DEPARTMENT OF HEALTH

THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

MONITORING AUTHORITY

GUIDE TO UK GLP REGULATIONS 1999

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FOREWORD

Compliance with the principles of Good Laboratory Practice (GLP) is a legal requirement for test facilities that undertake health and environmental safety studies, and some other testing, that will be submitted to regulatory authorities for the purposes of risk assessment. The principles of GLP, and the procedures implemented within the United Kingdom to monitor GLP compliance are contained within Statutory Instrument No. 1999/3106, the Good Laboratory Practice Regulations 1999 (the GLP Regulations).

This Guide has been produced by the UK’s GLP Monitoring Authority (GLPMA) and provides additional information on the UK GLP compliance monitoring programme. It should be read in conjunction with the GLP Regulations.

INTRODUCTION

The GLP Regulations and the Guide apply to any test facility which conducts, or intends to conduct, a regulatory study. A regulatory study is a study for which the regulatory authority to whom the data will be submitted, requires that study to be conducted in compliance with the principles of GLP. This Guide may also be useful to those test facilities that conduct, or intend to conduct, work that supports a regulatory study.

GLP is concerned with the organisational processes and the conditions under which certain laboratory studies are planned, performed, monitored, recorded, archived and reported. Adherence by test facilities to the principles of GLP ensures the proper planning of studies and the provision of adequate means to carry them out. It facilitates the proper conduct of studies, promotes their full and accurate reporting, and provides a means whereby the validity and integrity of the studies can be verified. The application of GLP to regulatory studies assures the quality of the data generated and allows its use by Government regulatory authorities in hazard and risk assessment in particular of new substances.

The internationally accepted principles of GLP were developed by the Organisation for Economic Co-operation and Development (OECD). These GLP principles and other associated OECD documents were subsequently ratified by the European Commission and transposed into EC Directives. The GLP Regulations implement these Directives within the United Kingdom.

The UK GLP Monitoring Authority (GLPMA) has responsibility for monitoring test facilities for compliance with the principles of GLP. The work of the GLPMA is carried out by a unit within the Inspection and Enforcement Division of the Medicines Control Agency (MCA), which is an executive Agency of the Department of Health (DH).

The range of test facilities monitored by the GLPMA include those involved in the health and environmental safety testing of human and veterinary pharmaceuticals, agrochemicals, cosmetics, food and feed additives and industrial chemicals. The test items are frequently synthetic chemicals but may be of natural or biological origin, and in some circumstances may be living organisms.
The following numbered sections correspond to the numbered Regulations in the Statutory Instrument.

1. PREAMBLE, CITATION AND COMMENCEMENT

(1) The GLP principles originally adopted by the European Community (article 1.1 of Council Directive 87/18/EEC) were those published by OECD in 1982 in Chapter 2 of “Good Laboratory Practice in the Testing of Chemicals – Final report of the OECD Expert Group on Good Laboratory Practice”. Commission Directive 90/18/EEC also endorses some OECD recommended adaptions of the original principles that were published in OECD Environment Monograph No. 47 and which are also set out in the Annexes to that Directive. Modified versions of these texts (modified to take into account legislative drafting requirements) were contained in Schedules 1 and 2 of the Good Laboratory Practice Regulations 1997.

(2) Following further consideration of key aspects of GLP by an OECD Expert Group, a revised set of GLP principles and revised guidance for compliance monitoring procedures were approved by OECD Council Decision C(97)186(Final). The European Commission adopted these revised OECD documents and incorporated them into Commission Directives 1999/11/EC and 1999/12/EC in March 1999.


(4) Section 2(2) of the European Communities Act 1972 permits any necessary regulations to be made by designated Ministers or departments. The designation of which Ministers or departments may exercise the power to make regulations, and details of which matters may be so regulated, are specified in Statutory Instrument No. 1999/2788, the European Communities (Designation) (No.3) Order 1999. This Statutory Instrument that came into force on 15th November 1999 designates the Secretary of State as a Minister with responsibility for “Measures relating to good laboratory practice”.

(5) The GLP Regulations came into force on 14th December 1999.

2. INTERPRETATION

(1) The definitions cited in this section of the GLP Regulations are, in most cases, identical to the definitions contained within the original OECD texts and corresponding EC Directives. However, there are a number of definitions that have been amended to accord with current UK legislative drafting requirements.
(2) The most significant of these changes is the use of “regulatory study” to replace the term “non-clinical health and environmental safety study”. This was necessary because the definition of non-clinical health and environmental safety study in the revised OECD principles of GLP includes studies which look at the properties of a test item rather than its health or environmental safety. Because not all studies for which GLP compliance is required are concerned with safety, the terminology had to be changed. The definition of regulatory study is given in section 4 below.

