SCHEDULE 1 Regulation 2(1)

GOOD LABORATORY PRACTICE PRINCIPLES **[**[F1](BASED ON SECTION II OF ANNEX I TO THE EUROPEAN PARLIAMENT AND COUNCIL DIRECTIVE 2004/10/EC)**]**

F1 Words in Sch. 1 heading substituted (27.4.2004) by The Good Laboratory Practice (Codification Amendments Etc.) Regulations 2004 (S.I. 2004/994), regs. 1, **2(d)**

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 or 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 indivdual is identified as reponsible 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 responsiblity to comply with the intructions 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 sytems 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—

Test and reference items

(a) receipt, identification, labelling, handling, sampling and storage;

Apparatus, materials and reagents

(b) (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;

Record keeping, reporting, storage, and retrieval

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

Test system (where appropriate)

(d) (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;

Quality assurance procedures

(e) 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—

Identification of the study, the test item and the reference item

(a) (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;

Information concerning the sponsor and the test facility

(b) (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;

Dates

(c) (i) the date of approval of the study plan by signature of the study director,

(ii) the proposed experimental starting and completion dates;

Test methods

(d) reference to OECD test guideline or other test guideline or method to be used;

Issues (where applicable)

(e) (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, measurments, observations and examinations to be performed, and statistical methods to be used (if any);

Records

(f) 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—

Identification of the regulatory study, the test item and the reference item

(a) (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;

Dates

(c) experimental starting and completion dates;

Statement

(d) 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;

Description of materials and test methods

(e) (i) description of methods and materials used,

(ii) reference to OECD test guidelines or other test guidelines or methods;

Results

(f) (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;

Storage

(g) 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 speciments 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 CONDUCTOF TEST FACILITY INSPECTIONS AND STUDY AUDITS **[**[F2](BASED ON PART OF PART B OF ANNEX I TO THE EUROPEAN PARLIAMENT AND COUNCIL DIRECTIVE 2004/9/EC)**]**

F2 Words in Sch. 2 heading substituted (27.4.2004) by The Good Laboratory Practice (Codification Amendments Etc.) Regulations 2004 (S.I. 2004/994), regs. 1, **2(e)**

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—

(0) 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 detemination 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.

Changes to legislation:
There are currently no known outstanding effects for the The Good Laboratory Practice Regulations 1999.