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 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;

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;

(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.