3. THE GOOD LABORATORY PRACTICE MONITORING AUTHORITY

(1) The GLP Regulations define the Good Laboratory Practice Monitoring Authority as the body responsible for enforcing compliance with the Regulations. It consists of the Secretary of State for Health, the National assembly for Wales, the Scottish Ministers and as respects Northern Ireland the Department of Health, Social Services and Public Safety - either acting alone, or any two or more of them acting jointly. They may appoint such persons as they think necessary for the proper discharge of their functions.

(2) In practice, these functions are discharged by the GLPMA which is the management body with responsibility for monitoring GLP compliance within the UK. In this capacity it is responsible for administering the UK GLP compliance programme. This involves the inspection of test facilities that are members, or prospective members, of the compliance programme, and for conducting study audits on behalf of regulatory authorities.

(3) The GLP MA deals with all enquiries on GLP from UK and overseas regulatory authorities. It also acts as a contact point and provides information, advice and guidance to industry, test facilities, sponsors of studies and the public on any aspect of GLP. To this end, the GLPMA may publish from time to time guidance on the interpretation or application of GLP principles in particular situations or circumstances.

(4) GLP is not treated as a reserved matter under the Scotland Act 1998 or the Northern Ireland Act 1998. Except where the functions of the GLPMA relate to matters reserved to the Westminster Parliament (for example, international relations), its functions fall within an area of devolved competence in respect of those countries. This is reflected in arrangements for enforcing compliance with the GLP Regulations, arrangements which also confer on the National Assembly for Wales identical enforcement powers to those of the Secretary of State for Health, the Northern Ireland Assembly and the Scottish Ministers. As regards international relations, the Head of the GLPMA represents the UK on GLP matters at EU and OECD meetings, and the GLPMA will remain the contact point for communication with overseas regulatory authorities on GLP matters. However, in its conduct of international relations the GLPMA follows the relevant concordats agreed with the devolved Governments.
The GLPMA consists of a Unit Head and inspectors, appropriately qualified, with relevant experience, and with knowledge of relevant sectors of industry. They are familiar with the GLP Regulations and the principles of GLP, the standards necessary to comply with these Regulations and principles, and with the regulatory requirements of authorities in the UK and overseas.

In situations where it is suspected that a criminal offence may have been committed, the GLPMA may need to commission the assistance of other appropriate DH officials, appropriate officials in the devolved administrations, or the police, to carry out the necessary investigations.

Any investigations into possible breaches of the Regulations would usually be coordinated by the GLPMA. However, if the investigation results in legal action being taken through the courts, responsibility for this action may be assumed by the appropriate authorities in Scotland, Wales or Northern Ireland if the alleged offence occurred there.

**4. REQUIREMENT TO BE A MEMBER OR A PROSPECTIVE MEMBER OF THE UK GLP COMPLIANCE PROGRAMME**

The GLP Regulations require that any test facility which conducts, or intends to conduct, a “regulatory study” must be a member, or prospective member, of the UK GLP compliance programme. A “regulatory study” is defined as:

A non-clinical experiment or set of experiments –

(a) in which an item is examined under laboratory conditions or in the environment in order to obtain data on its properties or its safety (or both) with respect to human health, animal health or the environment;

(b) the results of which are, or are intended, for submission to the appropriate regulatory authorities; and

(c) compliance with the principles of good laboratory practice is required in respect of that experiment or set of experiments by the appropriate regulatory authorities (whether or not compliance with the said principles in respect of that experiment or set of experiments is also a legislative requirement).

Current European Directives do not require laboratory tests to support human clinical trials or efficacy trials on plant protection products to be conducted according to the principles of GLP.
(3) Operators of test facilities must ensure that regulatory studies are not carried out at their premises unless they are a member or prospective member of the UK GLP compliance programme in respect of those premises. Some operators may be members of the compliance programme, but only in respect of defined parts of their test facility. If they subsequently intend to carry out a regulatory study at another part of their test facility not covered by their membership, they must apply for prospective membership of the compliance programme in respect of that additional part of the test facility before conducting regulatory studies there.

(4) There may be circumstances when the operator of a test facility wishes to join the compliance programme because they will be undertaking testing for which current EC Directives do not require GLP compliance, but for which the regulatory authority to whom the data will be submitted has stipulated that the work should be GLP compliant. If this testing constitutes a regulatory study as defined in paragraph 4.(1) then the test facility may be admitted to the compliance programme. They will be treated on the same basis as those test facilities conducting regulatory studies for which GLP compliance is a legislative requirement.

