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**S T A T U T O R Y I N S T R U M E N T S**

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**1999 No. 3106****HEALTH AND SAFETY****The Good Laboratory Practice Regulations 1999**

*Made* - - - - - *18th November 1999*

*Laid before Parliament* *19th November 1999*

*Coming into force* - - *14th December 1999*

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The Secretary of State, being a Minister designated<sup>(a)</sup> for the purposes of section 2(2) of the European Communities Act 1972<sup>(b)</sup> in relation to measures relating to good laboratory practice, in exercise of the powers conferred by the said section 2(2)<sup>(c)</sup>, and of all other powers enabling him in that behalf, hereby makes the following Regulations—

### Citation and commencement

1. These Regulations may be cited as the Good Laboratory Practice Regulations 1999 and shall come into force on 14th December 1999.

### Interpretation

- 2.—(1) In these Regulations, unless the context otherwise requires—

“batch” means a specific quantity or lot of a test or reference item produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character;

“experimental starting date” means the date on which the first study specific data are collected;

“experimental completion date” means the last date on which data are collected from the study;

“good laboratory practice instrument” means a document which comprises, or includes—

- (a) an endorsement by a monitoring authority of a claim by a test facility that the tests that it carries out comply with the principles of good laboratory practice;
- (b) a statement by a monitoring authority on the level of adherence of a test facility or a test site to the principles of good laboratory practice (including a statement that the facility or site has been found to be operating in compliance with the said principles or with these Regulations);
- (c) a statement by any other person for submission, or which may be submitted, to a regulatory authority on the level of adherence of a test facility or test site, or any part of a test facility or test site, to the principles of good laboratory practice (including a statement that the facility or site operates in compliance with the said principles or with these Regulations);
- (d) a statement by any person for submission, or which may be submitted, to a regulatory authority that he is a member of the United Kingdom good laboratory practice compliance programme;
- (e) a report issued by a monitoring authority as a result of a study audit or a test facility or test site inspection;
- (f) a statement by any person for submission, or which may be submitted, to a regulatory authority about the level of adherence of a regulatory study, or any phase of a

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(a) S.I. 1999/2788.

(b) 1972 c.68.

(c) Measures relating to good laboratory practice are not a reserved matter under the Scotland Act 1998 (c.46). Therefore, as regards Scotland, see section 57(1) of the 1998 Act which provides that despite the transfer to the Scottish Ministers by virtue of section 53 of that Act of functions in relation to observing and implementing Community law, any function of a Minister of the Crown in relation to any matter (including, therefore, in relation to measures relating to good laboratory practice) shall continue to be exercisable by him as regards Scotland for the purposes specified in section 2(2) of the European Communities Act 1972.

regulatory study, to the principles of good laboratory practice (including a statement that the study, or phase of a study, was conducted in compliance the said principles or with these Regulations),

and for the purposes of this definition, the “principles of good laboratory practice” means the said principles howsoever described;

“master schedule” means a compilation of information to assist in the assessment of workload and for the tracking of studies at a test facility;

“monitoring authority” means an authority in any country or territory which is responsible (either solely or jointly with other such authorities) for monitoring the good laboratory practice compliance of test facilities;

“OECD” means the Organisation for Economic Co-operation and Development;

“OECD test guideline” means a test guideline which the OECD has recommended for use in its member countries;

“operator”, in relation to a test facility, means the person having control of the test facility;

“premises”, in relation to a test facility, includes field sites at which phases of regulatory studies are conducted;

“principal investigator” means an individual who, for a multi-site regulatory study, acts on behalf of the study director and has defined responsibility for one or more delegated phases of the study;

“principles of good laboratory practice” means—

- (a) the principles of good laboratory practice set out in Schedule 1, which are based on the Good Laboratory Practice Principles set out in Section II of the Annex to Council Directive 87/18/ECC(a) on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances, as amended by Commission Directive 1999/11/EC(b) adapting to technical progress the principles of good laboratory practice as specified in Council Directive 87/18/EEC; read with
- (b) the revised guidance for the conduct of test facility inspections and study audits set out in Schedule 2, which is based on part of the Revised Guidance for the Conduct of Test Facility Inspections and Study Audits in the Annex to Council Directive 88/320/EEC(c) on the inspection and verification of good laboratory practice (GLP), as amended by Commission Directive 1999/12/EC(d) adapting to technical progress for the second time the Annex to Council Directive 88/320/EEC;

“quality assurance programme” means a defined system, including personnel, which is independent of study conduct and is designed to assure test facility management of compliance with the principles of good laboratory practice;

“raw data” means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a regulatory study;

“reference item” means any article used to provide a basis for comparison with a test item;

“regulatory authority” means any authority in any country or territory with legal responsibility for aspects of the control of chemicals or items of natural or biological origin;

“regulatory study” means 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);

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(a) OJ No. L 15, 17.1.1987, p. 29.

(b) OJ No. L 77, 23.3.1999, p. 8.

(c) OJ No. L 145, 11.6.1988, p. 35.

(d) OJ No. L 77, 23.3.1999, p. 22.

“short-term study” means a regulatory study of short duration with widely used, routine techniques;

“specimen” means any material derived from a test system for examination, analysis, or retention;

“sponsor” means a person who commissions, supports and/or submits a regulatory study;

“standard operating procedures” means the documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines;

“study completion date” means the date the study director signs the final report;

“study director” means the individual responsible for the overall conduct of the regulatory study;

“study initiation date” means the date the study director (first) signs the study plan;

“study plan” means a document which defines the objectives and experimental design for the conduct of a regulatory study, and includes any study plan amendments;

“study plan amendment” means an intended change to the study plan after the study initiation date;

“study plan deviation” means an unintended departure from the study plan after the study initiation date;

“test facility” means a facility which conducts or intends to conduct regulatory studies;

“test item” means an article that is the subject of a regulatory study;

“test site” means a location at which a phase of a regulatory study is conducted;

“test system” means any biological, chemical or physical system or a combination thereof used in a regulatory study;

“vehicle” means any agent which serves as a carrier used to mix, disperse, or solubilise the test or reference item to facilitate the administration or application to the test system.

- (2) In these Regulations, unless the context otherwise requires, a reference—
- (a) to a numbered regulation or Schedule is to the regulation in or Schedule to these Regulations bearing that number;
  - (b) in a regulation to a numbered or lettered paragraph is to the paragraph of that regulation bearing that number or letter; and
  - (c) in a paragraph to a numbered or lettered sub-paragraph is to the sub-paragraph in that paragraph bearing that number or letter.

### **The Good Laboratory Practice Monitoring Authority**

3.—(1) The body responsible for enforcing compliance with these Regulations shall be the Good Laboratory Practice Monitoring Authority, a body consisting of the Secretary of State for Health, the National Assembly for Wales, the Scottish Ministers and the Department of Health and Social Services for Northern Ireland.

(2) The functions of the Good Laboratory Practice Monitoring Authority may be performed by any one of the Secretary of State for Health, the National Assembly for Wales, the Scottish Ministers or the Department of Health and Social Services for Northern Ireland acting alone, or any two or more of them acting jointly.

(3) In accordance with the preceding provisions of this regulation, in these Regulations, “the Good Laboratory Practice Monitoring Authority” (“the GLPMA”) means any one or more of the Secretary of State for Health, the National Assembly for Wales, the Scottish Ministers and the Department of Health and Social Services for Northern Ireland, and, in the case of anything falling to be done by the GLPMA, means any one or more of them acting as mentioned in paragraph (2).

(4) The GLPMA may appoint such persons as they think necessary for the proper discharge by them of their functions, and those persons shall be appointed upon such terms and conditions (including conditions as to remuneration, benefits, allowances and reimbursement for expenses) as the GLPMA think fit.

**Requirement to be a member or a prospective member of the United Kingdom good laboratory practice compliance programme**

4. A regulatory study shall not be conducted at any premises of a test facility unless—
- (a) the operator of the test facility is regarded by virtue of regulation 5 or 6 as a member or a prospective member of the United Kingdom good laboratory practice compliance programme (hereafter referred to as “the UK GLP compliance programme”); and
  - (b) the operator’s membership or prospective membership of that programme is or is partly in respect of those premises,

and if a regulatory study is conducted at any premises in contravention of this regulation, the operator of that test facility shall be guilty of an offence.

