SCHEDULE 2

REVISED GUIDANCE FOR THE CONDUCTOF TEST FACILITY INSPECTIONS AND STUDY AUDITS **[**[F1](BASED ON PART OF PART B OF ANNEX I TO THE EUROPEAN PARLIAMENT AND COUNCIL DIRECTIVE 2004/9/EC)**]**

Textual Amendments

F1 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.

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