(5) Not all premises generating data that may be used in a regulatory study will necessarily need to be members of the compliance programme. Premises that are not in the UK cannot be in the UK programme but may of course be in the programme of the country in which they are situated. Premises involved solely in the production of background data, such as meteorological analysis, may not need to be in the programme.

(6) It is common practice that studies, or parts of studies, may be conducted by contract test facilities on behalf of a sponsor. In these circumstances the contract test facilities will only need to be in the compliance programme if they undertake work that amounts to a separate regulatory study. However, at the discretion of the GLPMA, a test facility that is conducting, or intends to conduct, work that constitutes a discrete phase of a regulatory study may be admitted to the compliance programme. It will be treated on the same basis as those test facilities conducting complete regulatory studies.

(7) Whether or not the contracted-out work constitutes a regulatory study may involve questions of fact and degree in each particular case. An example is where use is made in a regulatory study of data generated by a specialised technique which is only available at a particular laboratory. If the work carried out using the specialised technique is itself an experiment that fulfils the definition of regulatory study, then the laboratory conducting that work would need to be a member of the compliance programme.

(8) Test facilities that do not conduct, or intend to conduct, work that constitutes a regulatory study or a discrete part thereof are not required to work in accordance with the principles of GLP and will not therefore be admitted to membership of the UK GLP compliance programme.
Control and monitoring of contracted out work

(a) If the contracted-out work does not constitute a discrete regulatory study but only part of a regulatory study, the study director is responsible for ensuring that it is conducted in accordance with the principles of GLP. If the facility undertaking the contracted work is itself a member of the UK GLP compliance programme, it will not usually be necessary for representatives of the sponsoring test facility (i.e. the test facility at which the study director is located) to carry out any specific monitoring of the work carried out.

(b) If work that forms part of a regulatory study is contracted out to a test facility not in the compliance programme, and it is intended to claim compliance for that part of the study, then the sponsoring test facility must put into place quality assurance and management mechanisms to ensure that the contracted out work is done in accordance with GLP principles. In effect the contracted test facility will become part of the sponsoring test facility’s GLP system for that specific part of that study. This extension of the sponsoring test facility’s GLP system only applies to the piece of work in question and does not apply to the contracted test facility as a whole, or to any other work undertaken by them.

(c) The management mechanisms implemented by the sponsoring test facility must be operated to the satisfaction of the UK GLPMA. This will usually require the contracted-out work from each separate regulatory study to be monitored by representatives of study management and/or quality assurance from the sponsoring test facility. If this monitoring confirms that the contracted out work was conducted in accordance with GLP principles, then the study director may claim GLP compliance for the complete study, including the contracted out work. Conversely, if monitoring indicates that the work is not carried out in accordance with GLP principles then no claim of compliance can be made for this work.

(d) When a sponsoring test facility wishes to extend their GLP system to cover contracted out work, the GLPMA should be notified, in writing, of the test facility to be used, the regulatory studies concerned, and the type of work to be undertaken.

(e) If work that forms part of a regulatory study is contracted out to a test facility that is not a member of the compliance programme, unless this work is covered by an extension of the sponsoring test facility’s GLP system (as described in paragraphs a, b and c above) no claim of GLP compliance can be made for this work. The non-compliance of this work must be clearly stated in the study director statement included in the final study report.
(f) The situation is similar if an overseas test facility is contributing data towards a regulatory study being conducted by a UK test facility. Unless the overseas facility is a member of its own national GLP compliance programme, the UK test facility will need to monitor the work done overseas to ensure that it is done in accordance with GLP principles or no claim of GLP compliance can be made for this work.

(10) There may be circumstances in which the situation described in paragraph (f) above is reversed, i.e. a test facility in the UK is contributing data towards a regulatory study being conducted by an overseas test facility. It would not be a breach of the Regulations for the UK test facility to conduct this work without being a member of the compliance programme providing that the work did not constitute a discrete regulatory study as defined in paragraph 4.(1). However, if the UK test facility produced a GLP compliance statement for their work with the intention that this statement would be submitted to a regulatory authority, this could be a “false GLP instrument” and might constitute an offence under Regulation 12. (see section 12 for further information)

(11) In addition to the contracting out of study related work, it is also possible that other GLP activities might be contracted out to another organisation. Such activities might include provision of quality assurance services by a consultant; provision of computer system support; contract archiving; facility and/or equipment maintenance. In these situations there must be formal contracts and, if appropriate, detailed service level agreements which define the nature and extent of services to be provided.

(12) Test facility management is responsible for ensuring that any contracted out GLP activity is carried out in accordance with the GLP principles. When the contracted out service is fundamental to the overall GLP compliance of the test facility, e.g. archives or computer support, the UK GLPMA reserves the right to inspect these facilities.