**Prospective membership of the United Kingdom good laboratory practice compliance programme**

5.—(1) An operator of a test facility shall, for the purposes of these Regulations, be regarded as being a prospective member of the UK GLP compliance programme in respect of particular premises only if—

- (a) he has informed the GLPMA by notice in writing of the intention to conduct regulatory studies at those premises;
- (b) the GLPMA has in writing—
  - (i) acknowledged receipt of that notification, and
  - (ii) informed the operator that he is a prospective member of the programme in respect of those premises,

and he has not ceased to be regarded as a prospective member of the programme in respect of those premises by virtue of paragraph (2).

(2) An operator of a test facility shall cease to be regarded as a prospective member of the UK GLP compliance programme in respect of particular test facility premises if—

- (a) he is admitted to membership of the programme in respect of those premises by the GLPMA;
- (b) he informs the GLPMA in writing that he no longer conducts or intends to conduct regulatory studies at those premises; or
- (c) subject to paragraph (3), the GLPMA inform him in writing that they are not prepared to admit him to membership of the programme in respect of those premises.

(3) The GLPMA shall, before informing a prospective member of the UK GLP compliance programme they are not prepared to admit him to membership of the programme in respect of particular test facility premises—

- (a) inform the prospective member that they are considering taking such action and explain to him in writing the reasons why such action is being considered;
- (b) give the operator a specified period within which to make representations to the GLPMA; and
- (c) consider any representations which are duly made and not withdrawn,

unless, for either of the reasons set out in paragraph (4), it is necessary for the GLPMA to inform the prospective member immediately that they are not prepared to admit him to membership of the programme in respect of those premises.

- (4) The reasons referred to in paragraph (3) are that—
- (a) there is a failure to adhere to the principles of good laboratory practice at those premises which, in the opinion of the GLPMA, may contribute towards precipitating a danger to animal or human health or to the environment; or
  - (b) to ensure fulfilment of a Community obligation.

**Membership of the United Kingdom good laboratory practice compliance programme**

6.—(1) Subject to paragraph (2) and except where paragraph (5), (6) or (7) applies, the operator of a test facility shall be regarded as being a member of the UK GLP compliance programme in respect of particular test facility premises if—

- (a) he was regarded as being a member of the programme in respect of those premises immediately before these Regulations come into force by virtue of regulation 6 of the Good Laboratory Practice Regulations 1997(a); or
- (b) after having inspected those premises, the GLPMA have informed the operator in writing that they are admitting the operator to membership of the programme in respect of those premises.

(2) The operator of a test facility shall cease to be a member of the UK GLP compliance programme in respect of particular test facility premises if—

- (a) he has informed the GLPMA in writing that regulatory studies are no longer conducted at those premises; or
- (b) membership of the programme in respect of those premises has been withdrawn by the GLPMA in accordance with paragraph (3).

(3) Subject to paragraph (4), the GLPMA may by a notice in writing served on the operator of a test facility withdraw the operator's membership of the UK GLP compliance programme in respect of particular test facility premises if—

- (a) the operator, in the opinion of the GLPMA, no longer intends to conduct regulatory studies at those premises;
- (b) the operator is, in the opinion of the GLPMA, not capable of ensuring that the principles of good laboratory practice are adhered to at those premises; or
- (c) at those premises there is a failure to adhere to the principles of good laboratory practice which, in the opinion of the GLPMA, may contribute towards precipitating a danger to animal or human health or to the environment.

(4) Before serving a notice on an operator of a test facility under paragraph (3)(a) or (b), the GLPMA shall—

- (a) inform the operator in writing that they are considering serving such a notice and explain to him in writing the reasons why they are considering serving such a notice;
- (b) give the operator a specified period within which to make representations to him; and
- (c) consider any representations which are duly made and not withdrawn,

unless, in order to ensure fulfilment of any Community obligation, it is necessary for the GLPMA to serve the notice immediately.

(5) Where an operator of a test facility has ceased to be a member of the UK GLP compliance programme in respect of particular test facility premises on the grounds set out in paragraph (2)(a), or membership of the programme in respect of particular test facility premises has been withdrawn from him on the grounds set out in paragraph (3)(a), he shall again be regarded as being a member of the programme in respect of those premises if—

- (a) he has informed the GLPMA by notice in writing of the intention to conduct further regulatory studies at those premises;
- (b) he has become a prospective member of the programme in respect of those premises in accordance with the procedure set out in regulation 5; and
- (c) after having inspected those premises, the GLPMA has informed the operator in writing of his readmission to membership of the programme in respect of those premises.

(6) Where membership of the UK GLP compliance programme has been withdrawn from an operator of a test facility in respect of particular test facility premises on the grounds set out in paragraph (3)(b), he shall again be regarded as being a member of the programme in respect of those premises if—

- (a) he has informed the GLPMA by notice in writing of the intention to conduct further regulatory studies at those premises; and
- (b) the GLPMA—

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(a) S.I. 1997/654.

- (i) are of the opinion that the operator is capable of ensuring that the principles of good laboratory practice are adhered to at those premises, and
- (ii) have informed the operator in writing of his readmission to membership of the programme in respect of those premises.

(7) Where membership of the UK GLP compliance programme has been withdrawn from an operator of a test facility in respect of particular test facility premises on the grounds set out in paragraph (3)(c), he shall again be regarded as being a member of the programme in respect of those premises if—

- (a) he has informed the GLPMA by notice in writing of the intention to conduct further regulatory studies at those premises; and
- (b) the GLPMA—
  - (i) are of the opinion that the possible danger to animal or human health or to the environment which led to membership being withdrawn is no longer present, and
  - (ii) have informed the operator in writing of his readmission to membership of the programme in respect of those premises.

### **Requirement to adhere to the principles of good laboratory practice**

7.—(1) No person shall conduct a regulatory study at any premises of a test facility unless with regard to that study the principles of good laboratory practice are adhered to—

- (a) as respects the organisational structure surrounding the study; and
- (b) as respects the conditions under which the study is planned, performed, monitored, recorded, archived and reported.

(2) If the GLPMA have reasonable grounds for believing that a person has contravened paragraph (1) and is responsible for a serious deviation from the principles of good laboratory practice which may have affected the validity of a regulatory study, they may by a notice served on the operator of the test facility at whose premises the alleged contravention took place (in these Regulations referred to as a “warning notice”)—

- (a) state the GLPMA’s grounds for believing that the person—
  - (i) has contravened paragraph (1), and
  - (ii) is responsible for a serious deviation from the principles of good laboratory practice which may have affected the validity of a regulatory study;
- (b) specify the measures which, in the opinion of the GLPMA, the operator of the test facility must take in order to ensure that the serious deviation from the principles of good laboratory practice which may have affected the validity of a regulatory study will not recur;
- (c) require the operator of the test facility to take those measures, or measures which are at least equivalent to them, within such period as may be specified in the warning notice; and
- (d) inform the operator of the test facility of—
  - (i) his right of appeal against the warning notice under regulation 8,
  - (ii) the period within which such an appeal may be brought, and
  - (iii) the effect that such an appeal will have on any criminal proceedings relating to the operator’s alleged failure to comply with the warning notice.

(3) Any operator of a test facility who fails to comply with a warning notice shall, unless that notice has been withdrawn by the GLPMA or cancelled by a court, be guilty of an offence.

### **Appeals against warning notices**

8.—(1) An operator of a test facility who is aggrieved by a decision to serve a warning notice on him may appeal—

- (a) in England, Wales or Northern Ireland, to a magistrates’ court, and such an appeal shall be by way of complaint for an order; or
- (b) in Scotland, to a sheriff, and such an appeal shall be by summary application.

(2) The period during which such an appeal may be brought is—

- (a) one month from the date on which the warning notice was served on the operator desiring to appeal; or

(b) the period specified in the warning notice,  
whichever ends the earlier.

