step fails, the test facility may submit an appeal to the Supreme Chemical Council.

9. REFERENCES