5. PROSPECTIVE MEMBERSHIP OF THE UK GLP COMPLIANCE PROGRAMME

(1) There are two categories of “membership” of the programme: full membership and prospective membership. Prospective membership in most cases will be granted almost automatically, once an operator has informed the GLPMA in writing of his intention to conduct regulatory studies, or parts thereof, at particular premises. Prospective membership is granted by the GLPMA, acknowledging in writing receipt of the operator’s application, and informing him that he is a prospective member of the compliance programme. The GLPMA will then carry out an initial inspection of the test facility, usually within twelve weeks of prospective membership being granted.
(2) Any test facility operator who was advised by the GLPMA that they were a member, or prospective member, of the UK GLP compliance programme before the commencement of the 1999 GLP Regulations retain their membership status. They will remain members unless or until they withdraw voluntarily or have their membership withdrawn in accordance with regulations 5 and 6.

6. MEMBERSHIP OF THE UK GLP COMPLIANCE PROGRAMME

(1) If the initial inspection of a prospective member is satisfactory, the test facility operator will be admitted to full membership of the compliance programme in respect of those premises.

(2) If the GLPMA is considering a refusal to admit the operator to the compliance programme in respect of those premises, it is obliged, in accordance with regulations 5 and 6 –

(a) to inform the prospective member why membership is being refused

(b) to give the operator a specified period within which to make representations to the GLPMA, and

(c) consider any representations made,

unless the GLPMA has encountered a failure to comply with GLP principles that may precipitate a danger to animal or human health or to the environment, or the GLPMA is required for a reason under Community law to withdraw prospective membership immediately.

(3) Once prospective membership has been withdrawn, if an operator wishes to re-apply, he may do so, but rather than admitting them to prospective membership of the programme, the GLPMA will normally defer any decision on membership until after a further inspection. The GLPMA will usually make such an inspection within twelve weeks of receipt of the re-application (unless the GLPMA considered that the re-application was not justified). If the inspection confirms compliance with the principles of GLP, the operator will be admitted to full membership of the programme.

(4) If circumstance arise where the GLPMA takes the view that –

(a) the operator of a test facility who is a member of the programme in respect of particular premises is not capable of ensuring that GLP principles are adhered to at those premises, or
(b) at particular test facility premises there is a failure to adhere to GLP principles that may precipitate a danger to human or animal health or to the environment, or

(c) the operator is not conducting, and no longer intends to conduct work that constitutes a regulatory study or a discrete phase thereof,

then subject to the next paragraph, membership of the programme may be withdrawn in respect of those premises.

(5) Before withdrawing membership of the programme for the reasons given in paragraph 6.(4)(a) or (c) above, the GLPMA is obliged –

(a) to inform the member that such action is being considered and explain, in writing, the reasons for this course of action.

(b) to give the operator a specified period within which to make representations and

c) to consider any representations which are made.

(6) If the GLPMA are considering withdrawing membership of the programme for the reasons given in paragraph 6.(4)(b), there is no statutory requirement on the GLPMA to give the operator prior notice and an opportunity to make representations. However, the GLPMA will generally seek to do so, unless there are particular reasons why they need to withdraw membership immediately, for example because of an imminent risk of harm to animal health, human health or the environment.

(7) Where membership of the programme has been withdrawn in respect of particular premises, operators can apply to be re-admitted to the programme in relation to those premises.

(a) Where membership has been withdrawn because the operator was not considered capable of adhering to the principles of GLP at the test facility, the test facility can be re-admitted to the programme when the GLPMA is again of the opinion that the operator is capable of adhering to GLP principles at those premises.

(b) Where membership was withdrawn due to a possible danger to human or animal health or to the environment, the test facility can be re-admitted to the programme when that danger is no longer present.
(c) Where membership has been withdrawn because the test facility, or individual premises thereof, were not, in the opinion of the GLPMA, intending to conduct work that constituted all or part of a regulatory study, the operator can apply to be re-admitted to prospective membership of the programme when they demonstrate their intention to conduct further regulatory work at those premises. Application procedures will proceed as already described in paragraph 5(1).

7. REQUIREMENT TO ADHERE TO THE PRINCIPLES OF GLP

(1) Regulation 4 requires that any test facility which conducts, or intends to conduct, a “regulatory study” must be a member, or prospective member, of the UK GLP compliance programme. Regulation 7 requires any natural or legal person conducting a regulatory study at a test facility to adhere to the principles of GLP.