(3) On an appeal against a warning notice, a magistrates' or sheriff court may either cancel or affirm the notice and, if it affirms it, may do so either in its original form or with such modifications as the court may, in the circumstances, think fit.

(4) Pending the final disposal of an appeal, unless or until the appeal is withdrawn, any criminal proceedings relating the operator's alleged failure to comply with the warning notice shall be stayed or suspended.

#### **Powers of entry etc.**

9.—(1) For the purposes of enforcing compliance with these Regulations, a person appointed in accordance with regulation 3(4) shall have a right—

- (a) at any reasonable hour to enter any premises other than premises used only as a private dwelling house which he has reason to believe it is necessary for him to visit;
- (b) to carry out at those premises during that visit such inspections, examinations, tests and analyses as he considers necessary;
- (c) to require the production of and inspect any article or substances at the premises;
- (d) to require the production of, inspect and take copies of or extracts from any book, document, data or record (in whatever form it is held) at, or (in the case of computer data or records) accessible at, the premises;
- (e) subject to paragraph (5), to take possession of any article, substance, book, document, data, record (in whatever form they are held) at, or (in the case of computer data or records) accessible at, the premises;
- (f) to question any person whom he finds at the premises and whom he has reasonable cause to believe is able to give him relevant information;
- (g) to require any person to afford him such assistance as he considers necessary with respect to any matter within that person's control or in relation to which that person has responsibilities;
- (h) to require, as he considers necessary, any person to afford him such facilities as he may reasonably require that person to afford him,

but nothing in this paragraph shall be taken to compel the production by any person of a document of which he would, on grounds of legal professional privilege, be entitled to withhold production on an order for disclosure in an action in the High Court or, as the case may be, on an order for the production of documents in an action in the Court of Session.

(2) If a justice of the peace is satisfied by any written information on oath that there are reasonable grounds for entry into any premises other than premises used only as a private dwelling house for any purpose mentioned in paragraph (1), and—

- (a) admission to the premises has been or is likely to be refused and notice of intention to apply for a warrant under this subsection has been given to the occupier; or
- (b) an application for admission, or the giving of such notice, would defeat the object of the entry or that the premises are unoccupied or that the occupier is temporarily absent and it might defeat the object of the entry to await his return,

the justice may by warrant signed by him, which shall continue in force for a period of one month, authorise any person appointed in accordance with regulation 3(4) to enter the premises, if need be by force.

(3) A person appointed in accordance with regulation 3(4) entering any premises by virtue of paragraph (1) or of a warrant under paragraph (2) may take with him when he enters those premises such equipment as may appear to him necessary and any person who is authorised by the GLPMA to accompany him on that visit.

(4) On leaving any premises which a person appointed in accordance with regulation 3(4) is authorised to enter by a warrant under paragraph (2), that person shall, if the premises are unoccupied or the occupier is temporarily absent, leave the premises as effectively secured against trespassers as he found them.



(5) Where, pursuant to paragraph (1)(e), a person appointed in accordance with regulation 3(4) takes possession of any article, substance, book, document, data or record, he shall leave at the premises with a responsible person a statement giving particulars of the article, substance, book, document, data or record sufficient to identify it and stating that he has taken possession of it.

(6) Persons appointed in accordance with regulation 3(4) shall, when enforcing compliance with these Regulations, have regard to any relevant provision of the Revised Guidance for the Conduct of Test Facility Inspections and Study Audits set out in Part B of the Annex to Council Directive 88/320/EEC on the inspection and verification of good laboratory practice (GLP), as amended by Commission Directive 1999/12/EC adapting to technical progress for the second time the Annex to Council Directive 88/320/EEC.

### **Disclosure of confidential information**

10.—(1) A person who in the course of enforcing compliance with these Regulations gains access to commercially sensitive or other confidential information shall be guilty of an offence if, without lawful authority, he discloses that information.

(2) A person may disclose commercially sensitive or other confidential information to which he has had access in the course of enforcing compliance with these Regulations to—

- (a) the European Commission;
- (b) a monitoring authority;
- (c) a regulatory authority;
- (d) a police force;
- (e) a test facility or sponsor concerned with the inspection or study audit during the course of which the GLPMA gained access to that information.

(3) For the purposes of this regulation—

- (a) the names of test facilities or test sites which are or have been subject to an inspection as part of the UK GLP compliance programme;
- (b) the level of adherence of a test facility or test site to the principles of good laboratory practice of those laboratories as assessed by the GLPMA; and
- (c) the dates upon which study audits or test facility or test site inspections have been conducted,

shall not be considered to be confidential.

### **Obstruction etc. of authorised persons**

11.—(1) Subject to paragraph (2)—

- (a) any person who—
  - (i) intentionally obstructs a person appointed in accordance with regulation 3(4), or
  - (ii) without reasonable cause fails to comply with any requirement made of him by a person appointed in accordance with regulation 3(4),in circumstances where that person is acting in pursuance of any of his functions under these Regulations; or
- (b) any person who, in purported compliance with any such requirement as is mentioned in sub-paragraph (a)(ii), intentionally or recklessly furnishes information which is false or misleading in a material particular,

shall be guilty of an offence.

(2) Nothing in paragraph (1)(a)(ii) shall be construed as requiring any person to answer any question or give any information if to do so might incriminate him or, in the case of a person who is married, his spouse.

### **False good laboratory practice instruments**

12.—(1) A person who—

- (a) makes a false good laboratory practice instrument; or

- (b) makes a copy of an instrument which is, and which he knows or believes to be, a false good laboratory practice instrument,

with the intention that he or another shall use it to induce a regulatory authority to accept it as a genuine good laboratory practice instrument or a copy of a genuine good laboratory practice instrument shall be guilty of an offence.

- (2) A person who has in his possession—

- (a) a false good laboratory practice instrument which he knows or believes to be a false good laboratory practice instrument;
- (b) a copy of an instrument which he knows or believes to be a false good laboratory practice instrument,

with the intention that he or another shall supply it to a regulatory authority with the intention of inducing the regulatory authority to accept it as a genuine good laboratory practice instrument or a copy of a genuine good laboratory practice instrument shall be guilty of an offence.

- (3) A person who supplies to a regulatory authority—

- (a) a false good laboratory practice instrument which he knows or believes to be a false good laboratory practice instrument;
- (b) a copy of an instrument which he knows or believes to be a false good laboratory practice instrument,

with the intention of inducing the regulatory authority to accept it as a genuine good laboratory practice instrument or a copy of a genuine good laboratory practice instrument shall be guilty of an offence.

- (4) A good laboratory practice instrument is “false” for the purposes of this regulation if—

- (a) it is not that which it purports to be for any reason including where—
  - (i) it purports to have been made by a person who did not make it,
  - (ii) it purports to have been made in the form in which it is made by a person who did not in fact make it in that form,
  - (iii) it purports to have been altered in any respect on the authority of a person who did not in fact authorise the alteration in that respect; or
- (b) it includes information which is false or misleading in a material particular,

and a person shall be treated for the purposes of this regulation as making a false good laboratory practice instrument if he alters a good laboratory practice instrument so as to make it false in any respect (whether or not it is false in some other respect apart from that alteration).

- (5) A person may be guilty of an offence—

- (a) under paragraph (1) or (2) if the regulatory authority is outside the United Kingdom;
- (b) under paragraph (3) if the supply is from outside the United Kingdom to a United Kingdom regulatory authority or from within the United Kingdom to a regulatory authority outside the United Kingdom.

#### **Offences by bodies corporate and Scottish partnerships**

**13.** Where an offence under these Regulations 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—

- (a) any director, manager, secretary, partner or similar officer of the body corporate or Scottish partnership; or
- (b) any person who was purporting to act in any such capacity,

he as well as the body corporate or Scottish partnership shall be deemed to be guilty of that offence and he shall be liable to be proceeded against and punished accordingly.

#### **Defence of due diligence**

**14.** In any proceedings for an offence under any of the preceding provisions of these 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.