(2) The purpose of the GLP compliance programme is to monitor test facilities to ensure that they have implemented the necessary GLP procedures for the proper conduct of regulatory studies and are capable of assuring that the resulting data are of adequate quality. The programme encompasses test facility inspections and study audits carried out in accordance with the internationally agreed principles of GLP.

(3) A test facility, or individual laboratory areas within a test facility, may be engaged in the conduct of both regulatory studies (for which GLP compliance is required) and other work (for which GLP compliance is not required). In such situations, measures must be taken to ensure that the GLP compliance of the regulatory studies is not compromised by the conduct of the other work. In practice, this will usually require that all work is conducted to a uniform standard that is in accordance with the principles of GLP.

(4) Categories of inspections

Apart from the initial inspection, the inspections will fall into three categories:

(a) A system of regular, routine monitoring of test facilities, in principle on a two year cycle. Such monitoring will involve a general inspection of the test facility and a limited audit of ongoing or completed studies.

(b) Surveillance inspections of test facilities to monitor the effectiveness of any remedial actions implemented as a result of serious adverse inspection findings.
(c) Special test facility inspections and/or study audits at the request of regulatory authorities in this country or overseas, e.g. prompted by a query arising from the submission of data to that authority. Such requests will normally be for study audits but may sometimes involve test facility inspections. It will be for the regulatory authority concerned to identify and justify the need for any inspection or study audit that it has requested.

(5) **Inspection and study audit procedures**

(a) Operators of test facilities will normally be notified in advance of any inspections or audits which are to be carried out. However, under regulation 9 the GLPMA may, at their discretion, conduct any inspections or audits at any reasonable hour, at short notice or without prior notice.

(b) Study audits and directed inspections will normally take priority over the routine inspection programme.

(c) The wide variety of test facilities and diversity of study type means that inspectors will inevitably have to use their own judgement to assess the extent of compliance with the principles of GLP. Inspectors will nevertheless strive for a consistent approach in evaluating whether an adequate level of GLP compliance has been achieved.

(d) If serious deficiencies are identified during a routine facility inspection, directed inspection or study audit it may be necessary for the GLPMA to undertake surveillance inspections to ensure that the test facility continues to operate in accordance with the principles of GLP.

(e) In some instances study audits may suggest the need for a more general inspection of the test facility. In other instances, specific requests from regulatory authorities may be met from information derived from recently completed inspections, and further visits to the test facility concerned may not be necessary.

(f) During test facility inspections and study audits inspectors will have discussions with staff engaged in regulatory studies on any GLP points as they arise. A final meeting with management and relevant test facility personnel will normally be held in order that they may be informed of the outcome of the inspection or study audit. At this meeting a summary of the inspector’s findings will be presented.

(g) Mention may also need to be made of work that the inspector was unable to observe. This might include for example remote field trials stations that were not inspected during the inspection of the parent test facility, or laboratory areas that were not undertaking experimental work during the inspection.
(6) The GLPMA does not monitor:

(a) compliance with health and safety legislation at test facilities,

(b) compliance with animal welfare legislation at test facilities,

(c) the suitability of the design of studies, or the studies’ objectives,

(d) the suitability of the test system used for the purposes of identifying any particular hazardous property of a test item,

(e) the interpretation of the findings of the studies with respect to risks to human or animal health or the environment.

Test facility management is, however, reminded that the interests of the GLPMA and those of other inspectorates may overlap in some areas such as, for example, staff training, storage and labeling of chemicals, and general hygiene.

(7) Changes at test facilities

(a) The GLPMA should be informed, in writing, of any significant changes that happen with regards to the premises, activities or management of a test facility. Such changes might include construction of new or extended laboratory areas, intention to conduct additional (significantly different) study types, or major changes in key personnel.

(b) The GLPMA will consider the possible implications of the notified changes. If deemed appropriate, an inspector will visit the test facility in order to assess whether GLP compliance has been affected by the changes.

(c) When there have been very significant changes to the management of a test facility, e.g. as a result of acquisitions or mergers, it will usually be necessary for the GLPMA to revisit the test facility.

(8) Inspection and study audit reports

A full written report of the inspector’s findings will be provided to test facility management after completion of an inspection or audit. This report will indicate the nature of any deviations from the GLP principles or other deficiencies found at the time of inspection or audit. These may be deviations or deficiencies that are not sufficiently serious to affect the validity of studies emanating from the test facility, or they could be serious deviations or deficiencies that may, in the view of the inspector, affect the validity or integrity of studies emanating from the test facility.
If serious deviations or deficiencies are identified and the GLPMA is considering withdrawing prospective or full membership of the programme, the procedures described in section 6 will be initiated.

(9) **Warning notices**

If the GLPMA identifies serious deviations or deficiencies which in its opinion may have affected the validity of a regulatory study, a formal “warning notice” may be served on the operator of the test facility. This warning notice will state the GLPMA grounds for believing that the principles of GLP have not been adhered to, specify the measures that must be taken, require the operator of the test facility to undertake those measures (or measures equivalent to them) within a specified period, and outline his appeal rights under the Regulations. Failure to comply with a warning notice that has not been withdrawn by the GLPMA or cancelled by a court is an offence under regulation 7.

(10) **Responding to inspection and study audit reports**

(a) As soon as possible, and in any case no more than four weeks, a response to the inspection or audit report should be forwarded by test facility management to the GLPMA. This response should detail any action taken, or being taken, to rectify the GLP deviations or deficiencies reported by the inspector.

(b) The GLPMA will consider whether, in their opinion, the proposed remedial actions are appropriate to correct the deviations or deficiencies identified by the inspector. The operator will be informed, in writing, whether or not the proposed remedial actions are acceptable to the GLPMA.

(c) In the case of a routine inspection of a test facility that is a member of the compliance programme, when the GLPMA is satisfied that all deviations or deficiencies identified during the inspection have been corrected, a new GLP compliance statement will be issued.

(d) When the inspection was of a prospective member, once the GLPMA is satisfied that all deviations or deficiencies identified during the inspection have been corrected, the operator will be admitted to full membership of the programme in respect of specified premises and a GLP compliance statement will be issued.

(e) In the case of specific study audits the test facility will normally be invited to comment on the audit report before it is sent to the regulatory authority that requested the study audit. Any response to the audit report would normally be sent to the regulatory authority which requested the study audit with a courtesy copy sent to the GLPMA.

(f) In all cases the GLPMA reserves the right to carry out a re-inspection of a test facility before a GLP compliance statement is either issued or renewed.
(11) **GLP compliance statements**

Inspections do not result in the formal approval of test facilities to conduct regulatory studies. However, following a satisfactory inspection the GLPMA will normally issue a GLP compliance statement. This states the name and address of the test facility, the date of inspection, and an indication of the areas of expertise of that test facility.

(12) The areas of expertise that may appear on the compliance statement are:

- Analytical Chemistry
- Ecosystems
- Environmental Fate
- Environmental Toxicity
- Mutagenicity
- Toxicology
- Phys/Chem Tests

At the discretion of the GLPMA other test categories may be included if appropriate.

(13) The statement indicates that at the time of the inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at those facilities. The GLP compliance statement verifies that the test facility operates in accordance with the principles of GLP.

(14) In cases where there are only minor deviations from GLP principles which are not sufficiently serious to affect the validity or integrity of studies emanating from the test facility, it is considered reasonable for an inspector to report that the test facility is operating in accordance with GLP principles. These minor deviations or deficiencies will still need to be addressed as described in paragraph 7,(10) above.
8. COMPLAINTS AND APPEALS

(1) Any problems or misunderstandings between inspectors and test facility management arising from an inspection or study audit will normally be resolved in the meeting held at the end of the inspection or study audit. However, where problems persist and differences cannot be reconciled, test facility management may make representations against those findings of the inspectors that they consider unacceptable. Such representations should be made, in writing, to the Head of the GLPMA within the four week period described in paragraph 7.(10)(a). Appropriate steps will then be taken to achieve a mutually acceptable resolution of the problem.

(2) In the event that a test facility is not satisfied with the outcome of their representations in relation to any matter covered in the inspection or audit report, they should refer the matter to the Head of the Inspection & Enforcement Division of the Medicines Control Agency. In considering any representations, the views of expert assessors drawn from outside the Department of Health may be sought, on scientific or other matters. In seeking views, due account will be taken of the need for confidentiality.

(3) If a test facility is still not satisfied with their treatment they may wish to refer the matter to the Secretary of State for Health at Richmond House, 79 Whitehall, London SW1A 2NS.

(4) Where test facility management wishes to make representations about the manner in which an inspection or audit was conducted by the inspector, the same procedures should be followed.

(5) An operator of a test facility who is aggrieved by a decision to serve a warning notice on him may appeal through appropriate legal channels as described in regulation 8. Essentially, this involves an appeal to a magistrates’ court or, in Scotland, to a sheriff.

9. POWERS OF ENTRY

(1) Regulation 9 of the GLP Regulations empowers persons authorised in accordance with regulation 3 to enter premises and to require the production of data, etc. However, such authorised persons (usually inspectors from the GLPMA) will not normally enter any test facility premises, or attempt to gain access to data held by a test facility without the express permission of test facility management. Management of contract laboratories should ensure that sponsors are aware of these provisions concerning the inspectors’ authority to require production of study data.
(2) Authorised persons may also need to gain access to premises involved in a regulatory study but in respect of which membership of the GLP compliance programme is not required. They have the right, under the GLP Regulations, to enter any premises within the UK other than premises used solely as a private dwelling for the purposes of enforcing compliance with the GLP Regulations. However, as with premises of test facilities within the compliance programme, premises will not normally be entered without the express permission of the occupier.