**Penalties**

15. A person guilty of—
- (a) an offence under regulation 11(1)(a) shall be liable on summary conviction to a fine not exceeding level 3 on the standard scale;
  - (b) an offence under regulation 12 shall be liable—
    - (i) on summary conviction to a fine not exceeding the statutory maximum or to imprisonment for a term not exceeding three months or to both,
    - (ii) on conviction on indictment to a fine or to imprisonment for a term not exceeding two years or to both;
  - (c) any other offence under these Regulations shall be liable on summary conviction to a fine not exceeding level 5 on the standard scale or to imprisonment for a term not exceeding three months or both.

**Fees**

16.—(1) The GLPMA may charge operators of test facilities and operators of test facilities shall, if so charged, pay to the GLPMA such reasonable fees as the GLPMA may determine to cover the cost of providing inspections and services under these Regulations.

(2) The GLPMA may set those fees at levels such that they meet that part of the expenditure of the GLPMA which is reasonably attributable to the cost of inspecting and providing services under these Regulations to or on behalf of the person or class of person charged but the fees must not include any element of profit.

(3) Any such fee shall be payable within fourteen days following written notice from the GLPMA requiring payment of the fee.

(4) All unpaid sums due by way of, or on account of, any fees payable under this regulation shall be recoverable as debts due to the Crown.

- (5) The GLPMA may in exceptional circumstances—
- (a) waive payment of any fee or reduce any fee or part of a fee otherwise payable under this regulation;
  - (b) refund the whole or part of any fee paid pursuant to this regulation.

**Revocation**

17. The Good Laboratory Practice Regulations 1997 are hereby revoked.

Department of Health  
18th November 1999

*Alan Milburn*  
One of Her Majesty's  
Principal Secretaries of State

## SCHEDULE 1

Regulation 2(1)

GOOD LABORATORY PRACTICE PRINCIPLES  
(BASED ON SECTION II OF THE ANNEX TO COUNCIL DIRECTIVE 87/18/EEC,  
AS AMENDED BY COMMISSION DIRECTIVE 1999/11/EC)

## PART I

## TEST FACILITY ORGANISATION AND PERSONNEL

**Facility management's responsibilities**

1.—(1) Each test facility management should ensure that the principles of good laboratory practice are complied with in its test facility.

(2) As a minimum it should—

- (a) ensure that a statement exists which identifies the individuals within a test facility who fulfil the responsibilities of management as defined by the principles of good laboratory practice;
- (b) ensure that a sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of regulatory studies;
- (c) ensure the maintenance of a record of the qualifications, training, experience and job description for each professional and technical individual;
- (d) ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for those functions;
- (e) ensure that appropriate and technically valid standard operating procedures are established and followed, and approve all original and revised standard operating procedures;
- (f) ensure that there is a quality assurance programme with designated personnel and assure that the quality assurance programme is being performed in accordance with the principles of good laboratory practice;
- (g) ensure that for each study an individual with the appropriate qualifications, training and experience is designated by the management as the study director before the study is initiated. Replacement of a study director should be done according to established procedures, and should be documented;
- (h) ensure, in the event of a multi-site study, that, if needed, a principal investigator is designated, who is appropriately trained, qualified and experienced to supervise any delegated phase of the study. Replacement of the principal investigator should be done according to established procedures, and should be documented;
- (i) ensure documented approval of the study plan by the study director;
- (j) ensure that the study director has made the approved study plan available to the quality assurance personnel;
- (k) ensure maintenance of a historical file of all standard operating procedures;
- (l) ensure that an individual is identified as responsible for the management of the archives;
- (m) ensure maintenance of a master schedule;
- (n) ensure that test facility supplies meet requirements appropriate to their use in a study;
- (o) ensure for a multi-site study that clear lines of communication exist between the study director, principal investigator, quality assurance programme and personnel;
- (p) ensure that test and reference items are appropriately characterised;
- (q) establish procedures to ensure that computerised systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with the principles of good laboratory practice.

(3) When a phase of a study is conducted at a test site, test site management (if appointed) will have the responsibilities set out in sub-paragraph (2)(a) to (f), (h), (k) to (n), (p) and (q).

**Study director's responsibilities**

2.—(1) The study director is the single point of study control and has the responsibility for the overall conduct of the regulatory study and for its final report.

(2) These responsibilities should include, but not be limited to, the following functions. The study director should—

- (a) approve the study plan and any amendments to the study plan by dated signature;
- (b) ensure that the quality assurance personnel have a copy of the study plan and any amendments in a timely manner and communicate effectively with the quality assurance personnel as required during the conduct of the study;

- (c) ensure that study plans and amendments and standard operating procedures are available to study personnel;
- (d) ensure that the study plan and the final report for a multi-site study identify and define the role of any principal investigators and any test facilities and test sites involved in the conduct of the study;
- (e) ensure that the procedures specified in the study plan are followed, and assess and document the impact of any deviations from the study plan on the quality and integrity of the study, and take appropriate corrective action if necessary; and acknowledge deviations from standard operating procedures during the conduct of the study;
- (f) ensure that all raw data generated are fully documented and recorded;
- (g) ensure that computerised systems used in the study have been validated;
- (h) sign and date the final report to indicate acceptance of responsibility for the validity of the data and to indicate the extent to which the study complies with the principles of good laboratory practice;
- (i) ensure that after completion (including termination) of the regulatory study, the study plan, the final report, raw data and supporting material are archived.

#### **Principal investigator's responsibilities**

3. The principal investigator will ensure that the delegated phases of the study are conducted in accordance with the applicable principles of good laboratory practice.

#### **Study personnel's responsibilities**

4.—(1) All personnel involved in the conduct of the regulatory study must be knowledgeable in those parts of the principles of good laboratory practice which are applicable to their involvement in the study.

(2) Study personnel will have access to the regulatory study plan and appropriate standard operating procedures applicable to their involvement in the study. It is their responsibility to comply with the instructions given in these documents. Any deviation from these instructions should be documented and communicated directly to the study director and/or, if appropriate, the principal investigator.

(3) All study personnel are responsible for recording raw data promptly and accurately and in compliance with these principles of good laboratory practice, and are responsible for the quality of their data.

(4) Study personnel should exercise health precautions to minimise risk to themselves and to ensure the integrity of the regulatory study. They should communicate to the appropriate person any relevant known health or medical condition in order that they can be excluded from operations that may affect the study.

## **PART II**

### **QUALITY ASSURANCE PROGRAMME**

#### **General**

1.—(1) The test facility should have a documented quality assurance programme to assure that regulatory studies performed are in compliance with the principles of good laboratory practice.

(2) The quality assurance programme should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.

(3) This individual or these individuals should not be involved in the conduct of the regulatory study being assured.

#### **Responsibilities of the quality assurance personnel**

2. The responsibilities of the quality assurance personnel should include, but not be limited to, the following functions. They should—

- (a) maintain copies of all approved study plans and standard operating procedures in use in the test facility and have access to an up-to-date copy of the master schedule;
- (b) verify that the study plan contains the information required for compliance with the principles of good laboratory practice. The verification should be documented;
- (c) conduct inspections to determine if all studies are conducted in accordance with the principles of good laboratory practice. Inspections should also determine that study plans and standard operating procedures have been made available to study personnel and are being followed. Inspections can be of three types, as specified by quality assurance programme standard operating procedures—

- study based inspections,
  - facility based inspections,
  - process based inspections,
- and records of such inspections should be retained;
- (d) inspect the final reports to confirm that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the regulatory study;
  - (e) promptly report any inspection results in writing to management and to the study director, and to any principal investigator and the respective management, when applicable;
  - (f) prepare and sign a statement, to be included with the final report, which specifies the types of inspections and their dates, including the phase of a study inspected, and the dates inspection results were reported to management and the study director and any principal investigators, if applicable. This statement would also serve to confirm that the final report reflects the raw data.

### PART III FACILITIES

#### **General**

1.—(1) The test facility should be of suitable size, construction and location to meet the requirements of the regulatory study and to minimise disturbance that would interfere with the validity of the regulatory study.