(3) The GLP Regulations also contain reserve powers to obtain a warrant from a justice of the peace authorising entry where admission has been or is likely to be refused, where an application for admission, or the giving of notice, would defeat the object of entry, or in relation to unoccupied premises.

(4) The role of non-GLPMA staff in inspections or study audits

(a) The GLPMA may occasionally invite (in accordance with its powers under regulation 9) official representatives of other authorities to participate as observers in an inspection or study audit. The policy of the GLPMA is that such invitations will only normally be made with the consent of the test facility.

(b) Inspectors may also need to seek the assistance of specialists, especially when conducting study audits. If this is done, specialists may be drawn from appropriate Government departments, Government agencies, NHS hospitals, universities, or private consultancy organisations.

(c) Specialists, from wherever they are drawn, will be required to give an undertaking in writing not to use or disclose any information they may acquire in the course of an inspection or audit. Test facilities and sponsors will be informed of the identity of the specialists and the reasons why they are being involved.

10. DISCLOSURE OF CONFIDENTIAL INFORMATION

(1) Inspectors and other authorised persons may have access to highly confidential, commercially valuable information whilst conducting inspections and audits. To ensure that confidentiality is maintained:

(a) inspectors will carry warrants during inspections and study audits and can be called upon to produce them. Other authorised persons will have appropriate means of identification provided by the GLPMA.
(b) inspectors will, if requested by the test facility, sign to confirm receipt of any documents removed from the premises following an inspection or audit. In all cases, where inspectors use their powers to take possession of any article, substance, book, document, data or record, they are required to leave with a responsible person a statement giving particulars of the whatever has been taken (regulation 9(5).

(c) all information acquired by inspectors and/or held by the GLPMA is treated confidentially.

(2) Access to information and reports held by the GLPMA is generally restricted to the staff of the GLPMA and its line management, and no information will be disclosed to anyone else without proper lawful authority for doing so. There are certain authorities to whom confidential information can lawfully be released, and some information that is not considered to be confidential.

(3) The GLP Directives stipulate that the following information should not be considered confidential and consequently it may be released by the GLPMA. This information is –

   (a) the names of test facilities which are or have been subject to an inspection as part of the UK GLP compliance programme;

   (b) the good laboratory practice compliance status of those test facilities; and

   (c) the dates upon which test facility inspections or study audits have been conducted.

(4) The GLPMA may, in the performance of its legal duties, disclose confidential information to the European Commission, another GLP monitoring authority, a regulatory authority, a police force or to a test facility or sponsor concerned with a particular inspection or study audit. In addition, compliance statements and summaries of routine inspections and/or reports of specific study audits will be made available by the GLPMA to regulatory authorities if so requested. Copies of GLP compliance statements and audit reports will also be made available to the facility inspected and to sponsors of the studies audited.
(5) In cases where the GLPMA has the proper legal authority to disclose information held about a test facility but is not obliged to do so, the GLPMA will give due regard to the importance of protecting sensitive commercial information which would be useful to one of the test facility’s commercial competitors if it entered the public domain. Similar provisions will be applied to information relating to personnel involved in the conduct of studies. The Government’s position on disclosure of information is set out in the “Code of Practice on Access to Government Information” by which the GLPMA is bound.

11. OBSTRUCTION OF AUTHOURISED PERSONS

(1) As indicated in section 9, authorised persons have certain rights of access to test facilities. Should access be refused, the GLPMA may inform any regulatory authority that access has been refused and that the GLP compliance of that test facility cannot therefore be verified.

(2) Additionally, if an authorised person is refused access to any premises of a test facility, or is otherwise obstructed in the course of their duties, prosecution may be considered under regulation 11.

12. FALSE GOOD LABORATORY PRACTICE INSTRUMENTS

(1) The 1999 GLP Regulations include a new offence relating to the production, possession and submission to regulatory authorities of false good laboratory practice instruments. The most common examples of good laboratory practice instruments are-

(a) The statement of GLP compliance issued by the UK’s GLPMA or another national GLP monitoring authority following a test facility inspection.

(b) A letter, or other document, in which the UK’s GLPMA or another national GLP monitoring authority confirms that certain premises of a test facility operate in accordance with the principles of GLP, or that certain study types are conducted in accordance with the principles of GLP.

(c) The report issued by a GLP monitoring authority as a result of a site inspection or study audit.

(d) A statement included within a submission made to a regulatory authority in which it is claimed that a test facility, or premises thereof, operate in compliance with the principles of GLP.
A statement included within a submission made to a regulatory authority in which it is claimed that a regulatory study, or studies, had been conducted in accordance with the principles of GLP. This includes the study director GLP statement that forms part of each GLP study report. (and also any Principal Investigator statements made in respect of discrete phases of a study, if included within the report)

Making alterations or amendments to a good laboratory practice instrument which is intended for submission to a regulatory authority would constitute production of a false instrument.

Any good laboratory practice instrument that is misleading could also be considered to be a false instrument. For example a study director statement which claims GLP compliance for a study that is known to be significantly flawed could constitute a false instrument. It is therefore essential that study director statements clearly and accurately indicate any GLP deviations that might call into question the GLP compliance of the study or a part thereof.

When a test facility is undertaking a discrete phase of a study, under the control of a principal investigator, care must be taken to ensure that the GLP compliance statement produced by the principal investigator clearly indicates the scope of the work for which compliance is being claimed.

13. OFFENCES

The GLP Regulations describe the different offences that can be committed. Test facility management should be aware that if an offence is committed by a body corporate or Scottish partnership, and is proved to have been committed with the consent or connivance of, or to be attributable to any neglect on the part of any director, manager, partner or similar, then they, as well as the body corporate or Scottish partnership shall be deemed to be guilty of that offence.

14. DEFENCE OF DUE DILIGENCE

In any legal proceedings initiated under the GLP Regulations, it shall be a defence for the person charged to prove that he took all reasonable precautions and exercised all due diligence to avoid the commission of the offence.
15. PENALTIES

(1) If serious deviations from the principles of GLP are identified during a test facility inspection or study audit, the GLPMA may inform appropriate regulatory authorities. The test facility will, however, generally be informed before such action is taken.

(2) In most instances, the most effective and proportionate sanction against serious deviations from GLP principles will simply be refusal to grant GLP compliance statements until such time as appropriate remedial action has been taken. However, situations may arise where, because of aggravating circumstances, the GLPMA will need to consider withdrawing membership of the GLP compliance programme or issuing a warning notice.

(3) In the case of legal proceedings being initiated under the GLP Regulations, upon conviction the guilty party shall be punished in accordance with the schedules described in regulation 15. Details of the standard scale of fines may be obtained from a magistrates court.

16. FEES

(1) Test facilities that are members of the GLP compliance programme are charged fees, as determined by the GLPMA, to cover their costs. These fees are set at levels such that they meet that part of the expenditure of the GLPMA which is reasonably attributable to the costs of inspecting and providing services under the GLP Regulations. Such fees have to be paid within 14 days following written notice (i.e. an invoice) from the MCA requiring payment.

17. REVOCATION

(1) The 1997 Good Laboratory Practice Regulations and associated Code of Practice are replaced by the 1999 regulations and this Guide.
PERFORMANCE STANDARDS

CONDUCT OF GLPMA BUSINESS

(1) The GLPMA aims to provide an acceptable level of service and an effective complaints procedure. This is based on the following standards:

- All of the business conducted by the GLPMA will be carried out fairly and impartially. The GLPMA aims to provide a service that is accurate, courteous, efficient and positively helpful to the members of the GLP compliance programme. Staff will identify themselves by name at all times.

- Routine test facility inspections will be undertaken, in principle, on a two yearly cycle.

- A test facility will normally be given up to 10 working days notice of an intended inspection.

- A test facility will be informed in writing of the results of an inspection within 15 working days of the inspection.

- The GLPMA will carry out the initial inspection of a new test facility within twelve weeks of its being accepted as a prospective member of the GLP compliance programme.

- All correspondence sent to the GLPMA will be acknowledged, when necessary, within 5 working days. A reply will be sent to all enquiries within three weeks.

- Operation of a swift and effective complaints procedure.
Consultation and Communication

(2) The GLPMA has established Committees through which it is able to liaise with representatives of other regulatory authorities and industry trades associations.

(3) Any changes to the way in which the GLPMA operates will be discussed with other UK regulatory authorities and industry by means of their representatives on the relevant Committees.

(4) All enquiries concerning GLP should be addressed to:

GLP Monitoring Authority
Market Towers
1 Nine Elms Lane
London SW8 5NQ

Publication of Performance Standards

(5) At the end of each calendar year the GLPMA will publish the results of its performance against the standards of service set out in this document and also views on the effectiveness of the complaints procedure. This information will be made available via the industry representatives on the GLP Consultative Committee.