(2) The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each regulatory study.

#### **Test System Facilities**

2.—(1) The test facility should have a sufficient number of rooms or areas to assure the isolation of test systems and the isolation of individual projects, involving substances known or suspected of being biohazardous.

(2) Suitable facilities should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems.

(3) There should be storage rooms or areas as needed for supplies and equipment. Storage rooms or areas should be separated from rooms or areas housing the test systems and should provide adequate protection against infestation, contamination and deterioration.

#### **Facilities for handling test and reference items**

3.—(1) To prevent contamination or mix-ups, there should be separate rooms or areas for receipt and storage of the test and reference items, and mixing of the test items with a vehicle.

(2) Storage rooms or areas for the test items should be separate from rooms or areas containing the test systems. They should be adequate to preserve identity, concentration, purity, and stability, and ensure safe storage for hazardous substances.

#### **Archive Facilities**

4. Archive facilities should be provided for the secure storage and retrieval of study plans, raw data, final reports, samples of test items and specimens. Archive design and archive conditions should protect contents from untimely deterioration.

#### **Waste Disposal**

5. Handling and disposal of wastes should be carried out in such a way as not to jeopardise the integrity of regulatory studies. This includes provision for appropriate collection, storage and disposal facilities, and decontamination and transportation procedures.

### PART IV APPARATUS, MATERIALS AND REAGENTS

1. Apparatus, including validated computerised systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the regulatory study, should be suitably located and of appropriate design and adequate capacity.

2. Apparatus used in a regulatory study should be periodically inspected, cleaned, maintained, and calibrated according to standard operating procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement.

3. Apparatus and materials used in studies should not interfere adversely with the test systems.

4. Chemicals, reagents and solutions should be labelled to indicate identity (with concentration if appropriate), expiry date and specific storage instructions. Information concerning source, preparation date and stability should be available. The expiry date may be extended on the basis of documented evaluation or analysis.

## PART V TEST SYSTEMS

### Physical/Chemical

1.—(1) Apparatus used for the generation of physical/chemical data should be suitably located and of appropriate design and adequate capacity.

(2) The integrity of the physical/chemical test systems should be ensured.

### Biological

2.—(1) Proper conditions should be established and maintained for the storage, housing, handling and care of biological test systems, in order to ensure the quality of the data.

(2) Newly received animal and plant test systems should be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, the relevant lot should not be used in regulatory studies and, where appropriate, should be humanely destroyed. At the experimental starting date of a regulatory study, test systems should be free of any disease or condition that might interfere with the purpose or conduct of the study. Test systems that become diseased or injured during the course of a regulatory study should be isolated and treated, if necessary to maintain the integrity of the study. Any diagnosis and treatment of any disease before or during a regulatory study should be recorded.

(3) Records of source, date of arrival, and the arrival condition of test systems should be maintained.

(4) Biological test systems should be acclimatised to the test environment for an adequate period before the first administration or application of the test or reference item.

(5) All information needed to identify properly the test systems should appear on their housing or containers. Individual test systems that are to be removed from their housing or containers during the conduct of the regulatory study should bear appropriate identification, wherever possible.

(6) During use, housing or containers for test systems should be cleaned and sanitised at appropriate intervals. Any material that comes into contact with the test system should be free of contaminants at levels that would interfere with the regulatory study. Bedding for animals should be changed as required by sound husbandry practice. Use of pest control agents should be documented.

(7) Test systems used in field studies should be located so as to avoid interference in the regulatory study from spray drift and from past usage of pesticides.

## PART VI TEST AND REFERENCE ITEMS

### Receipt, handling, sampling and storage

1.—(1) Records including test item and reference item characterisation, date of receipt, expiry date, quantities received and used in regulatory studies should be maintained.

(2) Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured to the degree possible and contamination or mix-up are precluded.

(3) Storage containers should carry identification information, expiry date, and specific storage instructions.

### Characterisation

2.—(1) Each test and reference item should be appropriately identified (eg code, chemical abstracts service registry number (CAS number), name, biological parameters etc.).

(2) For each regulatory study, the identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test or reference items should be known.

(3) In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation between the sponsor and the test facility, to verify the identity of the test item subject to the study.

(4) The stability of test and reference items under storage and test conditions should be known for all regulatory studies.

(5) If the test item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined. For test items used in field studies (eg tank mixes), these may be determined through separate laboratory experiments.

(6) A sample for analytical purposes from each batch of test item should be retained for all regulatory studies except short-term studies.

## PART VII

### STANDARD OPERATING PROCEDURES

1. A test facility should have written standard operating procedures approved by test facility management that are intended to ensure the quality and integrity of the data generated by the test facility. Revisions to standard operating procedures should be approved by test facility management.

2. Each separate test facility unit or area should have immediately available current standard operating procedures relevant to the activities being performed therein. Published textbooks, analytical methods, articles and manuals may be used as supplements to these standard operating procedures.

3. Deviations from standard operating procedures related to the regulatory study should be documented and should be acknowledged by the study director and any principal investigators, as applicable.

4. Standard operating procedures should be available for, but not be limited to, the following categories of test facility activities. The details given under each heading are to be considered as illustrative examples—

(a) **Test and reference items**

receipt, identification, labelling, handling, sampling and storage;

(b) **Apparatus, materials and reagents**

(i) *apparatus*: use, maintenance, cleaning and calibration,

(ii) *computerised systems*: validation, operation, maintenance, security, change control and back-up,

(iii) *materials, reagents and solutions*: preparation and labelling;

(c) **Record keeping, reporting, storage, and retrieval**

coding of studies, data collection, preparation of reports, indexing systems, handling of data, including the use of computerised data systems;

(d) **Test system (where appropriate)**

(i) room preparation and environmental room conditions for the test system,

(ii) procedures for receipt, transfer, proper placement, characterisation, identification and care of test system,

(iii) test system preparation, observation and examinations, before, during and at the conclusion of the regulatory study,

(iv) handling of test system individuals found moribund or dead during the regulatory study,

(v) collection, identification and handling of specimens including necropsy and histopathology,

(vi) siting and placement of test systems in test plots;

(e) **Quality assurance procedures**

operation of quality assurance personnel in planning, scheduling, performing, documenting and reporting inspections.



PART VIII  
PERFORMANCE OF THE REGULATORY STUDY

**Study plan**

1.—(1) For each regulatory study, a written plan should exist prior to initiation of the study. The study plan should be approved by dated signature of the study director and verified for good laboratory practice compliance by quality assurance personnel as specified in paragraph 2(b) of Part II of this Schedule.

(2) As respects the study plan—

- (a) amendments to it should be justified and approved by dated signature of the study director and maintained with the study plan;
- (b) deviations from it should be described, explained, acknowledged and dated in a timely fashion by the study director and/or any principal investigators and maintained with the study raw data.

(3) For short-term studies, a general study plan accompanied by a study specific supplement may be used.

**Content of the Study Plan**

2.—(1) The study plan should contain, but not be limited to, the following information—

(a) **Identification of the study, the test item and the reference item**

- (i) a descriptive title,
- (ii) a statement which reveals the nature and purpose of the regulatory study,
- (iii) identification of the test item by code or name (IUPAC, CAS number, biological parameters etc.),
- (iv) the reference item to be used;

(b) **Information concerning the sponsor and the test facility**

- (i) name and address of the sponsor,
- (ii) name and address of any test facilities and test sites involved,
- (iii) name and address of the study director,
- (iv) name and address of any principal investigator, and the phase of the study delegated by the study director to, and under the responsibility of, the principal investigator;

(c) **Dates**

- (i) the date of approval of the study plan by signature of the study director,
- (ii) the proposed experimental starting and completion dates;

(d) **Test methods**

reference to OECD test guideline or other test guideline or method to be used;

(e) **Issues (where applicable)**

- (i) the justification for selection of the test system,
- (ii) characterisation of the test system, such as the species, strain, sub-strain, source of supply, number, body weight range, sex, age, and other pertinent information,
- (iii) the method of administration and the reason for its choice,
- (iv) the dose levels and/or concentration, frequency, duration of administration or application,
- (v) detailed information on the experimental design, including a description of the chronological procedure of the regulatory study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed, and statistical methods to be used (if any);

(f) **Records**

a list of records to be retained.

**Conduct of the Regulatory study**

3.—(1) a unique identification should be given to each regulatory study. All items concerning this regulatory study should carry this identification. Specimens from the study should be identified to confirm their origin. Such identification should enable traceability, as appropriate for the specimen and study.

(2) The regulatory study should be conducted in accordance with the study plan.

(3) All data generated during the conduct of the regulatory study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialled and dated.

(4) Any change in the raw data should be made so as not to obscure the previous entry, should indicate the reason for change and should be dated and signed or initialled by the individual making the change.

(5) Data generated as a direct computer input should be identified at the time of data input by the individual responsible for direct data entries. Computerised system design should always provide for the retention of full audit trails to show all changes to the data without obscuring the original data. It should be possible to associate all changes to data with the person having made those changes, for example by the use of timed and dated (electronic) signatures. Reasons for changes should be given.

## PART IX

### REPORTING OF REGULATORY STUDY RESULTS

#### General

1.—(1) A final report should be prepared for each regulatory study. In the case of short-term studies, a standardised final report accompanied by a study specific extension may be prepared.

(2) Reports of principal investigators or scientists involved in the regulatory study should be signed and dated by them.

(3) The final report should be signed and dated by the study director to indicate acceptance of responsibility for the validity of the data. The extent of compliance with these principles of good laboratory practice should be indicated.

(4) Corrections and additions to a final report should be in the form of amendments. Amendments should clearly specify the reason for the corrections or additions and should be signed and dated by the study director.

(5) Reformatting of the final report to comply with the submission requirements of a national registration or regulatory authority does not constitute a correction, addition or amendment to the final report.

#### Content of the Final Report

2. The final report should include, but not be limited to, the following information—

(a) **Identification of the regulatory study, the test item and the reference item**

- (i) a descriptive title,
- (ii) identification of the test item by code or name (IUPAC, CAS number, biological parameters etc.),
- (iii) identification of the reference item by name,
- (iv) characterisation of the test item including purity, stability and homogeneity;

(b) **Information concerning the sponsor and the test facility**

- (i) name and address of the sponsor,
- (ii) name and address of any test facilities and test sites involved,
- (iii) name and address of the study director,
- (iv) name and address of any principal investigators and the phase of the study delegated, if applicable,
- (v) name and address of scientists having contributed reports to the final report;

(c) **Dates**

experimental starting and completion dates;

(d) **Statement**

a quality assurance programme statement listing the types of inspections made and their dates, including the phases inspected, and the dates any inspection results were reported to management and to the study director and any principal investigators, if applicable. This statement would also serve to confirm that the final report reflects the raw data;

(e) **Description of materials and test methods**

- (i) description of methods and materials used,
- (ii) reference to OECD test guidelines or other test guidelines or methods;

(f) **Results**

- (i) a summary of results,
- (ii) all information and data required in the study plan,
- (iii) a presentation of the results, including calculations and determinations of statistical significance,
- (iv) an evaluation and discussion of the results and, where appropriate, conclusions;

(g) **Storage**

the location where the study plan, samples of test and reference items, specimens, raw data, and the final report are to be stored.

## PART X

## STORAGE AND RETENTION OF RECORDS AND MATERIALS

1.—(1) The following should be retained in the archives for the period specified by the appropriate regulatory authorities—

- (a) the study plan, raw data, samples of test and reference items, specimens and the final report of each regulatory study;
- (b) records of all inspections performed by the quality assurance programme, as well as master schedules;
- (c) records of qualifications, training, experience and job descriptions of personnel;
- (d) records and reports of the maintenance and calibration of apparatus;
- (e) validation documentation for computerised systems;
- (f) the historical file of all standard operating procedures;
- (g) environmental monitoring records.

(2) In the absence of a required retention period, the final disposition of any study materials should be documented. When samples of test and reference items and specimens are disposed of before the expiry of the required retention period for any reason, this should be justified and documented. Samples of test and reference items and specimens should be retained only as long as the quality of the preparation permits evaluation.

2. Material retained in the archives should be indexed so as to facilitate orderly storage and retrieval.

3. Only personnel authorised by management should have access to the archives. Movement of material in and out of the archives should be properly recorded.

4. If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archives of the sponsor of the regulatory study.

## SCHEDULE 2

Regulation 2(1)

REVISED GUIDANCE FOR THE CONDUCT  
OF TEST FACILITY INSPECTIONS AND STUDY AUDITS  
(BASED ON PART OF PART B OF THE ANNEX TO  
COUNCIL DIRECTIVE 88/320/EEC, AS AMENDED BY  
COMMISSION DIRECTIVE 1999/12/EC)

## PART I

## INSPECTION PROCEDURES

**Pre-inspection**

1.—(1) *Purpose:* to familiarise the inspector with the facility which is about to be inspected in respect of management structure, physical layout of buildings and range of studies.

(2) Prior to conducting a test facility inspection or study audit, inspectors should familiarise themselves with the facility which is to be visited. Any existing information on the facility should be reviewed. This may include previous inspection reports, the layout of the facility, organisation charts, study reports, protocols and *curricula vitae* (CVs) of personnel. Such documents would provide information on—

- the type, size and layout of the facility,
- the range of studies likely to be encountered during the inspection,
- the management structure of the facility.

(3) Inspectors should note, in particular, any deficiencies from previous test facility inspections. Where no previous test facility inspections have been conducted, a pre-inspection visit can be made to obtain relevant information.

(4) Test facilities may be informed of the date and time of an inspector's arrival, the objective of their visit and the length of time they expect to be on the premises. This could allow the test facility to ensure that the appropriate personnel and documentation are available. In cases where particular documents or records are to be examined, it may be useful to identify these to the test facility in advance of the visit so that they will be immediately available during the test facility inspection.

**Starting conference**

2.—(1) *Purpose:* to inform the management and staff of the facility of the reason for the test facility inspection or study audit that is about to take place, and to identify the facility areas, study(ies) selected for audit, documents and personnel likely to be involved.

(2) The administrative and practical details of a test facility inspection or study audit should be discussed with the management of the facility at the start of the visit. At the starting conference, inspectors should—

- outline the purpose and scope of the visit,
- describe the documentation which will be required for the test facility inspection, such as lists of on-going and completed studies, study plans, standard operating procedures, study reports, etc. Access to and, if necessary, arrangements for the copying of relevant documents should be agreed upon at this time,
- clarify or request information as to the management structure (organisation) and personnel of the facility,
- request information as to the conduct of studies not subject to principles of good laboratory practice in areas of the test facility where good laboratory practice studies are being conducted,
- make an initial determination as to the parts of the facility to be covered during the test facility inspection,
- describe the documents and specimens that will be needed for on-going or completed study(ies) selected for study audit,
- indicate that a closing conference will be held at the completion of the inspection.

(3) Before proceeding further with a test facility inspection, it is advisable for the inspector to establish contact with the facility's quality assurance unit.

(4) As a general rule, when inspecting a facility, inspectors will find it helpful to be accompanied by a member of the quality assurance unit.

(5) Inspectors may wish to request that a room be set aside for examination of documents and other activities.

### Organisation and personnel

3.—(1) *Purpose:* to determine whether the test facility has sufficient qualified personnel, staff resources and support services for the variety and number of studies undertaken, whether the organisational structure is appropriate, and whether management has established a policy regarding training and staff health surveillance appropriate to the studies undertaken in the facility.

- (2) The management should be asked to produce certain documents, for example—
- floor plans,
  - facility management and scientific organisation charts,
  - CVs of personnel involved in any types of studies selected for the study audit,
  - lists of on-going and completed studies with information on the type of study, initiation/completion dates, test system, method of application of test item and name of study director,
  - staff health surveillance policies,
  - staff job descriptions and staff training programmes and records,
  - an index to the facility's standard operating procedures,
  - specific standard operating procedures related to the studies or procedures being inspected or audited,
  - lists of the study directors associated with the study(ies) being audited.
- (3) The inspector should check, in particular—
- lists of on-going and completed studies to ascertain the level of work being undertaken by the test facility,
  - the identity and qualifications of the study directors, the head of the quality assurance unit and other personnel,
  - the existence of standard operating procedures for all relevant areas of testing.

### Quality assurance programme

4.—(1) *Purpose:* to determine whether the mechanisms used to assure management that regulatory studies are conducted in accordance with the principles of good laboratory practice are adequate.

(2) The head of the quality assurance unit should be asked to demonstrate the systems and methods of quality assurance inspection and monitoring of studies, and the system for recording observations made during quality assurance monitoring. Inspectors should check—

- the qualifications of the head of quality assurance, and of all quality assurance staff,
- that the quality assurance unit functions independently from the staff involved in the studies,
- how the quality assurance unit schedules and conducts inspections, how it monitors identified critical phases in a study, and what resources are available for quality assurance inspections and monitoring activities,
- that where studies are of such short duration that monitoring of each study is impracticable, arrangements exist for monitoring on a sample basis,
- the extent and depth of quality assurance monitoring during the practical phases of the study,
- the extent and depth of quality assurance monitoring of routine test facility operation,
- the quality assurance procedure for checking the final report to ensure its agreement with the raw data,
- that management receives reports from quality assurance concerning problems likely to affect the quality or integrity of a study,
- the actions taken by quality assurance when deviations are found,
- the quality assurance role, if any, if studies or parts of studies are done in contract laboratories,
- the part played, if any, by quality assurance in the review, revision and up-dating of standard operating procedures.

### Facilities

5.—(1) *Purpose:* to determine if the test facility, whether indoor or outdoor, is of suitable size, design and location to meet the demands of the studies being undertaken.

- (2) The inspector should check that—
- the design enables an adequate degree of separation so that, for example, test substances, animals, diets, pathological specimens etc. of one study cannot be confused with those of another,

- environmental control and monitoring procedures exist and function adequately in critical areas, for example, animal and other biological test systems rooms, test item storage areas, laboratory areas,
- the general housekeeping is adequate for the various facilities and that there are, if necessary, pest control procedures.

#### **Care, housing and containment of biological test systems**

6.—(1) *Purpose:* to determine whether the test facility, if engaged in studies using animals or other biological test systems, has support facilities and conditions for their care, housing and containment which are adequate to prevent stress and other problems which could affect the test system and hence the quality of data.

(2) A test facility may be carrying out studies which require a diversity of animal or plant species as well as microbial or other cellular or sub-cellular systems. The type of test systems being used will determine the aspects relating to care, housing or containment that the inspector will monitor. Using his judgment, the inspector will check, according to the test systems, that—

- there are facilities adequate for the test systems used and for testing needs,
- there are arrangements to quarantine animals and plants being introduced into the facility and that these arrangements are working satisfactorily,
- there are arrangements to isolate animals (or other elements of a test system, if necessary) known to be, or suspected of being, diseased or carriers of disease,
- there is adequate monitoring and record-keeping of health, behaviour or other aspects, as appropriate to the test system,
- the equipment for maintaining the environmental conditions required for each test system is adequate, well-maintained, and effective,
- animal cages, racks, tanks and other containers, as well as accessory equipment, are kept sufficiently clean,
- analyses to check environmental conditions and support systems are carried out as required,
- facilities exist for removal and disposal of animal waste and refuse from the test systems and that these are operated so as to minimise vermin infestation, odours, disease hazards and environmental contamination,
- storage areas are provided for animal feed or equivalent materials for all test systems, that these areas are not used for the storage of other materials such as test items, pest control chemicals or disinfectants, and that they are separate from areas in which animals are housed or other biological test systems are kept,
- stored feed and bedding are protected from deterioration by adverse environmental conditions, infestation or contamination.

#### **Apparatus, materials, reagents and specimens**

7.—(1) *Purpose:* to determine whether the test facility has suitably located, operational apparatus in sufficient quantity and of adequate capacity to meet the requirements of the tests being conducted in the facility, and that the materials, reagents and specimens are properly labelled, used and stored.

(2) The inspector should check that—

- apparatus is clean and in good working order,
- records have been kept of operation, maintenance, verification, calibration and validation of measuring equipment and apparatus (including computerised systems),
- materials and chemical reagents are properly labelled and stored at appropriate temperatures and that expiry dates are not being ignored. Labels for reagents should indicate their source, identity, concentration and/or other pertinent information,
- specimens are well identified by test system, study, nature and date of collection,
- apparatus and materials used do not alter to any appreciable extent the test systems.

#### **Test systems**

8.—(1) *Purpose:* to determine whether adequate procedures exist for the handling and control of the variety of test systems required by the studies undertaken in the facility, for example, chemical and physical systems, cellular and microbic systems, plants or animals.

(2) As regards physical and chemical systems, the inspector should check that—

- where required by study plans, the stability of test and reference items was determined and that the reference items specified in test plans were used,
- in automated systems, data generated as graphs, recorder traces or computer print-outs are documented as raw data and archived.

(3) As regards biological test systems, taking account of the relevant aspects referred to above relating to care, housing or containment of biological tests systems, the inspector should check that—

- test systems are as specified in study plans,
- test systems are adequately and, if necessary and appropriate, uniquely identified throughout the study, and that records exist regarding receipt of the test systems and document fully the number of test systems received, used, replaced or discarded,
- housing or containers of test systems are properly identified with all the necessary information,
- there is an adequate separation of studies being conducted on the same animal species (or the same biological test system) but with different items,
- there is an adequate separation of animal species (and other biological test systems) either in space or in time,
- the biological test system environment is as specified in the study plan or in standard operating procedures for aspects such as temperature, or light/dark cycles,
- the recording of the receipt, handling, housing or containment, care and health evaluation is appropriate to the test systems,
- written records are kept of examination, quarantine, morbidity, mortality, behaviour, diagnosis and treatment of animal and plant test systems or other similar aspects as appropriate to each biological test system,
- there are provisions for the appropriate disposal of test systems at the end of tests.

#### Test and reference items

9.—(1) *Purpose*: to determine whether the test facility has procedures designed—

- (a) to ensure that the identity, potency, quantity and composition of test and reference items are in accordance with their specifications; and
- (b) to properly receive and store test and reference items.

(2) The inspector should check that—

- there are written records on the receipt (including identification of the person responsible), and for the handling, sampling, usage and storage of test and reference items,
- test and reference item containers are properly labelled,
- storage conditions are appropriate to preserve the concentration, purity and stability of the test and reference items,
- there are written records on the determination of identity, purity, composition, stability, and for the prevention of contamination of test and reference items, where applicable,
- there are procedures for the determination of the homogeneity and stability of mixtures containing test and reference items, where applicable,
- containers holding mixtures (or dilutions) of the test and reference items are labelled and that records are kept of the homogeneity and stability of their contents, where applicable,
- when the test is of longer than four weeks duration, samples from each batch of test and reference items have been taken for analytical purposes and that they have been retained for an appropriate time,
- procedures for mixing substances are designed to prevent errors in identification or cross-contamination.

#### Standard operating procedures

10.—(1) *Purpose*: to determine whether the test facility has written standard operating procedures relating to all the important aspects of its operations, considering that one of the most important management techniques for controlling facility operations is the use of written standard operating procedures. These relate directly to the routine elements of tests conducted by the test facility.

(2) The inspector should check that—

- each test facility area has immediately available relevant, authorised copies of standard operating procedures,
- procedures exist for the revision and updating of standard operating procedures,
- any amendments or changes to standard operating procedures have been authorised and dated,
- historical files of standard operating procedures are maintained,
- standard operating procedures are available for, but not necessarily limited to, the following activities:
  - (i) receipt, determination of identity, purity, composition and stability, labelling, handling, sampling, usage, and storage of test and reference items,
  - (ii) use, maintenance, cleaning, calibration and validation of measuring apparatus, computerised systems and environmental control equipment,
  - (iii) preparation of reagents and dosing formulations,

- (iv) record-keeping, reporting, storage and retrieval of records and reports,
- (v) preparation and environmental control of areas containing the test systems,
- (vi) receipt, transfer, location, characterisation, identification and care of test systems,
- (vii) handling of the test systems before, during and at the termination of the study,
- (viii) disposal of test systems,
- (ix) use of pest control and cleaning agents,
- (x) quality assurance programme operations.

### Performance of the study

**11.**—(1) *Purpose:* to verify that written study plans exist and that the plans and the conduct of the study are in accordance with good laboratory practice principles.

- (2) The inspector should check that—
- the study plan was signed by the study director,
  - any amendments to the study plan were signed and dated by the study director,
  - the date of the agreement to the study plan by the sponsor was recorded (where applicable),
  - measurements, observations, and examinations were in accordance with the study plan and relevant standard operating procedures,
  - the results of these measurements, observations, and examinations were recorded directly, promptly, accurately and legibly and were signed (or initialled) and dated,
  - any changes in the raw data, including data stored in computers, did not obscure previous entries, included the reason for the change and identified the person responsible for the change and the date it was made,
  - computer-generated or stored data have been identified and that the procedures to protect them against unauthorised amendments or loss are adequate,
  - the computerised systems used within the study are reliable, accurate, and have been validated,
  - any unforeseen events recorded in the raw data have been investigated and evaluated,
  - the results presented in the reports of the study (interim or final) are consistent and complete and that they correctly reflect the raw data.

### Reporting of study results

**12.**—(1) *Purpose:* to determine whether final reports are prepared in accordance with good laboratory practice principles.

- (2) When examining a final report, the inspector should check that—
- it is signed and dated by the study director to indicate acceptance of responsibility for the validity of the study and confirming that the study was conducted in accordance with good laboratory practice principles,
  - it is signed and dated by other principal scientists, if reports from co-operating disciplines are included,
  - a quality assurance statement is included in the report and that it is signed and dated,
  - any amendments were made by the responsible personnel,
  - it lists the archive location of all samples, specimens and raw data.

### Storage and retention of records

**13.**—(1) *Purpose:* to determine whether the facility has generated adequate records and reports and whether adequate provision has been made for the safe storage and retention of records and materials.

- (2) The inspector should check—
- that a person has been identified as responsible for the archive,
  - the archive facilities for the storage of study plans, raw data (including that from discontinued good laboratory practice studies), final reports, samples, specimens and records of education and training of personnel,
  - the procedures for retrieval of archived materials,
  - the procedures whereby access to the archives is limited to authorised personnel and records are kept of personnel given access to raw data, slides, etc.,
  - that an inventory is maintained of materials removed from, and returned to, the archives,
  - that records and materials are retained for the required or appropriate period of time and are protected from loss or damage by fire, adverse environmental conditions, etc.



## PART II STUDY AUDITS

1. Test facility inspections will generally include, *inter alia*, study audits, which review on-going or completed regulatory studies. Specific study audits are also often requested by regulatory authorities, and can be conducted independently of test facility inspections. Because of the wide variation in the types of regulatory studies which might be audited, only general guidance is appropriate, and inspectors and others taking part in study audits will always need to exercise judgement as to the nature and extent of their examinations. The objective should be to reconstruct the study by comparing the final report with the study plan, relevant standard operating procedures, raw data and other archived material.

2. In some cases, inspectors may need assistance from other experts in order to conduct an effective study audit, for example where there is a need to examine tissue sections under the microscope.

3. When conducting a study audit, the inspector should—

- obtain names, job descriptions and summaries of training and experience for selected personnel engaged in the study(ies) such as the study director and principal scientists,
- check that there is sufficient staff trained in relevant areas for the study(ies) undertaken,
- identify individual items of apparatus or special equipment used in the study and examine the calibration, maintenance and service records for the equipment,
- review the records relating to the stability of the test items, analyses of test items and formulations, analyses of feed, etc.,
- attempt to determine, through the interview process if possible, the work assignments of selected individuals participating in the study to ascertain if these individuals had the time to accomplish the tasks specified in the study plan or report,
- obtain copies of all documentation concerning control procedures or forming integral parts of the study, including—
  - (i) the study plan,
  - (ii) standard operating procedures in use at the time the study was done,
  - (iii) log books, laboratory notebooks, files, worksheets, print-outs of computer-stored data, etc., checking calculations where appropriate,
  - (iv) the final report.

4. In studies in which animals (i.e. rodents and other mammals) are used, the inspector should follow a certain percentage of individual animals from their arrival at the test facility to autopsy. They should pay particular attention to the records relating to:

- animal body weight, food/water intake, dose formulation and administration etc.,
- clinical observations and autopsy findings,
- clinical chemistry,
- pathology.

## EXPLANATORY NOTE

*(This note is not part of the Regulations)*

These Regulations contain the legislative measures necessary for the implementation within the United Kingdom of Council Directive 87/18/EEC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances, as amended by Commission Directive 1999/11/EC adapting to technical progress the principles of good laboratory practice as specified in Council Directive 87/18/EEC, and for the implementation of Council Directive 88/320/EEC on the inspection and verification of Good Laboratory Practice (GLP), as amended by Commission Directive 1999/12/EC adapting to technical progress for a second time the Annex to Council Directive 88/320/EEC.

Regulation 2 is an interpretation provision. Amongst other definitions, there is a definition of the principles of good laboratory practice, a concept which is defined with reference to the principles set out in Schedule 1 to the Regulations and the operating procedures set out in Schedule 2. Regulation 3 sets out the arrangements for enforcing compliance with the Regulations by the good laboratory practice monitoring authority ("GLPMA").

Regulation 4 contains a requirement that regulatory studies must only be conducted at test facilities which are part of the United Kingdom good laboratory practice compliance programme. Regulation 5 deals with prospective membership of the programme by test facility operators in respect of particular test facility premises, and Regulation 6 deals with full membership of the programme.

Regulation 7 contains a requirement that regulatory studies shall be conducted in accordance with the principles of good laboratory practice. Where there are serious deviations from the principles, there is a procedure for serving warning notices on test facility operators requiring them to ensure that the serious deviation will not recur. Breach of such a notice is an offence, although there is an appeals procedure contained in Regulation 8, if an operator of a test facility is aggrieved by a decision to serve a warning notice on him.

Regulation 9 contains the powers to enable persons duly appointed by the GLPMA to enforce compliance with the provisions of the Regulations, including powers of entry. Regulation 10 contains rules relating to the disclosure of commercially sensitive or other confidential information which may come to light as a result of enforcement action taken under the Regulations. Impeding the work of a person duly appointed by the GLPMA who is acting in pursuance of any of his functions under the Regulations is made an offence under Regulation 11.

Regulation 12 contains offences relating to the production and supply to regulatory authorities of false good laboratory practice instruments. Regulation 13 relates to offences committed with the consent or connivance, or attributable to, bodies corporate or Scottish partnerships, and Regulation 14 is a general defence of due diligence in relation to any of the offences under the Regulations.

Regulation 15 is a penalties provision, and Regulation 16 gives the GLPMA powers to charge fees for inspections and services under the Regulations. Regulation 17 revokes the Good Laboratory Practice Regulations 1997.

A Regulatory Impact Assessment in relation to these Regulations has been prepared and copies may be obtained from the GLPMA, Room 1808, Market Towers, 1 Nine Elms Lane, London SW8 5NQ. A copy has also been placed in the library of each of the Houses of Parliament.



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**STATUTORY INSTRUMENTS**

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**1999 No. 3106****HEALTH AND SAFETY****The Good Laboratory Practice Regulations 1999**

£4.50

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Printed and published in the UK by The Stationery Office Limited  
under the authority and superintendence of Carol Tullo, Controller of  
Her Majesty's Stationery Office and Queen's Printer of Acts of Parliament.  
WO 5771 11/99 000000

ISBN 0-11-085544-2



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